Ministry of Environment of Denmark
Environmental Protection Agency

Analyses and risk assessment of endocrine disruptors in products for pregnant women and children

Survey of chemical substances in consumer products No. 189

June 2022

Publisher: The Danish Environmental Protection Agency

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ISBN: 978-87-7038-398-1

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Preface

Analysis and risk assessment of endocrine disruptors

In this project, chemical analyses of selected endocrine disruptors have been carried out in a wide range of consumer products. The project follows up on the survey and screening analyses carried out in the project "Survey of selected endocrine disruptors" carried out in 2020.

Results of the analyses and risk assessment are presented in this report.

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The project was funded by the Danish Environmental Protection Agency (Danish EPA).

The project was conducted from the end of May 2021 to the middle of January 2022.

Abbreviations

ADI	Acceptable Daily Intake
AF	Assessment Factor
AGD	Anogenital Distance
AO	Adverse Outcome
BMDL	BenchMark Dose Low
DNEL	Derived No-Effect Level
DMEL	Derived Minimal-Effect Level
EAS	Estrogenic, (anti-)androgenic, steroidsynthesis inhibiting
ECHA	European Chemicals Agency
ED	Endocrine Disruptor
EDC	Endocrine Disrupting Chemical
EFSA	European Food Safety Authority
GD	Gestation Day
KE	Key Event
LOAEL	Lowest-observed adverse effect level
LOD	Level Of Detection
LOQ	Level Of Quantification
MAF	Mixture Assessment Factor
MoA	Mode of Action
MIE	Molecular Initiating Event
NOAEL	No-Observed Adverse Effect Level
PBT/vPvB	PBT (persistent, bioaccumulative, toxic) and vPvB (very persistent, very bioaccumulative)
PoD	Point of Departure, e.g. NOAEL-value
RCR	Risk Characterization Ratio
SED	Systemic Exposure Dose
SVHC	Substances of Very High Concern
TDI	Tolerable Daily Intake
WoE	Weight of Evidence

Summary

This project carried out a hazard, exposure and risk assessment of the overall exposure of consumers to six different selected endocrine disruptors via selected consumer products as well as other products including food, food contact materials, medicinal products. The six focus substances of the project include:

1. Butylated hydroxylanisole (BHA), CAS No. 25013-16-5
2. Butylated hydroxytoluene (BHT), CAS No. 128-37-0
3. Butylparaben, CAS No. 94-26-8
4. Propylparaben, CAS No. 94-13-3
5. Octamethylcyclotetrasiloxane (D4), CAS No. 556-67-2
6. Bisphenol A (BPA), CAS No. 80-05-7

Background
In 2020, a survey of nine selected endocrine disruptors and/or substances suspected of being endocrine disruptors was prepared. The project was a survey and screening project, where screening analyses were carried out primarily to confirm or dismiss a content of the selected endocrine disruptors. As a result of the project, a focus on the above six focus substances was proposed for further work.

The present project is a follow-up to the above-mentioned survey and screening project, which focuses on six of nine endocrine disruptors and suspected endocrine disruptors. The six substances are listed above.

Purpose
The aim of this project is to perform chemical analyses and hazard, exposure and risk assessments on a substance-by-substance and/or collective basis for selected endocrine disruptors and suspected endocrine disruptors in products for pregnant women and children. Here, control analyses for specific substances regulated in legislation in selected product types were conducted. Finally, it has been investigated whether there is a difference in a possible risk on products purchased from Denmark, the EU or outside the EU.

The project focuses on the following three target groups:
1. Pregnant women (and therefore the unborn child)
2. Toddlers under the age of three
3. Children aged three years

Selection and purchase of products for chemical analysis
In this project, only chemical analyses of selected consumer products have been performed, while exposure to the six substances from medicinal products, food contact materials and food, are included in the final risk assessment in the form of knowledge from existing literature. Other sources of exposure, such as background exposure from the indoor environment, are not included in the risk assessment of this project.

Based on the survey and screening project from 2020 (Poulsen et al., 2020), a prioritisation was made of which product types should be analysed for which focus substances. The overall focus was on the following product types, with the relevant focus substances indicated in brackets:
- Plastics: plastic toys, dummy shields and mobile covers made from polycarbonate (BPA), plastic toys/rattlers (BHA and BHT)

- Silicone: Pop it, teething rings, iPad/tablet covers, wrist watch straps (D4)
- Textile: Socks, bodystockings, leggings/tights (BPA, butylparaben, propylparaben)
- Cosmetic products: body lotions, body oils, sunscreens and after sun products (butylparaben, propylparaben, BHA, BHT, D4)

The approach to the chemical analyses was to carry out screening analyses on the content of certain focus substances in consumer products made of plastic, silicone and textiles. Based on the results of the screening analyses, products were selected, and migration analyses were carried out for these selected products. For cosmetic products, quantitative content analyses were performed as the content concentration is used in the subsequent exposure calculations.

In total, 73 screening analyses were performed on plastic, silicone and textile products, 40 quantitative analyses on cosmetic products (of which 20 analyses were control analyses for the content of parabens), and 24 migration analyses (of which five analyses were control analyses for migration of BPA from toys).

Results of control analyses
Overall, the results of the control analyses carried out were that no infringements of the legislation were identified for either the migration of BPA from toys or the content of parabens in cosmetic products.

No migration of BPA above the detection limit of 0.006 mg/litre was identified in all five tested plastic toy products for children under 36 months. According to the Toys Statutory Order (Stat. Ord. 1800, 2020), the permitted migration limit value for BPA is 0.04 mg/litre. Thus, the migration limit was not exceeded for any of the products.

For the cosmetic products, 20 control analyses were performed for the content of parabens in cosmetic products. It was investigated whether there was compliance with the specific concentration limits for the specific parabens as well as the concentration limit for the sum of parabens. For all 20 cosmetic products examined, both the individual and the total concentration of the parabens were below the legal limit values. For propylparaben, concentrations above the permitted limit value were identified in three products, but taking into account the analytical uncertainty, the products remain within the permitted limit. Finally, other parabens banned by the Cosmetics Regulation were tested for, but not identified above the detection limit in any of the 20 products analysed.

Results of the chemical analyses
The results of the screening analyses for plastic, silicone and textile products are given in below. The same table also gives the overall results of the quantitative analyses for cosmetic products.

BHA was not identified in any of the plastic products and BHT in only one product (mobile cover). BPA was identified in a single dummy shield in small amounts, in three of eight mobile covers and in eight of a total of 21 textile products. Both butylparaben and propylparaben were identified in textile products, but propylparaben was identified most frequently (in 13 out of 21 textile products). D4 was identified in 17 of 32 silicone products, of which D4 was in all pop it products, but only in two of eight watch straps.

TABLE 1. Overview of results of screening analyses performed on plastic, silicone and textile products, as well as content analyses for cosmetic products. The number below each substance indicates the number of products containing the substance above the detection limit.

Material	Product type (number of products analysed)	BHT	BHA	BPA	Propyl-paraben	Butyl-paraben	D4
Plastic	Dummy shield (4)	0	0	1			
	Plastic toys (8)	0	0	0			
	Mobile covers (8)	1	0	3			
Silicone	Pop it (8)						8
	Teething rings (8)						3
	iPad/tablet cover (8)						4
	Watch straps (8)						2
Textiles	Children's socks (7)			4	4	2	
	Bodystocking (7)			2	5	1	
	Leggings/tights (7)			2	4	0	
Cosmetics	Body Lotion (12)	3	0		9	4	3*
	Body oil / stomach cream (1)	1	0		1	0	0*
	Sunscreen (6)	3	1		4	0	0*
	After sun product (1)	0	0		1	0	1*

* For the analyses of D4, analyses were performed on 20 other cosmetic products than the analyses for the parabens, BHA and BHT. In general, for D4, no D4 above the detection limit was analysed, but the results indicated that D4 could be present at a lower level than the detection limit.

Results of migration analyses

Based on the results of the screening analyses, selected migration analyses were performed for plastic, silicone and textile products. The results were that:

- No migration above the detection limit of BHT was identified from either of the two migration analyses of plastic products performed. Migration analyses for BHA were not performed as it was not identified in plastic products during the screening analyses.
- BPA was identified in one of two migration analyses performed. The migration was seen from one dummy shield. BPA was identified in the migration fluid from two of three textile samples.
- Propylparaben was identified in the migration fluid from two of three textile samples.
- No migration above the detection limit of D4 was identified from any of the 12 migration analyses performed on silicone products. This is consistent with D4 having a low solubility in water.

Hazard assessment

A thorough hazard assessment was carried out for the six selected substances and the assessment was that all six substances are endocrine disruptors. The focus was on effects via EATS modalities, i.e. effects related to (anti-) estrogenic (E), (anti-) androgenic (A), thyroid endocrine disrupting (T) and steroidogenic (S) modes of action. In addition, it was assessed and discussed how risk assessment could be made if it is assumed that there is no threshold for the endocrine disrupting effect, i.e. a Derived Minimal Effect Level (DMEL) based approach rather than a Derived No Effect Level (DNEL) based approach. The hazard assessment also included an evaluation of the relevance of the use of a mixture assessment factor (MAF), which can be used to account for possible contributions from other substances with the same effect or mode of action. This is because research on combination effects has shown that the risk is underestimated if only one substance at a time is considered in the risk assessment.

For each of the six substances, an assessment was made of the endocrine disrupting properties and determination of DNEL and DMEL for, respectively, thyroid endocrine disrupting activity and EAS-related activity. Due to a high degree of uncertainty regarding the publicly available data on propylparaben, a read across approach from data on butylparaben was used in the setting of DNEL/DMEL-values for this compound. Using this cautious approach is however also subject to some degree of uncertainty. For all substances, the conclusion is that evidence for endocrine disrupting mode of action has been found. The evidence is weaker for some substances (BHA, BHT) than for others (D4, BPA, butylparaben, propylparaben). For the six focus substances assessed in this project, neither the presence nor absence of a threshold has been identified. Therefore, a DMEL approach to the risk assessment can be applied for these six focus substances (according to the risk assessment approach in recent scientific reports).

In the risk assessment of this report, a MAF of 10 is used together with DNELs and DMELs. The size of the MAF is open for discussion, but in this project, a MAF of 10 is chosen as a starting point for discussion and calculations. This MAF takes into account other substances with similar effects, but not exposure to the same substance from multiple selected sources. In a recent report, the size of MAF has been calculated (modelled) for realistic chemical mixtures (especially in the aquatic environment). This report concludes that a MAF of 10 will be sufficiently protective for mixtures containing up to 30 chemicals (KEMI 2021).

The established DNELs and DMELs were used in the risk assessment in this report, since there is scientific justification for this approach (see above). However, it will be a political decision whether to use DNELs or DMELs, i.e. whether a future risk assessment is carried out on the basis of a threshold-based or non-threshold-based approach.
Research on combination effects (with a particular focus on endocrine disrupters) has shown that there is scientific evidence to consider possible contributions from other substances with the same mode of action in the risk assessment.
However, it will be a political decision whether to use MAF in future risk assessments. In the risk assessment of this report, both approaches (with and without MAF) have been used.

Exposure assessment
Contributions from selected sources of exposure for the six focus substances, aside from consumer products, have in this project included three categories: food, food contact materials and medicinal products. Much of the available data for food and food contact materials has proven to be uncertain for various reasons:

- partly because of the method used to determine the source exposure,
- partly because data findings are of older date, which leads to uncertainty regarding current exposure,
- and partly due to the origin of the data, as data from countries outside the EU cannot necessarily be considered representative of the European population, including Denmark.

The approach has, as far as possible, included data that are judged to represent a realistic exposure from the selected sources. However, in several cases, contributions from selected sources of exposure could be overestimated based on permitted limits for the two categories or due to lack of data.

Risk assessment
The risk assessment showed no risk for the use of cosmetic products for adults based on the detected contents of BHA, BHT, propylparaben, and butylparaben, using the DNEL-approach (method used under REACH R8). For children, a risk for endocrine disrupting effects was identified in relation to content of propylparaben in sunscreen (the same conclusion was seen for the cosmetic products using the normal risk assessment method for cosmetics (MoS calculations performed accordingly to SCCS Notes of Guidance (SCCS 2021a)).

However, the conclusions are different when the risk assessment, using the REACH DNEL/DMEL approach with and without MAF, are used and when contributions from selected sources of exposure are included in the risk assessment. Here it is evident that contributions from selected sources of exposure (in the form of contributions from food, food contact materials and medicinal products) with regard to the focus substances with the same mode of action dominate the overall RCR value, and the value is therefore dependent on data for these contributions.

For the risk assessment of other substances in other products (BPA and propylparaben in socks, tights, dummy shield and mobile covers; BHT in mobile covers and pop it toys for children under 3 years; D4 in toys, watch straps, iPad/tablet covers and teething rings), the migration analyses only measured quantifiable migration of propylparaben in two products ("DK-T 122, socks, target group children aged 3 years" and "DK-T 136, tights, target group children under the age of 3"). The other migration measurements showed no migration above the quantification limit. In risk calculations that include contributions from selected sources of exposure for propylparaben (which is based solely on exposure to medicinal products), the risk assessment shows that both products constitute a risk (RCR> 1). However, this risk is driven solely by the fact that the risks calculated for propylparaben via medicinal products all have RCR values > 1.

Conclusion

In the present project, the determined DNELs and DMELs used in the risk assessment, show that using a non-threshold-based approach (DMEL) results in a factor of 10 higher RCR values compared to a threshold-based approaches (DNEL). This means that a risk of endocrine disrupting effects will occur for more exposure scenarios, when a DMEL approach is used.

It is considered appropriate to use MAF, as the extent of single-acting substances and the contributions from different sources are not known. In the present project, quantification of contributions from selected sources of exposure for all six focus substances (BHA, BHT, propylparaben, butylparaben, BPA, D4) has proved to be very challenging. Calculating a realistic estimate of the contribution of selected sources of exposure to single-acting substances would require the identification of potential single-acting substances and updated data on the content of these substances in a variety of sources. As this is very difficult to achieve, a risk assessment alternative may be to apply a MAF to compensate for these unknown contributions.

Based on the analytical findings, it has not been possible to assess whether there is a difference in a possible risk from using products purchased from Denmark, the EU or outside the EU.

From the results from this report, it can be concluded that, regardless of the assessment method used, there is a risk of endocrine disrupting effects in children and pregnant women (and through the indirect exposure via the mother, to the unborn child), when exposure from consumer products are added to other product types. This is mainly due to exposure of endocrine disruptors through foods and medicines, whereas the risk contributions from the selected consumer products seem relatively limited (apart from possible contributions from sunscreen).

1. Introduction

Exposure of children and pregnant women to endocrine disruptors can affect the natural hormonal balance, which is problematic because the hormone-regulated development processes of organs are particularly sensitive. Studies show that children and pregnant women are widely exposed to endocrine disruptors and substances suspected of being endocrine disruptors. This knowledge is constantly being updated, and more substances are being studied and evaluated to have endocrine disrupting properties. Thus, the Danish EPA is continuously building on this knowledge and investigating the extent to which the substances are used in products for children and pregnant women.

1.1 Background

In 2020, a survey of nine selected endocrine disruptors and/or substances suspected of being endocrine disruptors was prepared. The project was a survey and screening project, where screening analyses were carried out primarily to identify the possible content of the selected endocrine disruptors. The 2020 project (Poulsen et al., 2020) identified some of the substances in the different products investigated, including D4 in silicone products, BHT in plastic products, BPA and propylparaben in textile products, and butylparaben and propylparaben in toys of the chemical mixture type. In addition, BHA, BHT, butylparaben and propylparaben were found to be used in cosmetic products.

The survey project from 2020 (Poulsen et al., 2020) started with a focus on nine selected substances but, based on the results of the survey and screening analyses, ended up with a list of six substances in total (D4, BHT, BHA, BPA, as well as propylparaben and butylparaben), which were proposed for further work in a follow-up project.

This project, which is a follow-up to the project carried out by Poulsen et al. (2020), will investigate and assess human health exposure to the six selected endocrine disruptors in a wide range of exposure sources to children and pregnant women.

The six substances that are the focus of the present project (and which are listed below in section 1.4 ”Delimitation”) cover both substances that are regulated with a limit value in the legislation for certain product types and substances that are not regulated with a limit value in the legislation. The restrictions and limit values applicable to the selected substances in focus are described in more detail in section 4 ”Legislative requirements”.

1.2 Purpose

The aim of the project is to conduct chemical analyses as well as perform exposure and risk assessments on a substance-by-substance and/or collective basis for selected endocrine disruptors in products for pregnant women and children. In addition, control analyses are carried out for specific substances regulated by legislation in selected product types. Furthermore, whether there is a difference in a possible risk on products purchased from Denmark, the EU or outside the EU is investigated.

1.3 Definitions

The six substances investigated in this project are endocrine disruptors or suspected endocrine disruptors. These six substances will be referred to as "focus substances" in the present

project to avoid the longer formulation "endocrine disruptors and/or suspected endocrine disruptors" in the report.

The WHO (WHO/IPCS, 2002) defines substances suspected of being endocrine disruptors as follows: "A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations".

The expert group on endocrine disrupters under REACH has concluded that a substance can be considered to be endocrine disrupting when there are harmful effects as well as an endocrine-disrupting mechanism of action, and when there is a probable connection between the two (harmful effect due to endocrine mechanism), (Danish EPA, 2021).

The project from 2020 (Poulsen et al., 2020), which forms the basis of the present project, is referred to as the survey project in this report.

The project purchased products from respectively DK, EU and non-EU, which are defined as follows:

- DK: Products purchased from a website or shop operated by a company with a Danish CVR/VAT no.
- EU: Products purchased from EU websites, but not from Danish shops or websites
- Non-EU: Products purchased from websites outside the EU

1.4 Delimitation

The project is limited to a risk assessment of the following six selected endocrine disrupting substances or substances suspected of being endocrine disrupting (focus substances):

- Butylated hydroxylanisole (BHA), CAS No. 25013-16-5
- Butylated hydroxytoluene (BHT), CAS No. 128-37-0
- Butylparaben, CAS No. 94-26-8
- Propylparaben, CAS No. 94-13-3
- Octamethylcyclotetrasiloxane (D4), CAS No. 556-67-2
- Bisphenol A (BPA), CAS No. 80-05-7

In addition, the project is limited to investigating products used by children and pregnant women. The project focuses on the following three target groups:

1. Pregnant women (and therefore the unborn child)
2. Toddlers under the age of three
3. Children aged three years

In the project, only consumer products are analysed, as this is the regulatory area of the Danish EPA. According to the Ministry of the Environment (2003), a consumer product is defined as a product purchased by a private consumer from a trader. Consumer products include all common household items, such as cosmetics, hygiene products, toys, cleaning products, household appliances, home furnishings and all other products typically used by private individuals. Excluded are medicinal products, medical devices, food and food contact materials.

2. Selection of product types for analysis

In this project on analysis and risk assessment of endocrine disruptors, only consumer products are analysed. Other products such as medicinal products, food contact materials and food are not analysed in the project, but information on the content and/or migration of the six focus substances is included in the subsequent exposure and risk assessments.

2.1 Consumer products containing the focus substances

In the survey project from 2020 (Poulsen et al., 2020), a survey of consumer products that may contain the six focus substances was conducted. The main findings from the survey are provided TABLE 2 below.

TABLE 2. Overview of possible occurrences of the six focus substances in consumer products of different materials

Focus substance	Plastic	Silicone	Textiles	Cosmetic products	Other
BPA	Used as a monomer in polycarbonate plastic (PC) and residues (unreacted) may be present.	No	Measured at low concentrations (µg/kg) in textiles, e.g. socks and bodystockings	Identified in some products at low concentrations. For example in wet wipes.	Hygiene products for women (panty liners, tampons)
Butylparaben	No	No	No	Used in a few products, e.g. face creams.	Chemical toys
Propylparaben	No	No	Measured at low concentrations (µg/kg) in socks	Used in some products, e.g. body lotion, hand cream.	Teething rings (the jelly/liquid) Chemical toys
BHA	Can be used as an additive in plastics (BHT more widely used)	No	No	Only used in a few products, e.g. powder	No
BHT	Used as an antioxidant in many types of plastics	No	No	Used in products such as sunscreen, body lotion, lip balms, deodorant Used as an antioxidant in perfume blends	Diapers Car seats Cushions Sanitary towels Mattresses Wax/polishes
D4	No	Used as a monomer in the manufacture of silicone	No	*Not allowed as an ingredient*	Squishy toys Mattresses Paints Wax/polishes

Based on the above results of the survey and the assessment of potential exposure, the following product types were selected, and a screening analysis was performed to investigate whether the focus substances could be identified in specific products or not. The results for detected substances are given in brackets in TABLE 3 below.

TABLE 3. Identified content of focus substances in selected consumer products (Poulsen et al., 2020)

Focus substance	Plastic	Silicone	Textiles	Chemical toys
BPA	-	-	Children's socks (2 of 9) Adult socks (1 of 6) Underpants (0 of 6)	-
Butylparaben	-	-	Children's socks (0 of 9) Adult socks (0 of 6) Underpants (0 of 6)	Finger paint (0 of 10) Soap bubble solution (2 of 11)
Propylparaben	-	-	Children's socks (2 of 9) Adult socks (2 of 6) Underpants (0 of 6)	Finger paint (0 of 10) Soap bubble solution (2 of 11)
BHA	Plastic toys (0 of 8) Mobile covers (0 of 6) Pacifiers (0 of 3)	Plastic toys (0 of 8) Mobile covers (0 of 6) Pacifiers (0 of 3)	-	-
BHT	Plastic toys (3 of 8) Mobile covers (1 of 6) Pacifiers (0 of 3)	Plastic toys (0 of 8) Mobile covers (0 of 6) Pacifiers (0 of 3)	-	-
D4	Mobile covers (1 of 6) Pacifiers (0 of 3)	Teething rings (4 of 8) iPad/tablet cover (4 of 5) Pacifiers (0 of 5)	-	-

- means that no analysis has been carried out for the substance in question in the product type

Based on the findings of the survey project, the following comprehensive list of consumer product types was compiled, which would be relevant for further investigation in the present project. The list below has therefore been used as a starting point for the selection and prioritisation of products in the present project:

For babies:
- D4 in silicone teething rings
- BHT in plastic toys (e.g. rattles and other toys for babies/toddlers)
- BPA in children's socks
- BPA in the pacifier shields
- Butylparaben and propylparaben in gel-filled teething rings
- BHT, propylparaben and butylparaben in cosmetic products

For children:
- D4 in silicone iPad and tablet covers
- D4 in other silicone products (toys – e.g. Pop it)
- BHT in plastic toys

- BHT in plastic mobile covers
- BPA in mobile covers (polycarbonate (PC))
- BPA and propylparaben in children's socks
- Butylparaben and propylparaben in soap bubble liquids
- BHT, propylparaben and butylparaben in cosmetic products

For pregnant women:
- D4 in silicone iPad and tablet covers
- BPA and propylparaben in adult socks
- BPA in mobile covers (PC)
- BHT in plastic mobile covers
- BHT, propylparaben and butylparaben in cosmetic products

2.2 Choice of product types in focus

The above product types are thus a comprehensive list of product types that could be relevant for analysis and risk assessment based on the survey project. However, it is important in this project to prioritise efforts so that there is room to analyse a certain number of products of each product type.

In this project, chemical analyses of the substances concerned in selected product types have been omitted for the reasons mentioned below:
- Parabens in finger paints, as neither butylparaben nor propylparaben was identified in the screening analyses in 2020.
- Parabens in soap bubble gels, as exposure will typically be limited (limited skin contact). Butylparaben and propylparaben were also identified in only 2 of 11 products in the screening analyses in 2020.
- D4, BHA and BHT in pacifiers, as none of the substances were identified in the screening analyses in 2020. However, the pacifier shield was not tested for BPA, since the analysis of the pacifier shield would be relevant.
- Possibly butylparaben and propylparaben in gel-filled teething rings, as it is expected that the substances are used as preservatives in the gel and therefore will probably migrate in small quantities from the plastic material.
- BHT in mobile covers, as higher levels of BHT were identified in plastic toys than in mobile phone covers. Exposure from plastic toys for babies/toddlers is expected to be higher than from mobile phone covers, as children are expected to put the toys in their mouths. However, BPA was not investigated in mobile covers in the survey project, so analysis of mobile covers made of polycarbonate would be relevant.

In TABLE 4 below is a list of product types selected for analysis in this project, and for which of the focus substances they are analysed.

TABLE 4. Overview of the priority analyses in this project – broken down by substances and product types

Focus substance	Plastic	Silicone	Textiles	Cosmetic products
BPA	Plastic toys made of polycarbonate Pacifier shield made of polycarbonate	-	Children's socks Bodystockings Tights/leggings	-

Focus substance	Plastic	Silicone	Textiles	Cosmetic products
	Mobile covers made of polycarbonate			
Butylparaben	-	-	Children's socks Bodystockings Tights/leggings	Body lotions Body oils Lotion for stretch marks Sunscreens
Propylparaben	-	-	Children's socks Bodystockings Tights/leggings	Body lotions Body oils Lotion for stretch marks Sunscreens
BHA	Plastic toys, e.g. rattles	-	-	Body lotions Body oils Lotion for stretch marks Sunscreens
BHT	Plastic toys, e.g. rattles	-	-	Body lotions Body oils Lotion for stretch marks Sunscreens
D4	-	Pop it iPad/tablet covers Teething rings/teething toys Watch straps	-	Body lotions Body oils Lotion for stretch marks Sunscreens

- means not analysed

2.3 Other products containing focus substances

In this project, the chemical analyses are limited to the focus substances in consumer products. This means that no analyses have been carried out on the focus substances in food, food contact materials (FCMs) and medicinal products. However, the survey project (Poulsen et al., 2020) showed that the focus substances have also been identified in food, FCM and medicinal products (see TABLE 5), so exposure from these is also included in the exposure and risk assessments in the present project. This is done by using exposure data from the literature.

TABLE 5. Findings on the use of the focus substances in food, food contact materials (FCM) and medicinal products in the survey project (Poulsen et al., 2020)

Focus substance	Food	FCM	Medicinal products/dietary supplements
BPA	May migrate into food from FCM. Data from DVFA are available.	Used in lacquers for metal packaging and as monomers for plastics of the polycarbonate type.	-
Butylparaben	Not approved as a food additive.	Not approved for use as an additive in FCM made of plastic.	Found in a few medicinal products.

Focus substance	Food	FCM	Medicinal products/dietary supplements
Propylparaben	Not approved as a food additive.	Approved for use as an additive in FCM made of plastic.	Found in a number of medicinal products. Data from DMA are available.
BHA	Permitted as a food additive at a certain concentration in a number of foods. For example in chewing gum.	Permitted as an additive to FCM made of plastic. Contamination from plastic foil and laminate investigated. Data from DVFA are available.	Found in a number of medicinal products. Data from DMA are available. Previously seen used in vitamin pills.
BHT	Permitted as a food additive at a certain concentration in a number of foods. For example in chewing gum.	Permitted as an additive to FCM made of plastic. Contamination from plastic foil and laminate investigated. Data from DVFA are available.	Found in a number of medicinal products. Data from DMA are available. Previously seen used in vitamin pills.
D4	Not allowed.	There are no specific rules for ingredients in FCM made of silicone. Data from DVFA are available.	-

- = not observed applied. DVFA = The Danish Veterinary and Food Administration. DMA = The Danish Medicines Agency.

3. Products selected for purchase

In cooperation with the Danish EPA, it was decided that the following types of consumer products should be analysed for the mentioned focus substances (indicated in brackets):

- Plastic products – 20 products in total divided into:
  - Mobile covers made of polycarbonate (BPA)
  - Pacifier shields made of polycarbonate (BPA)
  - Plastic toys/rattles/teething rings (BHT, BHA, BPA)
- Silicone products – 32 products in total divided into:
  - Pop it (D4)
  - iPad/tablet covers (D4)
  - Teething rings (D4)
  - Watch straps (D4)
- Textile products – 21 products in total divided into:
  - Socks (BPA, propylparaben and butylparaben)
  - Tights/leggings (BPA, propylparaben and butylparaben)
  - Bodystockings (BPA, propylparaben and butylparaben)
- Cosmetics – 40 products in total, divided into:
  - Body lotions/body oils (D4 and/or, BHT, BHA, propylparaben and butylparaben)
  - Lotion for stretch marks (D4 and/or, BHT, BHA, propylparaben and butylparaben)
  - Sunscreen/after sun lotion (D4 and/or, BHT, BHA, propylparaben and butylparaben)

In addition, 5 control analyses of migration of BPA were performed for selected toys intended for use by children at/under 36 months or in other toys intended to be put in the mouth. The toys were divided into plastic toys and rattles.

3.1 Procedure for purchasing products

The above product types were selected for chemical analyses in the present project. Based on this choice, a search was made for products to purchase. A list of 250 products was drawn up, divided into the selected product types, of which 119 products were initially selected and purchased in cooperation with the Danish EPA. Purchases were distributed relatively evenly between the different product types. However, the lotion for stretch marks (for pregnant bellies) and pacifier shield product types were deliberately reduced in number, as both product types are available to a limited extent on the market. Extra products were deliberately purchased in case products were not received before the start of the analyses.

For example, some of the products purchased consisted of both plastic and silicone part, so both types of materials were analysed in those products. In addition, several of the cosmetic products, according to the information available on the website, contained, e.g. both a silicone compound (so analysis for D4 was relevant), as well as BHT and/or propylparaben and butylparaben.

Although non-EU products were ordered seven weeks before the start of the analyses, there were still some non-EU products that did not arrive. A total of 12 non-EU products failed to arrive (mainly plastic products, but also some silicone products). For this reason, Danish silicone products (watch straps) were purchased to ensure the same number of analyses. The equal

distribution between non-EU, EU and DK products was thus not achieved. Neither equal distribution between plastic and silicone products nor the equal distribution of each type of product was achieved. In total, 118 analyses were performed on the 114 products that ended up being analysed.

3.2 Criteria for the procurement of the products

The following criteria were generally considered important when prioritising the purchase of the products:

- A roughly equal distribution of products was purchased from respectively DK, EU and non-EU. Some extra products from non-EU were purchased in case the products would not be delivered before the analyses were to be started.
- The above number of products was purchased in the four main areas (plastic products, silicone products, textile products and cosmetic products).
- Products were generally sourced from different producers, but the search for product examples showed a clear tendency for the same producers to use certain materials/ingredients for some product types. This was particularly the case for cosmetic products, where some manufacturers only use e.g. butylparaben and propylparaben in their products. The same was, to some extent, also valid for textiles, where certain brands use blended textiles while other producers use pure cotton only.
- In general, products were purchased from various websites. However, for purchases of products from the EU and non-EU in particular, there is a clear predominance for specific websites such as Amazon and Wish, as these types of websites deliver to Denmark. In relation to the survey project, there are a few previously used websites in the EU that no longer deliver to Denmark.

In addition, several criteria were applied to the procurement of the different product types for the main product categories (plastic, textile, silicone and cosmetics). These are described in more detail in the individual sections below.

3.2.1 Criteria for the procurement of plastic products

Selected product types made from plastic material that were focused on were:

- Mobile covers made of PC plastic
- Pacifier shields made of PC plastic
- Plastic toys/rattles/teething rings
- Plastic toys intended for use by children of 36 months or less, or in other toys intended to be put in the mouth

For pacifier shields and mobile covers, only products where the website indicated that the products are made of polycarbonate plastic or contain polycarbonate were purchased. For example, several mobile covers are a blend of TPU (thermoplastic polyurethane) and PC (polycarbonate). However, for pacifier shields, some clear plastic products were also purchased, as in many cases, there was no information on the material used for the pacifier shields.

For plastic toys/teething rings, the focus was on both the type of plastic and different target groups (under three years of age and from three years of age). The results of the survey project showed that some products made of ABS could contain BHT, which is why toys made of ABS have also been selected.

For toys used in control analyses for migration of BPA, there was a search for polycarbonate toys. However, the type of plastic is rarely specified for toys, so the focus here was on purchasing products made of clear plastic (which is typical for polycarbonate) or recycled plastic.

In general, for most plastic products, the specific plastic material from which the products were made was not indicated. Typically it just said "plastic". For example, it was impossible to find pacifiers that indicated the type of plastic the pacifier shield was made of, so a decision was made to purchase a few products for sampling. Thus, the products purchased were selected if they consisted of clear plastic or were transparent to lightly coloured plastic.
It was also challenging to find enough products for the other polycarbonate plastic products (mobile covers and plastic toys). In most cases, mobile covers are made of the plastic material TPU or a mixture of TPU and polycarbonate. A few products made from pure polycarbonate were identified, otherwise blended products were purchased.

3.2.2 Criteria for the procurement of silicone products

Selected product types made from silicone material that were focused on were:

- Pop it toys
- iPad/tablet covers
- Teething rings
- Watch straps

The products purchased were either labelled as being made of silicone and/or the product descriptions and pictures strongly suggested that the product was made of silicone.

3.2.3 Criteria for the procurement of textiles

Selected product types made from textile material that were focused on were:

- Socks
- Tights/leggings
- Bodystockings

Based on the 2020 survey project and studies by Freire et al. (2019) and Xue et al. (2017), it suggests that the highest levels of BPA are to be expected in synthetic materials such as polyester and elastane/spandex rather than products made of 100% cotton. In addition, BPA is reported to be more prevalent in coloured textiles, and to a lesser extent, in white textiles. Thus, only coloured fabrics containing polyester and/or elastane/spandex were purchased.

The survey project from 2020 identified BPA in socks, and in the study by Xue et al. (2017), BPA was identified in both socks and body stockings. These product types are therefore purchased for analysis in the present project. In addition, tights and leggings are also purchased as they are frequently used by toddlers and pregnant women and have long-lasting skin contact.

In general, it was a challenge to identify body stockings made of blended fabrics containing polyester and/or elastane/spandex. The majority of bodystockings are made of 100% cotton, but textile products consisting of blended fabrics were successfully sourced. Socks and tights/leggings are also generally made of mixed fabrics.

3.2.4 Criteria for the procurement of cosmetic products

Selected types of cosmetic products that were focused on were:

- Body lotions/body oils
- Lotion for stretch marks
- Sunscreens and after-sun lotions

These product types were selected partly because of their relevance to the three target groups of this project and because of the frequent and high (in many cases daily) exposure. In addition, a data extract from the Danish Consumer Council “Tænk Kemi”[1] app "Kemiluppen" confirmed that the selected focus substances are used in the types of cosmetic products mentioned above.

In addition, the focus was on products declared with the content of D3, D4, D5, D6 and D7, as well as dimethicone and cyclomethicone, as they according to Larsen et al. (2021), may contain D4 and residues thereof.
When searching websites for products containing the above ingredients, the INCI names of the siloxanes were used, i.e. cyclotrisiloxane (D3), cyclotetrasiloxane (D4), cyclopentasiloxane (D5), cyclohexasiloxane (D6) and cycloheptasiloxane (D7).

Extracts from the Danish Consumer Council's database behind "Kemiluppen" are described in more detail in the section below. A selection of substances that may be present in cosmetic products (BHA, BHT, butylparaben and propylparaben) and the siloxane compounds listed above were extracted.

The data extract from the database of the Danish Consumer Council was actively used to identify products with a possible content of the selected substances in focus in this project. Most of the products are purchased based on the ingredient lists available on the website, but some products are also purchased based on information from "Kemiluppen".

3.2.4.1 Data extract from Danish Consumer Council's database "Kemiluppen"

The Danish Consumer Council “Tænk Kemi” has developed an app, "Kemiluppen", where it is possible to get a cosmetic product rating (A, B and C) based on the Danish Consumer Council's rating of the ingredients declared on the product. The database behind the Kemiluppen contains information on all ingredients declared in the approximately 13,400 products included in the Kemiluppen (as of July 2021), all of which can be found on the Danish market. The project group, therefore, contacted the Danish Consumer Council “Tænk Kemi”, which has made an extract of which and how many products contain the selected substances. The search results for the selected substances are presented in TABLE 6 below (the percentage of the total number of products is given in brackets).

In general, only certain websites or specific brands of cosmetic products listed the ingredients on the website itself. Some Danish cosmetic products have been purchased based on information from the data extract from the Danish Consumer Council “Tænk Kemi”.

TABLE 6. Extract from the Danish Consumer Council “Tænk Kemi” database Kemiluppen regarding the use of the selected substances in cosmetic products in Denmark

Name of substance	Number of products in Kemiluppen (% of total number of products (approx. 13,400) in Kemiluppen)	Mainly used in the following types of products (number of products of this type)
Butylparaben	90 (0.7%)	Face care (14) – of this, face cream (5) Hair care (4) Foundation/powder (30)

[1] The Danish Consumer Council is named ”Tænk” in Danish (“Think” in English), and the data used is from the department “Kemi” (English: Chemistry”).

Name of substance	Number of products in Kemiluppen (% of total number of products (approx. 13,400) in Kemiluppen)	Mainly used in the following types of products (number of products of this type)
		Concealer/corrector (8) Mascara (7) After sun lotion (1)
Propylparaben	348 (2.6%)	Face care (37) – of this, face cream (18) Lip balm (7) Hair care (27) – of this, wax/hairspray (7) Blush/highlighter (16) Foundation (31) Mascara (36) Powder (39) Eye shadow (18) Body Lotion (46) Hand cream (20) Sunscreen/after-sun lotion (5) Toothpaste (1)
BHA	21 (0.2%)	Powder (7) Lipstick/lip balm (1) Hair mousse (2) Foot cream (1) Ointment (1) Eye shadow (2) Mascara (2) Nail polish (1)
BHT	902 (6.7%)	Face care (202) – of this, face cream (88) and lip balm (43) Baby perfume (2) Shaving/hair removal women (33) Hair care (44) – of this, wax/hairspray (25) Foundation/powder (54) Lipstick/lipgloss (24) Perfume (35) Body Lotion (26) Hand cream (17) Body oil (3) Sunscreen/after-sun products (14) Deodorant (177)
D3	1 (0.01%)	Hair care (1)
D4*	7 (0.1%)	Hair care - cream/conditioner/serum/oil (3) Foundation (3) Face care (1)
D5**	748 (5.6%)	Face care (141) – of this, face cream (61) Hair care (103) – of this, wax/hairspray (15) Foundation/powder (119) Mascara (15) Body care (70) – of this, hand care (19) Sun products/after-sun products (22)

Name of substance	Number of products in Kemiluppen (% of total number of products (approx. 13,400) in Kemiluppen)	Mainly used in the following types of products (number of products of this type)
		Deodorant (105)
D6**	229 (1.7%)	Face care (77) – of this, face cream (43) Hair care (13) – of this, hairspray (3) Foundation (47) Mascara (4) Eye shadow (3) Body care (23) – of this, hand care (5) Sun products/after-sun products (21)
D7	1 (0.01%)	Scrub (1)
Cyclomethicone	123 (0.9%)	Face care (12) – of this, face cream (6) Baby lotion (1) Hair care (26) – of this, hairspray/wax (3) Foundation (3) Body cream/lotion (5) Hand care (1) Sun products (3)
Dimethicone	2550 (19.0%)	Face care (641) – of this, face cream (429), BB/CC cream (37), lip balm (9), mask (42), serum (31) and eye care (50) Baby wipes (5) Shaving cream/wax (6) Hair care (145) – of this, hairspray/wax (51) Foundation/powder (230) Lipstick (23) Mascara (29) Nail polish (40) Eye shadow (73) Body care (452) – of this, cream/lotion (278), hand care (122), foot care (26), Sun products/after-sun products (150)

* D4 has been banned recently (last half of 2019), and information on this may therefore be outdated, according to the Danish Consumer Council.
** A general restriction of respectively D4, D5 and D6 are on the way. The limit value of 0.1% w/w will apply to all consumer and professional products and is expected to be adopted during 2021 (ECHA, 2020a).

As can be seen from the extract from the Danish Consumer Council "Tænk Kemi", dimethicone is clearly the most widely used of the relevant substances and occurs most frequently in facial and body care products. In addition, there are many occurrences of respectively D5, D6 and cyclomethicone. These substances are included in the analysis as some impurities of D4 are expected in the ingredients.

Propylparaben is more frequently used in cosmetic products than butylparaben, but butylparaben is nevertheless used in about 90 out of the 13,400 products and mainly in face care and foundation products.

Compared to the corresponding data extract in 2020, there has been a reduction in the number of products with butylparaben and propylparaben respectively. The use of butylparaben

has gone from 108 to 90 products, while propylparaben has gone from 444 to 348 products. In contrast, there is an increase in the number of products containing BHA (from 14 to 21 products) and BHT (from 898 to 902 products).

3.3 Overview of the analysed products

A total of 114 products were analysed and they are distributed as indicated in TABLE 7 for the different product types and respectively DK, EU and non-EU. As mentioned earlier, there were a number of ordered products that did not arrive before the analyses, so the distribution between DK, EU, non-EU, as well as the distribution between the individual product types is skewed in some cases.

TABLE 7. Distribution of the analysed products by type of product and DK, EU and non-EU

Material	Product type	DK	EU	non-EU	Sum
Plastic	Mobile covers	4	3	1	8
	Plastic toys/rattles/teething rings	4	4	0	8
	Pacifiers (shield)	2	2	0	4
Plastic (control migration)	Plastic toys/rattles	5	-	-	5
Silicone	Teething rings/teething toys	3	3	2	8
	iPad/tablet cover	3	3	2	8
	Pop it	3	3	2	8
	Watch straps	8	0	0	8
Textiles	Bodystocking/baby's sleeping suit	3	2	2	7
	Socks	3	1	3	7
	Tights/leggings	3	2	2	7
Cosmetic products	Body lotions/body oils	6	7	6	19
	Lotion for stretch marks (stomach)	1	-	1	2
	Sunscreens/after-sun products	4	7	4	15
Sum		**52**	**37**	**25**	**114**

As shown in TABLE 7, there is a predominance of Danish purchased products since 12 non-EU products did not arrive before the start of the analyses. Watch straps are therefore only purchased in Denmark. The same applies to products for the controling of the Toy Regulation (for migration of BPA). Purchases have been made with a view of achieving a fairly even distribution between the various product types. However, fewer pacifiers and fewer lotions for stretch marks (for stomach) have been purchased from the start, and with a combination of a number of non-EU products not arriving before the start of the analyses, there is a skewed distribution, especially for plastic products. Cosmetic products are predominant in quantity compared to the other product types for several reasons: Firstly, a number of control analyses were performed. Secondly, up to four substances were analysed in some products. Thirdly, there is typically a high exposure when using these products (leave-on).

TABLE 8 below shows how the 114 purchased products are distributed among the three target groups:

- Pregnant
- Children aged three years
- Children under the age of three

However, it should be pointed out that some products can be used by several or all target groups, e.g. cosmetic products, mobile covers, tablet covers and toys. The products are listed under the target group to which they primarily belong. For example, socks purchased in size two are listed in the column for children under three years of age, but the same socks are available in larger sizes for children aged three. Similarly, cosmetic products with the word "baby" in the product name are listed in the column for children under three. However, children aged three and pregnant women can still use them.

TABLE 8. Distribution of the purchased products by product type and target group

Material	Product type	Children under the age of three	Children aged three years	Pregnant	Sum
Plastic	Mobile covers	-	-	8	8
	Plastic toys/rattles/teething rings	4	4	-	8
	Pacifiers (shield)	4	-	-	4
Plastic control migration	Plastic toys/rattles	5	-	-	5
Silicone	Teething rings/teething toys	8	-	-	8
	iPad/tablet cover	-	8	-	8
	Pop it	1	6	1	8
	Watch straps	-	-	8	8
Textiles	Bodystocking/baby's sleeping suit	6	1	-	7
	Socks	4	3	-	7
	Tights/leggings	4	3	-	7
Cosmetic products	Body lotion/body oil	1	-	18	19
	Lotion for stretch marks	-	-	2	2
	Sunscreen/after-sun products	3	1	11	15
Sum		**40**	**26**	**48**	**114**

- means that no products in this category have been purchased for this target group. However, this does not mean that the target group cannot use the product. For example, children aged three also use their parents' mobile phones (and have contact with mobile covers), but the primary target group is pregnant women.

It can be seen in TABLE 8 that the distribution of products purchased for the different target groups is predominantly for children under the age of three and for pregnant women. This is because these target groups (toddlers and unborn babies) are thought to be most vulnerable to endocrine disruptors, toddlers tend to put things in their mouths (and thus are subject to a greater exposure), and some of the selected product types are exclusively aimed at these specific target groups (e.g. pacifiers, teething rings/rattles, bodystockings, lotions for stretch marks).

4. Legislative requirements

This chapter briefly describes the legislative requirements for the six focus substances in the selected product types.

The specific legislative requirements applicable to the focus substances in the product types analysed are illustrated in TABLE 9 below and are detailed separately in the sections below the table. In addition, general safety regulations apply to products marketed in the EU and Denmark (see section 4.1 ”Legislation in general”), which are not included in the overview.

Overall, it appears from TABLE 9, that, with the exception of cosmetic products, there are no legal limit values for the focus substances in the selected product types.

TABLE 9. Overview of specific legislative requirements in the EU for the six focus substances for the selected product types. Fields with a green background are the product types that have been investigated for the listed substances in this project.

Substance / Product type	BHA / BHT	D4*	Butylparaben/ propylparaben	BPA
Teething rings/teething toys made of plastic and silicone	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)	Toys: SML** = 0.04 mg/l
Plastic toys	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)	Toys: SML** = 0.04 mg/l
Pacifiers	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)
Mobile cover	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)
Silicone toys (Pop It)	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)
IPad and tablet covers	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)
Watch straps	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)
Textiles	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)	No limit value (set by law)
Cosmetic products	No limit value (set by law)	Not to be used	EU and DK: Max 0.14%, however, not to be used in leave-on products for the diaper area DK: Not to be used in products intended for children under three years of age	Not to be used

* For D4, there is a restriction proposal, which has not yet been examined by the Commission (see details under section 4.2.2 on D4)
** SML stands for Specific Migration Limit

4.1 Legislation in general

The Danish law on products and market surveillance[2] (LOV nr. 799, 2020) implements parts of the EU Directive 95/2001 on general product safety. The law on products and market surveillance only allows products to be made available in the EU that comply with the law and do not pose a risk. The composition of the product and thus the content of chemical substances also play a role in assessing whether a product presents a risk.

The Product Law does not apply to the safety aspects where other product-specific legislation has already laid down provisions regarding safety.

4.2 Legislation for the six substances in the product types studied

Below is a description of which legislation is in force or on the way for the individual substances.

4.2.1 BHA and BHT

For BHA and BHT, no specific restrictions have been set for their content in plastic, silicone, textile or cosmetic products. However, BHA and BHT are regulated in food, food contact materials and medicinal products (see later).

4.2.2 D4

For D4, no specific restrictions have been set for its content in plastic, silicone or textile products, but D4 is regulated in:

- Cosmetics via the Cosmetics Regulation (EU Regulation No 1223, 2009)[3]. D4 is listed in Annex II of the Cosmetics Regulation, and the substance is therefore prohibited for use in cosmetic products.

In addition, in March 2019, a restriction proposal was made under the REACH Regulation for the siloxane compounds D4, D5 and D6. The proposal is for a fairly broad restriction on the use of D4 (as well as D5 and D6) in various products, both for consumers and professional contexts. The restriction proposal is expected to be considered in 2021, and if adopted, there will be a transition period before the restriction applies.

4.2.3 Butylparaben and propylparaben

For parabens, no specific restrictions have been set for the content of the selected material types (other than cosmetic products). Not even in toy products. Butylparaben and propylparaben are regulated in:

- Cosmetics via the Cosmetics Regulation. Both butylparaben and propylparaben are allowed to be used in cosmetic products at a maximum concentration of 0.14%. However, the two substances must not be used in leave-on products intended for use in the diaper area of children under the age of three.

[2] "Lov om produkter og markedsovervågning". English title: Law on products and market surveillance. lov nr. 799 af 9.6.2020 (https://www.retsinformation.dk/eli/lta/2020/799). Hereinafter referred to as the "Product Law".

[3] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (EU Regulation 1223/2009). Referred to as the "Cosmetics Regulation".

- In Denmark, the use of butylparaben, propylparaben, isopropylparaben and isobutylparaben in cosmetic products intended for children under the age of three is prohibited[4] (Stat. Ord. no. 1217, 2013).

4.2.4 BPA

For BPA, no specific limit values have been set for textiles or products made of plastic or silicone (other than toys made of these materials). However, BPA is regulated in:

- Toys covered by the Toy Regulation[5] (Stat. Ord. no. 1800, 2020) in Appendix C of Annex II, which includes toys intended for use by children of/under 36 months, or in other toys intended to be put in the mouth. The migration limit value for BPA is 0.04 mg/litre in accordance with the methods laid down in standards EN 71-10:2005 and EN 71-11:2005 on organic chemical substances.
- Cosmetics in Annex II of the Cosmetics Regulation, which states that the use of BPA in cosmetic products is prohibited.

4.3 Legislation in areas other than consumer products

In addition to the consumer products studied, this project will also consider possible exposure to the six focus substances from other areas such as FCM, food and medicinal products. The legislation for these areas for the six focus substances is therefore described below.

4.3.1 Food contact materials (FCM)

The following legislation is relevant to the focus substances in FCM:

- FCM made of plastic in the EU Commission's regulation on plastic food contact materials (EU Regulation No 10, 2011)[6]. BHA and BHT are permitted for use as additives or processing aids in the production, and a specific migration limit has been set for them (30 mg/kg for BHA and 3 mg/kg for BHT - see also Appendix 1).
- FCM made of plastic in the regulation on plastic food contact materials: Propylparaben can be used as an additive or processing aid, but there is no specific migration limit value for the substance (see Appendix 1)).
- FCM made of plastic in the regulation on plastic food contact materials. BPA is permitted as a monomer, and a specific migration limit value of 0.05 mg/kg has been set. In addition, BPA is regulated as a surface treatment agent (see Appendix 1)).

No regulation exists for the other focus substances.

4.3.2 Food

The legislation below is relevant to the focus substances in food:

- Additives according to EU Regulation 1333/2008 on food additives (reproduced in the EU database on permitted food additives). BHA and BHT are permitted for use as food additives in certain foods such as fats, oils, spices and chewing gum (see the full list in Appendix 2).

4.3.3 Medicinal products

For medicinal products where only the two parabens and the two antioxidants (BHA and BHT) are used, the addition of this type of substances must be justified and documented. Otherwise,

[4] Danish Statutory Order no 1217 of 11 October 2013 prohibiting the import, sale and use of certain parabens in cosmetic products for children under the age of three.

[5] Danish Statutory Order no 1800 of 3 December 2020 on safety requirements for toys (hereinafter: the Toy Regulation)

[6] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food (hereinafter: "the Regulation on Food Contact Materials")

the addition of these substances will not be accepted. This is generally described in the European Pharmacopoeia (Ph. Eur.) and in Annex 2 to the EU Guideline ("Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product") (EMA, 2007). The Danish Medicines Agency has informed about the following requirements for the two parabens and the two antioxidants in medicinal products:

- An internal limit of 0.02% has been set for propylparaben in medicinal products. The content must always be justified, but higher content must be further justified toxicologically.
- There is no equivalent limit for butylparaben, but it is hardly used in medicinal products.
- For BHA and BHT, no limit value for content has been set, but their addition must be justified and documented in relation to development work regarding the composition. The need for addition must be demonstrated, otherwise the antioxidants are not allowed.

5. Use scenarios

This section describes use scenarios for the purchased products based on an overall knowledge of the product types. Subsequently, the use scenarios will be used directly or in a modified way to conduct concrete exposure scenarios for the actual products being analysed. Generic use scenarios are developed for the following product types:

- Pop it toys
- iPad/tablet/mobile covers
- Teething rings
- Plastic toys
- Pacifiers (pacifier shield)
- Socks, bodystockings/baby's sleeping suits and tights/leggings
- Cosmetic products (leave-on products for pregnant women, babies and children)

For each product type, the target group and the expected use scenario of the product are indicated. The use scenario covers expected use, duration in hours per day and the exposure pathway. This is used in order to decide which analytical methods can provide the best basis for a subsequent exposure assessment.

The exposure of chemical substances from a newly produced/unpackaged product is expected to be higher than for an older product, as the migration rate of chemical substances typically decreases over time. The products in this project are analysed by a single migration measurement, which means that the change in migration over time is not taken into account. The exposure estimates calculated from the migration analyses are thus based on the initial migration rate from the products, which must be considered as a worst case scenario.

Furthermore, the assessment of the analytical methods is based on the fact that migration tests are only performed on a specific product in one type of migration fluid – either artificial sweat or artificial saliva since the focus is on the main exposure route according to the usage pattern. For most substances, it is assumed that there is not a very large difference between migration in sweat and saliva, which is why carrying out migration in both liquids is generally not recommended.

If the individual migration analysis results in an inadequate risk assessment, it may be appropriate to follow up with additional migration measurements. Such migration measurements could reveal the evolution of migration over time or determine the migration in several types of migration fluids.

5.1 Pop it toys

Silicone plates, also called Pop it fidgets/toys, have become very popular with children recently. Pop it toys come in many different sizes, colours and models and are shaped, for example, as recognisable characters (e.g. animals, teddy bears and mythical creatures) and various types of food (e.g. ice cream and fruit). The child uses the toy to "pop" small hemispheres/bubbles a la bubble wrap. The bubbles are pressed from one side of the plate to the other, so the plate can be reused again and again.

Pop it toys are expected to be used by children as young as six years old. However, it is considered that the toys can also be used by younger children (three-year-olds) as the products are typically very colourful and excitingly designed. In general, the product is not considered to

be aimed at toddlers (less than three years old). However, a single pop it toy intended for children under the age of three has been purchased in this project.

Typical play with the products is expected to be centred on "popping"/pressing the bubbles on the plates. Children can use it as a relaxing toy where they press down the bubbles themselves, and they can use it in their play, for example, in games involving two or more players. A game can take the form of each player taking turns to press 1-4 consecutive bubbles at a time, and whoever is left with the last bubble loses the game. Once all the bubbles are pressed down, you can turn the plate over and start again.

For skin contact, a daily play with pop it toys of typically 2 hours per day is assessed. In some cases, the pop it product is not just a toy, and in the present project pop it products have been purchased that function as mobile covers and wristbands. In such cases, the pattern of usage is likely to be different from what is described above.
As for mobile covers (see below), it is estimated that a child as young as six years old uses a phone for 2 hours a day, which, together with estimated daily play with the product, gives a total exposure of 4 hours a day.

For a pop it product designed as a wristband, a significantly longer period of daily use is assessed, as it is expected that a child as young as six years old uses the wristband 24 hours a day.

For one pop it toy, for use by children under the age of three, the use scenario is assessed to be identical to the scenario for plastic toys in this age group (see Chapter 5.4).

5.1.1 Exposure path

Exposure from the toy is assessed to occur primarily via skin contact, where the chemical substances on the outside of the pop it toy are transferred to the palm via a sweaty hand. From the palm, it is expected that in children, exposure could occur through the mouth due to sucking of the fingers or if the product is put directly in the mouth.

5.1.2 Exposure time

In order to obtain the most optimal exposure assessment of the target groups, it is considered appropriate to perform migration tests of the toys in artificial sweat for up to 2 hours at body temperature. For mobile cover pop it products, it is considered appropriate to perform migration testing of the toy in artificial sweat for up to 4 hours, and for wristband pop it products, it is considered appropriate to perform migration testing in artificial sweat for up to 24 hours. For the individual product for children under the age of three, the same migration test is used as for toys for children under the age of three; migration test in artificial saliva for 3 hours.

This would provide data illustrating the maximum exposure that could occur (i.e. worst case), assuming that release from the entire surface of the toy is transferred to the hands.

5.2 Mobile/iPad/tablet covers

Adults, including pregnant women, are considered to be the primary target group for mobile phones/tablets. However, it is to be expected that young children as young as three years of age and younger will at times use mobile phones and/or tablets.

In a report previously published by the Danish EPA, the use of mobile phones/mobile covers has been assessed (Knudsen and Christensen, 2014; Strandesen et al., 2015). With the evolution of smartphones, where younger age groups are acquiring smartphones, and with the significantly increased range of services and features available on smartphones, the 2014 and

2015 data on phone usage can no longer be considered representative. The most recent data obtained by web-based search are given below.

The survey Mobile Life (2017) conducted by Index Danmark A/S states that 15-29-year-old Danes use their mobile phones on average two hours a day, excluding regular telephony.
DR describes a 17-year-old girl who uses her mobile phone for up to 8 hours a day (DR, 2018).
For children aged three and six respectively, no concrete figures have been found, but usage of up to 4 hours per day must be considered likely as a worst case scenario.

The pattern of usage for both pregnant women and children is thus daily use for up to 8 hours and 4 hours, respectively.

5.2.1 Exposure path

Exposure from mobile/tablet covers is assessed to occur primarily via skin contact, where the chemical substances on the outside of the mobile/tablet cover are transferred to the palm via a sweaty hand. Especially in children, exposure from the palm of the hand may occur through the mouth due to the sucking of the fingers.

5.2.2 Exposure time

In order to obtain the most optimal exposure assessment of the target groups, it is considered appropriate to perform migration tests of mobile covers in artificial sweat for up to 8 hours at body temperature. This would provide data illustrating the maximum exposure, assuming that release from the entire cover is transferred to the hands.

5.3 Teething rings

Teething rings are used to soothe babies during teething. The primary target group is thus babies up to two years of age.

It is assumed that the baby has access to the teething ring all the time and that the baby, when awake, has it in and out of their mouth several times during the day.
In an assessment of phthalates, ECHA (2013) states that a study on children's sucking behaviour found that children aged up to 18 months of age on average are sucking on teething rings and other plastic toys for 48 minutes per day and that the maximum sucking time was 200 minutes per day.
The pattern of usage is thus considered to be daily use for up to 200 minutes per day.

5.3.1 Exposure path

The baby is exposed to the chemical substances potentially released from the teething ring by the release of the substances into the saliva, much of which is swallowed. The rest of the exposure is estimated to occur primarily through saliva on the fingers/hand with the teething ring and skin around the mouth.
As a rule, it is not considered realistic that the child bites off small pieces of the teething ring. However, the quality and possibility of biting off pieces of the procured products should be assessed individually.

5.3.2 Exposure time

In order to obtain the most optimal exposure assessment, it is considered appropriate to perform migration tests of the teething ring (the area of the teething ring estimated to enter the mouth) with artificial saliva for up to 200 minutes at body temperature. This would provide data illustrating the maximum exposure, assuming that release from the teething ring will be highest at the start of use, before the first wash/cleaning.

5.4 Plastic toys

For plastic toys, toys are purchased both for children under the age of three and for three-year-old children. The types of toys vary but include cars, animals, tools, mobile phones, stacking rings, shape-sorting boxes and musical instruments (microphone).

The target groups for plastic toys are therefore children under the age of three and for three-year-old children. As plastic toys recommended for children over the age of three can easily end up in the hands of younger siblings, it is not considered relevant to make a clear distinction between these two groups in the context of a risk assessment.

For plastic toys, the typical use scenario would be skin contact with hands for children both under and over the age of three.

5.4.1 Exposure path

Exposure to chemical substances can occur through skin contact - typically the hands. Chemical substances from toys can migrate to the skin surface via a layer of sweat on the skin. However, the closest contact between plastic toys and toddlers is estimated to occur when children suck the toy, wetting the toy with saliva, which is then swallowed.

For children under the age of three
EHCA (2013) states in an assessment of phthalates that in a study of children's sucking behaviour (Juberg et al. (2001)) one found that children aged up to 18 months sucked on average on plastic toys and teething rings for 48 minutes per day and that the maximum sucking time was 200 minutes per day. SCHEER recommends in their final report on squishy toys (SCHEER, 2021), an oral exposure for three hours, for children up to three years of age.

For children over the age of three
ECHA (2013) does not provide estimates for sucking behaviour for children over the age of three. However, for children aged two, reference is made to Smith and Norris (2002), who found an average sucking time of toys of 43 minutes per day and a maximum sucking time of 178 minutes per day for two-year-old children.

As mentioned, it is expected that younger children will also be able to play with this toy. Hence, for both age groups, the starting point is daily exposure through saliva for three hours as used by SCHEER (2021).

5.4.2 Exposure time

In order to obtain the most optimal exposure assessment, it is considered appropriate to perform migration tests of the plastic toy (the area of the toy estimated to enter the mouth) with artificial saliva for 3 hours at body temperature. This would provide data illustrating the maximum exposure, assuming that the release from the plastic toy will be highest at the beginning of the product's useful life.

5.5 Pacifier shield

A pacifier typically consists of a rubber or silicone nipple, a shield and usually a ring. In the present study, the focus is on the pacifier shield. The primary target group is children up to three years of age.

The OECD has published a report that reviews and updates available information focusing on oral exposure of chemical substances to children from objects intended for oral exposure (OECD 2019). In this document, the maximum exposure time of pacifier shields is given as 7.7 hours per day. Typical exposure varies, with the highest estimated to be 3.6 hours per day.

5.5.1 Exposure path

Babies'/children's potential exposure to chemical substances from the pacifier shield when using pacifiers will occur when the child has the pacifier in their mouth, where there will be contact with the shield, both when handling the pacifier and when having the pacifier in their mouth. When they have the pacifier in their mouth, part of the shield will contact saliva from the mouth, and part of this saliva will be swallowed. In addition, part of the shield will be in direct contact with the skin around the mouth.
A previous study on the release of chemical substances in pacifiers (Lassen et al., 2011) assumes that the child has oral and dermal contact with approximately 25% of the surface of the pacifier, corresponding to half of the part of the pacifier facing the mouth. However, it was considered that the main contact surface is between the face and the shield.

5.5.2 Exposure time

In order to obtain the most optimal exposure assessment, it is considered appropriate to perform migration tests of the pacifier shield (with artificial saliva for up to 7.7 hours at body temperature). This would provide data illustrating the maximum exposure, assuming that the release from the pacifier shield will be highest at the start of use and before the first wash/cleaning.

5.6 Textiles for children

Textiles for children here include socks, bodystockings/baby's sleeping suit and tights/leggings.
Textiles purchased in this project are for children, mainly under the age of three, but some products are also purchased for older children (three years old).

The pattern of usage is expected to be:
Bodystockings/baby's sleeping suit (children under 1 years old): All day
Socks (children under the age of three and three-year-olds): All day except when the child is asleep, which is about 13-14 hours a day. Tights/leggings (children under the age of three and children aged three): All day except when the child is asleep, which is approximately 13-14 hours a day[7].
However, it cannot be excluded that in some cases children use socks and tights/leggings for a whole day, therefore the maximum time of use for all textiles is set at 24 hours per day.

5.6.1 Exposure path

Children up to three years of age: the potential exposure for babies/children under age three from textiles will be through the direct dermal contact surface, for which it can also be expected that the children will suck on the clothes to some extent.
Children aged three years: The potential exposure for children will be through direct dermal contact. It is not expected that there will be significant exposure through the sucking of clothing.

5.6.2 Exposure time

In order to obtain the most optimal exposure assessment, it is considered appropriate to perform migration tests of the textiles with artificial sweat for up to 24 hours at body temperature. This would provide data illustrating the maximum exposure that could occur, assuming that the release from the textiles will be highest at the start of the use of new clothes and before the first wash.

[7] Sleep patterns in children under the age of three - Patienthåndbogen ("Patient's Handbook") at sundhed.dk

5.7 Cosmetic products

The cosmetic products purchased in the project are body lotions, sunscreens, body oils, lotions for stretch marks (for pregnant women) and after sun products.

Products purchased in this category are for children under age three and three-year-olds, as well as for pregnant women.

The products are leave-on products and are expected to be applied on large parts of the body or the whole body daily. A few lotions for stretch marks have been purchased and are thus expected to be used exclusively on a pregnant stomach.

5.7.1 Exposure path

Exposure to the chemical substances in cosmetic products occurs primarily through direct dermal contact.

5.7.2 Exposure time

Migration analyses are not relevant for this product type. The relevant calculation for the use of individual cosmetic products is based on the content analyses and the SCCS Notes of Guidance (SCCS, 2021).

5.8 Wristwatch straps

The wristwatch straps purchased in the project are with the target group of pregnant women.

5.8.1 Exposure path

Exposure to the chemical substances from a watch strap occurs through direct dermal contact.

5.8.2 Exposure time

The use of a watch has evolved with today's technology not only to be used during waking hours, but also when the user is sleeping. A watch strap is expected to be used for up to 24 hours a day.
In order to obtain the most optimal exposure assessment, it is considered appropriate to perform migration tests of the watch straps with artificial sweat for up to 24 hours at body temperature. This gives a worst case value for daily exposure, as the daily migration of substances is expected to decrease with prolonged use.

6. Screening analyses

Screening analyses were performed on products made of plastic, silicone and textile materials. The purpose of the screening analyses was solely to identify a possible content of the focus substances and, based on this knowledge, to select products for subsequent migration analyses, where a possible migration is quantified for use in the risk assessment.

Screening analyses were performed on the following products (with the relevant focus substances in brackets):

- Plastic products – 20 products in total divided into:
  - Mobile covers made of polycarbonate (BPA)
  - Pacifier shields made of polycarbonate (BPA)
  - Plastic toys/rattles/teething rings (BHT, BHA, BPA)
- Silicone products – 32 products in total divided into:
  - Pop it (D4)
  - iPad/tablet covers (D4)
  - Teething rings (D4)
  - Watch straps (D4)
- Textile products – 21 products in total divided into:
  - Socks (BPA, propylparaben and butylparaben)
  - Tights/leggings (BPA, propylparaben and butylparaben)
  - Bodystockings (BPA, propylparaben and butylparaben)

Analytical methods and results are described in more detail below.

6.1 Screening analyses on plastic products

A screening analysis (single determination) for BHA, BHT and BPA in plastics was performed using GC-MS. The method is based on an ASTM standard for the determination of BHT in plastics and is thus a method optimised for BHT. The method is also used to screen for BPA and BHA. BHA is expected to be highly soluble in cyclohexane, just like BHT. In contrast, BPA has a lower solubility in cyclohexane than BHT and BHA, but it is expected that up to 50 mg/l corresponding to 450 mg/kg BPA can be detected in plastic samples.

Approximately a sample of 1.5 g was comminuted and extracted with cyclohexane at room temperature on a shaking table (according to ASTM D 4275-17). Methyl myristate (methyl tetradecanoate) was used as an internal standard. Subsequently, the extract was analysed using GC-MS. The limit of detection (LOD) is estimated to be about 5 mg/kg for BHT, about 6 mg/kg for BHA and about 50 mg/kg for BPA.

The results of the screening analyses are presented in TABLE 10 below. The content is not quantified precisely, but an approximate level is given in the form of ranges.

TABLE 10. Screening analysis of plastic products for the content of BHT, BHA and BPA

Product no.	Product type	Target group	BHT (mg/kg)	BHA (mg/kg)	BPA (mg/kg)
EU-P 3	Pacifier shield	Children under the age of three	≤ 5	≤ 6	≤ 50

Product no.	Product type	Target group	BHT (mg/kg)	BHA (mg/kg)	BPA (mg/kg)
EU-P 4	Pacifier shield	Children under the age of three	≤ 5	≤ 6	≤ 50
DK-P 5	Pacifier shield	Children under the age of three	≤ 5	≤ 6	≤ 50
DK-P 6	Pacifier shield	Children under the age of three	≤ 5	≤ 6	≤ 50
DK-P 18	Plastic toys	Children under the age of three	≤ 5	≤ 6	≤ 50
DK-P 19	Plastic toys	Children under the age of three	≤ 5	≤ 6	≤ 50
DK-P 20	Plastic toys	Children aged three years	≤ 5	≤ 6	≤ 50
DK-P 21	Plastic toys	Children aged three years	≤ 5	≤ 6	≤ 50
DK-P 32	Mobile covers	Pregnant women	≤ 5	≤ 6	≤ 50
DK-P 33	Mobile covers	Pregnant women	≤ 5	≤ 6	≤ 50
DK-P 34	Mobile covers	Pregnant women	5 - 50	≤ 6	≤ 50
DK-P 35	Mobile covers	Pregnant women	≤ 5	≤ 6	≤ 50
EU-P 14	Plastic toys	Children under the age of three	≤ 5	≤ 6	≤ 50
EU-P 15	Plastic toys	Children under the age of three	≤ 5	≤ 6	≤ 50
EU-P 16	Plastic toys	Children aged three years	≤ 5	≤ 6	≤ 50
EU-P 17	Plastic toys	Children aged three years	≤ 5	≤ 6	≤ 50
EU-P 29	Mobile covers	Pregnant women	≤ 5	≤ 6	≤ 50
EU-P 30	Mobile covers	Pregnant women	≤ 5	≤ 6	≤ 50
EU-P 31	Mobile covers	Pregnant women	≤ 5	≤ 6	≤ 50
NEU-P 28	Mobile covers	Pregnant women	≤ 5	≤ 6	≤ 50

It can be seen in TABLE 10 that neither BPA nor BHA are identified above the detection limit in any of the 20 plastic products purchased, while BHT is identified in one product (a mobile cover). The mobile cover containing BHT was purchased in Denmark but manufactured in China. For BPA, the choice of cyclohexane as extraction solvent, cf. BPA's poorer solubility, can have had an impact.

Due to the relatively high detection limit of BPA and an expected lower solubility of BPA in the solvent used for the extraction, the extract was run on LC-MS^2 to obtain a lower detection limit. This meant that BPA was identified at lower levels in some products, as indicated in TABLE 11 below.

TABLE 11. Screening analysis of plastic products using LC-MS^2 for the content of BPA

Product no.	Product type	Target group	BPA (mg/kg)
EU-P 3	Pacifier shield	Children under the age of three	0.06 - 0.2
EU-P 4	Pacifier shield	Children under the age of three	≤ 0.06
DK-P 5	Pacifier shield	Children under the age of three	≤ 0.06
DK-P 6	Pacifier shield	Children under the age of three	≤ 0.06
DK-P 18	Plastic toys	Children under the age of three	≤ 0.06
DK-P 19	Plastic toys	Children under the age of three	≤ 0.06
DK-P 20	Plastic toys	Children aged three years	≤ 0.06
DK-P 21	Plastic toys	Children aged three years	≤ 0.06
DK-P 32	Mobile covers	Pregnant women	≤ 0.06
DK-P 33	Mobile covers	Pregnant women	0.06*
DK-P 34	Mobile covers	Pregnant women	≤ 0.06
DK-P 35	Mobile covers	Pregnant women	0.06 - 0.2
EU-P 14	Plastic toys	Children under the age of three	≤ 0.06
EU-P 15	Plastic toys	Children under the age of three	≤ 0.06
EU-P 16	Plastic toys	Children aged three years	≤ 0.06
EU-P 17	Plastic toys	Children aged three years	≤ 0.06
EU-P 29	Mobile covers	Pregnant women	0.06 - 0.2
EU-P 30	Mobile covers	Pregnant women	≤ 0.06
EU-P 31	Mobile covers	Pregnant women	≤ 0.06
NEU-P 28	Mobile covers	Pregnant women	≤ 0.06

* For DK-P 33 the level is just around the detection limit. Therefore the identification of BPA is not certain. I.e. it looks like BPA, but the concentration in the sample is so low that this cannot be determined with certainty.

Based on the results, it is proposed that migration analysis be carried out on the following products, i.e:

- DK-P 34 - mobile cover (migration of BHT for 8 hours)
- DK-P 29 - mobile cover (migration of BPA for 8 hours)
- EU-P 3 - pacifier shield (migration of BPA for 7.7 hours)

6.2 Screening analyses on silicone products

Screening analyses (single determinations) were performed for D4 in the silicone products.

D4 is usually analysed using gas chromatography. The challenge of this analysis is that the column is coated with silicone (polydimethylsiloxane). It is a known phenomenon that the gas chromatographic column "bleeds" silicone compounds, i.e. it releases some of the coating material during the analysis itself. These compounds can also form cyclic silicone compounds during heating of the column, giving false-positive results. If a silicone product contains linear siloxanes with a silanol group, these linear siloxanes can also be converted to cyclic siloxanes

under conditions such as those found in the injector of the analysis equipment where elevated temperatures are present.

For this reason, an analytical method is used in which 0.4 g of the silicone product is comminuted, and an extraction is carried out with internal standard dissolved in acetonitrile and dimethylacetamide for two hours on a shaking table. The extract is then diluted with hexane and a silylating reagent (MSTFA, N-methyl, N-trimethylsilyl trifluoroacetamide) is added to the extract. The sample is then incubated for 30 minutes at 80 °C. The silylating reagent (MSTFA) reacts with any silanol groups present in linear siloxanes, which can then no longer form cyclic siloxanes. The extract is then analysed using a GC-MS.

As a control, several analyses were performed with so-called blank tests to check for the formation of cyclic siloxanes on the column and to determine blank values. Controls were also used and a known amount of D4 was added to selected samples to determine the recovery of the assay. Undecan was used as the internal standard as the isotope label D4 could not be obtained within a reasonable time. The detection limit was measured at 30 mg/kg based on the standard deviation of the lowest concentration in the standard range.

The results of the screening analyses are presented in TABLE 12 below. The content is not quantified precisely, but an approximate level is given in the form of ranges. For all silicone samples, they are taken from the area of the product where the highest contact is expected, e.g. on the ears of a teething ring formed as an animal and on the edge of an iPad/tablet cover or from the part of the product that accounted for the highest amount of silicone (e.g. the most commonly used colour).

TABLE 12. Screening analysis of silicone products for the content of D4

Product Lab no.	Product type	Target group	D4 (mg/kg)
DK-S 57	PopIt	Children aged three years	200 - 500
DK-S 58	PopIt	Children aged three years	200 - 500
DK-S 72	Teething rings/teething toys	Children under the age of three	≤ 30
DK-S 87	iPad/tablet cover	Children aged three years	≤ 30
DK-S 88	iPad/tablet cover	Children aged three years	≤ 30
DK-S 89	iPad/tablet cover	Children aged three years	30 - 200
DK-S 73	Teething rings/teething toys	Children under the age of three	≤ 30
DK-S 56	PopIt	Children under the age of three	30 - 200
DK-S 74	Teething rings/teething toys	Children under the age of three	30 - 200
DK-S 201	Watch strap	Pregnant women	30 - 200
DK-S 202	Watch strap	Pregnant women	200 - 500
DK-S 203	Watch strap	Pregnant women	≤ 30
DK-S 204	Watch strap	Pregnant women	≤ 30
DK-S 205	Watch strap	Pregnant women	≤ 30
DK-S 206	Watch strap	Pregnant women	≤ 30
DK-S 207	Watch strap	Pregnant women	≤ 30
DK-S 208	Watch strap	Pregnant women	≤ 30

Product Lab no.	Product type	Target group	D4 (mg/kg)
EU-S 53	PopIt	Children aged three years	200 - 500
EU-S 54	PopIt	Pregnant women	30 - 200
EU-S 55	PopIt	Children aged three years	200 - 500
EU-S 69	Teething rings/teething toys	Children under the age of three	200 - 500
EU-S 70	Teething rings/teething toys	Children under the age of three	≤ 30
EU-S 71	Teething rings/teething toys	Children under the age of three	200 - 500
EU-S 84	iPad/tablet cover	Children aged three years	200 - 500
EU-S 85	iPad/tablet cover	Children aged three years	30 - 200
EU-S 86	iPad/tablet cover	Children aged three years	≤ 30
NEU-S 50	PopIt	Children aged three years	200 - 500
NEU-S 51	PopIt	Children aged three years	30 - 200
NEU-S 66	Teething rings/teething toys	Children under the age of three	30 - 200
NEU-S 68	Teething rings/teething toys	Children under the age of three	≤ 30
NEU-S 81	iPad/tablet cover	Children aged three years	> 500
NEU-S 82	iPad/tablet cover	Children aged three years	≤ 30
Number of products with content above the detection limit			
Total			18
Divided by where the products are purchased			DK: 7 of 17 EU: 7 of 9 NEU: 4 af 6
Divided by product type			Teething rings: 4 of 8 iPad/tablet cover: 4 of 8 PopIt: 8 of 8 Watch straps: 2 of 8

It can be seen in TABLE 12 that D4 was identified in concentrations above the detection limit in 18 of the 32 silicone products purchased. In percentage terms, there is a larger share of the products from respectively EU and non-EU that contain D4 than for Danish products. However, significantly more Danish products were purchased, so no conclusions can be drawn with certainty. Some of the Danish products containing D4 are produced in China, but there is a lack of information on where many of the products are manufactured.

All eight PopIt products contain D4, and most of them in high amounts, whereas only two of eight watch straps contain D4 above the detection limit. For both teething rings and iPad/tablet covers, half of the products purchased contain D4 above the detection limit.

Based on the above results, it is suggested that migration analyses be performed for the products below. In the selection process, emphasis has been placed on choosing several products of the same product type and with different migration times. Product type and suggested migration times from chapter 5 “Use scenarios” are also indicated in the list below.

- NEU-S 50 - PopIt (migration of D4 for 2 hours)
- EU-S 53 - PopIt (migration of D4 for 2 hours)
- DK-S 56 - PopIt (migration of D4 for 2 hours)
- DK-S 54 - PopIt bracelet (migration of D4 for 24 hours)

- DK-S 201 - Watch strap (migration of D4 for 24 hours)
- DK-S 202 - Watch strap (migration of D4 for 24 hours)
- NEU-S 81 - iPad/tablet cover (migration of D4 for 8 hours)
- EU-S 84 - iPad/tablet cover (migration of D4 for 8 hours)
- DK-S 89 - iPad/tablet cover (migration of D4 for 8 hours)
- EU-S 71 - Teething ring (migration of D4 for 200 minutes)
- NEU-S 66 - Teething ring (migration of D4 for 200 minutes)
- DK-S 74 - Teething ring (migration of D4 for 200 minutes)

6.3 Screening analyses on textile products

Screening analyses (single determinations) were carried out for the content of BPA, butylparaben and propylparaben in the textile products.

BPA, butylparaben and propylparabe are determined in textiles using LC-MS^2. The analysis is performed by adding a mixture of acetone and dichloromethane to small pieces of textile, together with an isotope-labelled internal standard. The sample is extracted by ultrasound and filtered. After that, water is added and then evaporated. The evaporated sample is redissolved in methanol and subsequently analysed using liquid chromatography with mass spectrometric detection, LC-MS^2.

The detection limit is estimated to be 30 µg/kg for BPA and 2 µg/kg for parabens.

The results of the screening analyses are presented in TABLE 13 below. The content is not quantified precisely, but an approximate level is given in the form of ranges.

TABLE 13. Screening analysis of textile products for BPA, butylparaben and propylparaben content

Product no.	Product type	Target group	BPA (mg/kg)	Butylparaben (mg/kg)	Propylparaben (mg/kg)
EU-T 103	Bodystockings/baby's sleeping suit	Children under the age of three	≤ 0.03	≤ 0.002	≤ 0.002
EU-T 104	Bodystockings/baby's sleeping suit	Children under the age of three	0.03 - 0.2	≤ 0.002	0.002 - 0.05
DK-T 105	Bodystockings/baby's sleeping suit	Children aged three years	≤ 0.03	0.002 - 0.05	≤ 0.002
DK-T 106	Bodystockings/baby's sleeping suit	Children under the age of three	0.03 - 0.2	≤ 0.002	0.002 - 0.05
DK-T 107	Bodystockings/baby's sleeping suit	Children under the age of three	≤ 0.03	≤ 0.002	0.002 - 0.05
DK-T 120	Socks	Children under the age of three	≤ 0.03	≤ 0.002	≤ 0.002
DK-T 121	Socks	Children under the age of three	≤ 0.03	0.002 - 0.05	≤ 0.002
DK-T 122	Socks	Children aged three years	10 – 100	0.002 - 0.05	0.002 - 0.05
DK-T 136	Tights/leggings	Children under the age of three	0.2 – 1	≤ 0.002	0.002 - 0.05

Product no.	Product type	Target group	BPA (mg/kg)	Butylparaben (mg/kg)	Propylparaben (mg/kg)
DK-T 137	Tights/leggings	Children aged three years	≤ 0.03	≤ 0.002	0.002 - 0.05
DK-T 138	Tights/leggings	Children aged three years	0.03 - 0.2	≤ 0.002	≤ 0.002
EU-T 118	Socks	Children under the age of three	0.03 - 0.2	≤ 0.002	0.002 - 0.05
EU-T 134	Tights/leggings	Children aged three years	≤ 0.03	≤ 0.002	≤ 0.002
EU-T 135	Tights/leggings	Children under the age of three	≤ 0.03	≤ 0.002	≤ 0.002
NEU-T 101	Bodystockings/baby's sleeping suit	Children under the age of three	≤ 0.03	≤ 0.002	0.002 - 0.05
NEU-T 102	Bodystockings/baby's sleeping suit	Children under the age of three	≤ 0.03	≤ 0.002	0.002 - 0.05
NEU-T 115	Socks	Children aged three years	0.03 - 0.2	≤ 0.002	0.002 - 0.05
NEU-T 116	Socks	Children aged three years	1 – 10	≤ 0.002	0.002 - 0.05
NEU-T 117	Socks	Children under the age of three	≤ 0.03	≤ 0.002	≤ 0.002
NEU-T 132	Tights/leggings	Children under the age of three	≤ 0.03	≤ 0.002	0.002 - 0.05
NEW-T 133	Tights/leggings	Children under the age of three	≤ 0.03	≤ 0.002	0.002 - 0.05
Number of products with content above the detection limit					
Total			8	3	13
Divided by where the products are purchased			DK: 4 of 9 EU: 2 of 5 NEU: 2 of 7	DK: 3 of 9 EU: 0 of 5 NEU: 0 of 7	DK: 5 of 9 EU: 2 of 5 NEU: 6 of 7
Divided by product type			Socks: 4 of 7 Tights: 2 of 7 Bodyst.: 2 of 7	Socks: 2 of 7 Tights: 0 of 7 Bodyst.: 1 of 7	Socks: 3 of 7 Tights: 4 of 7 Bodyst.: 5 of 7

It can be seen in TABLE 13 that BPA is identified in eight of the 21 textile products purchased, while parabens are identified in 15 products (propylparaben in 13 products, but butylparaben in only three products – both parabens are identified in one product). In general, very low levels have been identified for all three substances. The parabens are maximally identified with an approximate content in the range 0.002 - 0.05 mg/kg, corresponding to 2 - 50 ppb. For BPA, five of the eight products have measured approximate levels in the range 0.03 - 0.2 mg/kg, while three products contain higher levels of BPA with approximate levels in the ranges: 0.2 - 1, 1 - 10 and 10 - 100 mg/kg. Two of these three products with higher BPA content were purchased in Denmark, but all three products with high BPA content were produced in China.

In relation to the selection of products for subsequent migration analysis, the selection of the three products with the highest content of BPA is proposed. It is considered unlikely that detectable migration of the low levels of paraben could occur. However, the same three products with the highest content of BPA also contain propylparaben, i.e. any migration of propylparaben could be identified by the same migration analysis as well. In other words, the following

products are proposed for migration analysis. Product type and suggested migration times from chapter 5 ”Use scenarios” are also indicated.

- DK-T 122 - socks (migration of BPA and propylparaben for 24 hours)
- DK-T 136 - leggings (migration of BPA and propylparaben for 24 hours)
- NEU-T 116 - socks (migration of BPA and propylparaben for 24 hours)

7. Quantitative analyses

Quantitative analyses were performed on all cosmetic products. The analyses aimed to identify the levels of the focus substances in cosmetic products and to check whether the permitted concentrations according to the Cosmetics Regulation were complied with. Knowledge on content concentrations is directly used in the subsequent risk assessment, as only leave-on products were investigated.

Quantitative analyses were performed on the following products (with the relevant focus substances in brackets):

- Cosmetic products – 40 analyses in total, divided into:
  - Body lotions/body oils (D4 and/or, BHT, BHA, propylparaben and butylparaben)
  - Lotions for stretch marks (D4 and/or, BHT, BHA, propylparaben and butylparaben)
  - Sunscreen/after sun lotion (D4 and/or, BHT, BHA, propylparaben and butylparaben)

The 40 analyses were distributed as follows:

- 20 analyses for the content of D4 in the above types of cosmetic products
- 20 analyses for the content of BHT, BHA, propylparaben and butylparaben in the above types of cosmetic products

Analytical methods and results are described in more detail below.

7.1 Method of analysis

In cosmetic products, quantitative analyses of BHA, BHT, D4, and parabens are performed. As control analyses, analyses are performed for the content of the focus substances butylparaben and propylparaben and the content of other parabens, which are either banned or restricted in cosmetic legislation. Finally, control analyses for the content of D4 were also performed.

D4 is a relatively non-polar substance that requires special sample preparation, as there is a risk of ring formation of any linear siloxanes present in the products by injection into GC-MS, as mentioned before under screening analyses for silicone products. Therefore, a different analytical method is used for D4 than for the other substances in cosmetic products. The test preparation for D4 is described previously for silicone products in section 6.2 ”Screening analyses on silicone products”.

The analysis of BHA, BHT and parabens includes a purification of the sample, where oils and water are retained/separated and the analytes are extracted.

Method of analysis for BHA, BHT and parabens

The sample was purified by retaining the oils and water and extracting the analytes. 0.1 g of sample was weighed, internal standard added and mixed with sodium sulphate and Florisil. It was then extracted with ethyl acetate, and cloudy samples were filtered through a 0.45 µm PTFE syringe filter before analysis.

Duplicate determinations of samples, controls, blanks and standard addition to selected samples were performed, and the method was validated. Calibration was done using deuterated internal standards (BHT-d3 (m/z 208/223) and butylparaben-d4 (m/z 125/142)) and by cantification on the specific ions for BHT (m/z 205/220), BHA (m/z 165/137), methylparaben (m/z 121/152), ethylparaben (m/z 121/138), propylparaben (m/z 121/138), butylparaben (m/z

121/138) and benzylparaben (m/z 121/91). The other parabens were identified by their mass spectra and retention time.

The detection limit for BHA was 0.001% and for BHT 0.0001%. The corresponding limits of quantification (LOQ) are 0.004% for BHA and 0.0003% for BHT. The detection limit for the parabens is substance dependent. However, it is estimated to be between 2 mg/kg and 10 mg/kg for methylparaben, ethylparaben, propylparaben and butylparaben and 20 mg/kg for benzylparaben, with an estimated relative uncertainty of 20%. However, it should be noted that for some samples the limit of quantification for BHA is 0.012%. This is because these samples had a high content of BHT and the method was optimised to correctly quantify the higher amount of BHT. In addition, a higher detection limit for BHT has been specified for individual samples, which is due to circumstances during the sample preparation.

Method of analysis for D4
For the determination of D4, basically the same procedure is used as mentioned in the screening analyses for the silicone products, where any linear siloxanes present are silylated in the extract using MSTFA before analysis using a GC-MS. The analysis was performed according to the method described in the International Journal for Cosmetic Science, 2017 (no. 39, 580-588).

400 mg of product was first added to a mixture of polar solvents with internal standard, after which a non-polar solvent (hexane) was added and mixed on a Vortex mixer. A subset of the hexane extract was added to the silylating reagent and then analysed using a GC-MS.

The detection limit for D4 was 30 mg/kg. The analysis uncertainty is estimated to be 20% relatively.

7.2 Results for the content of BHT, BHA, propylparaben and butylparaben and control analyses

The results of the quantitative analyses for the content of BHT, BHA, propylparaben and butylparaben in the 20 selected cosmetic products are given in TABLE 14 below.

All the cosmetic products analysed were purchased precisely because, according to the ingredients list, they contained one of the four substances, i.e. either BHA, BHT, propylparaben or butylparaben. The contents according to the ingredients list of the products are listed in TABLE 14 below).

TABLE 14. Quantitative analysis of cosmetic products for BHA, BHT, propylparaben and butylparaben content. Other parabens include isopropylparaben, isobutylparaben, pentylparaben, phenylparaben and benzylparabens.

Product Lab no.	Product type	Target group	Contents of BHA or BHT, respectively according to ingredients list	BHA (%)	BHT (%)	Content of parabens according to the ingredients list	Propylparaben (%)	Butylparaben (%)	Methylparaben and ethylparaben (%)	Other parabens (%)	Sum of all parabens (%)
NEU-K 171	Body lotion	Pregnant women	BHT	≤ 0.004	0.058	No	No	No	No	No	≤ LOD
NEU-K 181	Body oil	Pregnant women	BHT	≤ 0.004	0.023	Propylparaben	0.098	No	No	No	0.10
EU-K 183	Body lotion	Pregnant women	No	≤ 0.004	≤ 0.0005	Methylparaben Propylparaben Butylparaben	0.099	0.025	Methyl: 0.17	No	0.30
EU-K 182	Body lotion	Pregnant women	No	≤ 0.004	≤ 0.0003	Methylparaben Propylparaben Butylparaben	0.095	0.021	Methyl: 0.25	No	0.36
DK-K 187	Body lotion	Pregnant women	No	≤ 0.004	≤ 0.0003	Methylparaben Propylparaben	0.091	No	Methyl: 0.13	No	0.22
NEU-K 192	After sun	Pregnant women	No	≤ 0.004	≤ 0.0005	Methylparaben Propylparaben	**0.15**	No	Methyl: 0.13	No	0.27
EU-K 168	Sunscreen	Pregnant women	No	≤ 0.004	≤ 0.0003	Methylparaben Propylparaben	0.066	No	Methyl: 0.33	No	0.40
EU-K 195	Sunscreen	Pregnant women	No	≤ 0.004	≤ 0.0005	Methylparaben Propylparaben	**0.17**	No	Methyl: 0.23	No	0.40
EU-K 196	Sunscreen	Pregnant women	BHA	0.008	≤ 0.0003	**No**	0.046	No	Methyl: 0.092	No	0.14
NEU-K 172	Body lotion	Pregnant women	No	≤ 0.004	≤ 0.0005	Propylparaben Methylparaben Butylparaben	0.090	0.036	Methyl: 0.35	No	0.48

Product Lab no.	Product type	Target group	Contents of BHA or BHT, respectively according to ingredients list	BHA (%)	BHT (%)	Content of parabens according to the ingredients list	Propylparaben (%)	Butylparaben (%)	Methylparaben and ethylparaben (%)	Other parabens (%)	Sum of all parabens (%)
NEU-K 180	Body lotion	Pregnant women	No	≤ 0.004	≤ 0.0005	Methylparaben Ethylparaben Propylparaben Butylparaben	0.021	0.045	Methyl: 0.13 Ethyl: 0.055	No	0.25
NEU-K 193	Sunscreen	Children under the age of three	BHT	≤ 0.004	0.047	Methylparaben Ethylparaben Propylparaben	**0.17**	No	Methyl: 0.34 Ethyl: 0.14	No	0.65
EU-K 173	Body lotion	Pregnant women	No	≤ 0.004	≤ 0.0003	Methylparaben Propylparaben	0.054	No	Methyl: 0.20	No	0.25
DK-K 174	Body lotion	Pregnant women	BHT	≤ 0.004	≤ 0.0005	**No**	0.0002	No	No	No	0.0002
DK-K 176	Body lotion	Pregnant women	No	≤ 0.004	≤ 0.0003	Methylparaben Propylparaben	0.092	No	Methyl: 0.16	No	0.25
DK-K 198	Sunscreen	Pregnant women	BHT	≤ 0.012*	0.008	No	No	No	No	No	≤ LOD
EU-K 184	Body lotion	Pregnant women	BHT	≤ 0.012*	0.048	No	No	No	No	No	≤ LOD
DK-K 185	Body lotion	Pregnant women	BHT	≤ 0.012*	0.051	No	No	No	No	No	≤ LOD
DK-K 186	Body lotion	Pregnant women	No	≤ 0.004	≤ 0.0003	Methylparaben Propylparaben	0.043	No	Methyl: 0.18	No	0.22
DK-K 197	Sunscreen	Pregnant women	BHT	≤ 0.004	0.003	No	No	No	No	No	≤ LOD
Number of products with content above the detection limit				**1**	**7**		**15**	**4**	**13 / 2**	**0**	

* for some samples, the limit of quantification for BHA is higher, which is because these samples had a high content of BHT since the method was optimised to quantify the higher amount of BHT correctly

It can be seen in TABLE 14 that BHA and BHT were identified in concentrations above the detection limit in one and seven of the 20 cosmetic products purchased, respectively. The number of products containing BHA and BHT are consistent with the ingredients list on the product. The highest and only identified content of **BHA** is 0.008%. The **BHT** content is between 0.0003% and 0.06%. BHA and BHT have previously been studied in cosmetic products in the survey project on "Exposure of children and unborn children to selected chemical substances" (Larsen et al., 2017), where BHT was identified in levels between 0.0002 and 0.32%, and BHA in a single product of 0.004%. Therefore, the levels identified in this project are on par with previous analyses. However, BHT was not identified in the higher concentrations (above 0.1%) in this current project. This project shows, in line with the previous project, that the use of BHT is much more widespread compared to BHA in cosmetic products in general.

For **parabens**, propylparaben and butylparaben were identified in concentrations above the detection limit in 15 and four of the 20 cosmetic products purchased, respectively. The highest identified content of propylparaben and butylparaben is 0.17% and 0.044%, respectively.

It can be seen that there is generally a good correlation between the analytical results and the content according to the list of ingredients on the packaging of the products[8]. There are two products where the analysed content of parabens does not match the content according to the ingredients list:

- For EU-K 196, there is no paraben content according to the product's list of ingredients, despite the fact that a total paraben content of 0.14% and a content of both methylparaben and propylparaben in concentrations of 0.092% and 0.046% respectively have been identified.
- For DK-K 174, there is no paraben content according to the product's list of ingredients, despite the fact that a propylparaben content of 0.0002% has been identified.

Several parabens are regulated in Annex V of the Cosmetics Regulation, a list of preservatives allowed to be used in cosmetic products. The maximum authorised concentration (such as acid) of a mixture of the parabens mentioned in reference numbers 12 and 12a of Annex V to the Cosmetics Regulation is 0.8% (with the sum of butylparaben and propylparaben and their salts not exceeding 0.14%). This legal requirement is met for all 20 products analysed, with a maximum total paraben content of 0.65%.
Methylparaben and ethylparaben are each permitted at a concentration of 0.4% (as acid in ester form). This legal requirement is also met for all 20 products analysed. The maximum content of methylparaben is 0.38% and the maximum content of ethylparaben is 0.14%.
The limit for butylparaben and propylparaben is also met for all 20 analysed products, taking into account the analytical uncertainty. The content of butylparaben for the analysed products is maximum 0.044%, whereas the content of propylparaben is 0.15%, 0.17% and 0.17%, respectively, in the products NEU-K 192, EU-K 195 and NEU-K 193. These three concentrations are thus above the permitted 0.14%, but taking into account the uncertainty of the analyses, the levels are within the permissible limit.
Finally, other parabens banned by the Cosmetics Regulation were tested for, but not identified above the detection limit in any of the 20 products analysed.

7.3 Results for D4 content

The results of the quantitative analyses for the content of D4 in the 20 selected cosmetic products are given in TABLE 15 below.

[8] Packaging here means both primary packaging (the container itself) and secondary packaging (outer packaging) where such outer packaging was used.

TABLE 15. Quantitative analysis of cosmetic products for the content of D4

Product Lab no.	Product type	Target group	Content of silicone compound according to the ingredients list	D4 (mg/kg)
NEU-K 150	Body lotion	Pregnant women	Dimethicone	≤ 30
NEU-K 158	Lotion for stretch marks	Pregnant women	Dimethicone	≤ 30
EU-K 153	Body lotion	Pregnant women	Dimethicone Cyclopentasiloxane	≤ 30
EU-K 162	Sunscreen	Pregnant women	Dimethicone	≤ 30
EU-K 163	After sun	Pregnant women	Dimethicone Cyclohexasiloxane	≤ 30**
EU-K 154	Body lotion	Pregnant women	*None**	≤ 30
DK-K 187	Body lotion	Pregnant women	Dimethicone	≤ 30**
NEU-K 160	Sunscreen	Children under the age of three	Dimethicone	≤ 30
NEU-K 161	Sunscreen	Children aged three years	Dimethicone	≤ 30
NEU-K 151	Body lotion	Children under the age of three	Dimethicone	≤ 30
EU-K 164	Sunscreen	Pregnant women	Dimethicone	≤ 30
EU-K 152	Body lotion	Pregnant women	Dimethicone	≤ 30
EU-K 194	Sunscreen	Children under the age of three	Dimethicone	≤ 30
EU-K 168	Sunscreen	Pregnant women	Dimethicone	≤ 30
NEU-K 172	Body lotion	Pregnant women	Cyclopentasiloxane Dimethicone	≤ 30**
DK-K 175	Body lotion	Pregnant women	Dimethicone	≤ 30
DK-K 198	Sunscreen	Pregnant women	Dimethicone	≤ 30
DK-K 169	After sun	Pregnant women	*None**	≤ 30
DK-K 185	Body lotion	Pregnant women	Cyclohexasiloxane	≤ 30**
DK-K 186	Body lotion	Pregnant women	Dimethicone	≤ 30
Number of products with content above the detection limit				
Total				0

* Means that, despite information on the website at the time of purchase, the product did not contain a silicone compound after all (according to the ingredients list on the product).

** A possible content of D4 has been identified at levels below the detection limit.

It can be seen in TABLE 15 that D4 is not identified in concentrations above the detection limit in any of the 20 purchased cosmetic products. However, a possible content of D4 was identified in four products. The content of these four products is lower than the detection limit, which is relatively high due to the method blind, and the content can therefore not be specified with certainty. Method blind means that the column material contributes with a blind value. Without this blind value, much lower amounts would be seen, but because of the blind value, the uncertainty on samples with low D4 content becomes very high. Since the detection limit is calculated based on a known low content sample, this blind value means a higher detection limit.

It should be noticed that D4 previously has been identified in several cosmetic products in a former survey carried out by the Danish EPA (Larsen et al., 2021). D4 was identified as e.g.

impurities from other silicone compounds. The concentrations identified in the cosmetic products in the previous project were between 50 and 5900 mg/kg. In this previous project another method was used for the chemical analysis using a different solvent and without the used silylating reagent, when comparing the method used in the present project. The silylating reagent was used in the present project due to discussions of the method of analysis in the former project (Larset et al., 2021). It has not been clarified which method that is most accurate nor whether the two different methods of analysis will produce different results. The Danish EPA plans to follow up on this subject, but this will take place after publication of this report.

All the analysed cosmetic products were purchased precisely because they contained some kind of silicone compound according to the ingredients list (also mentioned in TABLE 15 above). However, upon receipt, two products were found not to contain a silicone compound according to the ingredients list. Despite this, these two products were analysed when they were selected for control analyses by the Swedish Chemicals Agency.

Annex II of the Cosmetics Regulation prohibits the use of D4 as an ingredient in cosmetic products. However, according to (Larsen et al., 2021) cyclic siloxanes such as D4 can occur as residues in other cyclic and linear siloxanes, e.g. dimethicone. Furthermore, Article 17 of the Cosmetics Regulation regarding traces of prohibited substances states that the unintentional presence of a small quantity of a banned substance (in this case D4) originating from impurities, the manufacturing process, storage or transfer from packaging, which is technically unavoidable under good manufacturing practice (GMP), may be allowed provided that the cosmetic product is safe to use according to Article 3 of the Cosmetics Regulation. Thus, no specific limit has been set for the permitted concentration of traces of banned substances, but this will instead depend on a safety assessment of the product, which is required for all cosmetic products under Article 10 of the Cosmetics Regulation.

It can be seen that for those products that may contain D4 in small amounts, in three out of four cases, the content of other cyclic siloxanes is also indicated, where D4 may be an impurity.

8. Migration analysis

The migration analyses described below were carried out in agreement with the Danish EPA. Five products were pre-purchased and selected for control analyses for migration of BPA from toys. The remaining products were selected based on the results of the screening analyses and were distributed among the products purchased from plastic, silicone and textile, respectively, based on the results of the screening analyses.

8.1 Selection of products for migration analysis

Optimally, it would make sense to perform migration analyses to the relevant migration medium, i.e. artificial saliva or artificial sweat, respectively, depending on the use of the product. However, this would require a disproportionate number of combinations of migration analyses (combinations of different substances and migration fluids) compared to the allocated analysis budget. For this reason, a single migration fluid was focused on.

According to the Danish Statutory Order on Toys (Statutory Order no. 1800 of 3 December 2020, Appendix C) EN 71-10:2005 and EN 71-11:2005 must be used for the migration of BPA from toys. According to EN 71-10:2005, water (deionised) must be used as migration fluid for the migration analysis of BPA in toys. In addition, EN 71-10:2005 uses stirring at migration, probably to simulate a sucking motion when the toy is placed in the mouth of toddlers. For this reason, the use of water was decided on as migration fluid for all other migration analyses, i.e. for the products listed below.

Although stirring should be used according to EN 71-10:2005, the choice of shaking tables was decided on in cooperation with the Danish EPA for the other migration analyses when dealing with products that toddlers put in their mouths (toys, pacifier shields and teething rings). The shaking table was chosen as it seems more realistic than stirring in simulating children sucking on the products. For products not expected to enter the mouth (in children), static migration conditions were used, i.e. the product was immersed in the migration fluid for the specified migration time. The selected products for the migration analyses and the selected migration conditions are listed in TABLE 16 below.

TABLE 16. Selected products and migration conditions for the migration analyses. The table is sorted by the substance analysed (third column). The listed migration times are derived from exposure times given in chapter 5.

Product no.	Product type	Substance	Migration time	Migration fluid	Other conditions
Control analyses according to EN 71-10:2005 and EN 71-11:2005					
DK-P 41	Toys	BPA	1 hour	Water, deionised	20 °C, stirring, 100 ml liquid
DK-P 42	Toys	BPA	1 hour	Water, deionised	20 °C, stirring, 100 ml liquid
DK-P 43	Toys	BPA	1 hour	Water, deionised	20 °C, stirring, 100 ml liquid
DK-P 44	Toys	BPA	1 hour	Water, deionised	20 °C, stirring, 100 ml liquid
DK-P 45	Toys	BPA	1 hour	Water, deionised	20 °C, stirring, 100 ml liquid

Product no.	Product type	Substance	Migration time	Migration fluid	Other conditions
Other migration analyses					
DK-T 122	Socks	BPA Propylparaben	24 hours	Water, deionised	37 °C, static, covered with liquid
DK-T 136	Tights/leggings	BPA Propylparaben	24 hours	Water, deionised	37 °C, static, covered with liquid
NEU-T 116	Socks	BPA Propylparaben	24 hours	Water, deionised	37 °C, static, covered with liquid
EU-P 3	Pacifier shield	BPA	7.7 hours	Water, deionised	37 °C, shaking table, covered with liquid
DK-P 35	Mobile cover	BPA	8 hours	Water, deionised	37 °C, static, covered with liquid
DK-P 34	Mobile cover	BHT	8 hours	Water, deionised	37 °C, static, covered with liquid
DK-P 56	Pop It, baby	BHT	200 min.	Water, deionised	37 °C, shaking table, covered with liquid
DK-S 57	Pop it	D4	2 hours	Water, deionised	37 °C, shaking table, covered with liquid
EU-S 53	Pop it	D4	2 hours	Water, deionised	37 °C, shaking table, covered with liquid
DK-S 56	Pop It, baby	D4	200 min.	Water, deionised	37 °C, shaking table, covered with liquid
DK-S 54	Pop It, arm	D4	24 hours	Water, deionised	37 °C, static, covered with liquid
DK-S 201	Watch strap	D4	24 hours	Water, deionised	37 °C, static, covered with liquid
DK-S 202	Watch strap	D4	24 hours	Water, deionised	37 °C, static, covered with liquid
NEU-S 81	iPad/tablet	D4	8 hours	Water, deionised	37 °C, static, covered with liquid
EU-S 84	iPad/tablet	D4	8 hours	Water, deionised	37 °C, static, covered with liquid
DK-S 89	iPad/tablet	D4	8 hours	Water, deionised	37 °C, static, covered with liquid
EU-S 71	Teething ring	D4	200 min.	Water, deionised	37 °C, shaking table, covered with liquid
NEU-S 66	Teething ring	D4	200 min.	Water, deionised	37 °C, shaking table, covered with liquid
DK-S 74	Teething ring	D4	200 min.	Water, deionised	37 °C, shaking table, covered with liquid

8.2 Methods of analysis

The substances for which migration analyses are carried out, i.e. BPA, propylparaben, BHT and D4, are analysed by the same methods as indicated in chapter 6 “Screening analyses” for plastic, silicone and textile products, respectively. The difference is that analysis is performed directly on the migration fluids for analysis of BPA and propylparaben and that the migration fluid is extracted with an organic solvent before analysis of respectively BHT or D4. Duplicate determinations have been applied to all migration analyses.

For the control analyses for the determination of migration of BPA from toys, EN 71-10: 2005 is followed, where the migration conditions are described (migration to deionized water for 1 hour with stirring and 20 °C), and EN 71-11: 2005, where analysis method and analysis equipment are described. According to EN 71-10:2005, a toy (product) of 10 cm^2 ± 1 cm^2 in surface area has to be used. Thus, the same size has been chosen for the other migration analyses as well. The surface area is calculated as both sides of the product (front and back) if the thickness is more than 0.5 mm. If the thickness is more than 1 mm, the surface area of the edges is calculated according to EN 71-10:2005 (section 6.3).

Therefore, in practice, a piece of the sample measuring 2.4 x 2 cm x 2 for the front and back (10 cm^2 ± 1 cm^2) is cut so that the surface of the edge of the product is included in the surface area. For textiles and other samples thinner than 0.5 mm, a piece of 5 x 2 cm (10 cm^2 ± 1 cm^2) was cut.

Samples are usually taken at the same location as for the screening analyses if this was possible. For the pop it samples, the edge of the product (a flat side) was used with the same colour distribution as for the screening analyses in order to determine the surface area. The sample is then placed in a 100 ml sample vial and sufficient migration fluid is used to cover the sample with liquid (10 or 20 ml) – with the exception of the control analyses for BPA migration from toys, where 100 ml migration fluid is used, as required by the standard EN 71-10:2005.

After the samples have been left at the specified migration conditions (shaking/stirring/static, temperature and time), they have been analysed by the same analytical methods as described previously for the individual substances. For the control analyses of migration of BPA from toys, according to EN 71-11:2005, HPLC equipment with both UV (DAD - diode array detector) and fluorescence detector must be used. Instead of the two detectors, $LC\text{-}MS^2$ was used for these migration analyses, which is more sensitive and selective as it measures the specific mass ions of BPA in addition to the retention time. The measurement range for the determination of BPA according to EN 71-11:2005 is 0.01 to 0.5 mg/l, and for FORCE's method M2.211, the measurement range is 0.002 to 1.0 mg/l.

8.3 Results – migration analysis

The analysis results for the migration analyses are given on the following pages. In all cases, duplicate determinations were performed, and the results are reported as an average of the two duplicate determinations performed.

8.3.1 Results for migration of BPA from toys (control analyses)

The results of the five control analyses carried out for BPA from toys are given in TABLE 17 below. The limit of detection (LOD) of the method is 20 ng/cm^2, while the limit of quantification (LOQ) is 60 ng/cm^2. For all five products, a level above the detection limit but below the quantification limit has been identified. The result is indicated as being below the quantification limit of 60 ng/cm^2. The relative expanded uncertainty of the method was determined to be 10 and 30% for high and low controls, respectively. The recovery of BPA in water spiked with known amounts of BPA is between 90 and 110%.

TABLE 17. Analytical results for migration of BPA from toys. Migration has been performed according to EN 71-10:2005, i.e. at 20 °C for 1 hour with stirring with 100 ml water and 10 cm^2 ± 1 cm^2.

Product no.	Product type	Migration (ng/cm^2)	Migration (µg/litre)
DK-P 41	Toys	< 60	< 6
DK-P 42	Toys	< 60	< 6
DK-P 43	Toys	< 60	< 6
DK-P 44	Toys	< 60	< 6
DK-P 45	Toys	< 60	< 6

It should be noted that it was not possible to obtain information on the type of plastic in the toy at the time of purchase, and therefore it was not possible to target purchases based on the content of the plastic type polycarbonate, where BPA is used as a monomer ("building block"). Therefore, products were analysed where the type of plastic looked like polycarbonate or toys made of recycled plastic where there could be a suspicion of possible residues of polycarbonate and/or BPA.

As can be seen from the results, BPA was not identified above the detection limit of 60 ng/cm^2 toy material, corresponding to approximately 6 µg/l migration fluid. According to the Toys Statutory Order[9] (Stat. Ord. 1800, 2020), the migration limit value for BPA from toys is 0.04 mg/litre, corresponding to 40 µg/l. This means that all five toy products sampled for migration analysis comply with the migration limit value for toys laid down in the Toys Statutory Order.

8.3.2 Results for migration of BPA and propylparaben

The results of the migration analyses carried out for BPA in textile and plastic products and for propylparaben in textile products are given in TABLE 18 below. The limit of detection (LOD) of the method is 2 ng/cm^2, while the limit of quantification (LOQ) is 6 ng/cm^2 for BPA, but the LOD and LOQ are 1 and 2 ng/cm^2 respectively for propylparaben.

For the product EU-P 3 (the pacifier shield), both LOD and LOQ are twice as high, as the product is not flat but curves, therefore more migration liquid had to be used to cover the product with the liquid.

The uncertainty of the method used in general is 10% - 30% for BPA and 10% for propylparaben. However, the uncertainty for both substances is much higher at the low concentrations close to the detection limit. The recovery of both BPA and propylparaben in water spiked with known amounts of BPA and propylparaben is between 90% and 110%.

[9] Danish Statutory Order no 1800 of 3 December 2020 on safety requirements for toys (hereinafter referred to as the Toys Statutory Order). The limit value for BPA applies to toys intended for use by children of 36 months or less or in other toys intended to be put in the mouth (according to Appendix C of Annex II).

TABLE 18. Analytical results for migration of BPA and propylparaben from textiles. Migration is performed according to the migration conditions listed in the table. The listed migration times are derived from exposure times given in chapter 5.

Product no.	Product type	Migration BPA (ng/cm^2)	Migration Propylparaben (ng/cm^2)	Migration conditions	Volume of migration fluid in ml
DK-T 122	Socks	< 6 *	3	24 hours, 37 °C, static, covered with liquid	10
DK-T 136	Tights/leggings	< 6	14	24 hours, 37 °C, static, covered with liquid	10
NEU-T 116	Socks	3 **	< 2	24 hours, 37 °C, static, covered with liquid	10
EU-P 3	Pacifier shield	< 12 ***	< 4 ***	7.7 hours, 37 °C, shaking table, covered with liquid	20
DK-P 35	Mobile cover	< 6	< 2	8 hours, 37 °C, static, covered with liquid	10

* BPA was determined in the migration fluid above the limit of detection (LOD) but below the limit of quantification (LOQ) indicated in the table.
** 20 cm^2 of substance is measured instead of 10 cm^2, which is why LOQ and LOD are lower
*** A larger volume had to be used to cover the pacifier shield with migration fluid. LOQ and LOD are therefore higher. BPA levels above the limit of detection (LOD) but below the limit of quantification (LOQ) have been determined in one of the two determinations.

Thus, migration of BPA was identified from two of three textiles examined, and migration of propylparaben from two of the three textiles examined (although not from the same textiles as for BPA). For the plastic products, migration of BPA from the pacifier shield was identified but at a level below the limit of quantification. Propylparaben was not identified in the migration fluid from the plastic products.

8.3.3 Results for migration of BHT from plastics

The results of the migration analyses performed for BHT in the two plastic products are given in TABLE 19 below. The limit of detection (LOD) of the method is 30 ng/cm^2, while the limit of quantification (LOQ) is 80 ng/cm^2 for BHT. The relative expanded uncertainty was determined to be 10% and 15% for low and high controls, respectively. The recovery of BHT in water spiked with known amounts of BHT is between 90% and 110%.

TABLE 19. Analytical results for migration of BHT in plastic products. Migration is performed according to the migration conditions listed in the table. The listed migration times are derived from exposure times given in chapter 5.

Product no.	Product type	Migration BHT (ng/cm^2)	Migration conditions	Volume of migration fluid in ml
DK-P 34	Mobile cover	< 30*	8 hours, 37 °C, static, covered with liquid	10
DK-P 56	Pop It, baby	< 30	200 min, 37 °C, shaking table, covered with liquid	10

* The analysis indicated the content of BHT in the migration fluid below the limit of detection (LOD).

Thus, no BHT was identified in the migration fluid above the detection limit for the two samples.

8.3.4 Results for migration of D4 from silicone

The results of the migration analyses carried out for D4 in the 12 silicone products are given in TABLE 20 below. The limit of detection (LOD) of the method is 2 µg/cm^2, while the limit of quantification (LOQ) is 6 µg/cm^2 for D4.

In general, 10 ml migration fluid was used for the migration analyses, but for some samples which were thicker, 20 ml was used to cover the whole product with the migration fluid.

TABLE 20. Analytical results for migration of D4 in silicone products. Migration is performed according to the migration conditions listed in the table. The listed migration times are derived from exposure times given in chapter 5.

Product no.	Product type	Migration D4 (µg/cm^2)	Migration conditions	Volume of migration fluid in ml
DK-S 57	Pop it	< 6	2 hours, 37 °C, shaking table, covered with liquid	10
EU-S 53	Pop it	< 6	2 hours, 37 °C, shaking table, covered with liquid	10
DK-S 56	Pop It, baby	< 6	200 min, 37 °C, shaking table, covered with liquid	10
DK-S 54	Pop It, arm	< 6	24 hours, 37 °C, static, covered with liquid	10
DK-S 201	Watch strap	< 6	24 hours, 37 °C, static, covered with liquid	10
DK-S 202	Watch strap	< 6	24 hours, 37 °C, static, covered with liquid	10
NEU-S 81	iPad/tablet	< 6	8 hours, 37 °C, static, covered with liquid	10
EU-S 84	iPad/tablet	< 6	8 hours, 37 °C, static, covered with liquid	10
DK-S 89	iPad/tablet	< 6	8 hours, 37 °C, static, covered with liquid	10
EU-S 71	Teething ring	< 12	200 min, 37 °C, shaking table, covered with liquid	20
NEU-S 66	Teething ring	< 6	200 min, 37 °C, shaking table, covered with liquid	10
DK-S 74	Teething ring	< 12	200 min, 37 °C, shaking table, covered with liquid	20

Thus, D4 was not detected in the migration fluid for any of the samples. As D4 is an insoluble (lipophilic) compound, its solubility in water is low (56 µg/litre at 23 °C). This means that only a very small amount of D4 (56 µg) can be dissolved in one litre of water at 23 °C. D4 is thus about 10,000 less soluble in water than propylparaben, and the likelihood of the substance migrating out of the samples in larger quantities is therefore expected to be low.
In the semi-quantitative analyses of the silicone products, D4 content of 200-500 ppm was found. With the migration method used, this corresponds to at least 30-40 times as much D4 potentially migrating into the migration fluid as the quantification limit of the method, if the entire content migrated. However, this is without taking into account the poor solubility of the substance in water.

It should be noted that migration analyses with D4 are complicated as the silicone compound is lipophilic and may tend to stick to the glass when migration fluid is transferred to a new test tube. Analyses of controls (migration fluid added with a known amount of D4) showed that the

residual concentration of D4 in the controls used was significantly lower in the 24-hour samples than in the other migration samples (at 2 hours, 200 minutes and 8 hours). This indicates that these conditions (24 hours of migration) are not optimal for D4 migration.
Therefore, as an additional control, new migration analyses were performed for all migration analyses listed above for the silicone products, where a piece of the silicone products was placed in a test tube and covered with migration fluid, after which the product was left under the listed conditions before analysis. A sample of the migration fluid was then taken directly from the test tube. The results here were identical, i.e. no migration of D4 above the detection limit was identified.

9. Hazard assessment

This chapter provides a thorough hazard assessment for the six selected endocrine disruptors and suspected endocrine disruptors. The hazard assessment must be relevant for children up to 3 years of age and pregnant women, as it must form the basis for the subsequent exposure and risk assessment for these groups. The hazard assessment was performed by National Food Institute at DTU (DTU Food).

The focus is on effects via EATS modalities, i.e. effects related to (anti-) estrogen (E), (anti-) androgen (A), thyroid disrupting (T) and steroid hormone synthesis disrupting (S) properties. In practice, most endocrine disrupting chemicals are known to have either estrogenic, anti-androgenic and / or steroidogenic disrupting action, while anti-estrogenic and androgenic action is rarely seen. The assessment of endocrine disrupting effect is based on principles described in ECHA / EFSA guidance (2018). Determination of derived no-effect levels (DNELs) and derived minimal effect levels (DMELs) follow principles in ECHA's Guidance on information requirements R.8 (ECHA 2012).

We present separate sections for the T modality and for EAS modalities in line with ECHA / EFSA guidance (2018). If relevant based on knowledge of mode of action, DNELs and DMELs are determined for each of these modalities. As a starting point, separate DNELs will not be determined for estrogen, anti-androgen, and steroid hormone disrupting effect, as research shows that substances that act via one or several of these modes of actions together, can cause similar endocrine disrupting effects (Christiansen et al. 2020). In line with this, the OECD guidance document 150 regarding evaluation of endocrine disruptors presents a number of examples of substances that shows more than one sort of endocrine action (OECD 2018). In this risk assessment project, it will therefore not be relevant to separate these effects. Therefore, in this project a $DNEL_{EAS}$ as well as $DMEL_{EAS}$ and $DNEL_{Thyr}$ as well as $DMEL_{Thyr}$ will be determined.

In addition, it is evaluated how risk assessment can be performed if it is assumed that there is no threshold for the endocrine disrupting effect as described in a report prepared by the Danish Centre on Endocrine Disrupters, CEHOS (Hass et al. 2019). It is also evaluated how simultaneous exposure to many endocrine disrupting compounds can be taken into account using a Mixture assessment factor (MAF), and the consequences of this are discussed.

In this project, both DNEL and DMEL values have been set. This is because a number of recent scientific reports suggest that risk assessment of endocrine disrupting chemicals should not follow the current threshold-based approaches (Hass et al. 2019; Demenix et al. 2020). According to REACH information requirements R.8, DNEL is used for substances where a safe threshold is assumed (i.e. a dose below which no adverse effect is expected), while DMEL is used for substances for which a threshold is not expected (ECHA 2012). For the endocrine disruptors, this is currently unresolved.

In 2019, international experts with research backgrounds and representatives of the European authorities prepared recommendations on how risk assessments should take into account gaps in current knowledge about the adverse effects of chemical substances, especially the endocrine disruptors (Hass et al. 2019). The report, which is based on several workshops, recommends including additional uncertainty factors in the risk assessment, e.g. to account for exposure during sensitive periods and lack of assessment of endocrine-sensitive endpoints. Furthermore, it is recommended to use a non-threshold based approach per default when

evaluating endocrine disruptors in cases where there is no knowledge of the presence or absence of a threshold. This is in line with current practice for risk assessment of carcinogenic chemicals and this approach is recommended to address specific uncertainties related to the assessment of endocrine disruptors.

One of the arguments that supports the notion that there is no biological threshold for endocrine disruptors is the very important organizing role hormones play during fetal and neonatal development, a time point where the homeostatic control is not effective or not yet developed. Despite continued discussions in recent years, there is still no agreement on whether the toxicological principle of a 'safe threshold' can be used to assess the safety of endocrine disruptors (EC 2020b). In 2019, the European Parliament adopted a non-binding resolution calling on the Commission to make more coherent regulation of endocrine disruptors in the EU. One of the points adapted in this Directive called on the Commission to: *draw up legislative proposals no later than June 2020 to insert specific provisions on EDC[10]s into Directive 2009/48/EC, similar to those on CMR substances but without any reference to thresholds of classification, as such thresholds are not applicable for EDCs* (EP, 2019). The issue of toxicological threshold is also mentioned in the working document of the Commission's fitness check of endocrine disruptors (EC 2020b). In here the different opinions among authorities and experts on the ability to demonstrate safe or unsafe use of endocrine disruptors using available methods in a risk assessment are discussed. Among other things, it is noted: "*at EU level, agencies and scientific committees may in principle conclude on a level below which no risk is identified, if the evidence for a specific substance allows a threshold to be established"* (EC 2020a).

9.1 Methods - hazard assessment

A literature search has been performed for each of the six selected substances with the aim of updating previous reports in relation to assessment of endocrine disrupting effects, and determination of a DNEL for endocrine disruption.

For each substance, tables have been prepared with information on a) data availability and literature search, b) assessment of endocrine disrupting effects, c) DNEL / DMEL determination and, d) possibly notes on any other effects of relevance to human health.

An overall assessment has been made of methods for risk assessment of endocrine disruptors, i.e. assessment of the use of DMEL versus DNEL depending on whether there is a threshold for endocrine disrupting effect. In addition, the use of the Mixture Assessment Factor, MAF, is assessed in risk assessment.

9.1.1 Data availability and literature search

For each of the six substances, previous reports that have assessed the endocrine disrupting effects and / or already established DNEL values with the focus on risk assessment of endocrine effect (TABLE 21). These have been included in the present report. In addition, a literature search was performed using keywords based on a search strategy described in the ECHA / EFSA guidance (2018). The search was used to identify studies for use in both assessment of endocrine disrupting effect and a determination of DNELs. Screening of the identified articles was done in three steps, in accordance with recommendations from ECHA / EFSA (2018): 1) screening of titles, 2) screening of abstracts, and 3) screening of full text articles.

In addition, the REACH registration for each substance was checked by look-ups in ECHA's public reporting database (ECHA dissemination site). The available study summaries for toxicological studies were reviewed in order to clarify whether references were made to studies

[10] EDC is short for an Endocrine Disrupting Chemical

that could contribute to the assessment of endocrine disrupting effect and / or DNEL determination for endocrine disrupting effect. The result of this review is described in the appendices for each substance. Overall, for the six selected compounds, most of data available in ECHA's public database was also reported in peer-reviewed publications, or had previously been included in hazard assessments carried out by expert panels from e.g. ESFA or in relation to the preparation of SVHC proposals. For those studies in ECHA's database that had not previously been published or included in hazard assessments, DTU found that the ECHA study summaries were not sufficient to assess the quality and robustness of the studies. In these cases, the results were not used for DNEL determinations. No further information on these studies was obtained from, e.g. the registrants.

See exact search string and available information in appendix for each substance.

9.1.2 Assessment of endocrine disrupting effects

The assessment of endocrine disrupting effects in this report generally follows the principles described for the assessment of endocrine disrupting effects of pesticides / biocides (ECHA / EFSA 2018). These principles are used to clarify whether a substance meets the WHO's definition of an endocrine disruptor. WHO's definition of an endocrine disruptor is: "*An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.*" (WHO/IPCS 2002). It must therefore be assessed whether the substance has 1) endocrine disrupting mode of action, 2) adverse effects, and 3) a biologically plausible relationship between endocrine disrupting mode of action and the adverse effects.

In practice, the assessment was performed differently for the 6 substances. Bisphenol A and Butylparaben were prior to this report already identified as "substance of very high concern" (SVHC) on the basis of their endocrine disrupting effects on human health, and for these two substances reference was therefore made to their respective SVHC reports. For Propylparaben, D4, BHA and BHT, assessments were made in accordance with the guidelines for assessment of endocrine disrupting effects of pesticides / biocides, cf. ECHA / EFSA (2018), however, reproduced in appendices in a compact version for each substance. For each of these substances, the following steps were performed in the assessment: 1) description of the evidence for endocrine disrupting mode of action, 2) description of evidence for the adverse effect on endocrine-relevant endpoints, 3) mode of action analysis. The principles of the "Lines of Evidence" description (ECHA / EFSA 2018) have been applied, but the description is more brief here. For each substance, the proposed mode of action was composed of a description of the Molecular Initiating events (MIE), Key Events (KE) and Adverse Outcomes (AO). Mode of action analysis, i.e. assessment of biologically plausible link between key events, has been presented for the modality (EAS or T) that was considered relevant for the individual substance.

Conclusions for each substance are summarized in a table (TABLE 22) that includes assessment of dose-response and temporal relationships, human relevance, and uncertainties. The main conclusions are also included here in the report.

9.1.3 DNEL and DMEL determination

DNEL and DMEL are determined for all six substances in accordance with REACH information requirements R.8 (ECHA 2012). Such a DNEL is used as a zero-effect level, below which exposures are assessed not to entail any risk, while DMEL is used as an effect level, below which exposures are assessed to entail a low and thus tolerable / acceptable risk when there is no lower threshold for effects.

The hazard assessment is carried out with a focus on endocrine disrupting effects, and one common DNEL is calculated for children and pregnant women. Children and pregnant women are the target groups of the project, as they are considered to be most vulnerable to endocrine disrupting effects via EATS modalities. Depending on the action(s) of the substances, one DNEL is determined for endocrine disrupting effect via T modality ($DNEL_{thyr}$) and one DNEL for endocrine disrupting effect via EAS modalities ($DNEL_{eas}$).

The DNEL determination in this project is based on no-observed adverse effect levels (NOAELs) from experimental animal studies, or on lowest-observed adverse effect levels (LOAELs) if a NOAEL could not be determined. In principle, benchmark dose low (BMDL) values could also be used, but there has not been sufficiently robust data for these values in this project (only for BPA in EFSA's calculation of TDI, but this was not on an endocrine disrupting effect). In the case of the use of LOAELs, an assessment factor (AF) in the order of 3 to 10 was used to take into account the uncertainty regarding the identification of NOAEL, cf. REACH guidance (ECHA 2012). The DNEL determination also includes uncertainty factors, which must take into account uncertainties from intra- and inter-species variation, nature and severity of the effect, as well as sensitivity of human (sub-) populations. For example, an additional uncertainty factor may have been included if no studies of effects have been carried out during development, but a risk assessment is wanted for pregnant women and children. Our starting point was a calculated internal dose, i.e. a DNEL that can be used in risk assessment across all exposure routes. This corresponds to principles used by e.g. SCCS, who do risk assessment on the basis of a systemic exposure dose, which is compared to a systemic "point of departure" (POD_{sys}). This can be BMDL, NOAEL or LOAEL adjusted with regard to systemic absorption (SCCS 2018). Therefore, exposure data have also been converted to an internal dose in order to be used in the risk assessment. This is relevant, for example, when using data from studies where absorption is not assumed to be 100%, e.g. dermal studies.

DNELs can be determined on the basis of several types of studies, i.e. both short-term and long-term studies as well as reproductive toxicology studies, including developmental toxicity studies. The effects used for the DNEL determination are considered to be specifically related to the endocrine disrupting action, and not secondary to maternal toxicity or general toxicity. These are most often studies with oral exposure, which is also generally the case for most of the cosmetic ingredients evaluated by SCCS (SCCS 2018). SCCS notes that if 100% absorption is assumed by oral exposure in the toxicological study, but the absorption is actually less, the risk will be overestimated.

DMELs can be determined according to the same principles as those used for DMEL determinations for carcinogenic chemicals, for which no threshold is assumed. There are two possibilities, 1) "Linearised approach" whereby an extrapolation is made from the incidence of harmful effects in human or animal experimental studies, to a human incidence of 10^{-6} for a given relevant harmful effect on health, or 2) "Large assessment factor" approach, which is done via the same principles as DNEL determination, but with the application of an additional uncertainty factor (R.8, p. 6). In both cases, for carcinogens T25 (tumour incidence 25%), BMD10 or BMDL10 is used as the reference dose for an effect level. In this context, BMD10 reflects the dose at which a tumour incidence of 10% is seen. BMDL10 also takes into account the uncertainty of this dose, as it is defined as the lower limit of the 95% confidence interval for BMD10. The choice of BMD or BMDL depends on the desired degree of caution / protection.

For example, a “linearized approach” will use a BMD(L)10 and an uncertainty factor for allometric scaling (e.g. 4 for rat to human) as well as an uncertainty factor of 100,000 for extrapolation from high to low risk. For the selected compounds, it was not possible to use the “Linearized approach”, as no relevant human or animal experimental data have been identified to ex-

trapolate to human risk of 10^{-6}. Such extrapolation requires effect data where there is a frequency of a relevant finding (e.g. 10% incidence corresponding to BMD(L)10. Such data are often not available for endocrine disruptors.

It was therefore decided that in this project DMELs were determined using the "Large assessment factor" approach. This approach is based on a BMD(L)10 as well as the use of the uncertainty factors (assessment factors) presented in R.8, table R 8-8, p. 44 (ECHA 2012). In the present project, BMD(L) values were not available as data could not be converted to this value. Instead, a NOAEL approach was used, or LOAEL if a NOAEL was not available. The ECHA guide (R.8) describes that a total AF of 10,000 can be used and consists of an assessment factor (AF) 10 for interspecies differences, an AF of 10 for intraspecies differences, an AF 10 for "nature of the carcinogenic process" and an additional AF of 10 because BMDL10 reflects an effect level and not a no-effect level. In this project, AF 10x10 was similarly used for inter- and intraspecies differences as well as an AF 10 for "nature of endocrine disrupting properties" (Hass et al. 2019). However, the additional assessment factor of 10 was not included as NOAELs (or LOAEL and extra AF) and thus a no-effect level, rather than an effect level what the use of BMDL would reflect.

The following steps describe the DNEL/DMEL determination for each substance (cf. R.8 p. 12) (ECHA 2012):

1. Identification of a "dose descriptor", i.e. NOAELs / LOAELs / BMD(L)10 for effects relevant to T or EAS modalities
2. Modification to internal dose, if necessary
3. Determination of DNEL using uncertainty factors
4. Determination of DMEL using uncertainty factors, including factor 10 for "nature of endocrine disrupting properties"

Details about DNEL and DMEL calculations are given in a separate appendix for each substance and are summarized in TABLE 23 below. It is noted that for propylparaben a read-across approach was made using data for butylparaben in the DNEL determination. This more cautious approach has been chosen because existing data for propylparaben are considered to be subject to a significant degree of uncertainty.

9.1.4 Mixture assessment factor

The new EU Chemicals Strategy focuses on handling combination effects (EC 2020a). Under REACH, the use of an uncertainty factor, called Mixture assessment factor, MAF, is proposed with regard to combination effects. Research into combination effects (especially on endocrine disruptors) has shown that there is scientific evidence to take this into account in a risk assessment. Combination effects include the total exposure to a variety of substances, and a risk assessment for combination effects should take into account the overall risk for substances with the same effect or mode of action. The combination effects thus do not include the total exposure of a substance from several sources, it is called "aggregate exposure". It is currently being discussed whether a MAF should be allocated to DNEL / DMEL or RCR (risk characterization ratio), i.e. as part of the hazard assessment or risk assessment. Quantitatively, it will not make any difference whether MAF is allocated to DNEL / DMEL or RCR. In this project, it was decided to allocate MAF to DNEL in line with the other assessment factors. The size of the MAF is also up for discussion, and in this project, a MAF of 10 was chosen as a starting point for discussions and calculations. This MAF takes into account other substances with similar effect, but not any background exposure of the same substance from several sources.

In a recent report, the size of MAF is calculated (modelled) for realistic chemical mixtures, especially in the aquatic environment. These analyses show that a MAF of 10 appears to be sufficiently protective for the majority (> 70%) of the mixtures, while a MAF of 20 covers 95% of the mixtures (KEMI 2021). The report mentions an uncertainty regarding human health. It is

concluded that a MAF of 10 will be sufficiently protective for mixtures with up to 30 chemicals (KEMI 2021).

9.1.5 Other effects

No search for literature describing other effects than endocrine disruption was performed. Notes on other effects relevant to human health were only included sporadically.

9.2 Results and discussion - hazard assessment

9.2.1 Data availability and literature search for the six substances.

For each compound, an overview of relevant reports has been compiled and a literature search has been performed as described in the corresponding appendix.

TABLE 21 below summarizes this information for the six substances.

TABLE 21. Overview of available data and literature search. See Appendix 3 to Appendix 8 for details and references.

	D4	BHA	BHT	BPA	Butylparaben	Propylparaben
Relevant reports	ED list (Hass et al 2018), SVHC documentation (ECHA 2016, ECHA 2021), CLH (ECHA, 2017), SCCS 2010, MST projects (Andersen et al. 2012, Larsen et al. 2017)	EFSA 2011, EFSA 2012. CEHOS SIN list (Hass et al. 2012), MST project (Larsen et al. 2017), DTU literature update to FVST 2020.	EFSA 2012, MST project (Larsen et al. 2017), DTU literature update to FVST 2020.	EFSA 2015, SVHC 2017, MST project (Larsen et al. 2017)	SIN list 2012, SCCS 2013, SVHC 2020, MST project (Larsen et al. 2017)	SCCS 2013, SCCS 2021, EMA 2015, MST project (Larsen et al. 2017)
Studies used in the assessment of endocrine disrupting effect	Reference to ED list, no recent studies found relevant	Review of 23 studies.	Review of 13 studies.	Not applicable, reference to SVHC	Referral to SVHC and supplemented with 15 studies	
Studies used in DNEL determination	Reference to Larsen et al. 2017, supplemented with new data from Jean & Plotztke 2017	Reference to Larsen et al. 2017, but re-evaluated and with new conclusions	Reference to Larsen et al. 2017 and EFSA 2012, new studies have been assessed but do not change DNEL.	Reference to EFSA 2015 and MST 2017 supplemented with new studies	Reference to MST 2017 supplemented with 7 studies	Read across from data on butylparaben in the DNEL determination.
Comments	Few relevant studies have been found in the ECHA database, but require closer inspection.	Few relevant studies have been found in the ECHA database, but require closer inspection	Several possible relevant studies have been found in the ECHA database, but require closer inspection	Focused approach in the selection of studies for use in the reassessment of DNEL.		The existing, publicly available data base for propyl paraben is considered to be subject to a high degree of uncertainty. Therefore, in the DNEL determination for this substance, a read across from data on butylparaben.

ED stands for Endocrine Disruptor

9.2.2 Overview of assessment of endocrine disrupting effects

The evidence for endocrine mode of action, adverse effect and mode of action analysis for the six substances are found in appendices for each substance. TABLE 22 below gathers information for the six substances.

TABLE 22. Overview of assessment of endocrine disruptors on the thyroid hormone system (T modality) and via estrogenic, (anti-) androgenic and steroid endocrine disrupting action (EAS modality). See Appendix 3 to Appendix 8 for details.

	D4	BHA	BHT	BPA	Butylparaben	Propylparaben
Endocrine disrupting Mode of action, T modality	-	Weak evidence, few in vitro and in vivo studies with varying conclusions	Weak evidence, no in vitro studies, no effect on hormones in vivo	T modality has not been further investigated, reference is made to SVHC document which shows clear signs of Thyroid effects in amphibians and less clear in fish	Moderate evidence, T relevant effects in vitro and in vitro.	Few studies, poorly studied
Adverse effect, T modality	Weak evidence, altered thyroid weight and histology in one single dose study.	Moderate evidence. Altered thyroid histology in rat and pig.	Moderate evidence. Altered thyroid weight and histology in two rat studies.	T modality is not further investigated in this report	No effect in one study, i.e. no effect or not adequately studied	Few studies, poorly studied
Mode of action analysis, T modality	Not relevant	Biologically plausible relationship between endocrine activity and adverse effect.	No knowledge of mode of action but in vivo adverse effect on thyroid	T modality is not further investigated in this report	Not relevant	Not relevant
Endocrine disrupting action, EAS modalities	Strong evidence for estrogenic action in vivo and in vitro.	Strong evidence for gonadotropin-disrupting action. Overall, moderate evidence for EAS related properties. Varying conclusions regarding estrogenic activity in vitro. Anti-estrogen in vivo (uterotrophic). Clear anti-androgenic action in vitro (three studies), but not in vivo (Hershberger).	Weak evidence. Varying effect pattern.	Strong evidence for estrogenic activity in vivo and in vitro.	Estrogen and possible anti-androgen and steroid synthesis inhibitors	Strong evidence for estrogenic action in vitro and in vivo, moderate evidence for anti-androgenic effect in vitro

	D4	BHA	BHT	BPA	Butylparaben	Propylparaben
Adverse effect, EAS modalities	Females: several findings of EAS relevant adverse effects in five studies. Males: increased incidence of testicular interstitial cell hyperplasia in a long-term study.	Females: Moderate effect - delayed vaginal opening and altered oestrus cycle. Males: short AGD, delayed puberty, decreased prostate weight, decreased sperm quality.	Weak evidence, few data available.	Strong evidence for adverse effects in several in vitro studies, e.g. on sperm quality and mammary gland tissue development.	Females: several studies show EAS related effects (not reviewed in SVHC document) Males: Decreased sperm quality and sperm count in offspring exposed during development in several, but not all studies.	Weak / maternal evidence of reproductive effects in published studies. Unpublished study reports have not been studied here, but may point to relevant adverse effects. Read-across re- from data on butylparaben is used here.
Mode of action analysis, EAS modalities	Biologically plausible relationship between endocrine activity and adverse effect.	Biologically plausible association between endocrine activity and adverse effect, for both males and females	Not relevant	Biologically plausible relationship between endocrine activity and adverse effect.	Biologically plausible relationship between endocrine activity and adverse effect.	Biologically plausible relationship between endocrine activity and adverse effect (Read across)
Overall conclusion in relation to the WHO definition of endocrine disrupting effect	Meets definition as endocrine disrupting via EAS modalities, but not T modality. Suspected endocrine disruptor via T modality, but so far only one study of thyroid effects has been identified.	Meets definition as endocrine disruptor via both T and EAS modalities	Suspected endocrine disrupting via T and EAS modalities (meeting definition of endocrine disrupting effect would require clearer findings in several studies).	Meets definition as endocrine disruptor via EAS modalities. T modality is not further investigated in this report	Meets definition as endocrine disrupting via EAS modalities, but not T modality.	Meets definition as endocrine disrupting via EAS modalities, but not T modality.

9.2.3 DNEL/DMEL determination, including use of mixture assessment factor

For each substance, details regarding DNEL and DMEL determination are given in separate appendices. TABLE 23 gathers information on DNELs and DMELs for each substance.

TABLE 23. DNELs and DMELs for endocrine disrupting effects for T modality (DNELthyr and DMELthyr) and EAS modalities (DNELeas and DMELeas). All figures are in µg / kg bw / day. See Appendix 3 to Appendix 8 for details.

	D4	BHA	BHT	BPA	Butylparaben	Propylparaben
$DNEL_{thyr}$	Not relevant	1000	250	Not evaluated	Not relevant	Not relevant
$DMEL_{thyr}$	Not relevant	100	25	Not evaluated	Not relevant	Not relevant
$DNEL_{eas}$	36	100	Not relevant	0.24	20	20
$DMEL_{eas}$	3.6	10	Not relevant	0.024	2	2

The use of mixture assessment factors, MAF, will be relevant for substances with and without a threshold. TABLE 24 calculates DNELs and DMELs where an additional MAF of 10 is included.

TABLE 24. Use of MAF of 10 in determining DNELs for endocrine disrupting effects for T modality ($DNEL_{thyr}$) or EAS modalities ($DNEL_{eas}$). All figures are in µg / kg bw / day. See Appendix 3 to Appendix 8 for details.

	D4	BHA	BHT	BPA	Butylparaben	Propylparaben
$DNEL_{thyr}$	Not relevant	100	25	Not evaluated	Not relevant	Not relevant
$DMEL_{thyr}$	Not relevant	10	2.5	Not evaluated	Not relevant	Not relevant
$DNEL_{eas}$	3.6	10	Not relevant	0.024	2	2
$DMEL_{eas}$	0.36	1	Not relevant	0.0024	0.2	0.2

9.2.4 Discussion of risk assessment methods, including DNEL vs DMEL approach and use of Mixture assessment factor

The same "point of departure" and standard assessment factors have been used for uncertainties in DNEL and DMEL determination. In addition, an additional AF of 10 for DMEL determination using the "Large assessment factor" approach. This choice of methods means that there is generally a factor of 10 difference between DNEL and DMEL. This difference between DNEL and DMEL could be smaller or larger if BMDL10 and another AF of 10 had been used in the DMEL determination, cf. principles in R.8. (ECHA 2012). However, it was not possible within the framework of this project to determine BMDL10 for the endocrine disrupting effects, because the experimental studies used did not contain a sufficient number of doses to derive a benchmark dose-response sequences, and that no relevant human data were identified for a BMDL determination.

In relation to the use of a Mixture Assessment Factor, MAF, such an additional factor of e.g. 10 can be used to take into account possible contributions from other substances with the same mode of action. The size of this MAF will be politically determined and it will differ from substance to substance whether this MAF is realistic or will lead to an over- or underestimation

of the risk. If there is a significant contribution to the risk from simultaneous exposure to substances with the same action or effect as a given substance, a MAF of e.g. 10 can improve the risk assessment, although there may still be some underestimation of the risk. If there is no significant contribution to the risk from simultaneous exposure to substances with the same mode of action or effect, the use of MAF of e.g. 10 will certainly lead to an overestimation of the risk. Recent studies in the field show that a MAF of 10 will be sufficient in most scenarios with realistic mixtures (KEMI 2021), but scientific research will continue with such studies in the coming years.

In a risk assessment, the use of the DMEL approach and MAF will lead to a 100 times higher RCR value than if the DNEL approach is used without the use of MAF. There will be situations where this has no bearing on the conclusion, i.e. if RCR values are below 1 (low / no risk) for both approaches, or if RCR values are above 1 (identified risk) for both approaches. In other situations, the conclusion will be different, depending on which approach is chosen.

9.3 Conclusion

For each of the six substances, an assessment of endocrine disrupting properties has been performed as well as a determination of DNEL and DMEL for, thyroid hormone disrupting properties and Estrogenic, (anti-)androgenic, steroidsynthesis disrupting properties, respectively.

For all substances, the conclusion is that evidence of endocrine disrupting action has been found. The evidence is weaker for some substances (BHA, BHT) than for others (D4, BPA, butylparaben, propylparaben). The report and its appendices provide an overview of the basis for these assessments as well as knowledge gaps.

The established DNELs and DMELs can be used in risk assessment, and it will be a political decision whether DNELs or DMELs are used, i.e. whether the risk assessment is carried out on the basis of a threshold-based or non-threshold-based approach. In this report, both approaches (both DNELs and DMELs) are used and the results are discussed.

A MAF of 10, has in this report been used in the risk assessment together with DNELs and DMELs. It will also be a political decision whether MAF should be used in future risk assessments, i.e. whether possible contributions from other substances with the same mode of action should be taken into account. In this report, both approaches (both with and without MAF) are used and the results are discussed.

10. Contribution from selected exposure sources

In the present project, exposure to the six selected focus substances from consumer products has been identified via chemical analyses. In addition, data on exposure levels of the six focus substances have been searched from selected sources of exposure. These comprises food, food contact materials (FCM) and medicinal products. This chapter contains data on exposure levels from food, FCM and medicinal products.

Data on contribution from food and FCMs to exposure to the six focus substances have been estimated on the basis of the latest data from the DTU National Food Institute about content in food as well as the latest content and exposure estimates in reports from EFSA.

The contribution of medicinal products to exposure to the six focus substances has been estimated from the content in medicinal products. Information was obtained through web-based search on the websites of the European Medicines Agency (EMA); data extracted by the Danish Medicines Agency; medicin.dk as well as a general internet search regarding the content of the substances in medicinal products. Based on this information, an exposure assessment has been performed for pregnant women and young children.

In cases where relevant data from consumer products have been found, these are included in the below tables. This applies for instance to BHT in cosmetics and BPA in toys. In general, however, it is important to note that only data for food, FCM and medicinal products are included in the exposure and risk assessment calculations. It is outside the scope of this project to carry out a more systematic study of all other potential sources of exposure to the six focus substances. In other words, the risk assessment includes exposure estimates for the three selected sources of exposure, food, FCM and medicinal products, as well as the analysis results for the consumer products.

For the three selected sources of exposure (food, FCM and medicinal products), the literature search has focused on reports containing an average estimate or a “worst case” assessment of the daily exposure of pregnant women/adults and/or children. This means, for example, that survey reports with exposure assessments of specific products/articles (such as selected toys and PUR foam products) are not included.

When sufficient data are available for the six focus substances, exposure levels have been established for the substances based on particularly exposed persons as well as more average exposure scenarios relevant for most pregnant women and young children. It is assumed that worst case exposure to several substances at the same time must be considered unrealistic, as worst case exposure to one substance rarely occurs (often equivalent to 95th percentile exposure). As a result, it is assessed that both types of exposure levels are needed to be able to establish realistic exposure scenarios in cases where the risk assessment must take into account the contributions of several single-acting substances, as worst case considerations for all substances at once are not considered realistic. The exposure assessment for the six focus substances includes exposure values for worst case (corresponding to 95th percentile exposures in many of the available public assessments called “opinions”) as well as average/median exposures.

Below is a table for each of the six focus substances, which summarises the average daily exposure to the substances from the consumer product types assessed as primary sources of exposure in Poulsen et al. (2020) as well as food, FCM and medicinal products. Data in the tables are reproduced directly from the reference, and data used for the further calculations are marked in **bold**. For children, one value has been selected for further calculations, as there is no data basis for dividing the exposure into children under 3 years and children of 3 years. As exposure data are lacking or there is insufficient exposure data for several of the substances, the estimated values are based on worst case considerations with a significant risk of overestimation.

10.1 Sources of exposure to BHA

BHA is used as an antioxidant in various consumer products including cosmetic products, but also products such as medicinal products and foods (Poulsen et al., 2020). In an earlier report by Larsen et al. (2017) cosmetic products, among others, were examined for content of BHA. BHA was found only in one product, out of a total of 24 analysed cosmetic products (body oil conc. 0.0039%) (Larsen et al. 2017). Larsen et al. (2017) referred to data from a campaign from the Danish Consumer Council, in which 11 products (out of 560 products) contained BHA (based on the content declaration), which corresponds to a percentage of 0.16%. Larsen et al. (2017) concluded that BHA contributes only marginally to the exposure of children and unborn children to total exposure through cosmetics, and that the substance must be considered rare in cosmetics. Consequently, cosmetic products are not considered a primary source of exposure in this report.

TABLE 25. Reference and relevant data for daily BHA exposure sources. Data for average daily exposure (average exposure) and for worst case exposure (worst case/95% exposure) are given directly from the reference. For the three exposure sources selected to be included in the risk assessment calculations (food, FCM and medicinal products), data used for further calculations are marked in **bold**.

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
EFSA 2012a	FCM Permitted in FCM of plastic as additive or excipient in production. Limit value for migration 30 mg/kg (Appendix 1).	Exposure data are calculated on the assumption of a daily intake of 1 kg of food wrapped in plastic with a maximum allowable migration value for BHA.	Adults/Pregnant women Estimate: 0.43 mg/kg bw/d (o) *	No applicable data	No data
			Children under 3 years Estimate: 2.5 mg/kg bw/d (o) *	No applicable data	No data
			Children 3 years Estimate: 2.5 mg/kg bw/d (o) *	No applicable data	No data
EFSA 2012a	Food Approved for use as a food additive in certain	EFSA (2012a) describes that there is very little data regarding actual content of BHA in foods,	Adults/Pregnant women Average: 0.03-0.12 mg/kg bw/d (o) ** High (95-perc.): 0.08-1.12 mg/kg bw/d (o) **	**0.03 mg/kg bw/d (o)****	0.08 mg/kg bw/d (o)**

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
	raw materials (eg fats, oils, spices and chewing gum) (Appendix 2).	and therefore exposure assessments are based on maximum permitted levels (MPLs). This results in a very conservative/careful calculation. The DTU National Food Institute considers EFSA's approach to be very conservative/cautious (Bredsdorff et al. 2020) **. However, as no other data are available, the lowest exposure value is used for the further calculations as worst case. The lowest value in the specified exposure data intervals is stated in "average exposure" and "worst case/95 per cent. exposure".	Children under 3 years Average: 0.04-0.023 mg/kg bw/d (o) ** High level: 0.14-0.57 mg/kg bw/day (o) **	**0.04 mg/kg bw/d (o)**, *****	0.14 mg/kg bw/day (o)**
			Children 3 years Average: 0.08-0.36 mg/kg bw/d (o) High level (95-perc): 0.26-0.60 mg/kg bw/d (o)	0.08 mg/kg bw/d (o)**, ***	0.26 mg/kg bw/d (o)**
Dialog with Danish Medicines Agency **** Poulsen et al. 2020	Medicinal products Use in medicinal products must be justified, otherwise the substance will not be allowed. No specific limit has been set for BHA.	In a project carried out by Poulsen et al. (2020) it was assessed that BHA is used in a number of medicinal products, including skin remedies, patches for allergy testing, hydrocortisone, acne remedies, creams for skin infections as well as agents for cholesterol treatment.	Adults/Pregnant women A realistic worst case exposure assessment (determined from the highest value in the range of the typical content) for BHA from drugs is estimated to be 5 units per day each containing 0.2 mg/unit. When ingesting 5 units, a total exposure will correspond to 1 mg/d (o). At a weight of 60 kg, it will result in a daily oral exposure corresponding to 0.017 mg/kg bw/d. Children ≤ 3 years		**0.017 mg/kg bw/d (o)**

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
		In direct dialogue with the Danish Medicines Agency, it was stated that BHA is present in 165 medicinal products *****. The Danish Medicines Agency states that the typical content per dosage unit (tablets, capsules) or g (creams, ointments) is 0.02-0.2 mg/unit.	A realistic worst case exposure assessment (determined on the basis of the highest value in the range of the typical content) for BHA from medicinal products is considered to be relevant for creams, eg creams for skin infections. A cream is assumed to be applied 2-3 times a day, estimated to be 1 g/time as the worst case consideration, ie 3 g of product per day. This results in a daily exposure of 0.6 mg BHA per day. At a weight of 8.9 kg, this results in a daily dermal exposure corresponding to 0.07 mg/kg bw/d (d).		**0.07 mg/kg bw/d (d)**

(d):dermal; FCM: Food contact materials; (o):oral

* It appears in a project carried out by Larsen et al. (2017) that the Danish Veterinary and Food Administration in connection with the project at the time informed that Danish data indicated that there is no migration of BHA from FCM. Therefore, exposure to BHA from FCM was not included in the overall exposure assessment. DTU National Food Institute considers EFSA's exposure assessment for BHA and BHT to be very overestimated (Bredsdorff et al. 2020). Furthermore, the DTU National Food Institute points out migration of BHA from FCM as being significantly lower (based on available migration studies) than EFSA's exposure estimates. The values from EFSA are therefore not used in the further calculations.

** DTU National Food Institute points out in their assessment of EFSA's exposure assessment (2012a) that BHA is either not used in food or is measured below the detection limit in food. Overall, the DTU National Food Institute assesses that the exposure assessment for BHA is very conservative/cautious (Bredsdorff et al. 2020). However, as no other data are available, the lowest reported exposure value is used for the further calculations.

*** As exposure data are very conservative/cautious, the lowest concentration for children is used for the further risk assessment calculations.

**** In connection with the present project, the Danish Medicines Agency has been a member of the follow-up group and contributed information regarding medicinal products that have been used for the exposure calculations.

***** Includes all strengths of the medicine as well as generic medicinal products, incl. parallel imported medicinal products. The exact quantitative content of excipients is in most cases confidential and therefore not searchable.

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
References: EFSA 2012a. SCIENTIFIC OPINION Statement on the safety assessment of the exposure to butylated hydroxyanisole E 320 (BHA) by applying a new exposure assessment methodology. EFSA Journal 2012;10(7):2759. Poulsen et al., 2020. Survey of selected endocrine disruptors. Survey of chemical substances in consumer products No. 183, 2020. Poulsen PB, Geschke S, Borregaard C, Merlin C. https://www2.mst.dk/Udgiv/publications/2020/10/978-87-7038-242-7.pdf					

10.2 Sources of exposure to BHT

BHT is used as an antioxidant in various consumer products. Poulsen et al. (2020) assessed that BHT is used primarily in perfumes, but also in plastic products. In Larsen et al. (2017), the exposure to BHT from cosmetics was determined on the basis of analyses of the product types body lotion (480 µg/kg bw/d (dermal), corresponding to 19.2 µg/kg bw/d (internal dose) as well as sunscreen and body lotion (2016 µg/kg bw/d (dermal), corresponding to 80.6 µg/kg bw/d (internal dose)). A more recent SCCS assessment (SCCS 2021b) is available, which contains calculations of an accumulated systemic exposure from cosmetics.

TABLE 26. References and relevant data for daily BHT exposure sources. Data for average daily exposure (average exposure) and for worst case exposure (worst case/95% exposure) are given directly from the reference. For the three exposure sources selected to be included in the risk assessment calculations (food, FCM and medicinal products), data used for further calculations are marked in **bold**.

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
EFSA, 2012b	FCM Allowed in FCM of plastic as additive or auxiliary substance in the production. Limit value for migration 3 mg/kg (Appendix 1).	EFSA has calculated the exposure using maximum permissible migration limits, assuming a daily intake of 1 kg of food. EFSA's calculations are therefore considered as worst case *.	Pregnant women Estimate: 0.05 mg/kg bw/d (o) Children 3 years Estimate: 0.2 mg/kg bw/d (o)	**0.05 mg/kg bw/d (o)*** **0.2 mg/kg bw/d (o)***	
Husøy et al. 2019	Food Approved for use as an additive to foods in certain raw materials (Appendix 2).	The report calculates the external exposure to BHT via food and beverages based on measurements from products. Data are therefore considered representative of BHT from food, and as a worst case the highest concentrations are stated in “average exposure”	Pregnant women Average: 1.6 - 2.5 µg/kg bw/d (o) High (95-perc.): 71-75 µg/kg bw/d (o)	**0.0025 mg/kg bw/d (o)**	0.075 mg/kg bw/d (o)

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
		and “worst case/95 per cent. exposure) ”.			
EFSA, 2012b	Food Approved for use as an additive to foods in certain raw materials (Appendix 2).	EFSA has calculated the exposure based on "maximum permitted levels" (MPLs) and it is thus considered worst case. EFSA's calculations for the average exposure are considered worst case, which is why the smallest value in the specified intervals is stated as the average exposure concentration. Data from Husøy et al. (2019) are considered more realistic, but as this report does not contain data for children, available data from EFSA (2012b) are used for the risk assessment calculations. **	Pregnant women Average: 0.01-0.05 mg/kg bw/d (o) High (95-perc.): 0.04-0.17 mg/kg bw/d (o) Children 3 years Average: 0.01-0.09 mg/kg bw/d (o) High (95-perc.): 0.05-0.30 mg/kg bw/d (o)	0.01 mg/kg bw/d (o)** **0.01 mg/kg bw/d (o)**	0.04 mg/kg bw/d(o)** 0.05 mg/kg bw/d (o)
Dialog with Danish Medicines Agency ****	Medicinal products Use in medicinal products must be justified, otherwise the substance will not be allowed.	In Poulsen et al. (2020) it was assessed that BHT is used in a number of medicinal products **** In a direct dialogue with the Danish Medicines Agency, it	Adults/Pregnant women A worst case exposure assessment for BHT from medicinal products is estimated to be 5 units per day containing 0.5 mg each. When ingesting 5 units, a total exposure will be equal to 2.5 mg/d (o). At a weight of 60 kg it will result in a daily	Not assessed	**0.04 mg/kg bw/d (o)**

Refer-ence	Exposure source and per-tinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
Poulsen et al. 2020		was stated that the typical content is in the range 0.03-0.5 mg/unit (tablets/capsules). For other medicinal products, the content is approx. 0.2 mg/g.	oral exposure corresponding to 0.04 mg/kg bw/d (o). Children ≤ 3 years A worst case exposure assessment for BHT from medicinal products is considered relevant for creams, eg use of anti-inflammatory agent (0.2 mg/g). A cream is assumed to be applied 2-3 times a day, estimated to be 1 g/time as the worst case consideration, ie up to 3 g/d. This results in a daily exposure up to 0.6 mg/d. At a weight of 8.9 kg this results in a daily dermal exposure corresponding to 0.07 mg/kg bw/d (d).	Not assessed	**0.07 mg/kg bw/d (d)**
Larsen et al. 2017	Cosmetics	Determined on the basis of analyses of the product types body lotion (0.48 mg/kg bw/d (d), corresponding to an internal dose of 0.019 mg/kg bw/d); sunscreen and body lotion (2.016 mg/kg bw/d, (d), corresponding to an internal dose of 0.0806 mg/kg bw/d.	Children under 3 years Average: 0.48 mg/kg bw/d (d) (corresponding to an internal dose of 0.019 mg/kg bw/d) High: 2.02 mg/kg bw/d (d) (corresponding to an internal dose of 0.081 mg/kg bw/d) Pregnant women Average: 0.3 mg/kg bw/d (d) (corresponding to an internal dose of 0.012 mg/kg bw/d) High: 1.260 mg/kg bw/d (d)	0.48 mg/kg bw/d (d) 0.3 mg/kg bw/d (d)	2.02 mg/kg bw/d (d)

Refer-ence	Exposure source and per-tinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
			(corresponding to an internal dose of 0.05 mg/kg bw/d)		1.26 mg/kg bw/d (d)

(d):dermal; FCM: Food contact materials; (o):oral

* DTU National Food Institute's assessment of EFSA's exposure assessment for BHA and BHT (Bredsdorff et al. 2020) is that EFSA's exposure estimates for BHT from FCM are very conservative/cautious.

** Exposure estimates from Husøy et al. (2019) are assessed by the DTU National Food Institute to be more realistic than EFSA's assessment, which is assessed as being very conservative/cautious (exposure assessment is calculated using "maximum permitted levels" (MPLs)) (Bredsdorff et al. 2020). In this report, data from Husøy et al. (2019) is used for the risk assessment calculations.

*** In connection with the present project, the Danish Medicines Agency has been a member of the follow-up group and has passed on information regarding medicinal products that have been used for the exposure calculations.

**** Including nicotine chewing gum (0.43-0.5 mg per chewing gum), painkiller for inhalation (0.01%), scabies, anti-inflammatory drug (0.2 mg/g), treatment of psoriasis (0 , 05-0.16 mg/g), herpes remedies, treatment of sun damage to the skin (2.0 mg/g), agents for vaginal estrogen deficiency (0.008 mg/vagitoria), treatment of vitamin D deficiency, dandruff shampoo, skin remedy (antibiotics) for skin infection, patches for allergy testing, hydrocortisone, remedies for urination problems and ADHD medication.

References: EFSA 2012b. Scientific Opinion on the re-evaluation of butylated hydroxytoluene BHT (E 321) as a food additive. EFSA Journal 2012;10(3):2588

Husøy, T., Andreassen, M., Lillegaard, I. T. L., Mathisen, G. H., Rohloff, J., Starrfelt, J., ... & Bruzell, E. M. (2019). Risk assessment of butylated hydroxytoluene (BHT). Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics of the Norwegian Scientific Committee for Food and Environment. VKM Report.

Larsen, PB; Boberg J, Poulsen PB, Mørck TA, Boyd HB, Andersen DN, Axelstad M, Hass U (2017) Exposure of children and unborn children to selected chemical substances MST survey of chemical substances in consumer products no. 158 ISBN: 978-87-93529-84-7 https://www2.mst.dk/Udgiv/publications/2017/04/978-87-93529-84-7.pdf

Poulsen et al., 2020. Survey of selected endocrine disruptors. Survey of chemical substances in consumer products No. 183, 2020. Poulsen PB, Geschke S, Borregaard C, Merlin C. https://www2.mst.dk/Udgiv/publications/2020/10/978-87-7038-242-7.pdf

10.3 Sources of exposure to butylparaben

Parabens are used as preservatives in a wide range of consumer products. In a 2019 report, RIVM in the Netherlands conducted a risk assessment of butylparaben in cosmetic products, foods, drugs and other sources such as toys and articles for toddlers (Hessel et al., 2019). The report assessed that cosmetic products, foods and medicinal products are primary sources of exposure to butylparaben, based on international data (medicinal products could not be included in the risk assessment due to lack of data).

TABLE 27. References and relevant data for butylparaben exposure sources. Data for average daily exposure (average exposure) and for worst case exposure (worst case/95% exposure) are given directly from the reference. For the three exposure sources selected to be included in the risk assessment calculations (food, FCM and medicinal products), data used for further calculations are marked in **bold**.

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
EU Regulation No 10/2011	FCM Not approved for FCM *			-	-
EU Regulation No 1333/2008	Food Not allowed as an additive in food **			-	-
Poulsen et al 2020	Medicinal products	Searching relevant databases did not give relevant hits. In Poulsen et al. (2020) the following medicinal products were listed as containing butylparaben (though without concentration): Hydrocortisone, herpes me-	In the present project it has not been possible to identify a contribution from medicinal products containing butylparaben, so a contribution of butylparaben from medicinal products has not been calculated.	No data	No data

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
		dicinal products and psoriasis medicinal products.			
Hessel et al. 2018	Cosmetics Max. 0.14% in rinse-off. Not to be used in leave-on products for the diaper area. Not to be used in Denmark in products for children under 3 years.	The exposure assessment for adults has been determined on the basis of a literature review and comparison with Dutch conditions. Exposure assessments for children have been established on the basis of actual measurements of products for children in the Netherlands.	Pregnant women Average: 0.02 mg/kg bw/d (d) High (97.5 perc.): 0.1 mg/kg bw/d (d) Children ≤ 3 years Average: 0.2 mg/kg bw/d (d) *	0.02 mg/kg bw/d (d) No data	0.1 mg/kg bw/d (d) 0.2 mg/kg bw/d (d)*
(d):dermal; FCM: Food contact materials					
* EU Regulation No 10/2011 on plastic materials and articles intended to come into contact with food contains Annex I, which is a list of approved substances that may be used in the manufacture of plastic materials and plastic articles to come into contact with food. Butylparaben is not listed. ** EU Regulation No. 1333/2008 on food additives contains Annex II, which is an EU list of food additives that are approved for use in food, as well as the conditions of use. Annex II is available on the EU website as a database of authorised food additives (Authorisation of additives (europa.eu)). Butylparaben is not listed. *** This value originates from data which are primarily calculated on the basis of content concentrations in wet wipes. Butylparaben is not allowed in products such as wet wipes and creams for the diaper area. However, this value is used as a worst case scenario, as there may be use of products for children that are not intended for this purpose. The measurements were made over 15 years ago, and it is also mentioned in the RIVM report that this figure may be misleading, as the use of butylparaben in products for children has been significantly reduced.					
References:					

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
EU Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives https://eur-lex.europa.eu/legal-con-tent/DA/TXT/PDF/?uri=CELEX:02008R1333-20200319&qid=1587622791269&from=EN EU Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food https://eur-lex.europa.eu/legal-content/DA/TXT/PDF/?uri=CELEX:02011R0010-20190829&qid=1587913393869&from=EN Hessel et al. 2018. Review on butylparaben: exposure, toxicity and risk assessment. With a focus on endocrine disrupting properties and cumulative risk assessment. RIVM Report 2018-0161. Poulsen et al., 2020. Survey of selected endocrine disruptors. Survey of chemical substances in consumer products No. 183, 2020. Poulsen PB, Geschke S, Borregaard C, Merlin C. https://www2.mst.dk/Udgiv/publications/2020/10/978-87-7038-242-7.pdf					

10.4 Sources of exposure to propylparaben

Propylparaben is used as a preservative, e.g. in cosmetic products, toys, medicinal products and food (Poulsen et al. 2020). In this report, information has been sought for exposure levels in toys and cosmetic products, as well as in FCM and medicinal products. Propylparaben is not permitted as an additive in foods. An earlier report, published by the Danish Environmental Protection Agency (Andersen et al. 2013), mentions exposure data for food, but as propylparaben is not permitted as a food additive (Appendix 2) and data from 2013 can be considered obsolete, these data are not used. For exposure levels in cosmetics, a more recent opinion of the SCCS was identified with dermal exposure levels.

TABLE 28. References and relevant data for daily sources of exposure to propylparaben. Data for average daily exposure (average exposure) and for worst case exposure (worst case/95% exposure) are given directly from the reference. For the three exposure sources selected to be included in the risk assessment calculations (food, FCM and medicinal products), data used for further calculations are marked in **bold**.

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
	FCM Allowed as an additive or excipient in plastic. No limit value (Appendix 1).			No data	No data
EU Regulation No 1333/2008	Food Not allowed as an additive in food **		Pregnant women 0.004 - 0.013 mg/kg bw/d (o) *	No applicable data	No applicable data
Dialog with Danish Medicines Agency***	Medicinal products The content of preservatives and antioxidants must always be justified regardless of the amount. Content higher	Searching relevant databases yielded sparse data. Therefore, data from a recent report have been used. In Poulsen et al. (2020) it was assessed that	Pregnant women As an example, remedies for acid reflux and heartburn are used: 0.02% (20 mg/100 ml = 0.2 mg/ml as daily dose. For example, 10 ml/meal (4 times a day) can be estimated, which will result in a daily dose of 8		**0.13 mg/kg bw/d (o)**

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
Poulsen et al. 2020	than 0.02% must be further justified toxicologically.	propylparaben is used in a number of medicinal products **** It is considered that a possible exposure from medicinal products containing propylparaben could be from agents for acid regurgitation/heartburn (6 mg/10 ml) in relation to pregnant women. This will also reflect a worst case oral exposure in relation to pregnant women. Typical concentration up to 0.02% (20 mg/100 ml = 0.2 mg/ml) in medicinal products.	mg/d (at a weight of 60 kg it will result in a daily oral exposure equivalent to 0.13 mg/kg bw/d (o) <u>Children</u> Remedies for acid reflux and heartburn (children under 3 years): 0.02% (20 mg/100 ml = 0.2 mg/ml as daily dose. As an example, a daily dose of 10 ml can be estimated, which will result in a daily dose of 2 mg/d (o). At a weight of 14 kg it will result in a daily oral exposure corresponding to: 0.14 mg/kg bw/d (o).		**0.14 mg/kg bw/d (o)**
SCCS 2021c	Cosmetics (max. 0.14%). Not to be used in leave-on products for the diaper area. Not to be used in Denmark in products for children under 3 years).	SCCS used calculation methods to determine a realistic and a conservative/cautious worst case scenario. Both are determined using maximum content concentrations. The exposure level for children is determined in a referenced study using lower body weight (not specified in SCCS) and assumption of intake of other products (not specified in SCCS)	<u>Pregnant woman</u> 0.44-0.49 mg/kg bw/d (d) <u>Children (no age group indicated)</u> 1.05 mg/kg bw/d (d)	0.44 mg/kg bw/d (d) 1.05 mg/kg bw/d (d)	0.49 mg/kg bw/d (d)
(d):dermal; FCM: Food contact materials; (o):oral					

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure

* These values are derived from data from food intake in the 1980s from the USA, where the regulation of parabens in food does not have/had the same restrictions as in the EU (Andersen-sen et al. 2013). In Andersen et al. (2012) it was concluded that the exposure of pregnant women to parabens from food is negligible. However, it was assessed that exposure from food produced abroad may occur. Based on these two studies, no useful average data have been found for food exposure of propylparabens.

** EU Regulation No. 1333/2008 on food additives contains Annex II, which is an EU list of food additives that have been approved for use in foods, as well as the conditions of use. Annex II is available on the EU website as a database of authorised food additives (Authorisation of additives (europa.eu)). Propylparaben is not listed.

*** In connection with this project, the Danish Medicines Agency has been a member of the follow-up group and has provided information regarding medicinal products that have been used for the exposure calculations.

**** Including hydrocortisone, herpes remedies, treatment of sun damage to the skin (0.2 mg/g), epilepsy medication (0.18 mg/ml - 3 mg/5 ml), creams against eczema, analgesic gel after circumcision of boys, allergy medicine (oral drops) (0.04-0.2 mg/ml), agents for potassium deficiency in the blood, mucolytic cough medicinal products, agents for acid re-flux/heartburn, agents for the treatment of vaginal flora (0.2 mg/g), scabies, nasal spray (for smoking cessation), painkillers for severe pain, treatment of frequent urination (0.2 mg/ml), acne remedies, patches for pain treatment (7 mg/patch), anti-inflammatory drugs (0.2 mg/ml), treatment of urinary tract infections, medicinal products for sore throats (0.24 mg/dose), ear drops for otitis media (0.3 ml/ml)

References:

EU Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives
https://eur-lex.europa.eu/legal-con-tent/DA/TXT/PDF/?uri=CELEX:02008R1333-20200319&qid=1587622791269&from=EN

Poulsen et al., 2020. Survey of selected endocrine disruptors. Survey of chemical substances in consumer products No. 183, 2020. Poulsen PB, Geschke S, Borregaard C, Merlin C. https://www2.mst.dk/Udgiv/publications/2020/10/978-87-7038-242-7.pdf

SCCS 2021b.Opinion on Propylparaben (PP). SCCS/1623/20. Adopted on meeting 30-31 March 2021.

10.5 Sources of exposure to D4

The use of D4 is considered to occur primarily in the production of silicone polymers. Thus, the substance may occur as a residual product in various silicone products. The exposure of D4 is documented to occur from several consumer products, among others, toys (Klinke et al., 2018) and mattresses (Poulsen et al. 2020b). As these reports do not include an assessment of an average exposure and do not include relevant estimation data for food, FCM or medicinal products, data from these reports are not included in the table below.

Occurrence of D4 in FCM and drugs has not been considered relevant as a source of exposure. It must be expected that there may be exposure from for instance baking tins, straws and the like consisting of silicone, but in the present project, however, no applicable exposure data from such silicone products have been identified. For foods, there are studies showing that D4 bioaccumulates and thus can be measured in aquatic foods such as fish (Greve et al., 2014). Consequently, exposure of D4 from food is expected to occur, but no data indicating the level of this have been identified. Contributions from these are not included in the present project.

TABLE 29. References and relevant data for daily D4 exposure sources. No data were found for the selected sources of exposure, FCM, food and medicinal products.

Refer-ence	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
	FCM		No data	-	-
	Food		No data	-	-
	Medicinal products (Not in use)		Not in use		
FCM: Food contact materials					

10.6 Sources of exposure to BPA

EFSA's Opinion from 2015 (EFSA 2015) contains an assessment of the exposure to BPA for different population groups based on age. The report contains exposure assessments for food and other sources. EFSA (2015) and the restriction dossier on the use of BPA in thermal paper (ANSES, 2014) review the broad use of BPA, as well as the many sources of exposure to BPA by the consumer. This includes air (both inside and outside), dust and drinking water, as well as food and FCM. EFSA (2015) concludes that the primary source of exposure in all population groups is food. The table below reviews the exposure from FCM, food, medicinal products and toys (children). Thermal paper is not included as the primary source of BPA exposure to the consumer, as its use is limited to a maximum of 0.02% by weight (the regulation applied in January 2020).

TABLE 30. References and relevant data for BPA exposure sources. Data for average daily exposure (average exposure) and for worst case exposure (worst case/95% exposure) are given directly from the reference. For the three exposure sources selected to be included in the risk assessment calculations (food, FCM and medicinal products), data used for further calculations are marked in **bold**.

Reference	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
EFSA 2015	Food incl. FCM Regulated as a surface treatment agent. Permitted in FCM of plastic as monomer with a specific limit value for migration of the substance of 0.05 mg/kg (described in Chapter 4)	See text above table	Pregnant women Average: 116-159 x10-6 mg/kg bw/d (o) High: 335-388x10-6 mg/kg bw/d (o) Children (6 months to 10 years) * Average: 290-375x10-6 mg/kg bw/d (o) High: 813-857x10-6 mg/kg bw/d (o)	**159 x 10^{-6} mg/kg bw/d (o)** **375x10^{-6} mg/kg bw/d (o)**	388x10^{-6} mg/kg bw/d (o) 857x10^{-6} mg/kg bw/d (o)
	Medicinal products	Not used in medicinal products			
EFSA 2015	Toys - oral exposure	The exposure is calculated assuming a migration to saliva of	Children under 1 year Average: 0.2x10-6 mg/kg bw/d (o)	0.2x10^{-6} mg/kg bw/d (o)	

Refer-ence	Exposure source and pertinent regulation	Notes to exposure data	Exposure data	Average exposure	Worst case/95-perct. exposure
	EU regulatory require-ments: Toys: SML = 0.04mg/l (described in Chapter 4)	0.14 µg per toy per day (average value for measured migration) using 0.5-2 toys per day.	High: 0.6x10-6 mg/kg bw/d (o) Children (1-3 years) Average: 0.01x10-6 mg/kg bw/d (o) High: 0.01x10-6 mg/kg bw/d (o)	$0.01x10^{6}$ mg/kg bw/d (o)	$0.6x10^{-6}$ mg/kg bw/d (o) $0.01x10^{-6}$ mg/kg bw/d (o)
FCM: Food contact materials; (o): oral.					
* EFSA (2015) also indicates exposure to infants 0-6 months. However, these data are not included as they are lower than the average exposure for children 6 months to 10 years of age.					
References: EFSA (2015). Scientific Opinion on the risks to public health related to the presence of bisphenol A(BPA) in foodstuffs: Executive summary. EFSA Journal 2015;13(1):3978					

11. Risk assessment method

11.1 Discussion of risk assessment method for the six focus substances

Based on the conclusions of the hazard assessment in Chapter 9, risk assessment methods for the six focus substances D4, BHA, BHT, BPA, butylparaben and propylparaben are discussed here.

In the hazard assessment, it was concluded that evidence of endocrine disrupting modes of action has been found for all substances. The evidence is weaker for some substances (BHA, BHT) than for others (D4, BPA, butylparaben, propylparaben). In relation to the derivation of DNEL and DMEL values (one total value for children and pregnant women), the focus is on effects via EATS modes of action. As concluded in the hazard assessment, research shows that substances that act via one or more EAS modes of actions can collectively cause sex-specific endocrine disrupting effects. As a result, it will not be relevant to separate these effects in the risk assessment, and DNEL/DMEL values have therefore been derived for T and overall for EAS modes of action, i.e. $DNEL_T$/$DMEL_T$ and $DNEL_{EAS}$/$DMEL_{EAS}$. One common DNEL/DMEL value has been calculated for children and pregnant women, who are the target group of the project, and who are considered to be most vulnerable to endocrine disrupting effects via EATS modes of action.

In relation to risk assessment of chemical substances with endocrine disrupting effects, the regulatory environment does not agree whether the risk assessment should be carried out on the basis of a threshold-based or a non-threshold-based approach (see Chapter 9). Based on a number of recent scientific reports, it is recommended that risk assessment of endocrine disrupting chemicals should be performed differently than for the current threshold-based approach (DNEL), i.e. with a non-threshold-based approach (DMEL).

For the selected endocrine disruptors, it was not possible to use a Linearized approach, as no relevant human or animal experimental data have been found to perform extrapolation to human risk of 10^{-6} (see Chapter 9). This non-threshold approach is recommended by default when evaluating endocrine disruptors in cases with no knowledge of the presence or absence of a threshold value. Furthermore, it is recommended to include additional uncertainty factors (AF) due to lack of knowledge about the endocrine disrupting effects of chemical substances (low sensitivity in test methods, lack of exposure in sensitive exposure windows, and non-monotonous dose-response relationships). For the six focus substances assessed in this project, neither the absence nor the presence of a threshold has been identified, so a DMEL approach to the risk assessment should be used (according to recent scientific reports).

In this project, both a DNEL and a DMEL value have been determined for the six focus substances using the Large assessment factor, which will be used in this risk assessment. According to REACH information requirements R.8, DNEL is used for substances for which a threshold is assumed, while DMEL is used for substances for which a threshold is not assumed (ECHA 2012). As a result, DNEL is used as a zero-effect level below which exposures are assessed not to entail a risk, while for DMEL an effect level is used below which exposures are assessed to entail a low but tolerable risk.

The derivation of DNEL and DMEL values as well as uncertainties regarding these are discussed in the following sections.

11.1.1 DNEL/DMEL

For the endocrine disrupting properties of the six focus substances, DNEL and DMEL values have been derived for each substance for a T endocrine disrupting mode of action and an EAS endocrine disrupting mode of action, respectively (see Chapter 9 regarding hazard assessment).

The derived DNEL and DMEL values are based on an internal dose, so values can be used in the risk assessment across all exposure routes. This approach follows the recommendations of SCCS (2021a) where risk assessment is performed on the basis of a systemic exposure dose, which is compared with a systemic point of departure (PODsys), i.e. NOAEL/LOAEL adjusted with respect to systemic absorption.

The determined DNELs and DMELs ($DNEL_T$/$DMEL_T$ and $DNEL_{EAS}$/$DMEL_{EAS}$) are used in the risk assessment (where risk characterization ratio (RCR) calculations are performed using both the DNEL and DMEL values). If a risk is identified, differences between the different methods will be discussed and the risk assessment may be modified.

11.1.2 Mixture assessment factor (MAF)

Today, there is considerable focus on managing the risk with regard to combination effects by simultaneous exposure to a number of chemical substances with the same mode of action or effect. Research into combination effects (especially with a focus on endocrine disruptors) has shown that there is scientific evidence to consider possible contributions from other substances with the same mode of action in the risk assessment. It is also proposed in REACH to use an additional uncertainty factor to allow for combination effects. This additional uncertainty factor is called MAF and takes into account other substances with a similar effect, but not an exposure of the same substance from several sources.

The size of the MAF is up for discussion, but in this report a MAF of 10 is set as a starting point in relation to the established DNEL/DMEL values (see Chapter 9). In a recent report, the size of the MAF is calculated (modelled) for realistic chemical mixtures, especially in the aquatic environment. These analyses show that a MAF of 10 appears to be sufficiently protective for the majority (> 70%) of the mixtures, while a MAF of 20 covers 95% of the mixtures (KEMI 2021). The report mentions an uncertainty regarding human health. It is concluded that a MAF of 10 will be sufficiently protective for mixtures with up to 30 chemicals (KEMI 2021).

It is currently being discussed whether a MAF should be allocated to DNEL/DMEL or RCR (risk characterization ratio), i.e. as part of hazard assessment or risk assessment. Quantitatively, it will not make a difference whether MAF is allocated to DNEL/DMEL or RCR. In this project, it has been decided to allocate MAF to DNEL in line with other assessment factors. If DMEL, which is 10 times lower than DNEL, and a MAF of 10 are used in the risk assessment, the RCR for a specific substance will be 100 x higher than if DNEL is used without the use of a MAF. That is, an RCR value of 0.01 using DNEL without MAF will be increased to an RCR value of 1 (i.e. pose a risk) if an approach with DMEL value and MAF is used. Thus, the applied approach will be very important for the conclusion of the risk assessment.

11.1.3 Conclusion regarding DNEL/DMEL values and MAF for use in the risk assessment

In the hazard assessment (Chapter 9), DNEL and DMEL values are derived and modified with an additional safety factor of 10 (MAF value). The modification has been made to take into account the risk of simultaneous exposure to a number of substances with the same mode of action (combination effects). In the risk assessment, DNEL and DMEL have been used both with and without modification with a MAF to illustrate whether it has an impact on a possible risk.

11.2 Procedure for risk assessment

The risk calculations in this report contain calculations of RCR partly with a DNEL approach, partly with a DMEL approach with and without a MAF. However, the MAF is not included in the calculations in which the exposure sources food, food contact materials (FCM) and medicinal products are included.

Below is an overview of the risk calculations in this report, followed by an in-depth explanatory text for the calculations.

Overview of risk calculations:

- **RCR - product, single substance**
  RCR for the individual exposure scenario (product). In these calculations, the RCR is calculated for each measurement from the analysis results. For each measurement there are eight RCR values ($DNEL_T$, $DMEL_T$, $DNEL_{EAS}$, $DMEL_{EAS}$, $DNEL_T$ w. MAF, $DMEL_T$ w. MAF, $DNEL_{EAS}$ w. MAF and $DMEL_{EAS}$ w. MAF). These calculations only show whether each of the six focus substances in the individual products constitutes a risk. Contributions from other sources of exposure (food, FCM and medicinal products) are therefore not included.

  These calculations are given in the following chapters:
  12.3 RCR - Cosmetic products, single substance
  12.4 RCR - Textiles, plastic and silicone products, single substance

- **RCR - selected sources of exposure**
  RCR is calculated for each of the focus substances for the selected sources of exposure: food, FCM and medicinal products but not for consumer products. Estimates of exposure from these sources of exposure are given in Chapter 10.

  Summarized RCR values have been calculated for each of the six focus substances, for each exposure source, as well as RCR values for the total exposure from all three exposure sources for focus substances with the same mode of action.

  For each of the six focus substances, eight RCR values have been calculated for each exposure source ($DNEL_T$, $DMEL_T$, $DNEL_{EAS}$, $DMEL_{EAS}$, $DNEL_T$ w MAF, $DMEL_T$ w MAF, $DNEL_{EAS}$ w MAF and $DMEL_{EAS}$ w MAF).

  A MAF is not included in the risk calculations for the total exposure from the three sources (food, FCM and medicinal products), as the MAF deals with exposure to other similar acting substances and should only be used in the calculations for individual substances.

  This shows the risk of endocrine disrupting effects for the individual sources of exposure to food, FCM and medicinal products. It is thus also clear whether the sum of exposure from several substances with a similar effect from the three sources can lead to endocrine disrupting effects.

  The six focus substances are added up according to their mode of action (Chapter 9).

  Sources of exposure - EAS mode of action includes D4, BHA, BPA, butylparaben and propylparaben.
  Sources of exposure - T mode of action includes BHA and BHT.

  These calculations are given in the following chapter:

12.5 RCR for selected sources of exposure (food, FCM and medicinal products)

- **RCR - product, single substance + sources of exposure** **(food, FCM and medicinal products)**
  RCR values for the individual exposure scenario (product) added up with the RCR values for the three selected exposure sources (food, FCM and medicinal products). For each product, an RCR value has previously been calculated for each measured focus substance (RCR - product, single substance) and this is added up with the total exposure contribution from the selected exposure sources. Depending on the mode of action of the focus substance, the total exposure contribution to focus substances is added up with an EAS or T mode of action. For this purpose, RCR values for single substances are calculated with MAF added with the exposure source contribution for the specific substance. Formulas appear in the explanatory text below.

  This will show whether the individual exposure from a specific product + contribution from selected exposure sources, overall, can constitute a risk. (Selected products that showed content/migration of several focus substances with the same mode of action were not added in these calculations. This was only relevant for cosmetic products and is explained in the following section).

  These calculations are given in the following chapter:
  12.6 RCR for products and sources of exposure (12.6.1 and 12.6.3)

- **RCR - product, several focus substances + sources of exposure** **(food, FCM and medicinal products)**
  As a content of several similar acting focus substances has been found in several of the cosmetic products, RCR values for the focus substances have been added for each of these products. For each product RCR values have been calculated, which add up analysis results for focus substances with the same mode of action with the total exposure contribution from the selected exposure sources.

  These calculations are given in the following chapter:
  12.6.2 RCR for the cosmetic products with several focus substances with the same mode of action

- **RCR - combined**
  Finally, the risk assessment calculates a combined exposure for each of the three target groups (children under 3 years, children 3 years and pregnant women/unborn children). This includes RCR values for similar acting substances measured in several consumer products (e.g. cosmetics and toys) as well as exposure from the three selected sources of exposure (food, FCM and medicinal products).

  These calculations are given in the following chapter:
  12.7 RCR for combined exposure for each target group

In relation to the risk assessment, the risk characterization ratio (RCR) is calculated on the basis of the substance exposure calculated for the highest measured substance concentration in the products (i.e. worst case) in relation to the calculated DNEL/DMEL values for the substance ($DNEL_T$/$DMEL_T$ and $DNEL_{EAS}$/$DMEL_{EAS}$). The following formula is used to calculations without MAF:

$RCR_{\text{product, single substance}}$ = exposure (substance 1) (µg/kg bw/d)/DN(M)EL (substance 1) (/g/kg bw/d)

With MAF

In relation to the risk assessment, RCR is calculated on the basis of the specific exposure in relation to the calculated DNEL/DMEL values using a MAF of 10 to allow for exposure from other substances with a similar effect. For each of the six substances, the worst case exposure estimates are compared with the relevant DNEL or DMEL values ($DNEL_{T\text{-}MAF}$/$DMEL_{T\text{-}MAF}$ and $DNEL_{EAS\text{-}MAF}$/$DMEL_{EAS\text{-}MAF}$) and RCR values are calculated to illustrate the degree of risk for the individual exposure scenarios/products:

$RCR_{product,\ single\ substance}$ = exposure (substance 1) (/g/kg bw/d)/DN(M)ELMAF (µg/kg bw/d)

When calculating RCR values, which include the selected exposure sources food, FCM and medicinal products, the calculated RCR is used based on the specific exposure/product in relation to derived DNEL/DMEL values with and without MAF.

For RCR values without MAF, the following formula has been used to include the selected sources of exposure for the risk assessment:

RCR (substance A) =

(product exposure (substance A)/DN(M)EL (substance A) +
(exposure from sources of exposure (substance A)/DN(M)EL (substance A)) +
(sum of RCR values for selected exposure sources for other focus substances with the same mode of action calculated with DN(M)EL values for these substances).

MAF is included in the calculations to allow for other substances with the same mode of action. The RCR values of a single focus substance with MAF (calculated for food, FCM, medicinal products and selected products) can be summed up to a total RCR value. For RCR values with MAF, the following formula is used:

RCR (substance A) =

(product exposure (substance A)/DN(M)EL (substance A) $_{w.\ MAF}$) +
(exposure from exposure sources (substance A)/DN(M)EL (substance A) $_{w.\ MAF}$)

Based on the calculated RCR values for the individual exposure scenarios (products), a total RCR value ($RCR_{total\ product}$) is determined for the individual products containing several focus substances at the same time by adding the total RCR contributions for substances with the same mode of action (EAS or T):

- $RCR_{product,\ total}$ = RCR (substance 1) + RCR (substance 2) + RCR (substance 3) ….

For each of the three target groups a combined risk calculation has been set up, which includes realistic worst case exposures from several of the analysed products containing the same or similar acting focus substances over the course of a day.

For all calculated RCR values, a value above 1 indicates a risk and is marked in **bold** in all tables.

11.2.1 Calculation of the Margin of Safety (MoS) for cosmetic products

In connection with a risk assessment of cosmetic products, SCCS (2021a) states that no harmonized guidelines for the assessment of endocrine disruptors are yet available. SCCS (2021a) states that endocrine disruptors should be hazard and risk assessed in line with other problematic chemical substances. The SCCS (2021a) does not set out any guidelines on how

to carry out a risk assessment of exposure to several similar acting substances. However, recent scientific reports suggest that risk assessment of endocrine disrupting chemicals should be performed differently than the current threshold-based approaches (Hass et al. 2019, Demenix et al 2020), and that combination effects should also be taken into account in the risk assessment (KEMI, 2021). Furthermore, it is recommended to include additional uncertainty factors in the risk assessment, e.g. to allow for exposure during sensitive periods and lack of hormone-sensitive endpoints (Hass et al. 2019) - see Chapter 9.1 for further discussion.

Risk assessment of the individual substance in a cosmetic product has been performed, according to SCCS (2021a), when calculating a margin of safety value (MoS):

MoS = PoDsys/SED

Where

PoDsys: is the point of departure value of the systemic exposure to the specific substance (i.e. an N(L)OAL value or a BMD value).

SED: is the calculated systemic exposure when using the cosmetic product.

Usually, a calculated MoS value above 100 is considered to indicate safe use.

This method is not suitable for risk assessment of several similar acting substances at the same time, as the addition of MoS values for several substances does not make sense, since a higher MoS value obtained by addition indicates greater safety than when exposed to a single substance. For risk assessment of cosmetic products with several similar acting substances, the calculations are therefore made with the RCR approach used in REACH. The MoS calculations can thus only be used to conclude on the risk of the individual substance in each cosmetic product.

Information on MoS calculations is only stated in an appendix to this report (see Appendix 9). In the following, however, a calculation example has been made of propylparaben in sunscreen for pregnant women based on the highest measured concentration.

<u>Calculation example - propylparaben (sunscreen, pregnant women - Product Lab no. EU-K 195)</u>

To calculate the MoS, the internal systemic dose (SED) is determined, which is calculated from the following in accordance with the SCCS Notes of Guidance (2021a):

$$SED = E_{product} \times C/100 \times DA_p/100$$

where Eproduct (mg/kg bw/day) is the estimated daily exposure, C (%) = the concentration of the substance and DAp (%) = dermal absorption.

According to SCCS (2021a), a daily consumption of 18 g/d is used in risk assessment of sunscreen. With a propylparaben content of 0.17%, a woman of 60 kg will thus be exposed to:

Exposure (external) = (18 g/d x 10^6 µg/g x 0.0017)/60 kg = 510 µg propylparaben/kg bw/d

Internal dose (µg/kg bw/d) = 510 µg BHA/kg/d x 3.7% = 19 µg propylparaben/kg bw/d

The MoS can then be calculated for the product, using the PoD value identified in the hazard assessment, Chapter 9, and the SED value calculated above.

Rat; several studies with perinatal oral exposure.
LOAEL: 10 mg/kg bw/d
NOAEL: 10/5 = 2 as an uncertainty factor of 5 (UF 5) is used to get from LOAEL to NOAEL in accordance with the SCCS Notes of Guidance (2021a) and the assessment in Chapter 9.
PoD: 2 mg/kg bw/d (internal dose assuming an oral absorption of 100%)
SED: 19 µg/kg bw/d (internal dose) = 0.019 mg/kg bw/d
MoS: 2/0.019 = 105

12. Risk assessment

The following sections contain the risk calculations of the analysis results.

12.1 Data for body weight used in the calculations

For pregnant women, a body weight of 60 kg is used as the standard weight for a woman (SCCS, 2021a).

For children aged 3 years, a weight of 14 kg is used. This is considered representative of this target group, as ECHA (2012) in their guidance document refers to RIVM (2014), which indicates a body weight of 12.4 kg for 2-3 years and 15.7 kg for a child of 3 -6 years based on the 25th percentile in the two age groups. The average body weight for the two age groups is thus 14 kg.

For children under 3 years, a weight of 8.9 kg is used. This is considered representative as the worst case for the target group, as ECHA (2016) in their guidance document refers to RIVM (2014), which states a body weight of 8 kg for a child of 6-12 months and 9.8 kg for a child at 1-2 years based on the 25th percentile in the two age groups. The average body weight for the two age groups is thus 8.9 kg.

12.2 Dermal/oral absorption of the six focus substances

The risk assessments are based on DN(M)EL values stated as internal dose (Chapter 9). For products with skin contact or exposure through the mouth it is important to know the degree of absorption through the skin or through the gastrointestinal tract to calculate the internal exposure dose (systemic dose) for the substances. Absorption of the six focus substances by dermal and oral exposure is reviewed below, as these two exposure pathways are relevant to the exposure scenarios.

12.2.1 BHT and BHA

In a new SCCS opinion of BHT (September 2021 - draft version) a dermal absorption of 0.4% has been identified. This is based on data from a new *in vitro* dermal absorption study (referred to as Eurofins (2020) in SCCS opinion (2021c)) conducted according to OECD test guideline 428 “Skin Absorption: In Vitro Method” (OECD, 2004). In the study, the dose applied to the skin was equivalent to 5 mg/cm2 (40 µg BHT). Although this is a draft SCCS opinion, it is considered relevant to use a dermal absorption of 0.4% for BHT. On the basis of comparable physical and chemical properties, including also structural properties, it is considered scientifically justified to also use a dermal absorption of 0.4% for BHA for the further calculations of internal dose.

Previously, Larsen et al. (2021) used a dermal absorption of 4% for BHT and BHA. The background for this is data from a Cosmetic Ingredient Review (2002), in which the dermal absorption is stated from an *in vivo* experiment with guinea pigs to a maximum of 4% BHT, measured from excretion of radioactive labelled BHT and metabolites in the urine. A similar absorption was suggested for BHA in this former report based on the same scientific justification. However, it is considered more relevant to use a dermal absorption of 0.4% based on the availability of the more recent test data performed in accordance with an OECD guideline study.

Oral absorption for BHT is stated in the new SCCS opinion (2021c), to be 100% when taken orally.

12.2.2 Propylparaben and butylparaben

For propylparaben and butylparaben, a dermal absorption of 3.7% is used as proposed in the latest SCCS opinion (2021b) as well as in Larsen et al (2017).

An absorption by oral ingestion is assumed to be 100% absorption in the calculations (SCCS, 2021).

12.2.3 D4

For D4, a dermal absorption of 0.5% and an oral absorption of 52% are applied, which are also used in Larsen et al. (2021) The dermal value has been selected on the basis of an SCCS opinion on D4 (2010), which concludes a dermal absorption of 0.5% for D4 based on *in vitro* and *in vivo* dermal absorption studies.

12.2.4 BPA

According to EFSA (2015), an oral absorption of 100% and a dermal absorption of 10% from thermal paper as matrix and 50% from cosmetics as matrix are used.

In this report, a dermal absorption of 10% has been used. This is considered most relevant for the calculations, as these (calculations for BPA) relate to a migration from a solid material and not a cosmetic product that is applied on the skin.

12.3 RCR - Cosmetic products, single substance

Content analyses have been performed on cosmetic products including sunscreen, body lotion, body oil and aftersun for pregnant women as well as sunscreen for children under 3 years.

Based on the measured contents of BHT, BHA, propylparaben and butylparaben reported in Chapter 7, exposure scenarios can be established for the four substances with regard to the use of cosmetic products. TABLE 14 shows that BHT was found in seven cosmetic products out of 20. However, products containing BHA, BHT and the two parabens were purchased intentionally.

The highest content of BHT of 0.058% (product Lab no. NEU-K 171) was found in body lotion for pregnant women, while the second highest content of 0.051% (product Lab no. DK-K 185) was also found in body lotion for pregnant women. These are both leave-on products that are used in relatively large amounts when applied. Use of these two products daily during a summer could thus constitute a realistic worst case scenario for exposure to BHT.

According to TABLE 14, BHA is found only in a single cosmetic product out of 20 - a sunscreen for pregnant women - and only in a very low concentration of 0.008% (product Lab no. EU-K 196). Consequently, exposure to BHA through cosmetics will contribute only marginally to BHT. It is therefore not considered relevant to make a more detailed exposure assessment of this substance, as the contribution will be insignificant compared to the contribution from BHT. In addition, the occurrence of the substance in cosmetics based on the analyses performed must be considered rare but is included for completeness and to illustrate a possible risk of occurrence of both BHT and BHA at the same time.

TABLE 14 shows that propylparaben was found in 15 out of 20 cosmetic products. The highest content of propylparaben (0.17%) was found in sunscreen for children under 3 years (product Lab no. NEU-K 193). For pregnant women, the highest content of propylparaben was identified in a sunscreen with a concentration of 0.17% (product Lab no. EU-K 195). Butylparaben was found in four cosmetic products (body lotion), all for pregnant women. Highest measured concentration was 0.045%, found in body lotion (product Lab no. NEU-K 180).

TABLE 15 shows that D4 was not found in the 20 purchased cosmetic products. However, a possible content of D4 in four products below the detection limit (30 mg/kg) was identified. Due to analytical issues with D4 (as described in Chapter 7.3), the analyses will be repeated using a different analysis method, but this will happen after the publication of this report.

In the following exposure calculations, the highest measured concentrations of the focus substances identified for the individual cosmetic products have been used across analyses of the individual cosmetic products. Based on these calculations, RCR calculations have been made in the following sections.

It is noted that for the cosmetic products, where several focus substances with the same mode of action (EAS) have been found, RCR calculations have also been made. The cosmetic products are body lotions for pregnant women where concentrations of both propylparaben and butylparaben have been measured (product numbers: EU-K 183; EU-K 182; NEU-K 172; NEU-K 180). In addition, both BHA and propylparaben have been found in sunscreen for pregnant women (product number: EU-K 196), both of which have an EAS-based mode of action. The RCR values for the cosmetic products are calculated based on the exposure calculations as well as the relevant DNELs and DMEL values as in the section below on exposure calculations (12.3.1), in which calculation examples are given for the highest measured concentrations of the focus substances identified for the individual cosmetic products across analyses of the individual cosmetic products. In the following, calculation examples of exposure calculations and RCR calculations are not given for the above-mentioned product numbers containing two focus substances. The specific RCR values for these cosmetic products can be found in section 12.6.2 (RCR for cosmetic products with several focus substances with the same mode of action).

12.3.1 Exposure calculations

In this section, exposure to the cosmetic products is calculated. In this project cosmetic products have been selected for two target groups, pregnant women/unborn children and children under 3 years of age, and calculation examples have been made of each product type (body lotion, sunscreen, aftersun, body oil) for the relevant target group.

In the following calculation examples of the specific external and internal dose, the highest measured concentrations identified for the individual cosmetic products have been used across analyses of the individual cosmetic products. A calculation example of a single substance is given for the individual cosmetic products. As D4 was not found in the analyses, a calculation example is given based on the detection limit of the analyses of 30 mg/kg. Since the analyses indicated a possible content below the detection limit, this can be considered worst case.

Based on the dermal absorption, the internal systemic dose (SED) can be calculated from the following in accordance with the SCCS Notes of Guidance (2021a):

$$SED = E_{product} \times C/100 \times DA_p/100$$

Where $E_{product}$ (mg/kg bw/day) is the estimated daily exposure, C (%) = the concentration of the substance and DA_p (%) = dermal absorption.

Internal dose = External exposure x absorption

In the examples below external exposures and internal doses (defined as SED) are calculated for pregnant women and children under 3 years.

Pregnant women/unborn children:

Body lotion (product NEU-K 180):
According to the Scientific Committee on Consumer Safety (SCCS (2021a)), a daily consumption of 7.82 g/d is used in risk assessment of body lotions. With a **butylparaben** content of 0.045%, a woman of 60 kg will thus be exposed to:

Exposure (external) =
(7.82 g/d x 10^6 µg/g x 0.00045)/60 kg = 59 µg butylparaben/kg bw/d

Internal dose (µg/kg bw/d) =
59 µg butylparaben/kg/d x 3.7% = 2.2 µg butylparaben/kg/d

Sunscreen (product EU-K 196):
According to SCCS (2021a), a daily consumption of 18 g/d is used in risk assessment of sunscreen. With a content of **BHA** of 0.008%, a woman of 60 kg will thus be exposed to:

Exposure (external) = (18 g/d x 10^6 µg/g/g x 0.00008)/60 kg = 24 µg BHA/kg bw/d

Internal dose (µg/g/kg bw/d) = 24 µg BHA/kg/d x 0.4% = 0.1 µg BHA/kg/d

It should be noted, however, that recommendations from the health authorities are application of 36 g corresponding to 72 g/day[11], [12]. This is four times higher than the 18 g/d used, as stated in SCCS (2021a). However, 18 g/d has been used in this report as it is recommended by SCCS, and the same amount has been used in previous risk assessments. However, this means that the exposure from sunscreens is probably underestimated, especially if the consumer follows recommendations from the health authorities regarding protection from the sun.

Aftersun (product NEU-K 192):
According to SCCS (2016), a daily consumption of 7.82 g/d is used in risk assessment of body lotion. Based on a comparable use scenario, it is estimated that the amount of aftersun is comparable to the amount of body lotion, in this case 7.82 g/d. This value will be used in the following calculation of the exposure scenario. With a content of 0.15% **propylparaben**, a woman of 60 kg will thus be exposed to:

Exposure (external) (7.82 g/d x 10^6 µg/g/g x 0.0015)/60 kg = 196 µg propylparaben/kg bw/d

Internal dose (µg/kg bw/d) = 196 µg propylparaben/kg/d x 3.7% = 7.3 µg propylparaben/kg/d

Body oil (product NEU-K 181):
According to SCCS (2021a), a daily consumption of 7.82 g/d is used in risk assessment of body lotions. Based on a comparable use scenario, it is estimated that the amount of body oil is comparable to the amount of body lotion, in this case 7.82 g/d. This value will be used in the following calculation of the exposure scenario. For body oil, a **propylparaben** content of 0.098% and a **BHT** content of 0.023% have been identified. A woman of 60 kg will thus be exposed to:

Exposure (external) propylparaben: (7.82 g/d x 10^6 µg/g x 0.00098)/60 kg = 128 µg propylparaben/kg bw/d

[11] Letter from the Ministry of Environment to SCCS dated 26 October 2021.

[12] https://www.sst.dk/-/media/Udgivelser/2019/Faktaark-solbeskyttelse/SolcremeX.ashx?la=da&hash=0AF74491A5027C0F2D30914C51FE032CC3D173CD (In Danish. Accessed December 2021).

Internal dose (propylparaben): 128 µg propylparaben/kg/d x 3.7% = 4.7 µg propylparaben/kg/d

Exposure (external) BHT: (7.82 g/d x 10^6 µg/g/g x 0.00023)/60 kg = 30 µg BHT/kg bw/d

Internal dose (BHT): 30 µg BHT/kg/d x 0.4% = 0.1 µg BHT/kg/d

It should be noted that in this example, BHT has also been found in addition to propylparaben. Calculations have been made for both focus substances as analyses have only been performed on one body oil product. In the following, RCR calculations have been made for these two substances in the body oil.

Children under 3 years:

Sunscreen (product NEU-K 193):
According to SCCS (2021a), the ratio between the surface area of the skin and body weight is 1.6 times greater in children aged 1 year compared to adults. With the same exposure per cm^2, the exposure will be 1.6 times higher per kg body weight for children of 1 year compared to adults. Using this as a benchmark and with a child of 1 year as an exponent of the group of children under 3 years, the exposure can be calculated.

According to SCCS (2021a), a daily consumption of 18 g/d is used in risk assessment of sunscreen. With a **D4** content of 0.003% (30 mg/kg) a child will thus be exposed to:

Exposure (external) (18 g/d x 10^6 µg/g x 0.00003)/60 kg x 1.6 = 14.4 µg D4/kg bw/d

Internal dose (µg/kg bw/d) = 14.4 µg D4/kg bw/d x 0.5% = 0.072 µg D4/kg bw/

The above exposure scenarios are considered realistic, as the highest measured concentrations identified for the individual cosmetic products have been used, as well as consumption quantities in accordance with the guidance document for cosmetic products (SCCS, 2021a).

The table below shows the exposure estimates for the highest measured concentrations in the cosmetic products across analyses of the individual cosmetic products.

For the cosmetic products with several focus substances with the same mode of action, contributions have been added for the individual substances in connection with an overall risk assessment. This is primarily in selected body lotions for pregnant women where concentrations of both propylparaben and butylparaben have been measured (product numbers: EU-K 183; EU-K 182; NEU-K 172; NEU-K 180), both of which have an EAS based mode of action. In addition, BHA and propylparaben have been found in a sunscreen for pregnant women (product number: EU-K 196), both of which have an EAS based mode of action.

TABLE 31. Exposure estimates for the highest measured concentrations of BHA, BHT, propylparaben and butylparaben in sunscreen, body oil, body lotion and aftersun for pregnant women and sunscreen for children under 3 across measurements for the product groups. As a result, there are different product numbers for the product groups as the highest measured concentrations are from different analyses for the different product groups. No D4 was identified above the detection limit. Exposure estimates of D4 for pregnant women and children under 3 years of age have been calculated for the same cosmetic products using the detection limit of 30 mg/kg (equivalent to 0.003%). The table lists the target group, body weight, dermal absorption as well as the external exposure and internal dose (see calculation examples in the previous text).

	Target group	Body weight (kg)	Concentration (%)	User scenario (g/d)	Exposure, external (µg/kg bw/d)	Dermal absorption (%)	Internal dose (SED) (µg/kg bw/d)
BHA (sunscreen) (EU-K 196)	Pregnant women	60	0.008	18	24	0.4	0.1
BHT (sunscreen) (DK-K 198)	Pregnant women	60	0.008	18	24	0.4	0.1
BHT (body oil) (NEU-K 181)	Pregnant women	60	0.023	7.82	30	0.4	0.12
BHT (body lotion) (NEU-K 171)	Pregnant women	60	0.058	7.82	76	0.4	0.3
BHT (sunscreen) (NEU-K 193)	Children under 3 years	(1.6)**	0.047	18	226	0.4	0.9
Butylparaben (body lotion) (NEU-K 180)	Pregnant women	60	0.045	7.82	59	3.7	2.2
Propylparaben (sunscreen) (EU-K 195)	Pregnant women	60	0.17	18	510	3.7	19
Propylparaben (body lotion) (EU-K 183)	Pregnant women	60	0.099	7.82	129	3.7	4.8
Propylparaben (aftersun) (NEU-K 192)	Pregnant women	60	0.15	7.82	196	3.7	7.3

	Target group	Body weight (kg)	Concentration (%)	User scenario (g/d)	Exposure, external (µg/kg bw/d)	Dermal absorption (%)	Internal dose (SED) (µg/kg bw/d)
Propylparaben (body oil) (NEU-K 181)	Pregnant women	60	0.098	7.82	128	3.7	4.7
Propylparaben (sunscreen) (NEU-K 193)	Children under 3 years	(1.6)**	0.17	18	816	3.7	30.2
D4 (sunscreen)*	Pregnant women	60	0.003	18	9	0.5	0.045
D4 (body lotion)*	Pregnant women	60	0.003	7.82	3.91	0.5	0.020
D4 (aftersun)*	Pregnant women	60	0.003	7.82	3.91	0.5	0.020
D4 (body oil)*	Pregnant women	60	0.003	7.82	3.91	0.5	0.020
D4 (sunscreen)*	Children under 3 years	(1.6)**	0.003	18	14.4	0.5	0.072

* As D4 was not found in the analyses, exposure based on the detection limit of the analyses of 30 mg/kg (0.003%) has been reported. Since the analyses indicated a possible content below the detection limit (of 30 mg/kg), this can be considered worst case. A specific product number for D4 is not specified. Exposure calculations have been made for each individual cosmetic product group.

** According to the Scientific Committee SCCS (2021a), the ratio between the surface area of the skin and body weight is 1.6 times greater in children aged 1 year compared to adults. With the same exposure per cm2, the exposure will be 1.6 times higher per kg body weight for children of 1 year compared to adults. Using this as a benchmark and with a child of 1 year as an exponent of the group of children under 3 years, the exposure can be calculated.

12.3.2 Risk characterization, single measurements (highest concentrations) across analyses of the cosmetic product groups

12.3.2.1 Sunscreen (pregnant women/unborn children)

In the tables below, RCR values are calculated to illustrate the degree of risk of exposure to focus substances from the cosmetic product groups. For all calculations, worst case exposure estimates have been used based on the highest measured concentrations for each of the focus substances in the individual cosmetic products across analyses within the individual cosmetic products. There are therefore different product numbers for sunscreen and body lotions for pregnant women. For aftersun and body oil for pregnant women, only one product number is given as only analyses of one product have been performed. The same applies to sunscreen for children under 3 years.

For D4, RCR values have been calculated based on the detection limit of the analyses of 30 mg/kg (0.003%). RCR calculations have been made for each individual cosmetic product group.

The calculated internal dose estimates from the previous table (TABLE 31) are used to calculate RCR values in relation to the relevant DNELs or DMELs with and without the use of MAF.

The calculation methods for the risk assessment are described in Chapter 11 "Risk assessment method"

The internal dose estimates (µg/kg/bw/d), as shown in the table below, are calculated in TABLE 31, and the DNEL and DMEL values shown (µg/kg/bw/d) are described in Chapter 9.

TABLE 32. DNELs for endocrine disrupting effects for T mode of action ($DNEL_T$) or EAS mode of action ($DNEL_{EAS}$) as well as corresponding RCR values with and without MAF in sunscreen for pregnant women. RCR values are for the highest measured concentrations of BHA, BHT and propylparaben across analyses of sunscreen for pregnant women. The RCR for D4 is based on the detection limit of the analyses, set at 30 mg/kg (0.003%). All figures are in internal doses and stated in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold.**

Product: Sunscreen	**Concentration** (%)	**Exposure** (µg/kg bw/d)	**$DNEL_T$** (µg/kg bw/d)	**$DMEL_T$** µg/kg bw/d	**$DNEL_{EAS}$** (µg/kg bw/d)	**$DMEL_{EAS}$** (µg/kg bw/d)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF*** ** $DNEL_T$	**RCR w. MAF*** ** $DMEL_T$	**RCR w. MAF*** ** $DNEL_{EAS}$	**RCR w. MAF*** ** $DMEL_{EAS}$
BHA (EU-K 196)	0.008	0.1	1000	100	100	10	0.0001	0.001	0.001	0.01	0.001	0.01	0.01	0.1
BHT (DK-K 198)	0.008	0.1	250	25	Not relevant	Not relevant	0.0004	0.004	-	-	0.004	0.04	-	-
Butylparaben	-	-	Not relevant	Not relevant	20	2	-	-	-	-	-	-	-	-
Propylparaben (EU-K 195)	0.17	19	Not relevant	Not relevant	20	2	-	-	0.95	**9.5**	-	-	**9.5**	**95**
D4	0.003*	0.045**	Not relevant	Not relevant	36	3.6	-	-	0.001	0.01	-	-	0.01	0.1

"-": no calculation
* D4: The detection limit is set at 30 mg/kg for the D4 analyses
** D4: (18 g/d x 106 x 0.00003/60 kg = 9 µg/kg bw/d x 0.5%/dermal absorption) = 0.045 µg/kg bw/d)
*** RCR values using MAF of 10

No risk of BHA or BHT (RCR <1) has been identified in sunscreen for pregnant women based on the highest measured concentrations of BHA, BHT and propylparaben across the analyses of sunscreen for pregnant women. For propylparaben, no risk (RCR <1) has been identified using DNEL (threshold approach) without the use of MAF. When using DMEL (non-threshold approach) with and without the use of MAF, a risk has been identified (RCR> 1). No risk of D4 has been identified based on the detection limit of the analyses.

12.3.2.2 Body lotion (pregnant women/unborn children)

TABLE 33. DNELs for endocrine disrupting effects for T mode of action ($DNEL_T$) or EAS mode of action ($DNEL_{EAS}$) as well as corresponding RCR values with and without MAF in body lotion for pregnant women. RCR values are for the highest measured concentrations of BHT, butylparaben and propylparaben, across the analyses for body lotion for pregnant women. The RCR for D4 is based on the detection limit of the analyses, set at 30 mg/kg (0.003%). All figures are in internal doses and in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold.**

Product: Body lotion	**Concentration** (%)	**Exposure** (µg/kg bw/d)	**$DNEL_T$** (µg/kg bw/d)	**$DMEL_T$** (µg/kg bw/d)	**$DNEL_{EAS}$** (µg/kg bw/d)	**$DMEL_{EAS}$** (µg/kg/d)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF*** ** $DNEL_T$	**RCR w. MAF*** ** $DMEL_T$	**RCR w. MAF*** ** $DNEL_{EAS}$	**RCR w. MAF*** ** $DMEL_{EAS}$
BHA	-	-	1000	100	100	10	-	-	-	-	-	-	-	-
BHT (NEU-K 171)	0.058	0.3	250	25	Not relevant	Not relevant	0.0012	0.012	-	-	0.012	0.12	-	-
Butylparaben (NEU-K 180)	0.045	2.2	Not relevant	Not relevant	20	2	-	-	0.105	**1.05**	-	-	**1.05**	**10.5**
Propylparaben (EU-K 183)	0.099	4.8	Not relevant	Not relevant	20	2	-	-	0.235	**2.35**	-	-	**2.35**	**23.5**
D4	0.003*	0.020**	Not relevant	Not relevant	36	3.6	-	-	0.0006	0.006	-	-	0.006	0.06

"-": no calculation
* D4: The detection limit is set at 30 mg/kg for the D4 analyses
** D4. (7.82 g/d x 106 x 0.00003/60 kg = 3.91 µg bw/kg/d x 0.5%/dermal absorption) = 0.020 µg/kg bw/d)
*** RCR values using MAF of 10 when setting DNEL values

No risk of BHT (RCR <1) has been identified in body lotions for pregnant women, based on the highest measured concentrations of BHT, butylparaben and propylparaben across the analyses of sunscreen for pregnant women. For butylparaben and propylparaben, no risk (RCR <1) has been identified using DNEL (threshold approach) without the use of MAF. When using DMEL (non-threshold approach) with and without the use of MAF, a risk has been identified (RCR> 1). No risk of D4 based has been identified on the detection limit of the analyses.

12.3.2.3 Aftersun (pregnant women/unborn children)

TABLE 34. DNELs for endocrine disrupting effects for T mode of action ($DNEL_T$) or EAS mode of action ($DNEL_{EAS}$) as well as corresponding RCR values with and without MAF in aftersun for pregnant women. RCR values are the highest measured concentration of propylparaben in aftersun for pregnant women. The RCR for D4 is based on the detection limit of the analyses, set at 30 mg/kg (0.003%). All figures are in internal doses and in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold**.

Product: Aftersun	**Concentration** (%)	**Exposure** (µg/kg bw/d)	**$DNEL_T$** (µg/kg bw/d)	**$DMEL_T$** µg/kg bw/d	**$DNEL_{EAS}$** (µg/kg bw/d)	**$DMEL_{EAS}$** (µg/kg bw/d)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF*** ** $DNEL_T$	**RCR w. MAF*** ** $DMEL_T$	**RCR w. MAF*** ** $DNEL_{EAS}$	**RCR w. MAF*** ** $DMEL_{EAS}$
BHA	-	-	1000	100	100	10	-	-	-	-	-	-	-	-
BHT	-	-	250	25	Not relevant	Not relevant	-	-	-	-	-	-	-	-
Butylparaben	-	-	Not relevant	Not relevant	20	2	-	-	-	-	-	-	-	-
Propylparaben (NEU-K 192)	0.15	7.3	Not relevant	Not relevant	20	2	-	-	0.36	**3.6**		**-**	**3.6**	**36**
D4	0.003*	0.020**	Not relevant	Not relevant	36	3.6	-	-	0.0006	0.006	**-**	**--**	0.006	0.06

"-": no calculation
* D4: The detection limit is set at 30 mg/kg for the D4 analyses
** D4: (7.82 g/d x 106 x 0.00003/60 kg = 3.91 µg/kg/d x 0.5%/dermal absorption) = 0.020 µg/kg bw/d)
*** RCR values using MAF of 10 when setting DNEL values

No risk of propylparaben (RCR <1) has been identified using DNEL (threshold approach) without the use of MAF in aftersun for pregnant women based on the highest measured concentration of propylparaben. When using DMEL (non-threshold approach) with and without the use of MAF, a risk has been identified (RCR> 1). No risk of D4 has been identified based on the detection limit of the analyses.

12.3.2.4 Body oil (pregnant women/unborn children)

TABLE 35. DNELs for endocrine disrupting effects for T mode of action ($DNEL_T$) or EAS mode of action ($DNEL_{EAS}$) as well as corresponding RCR values with and without MAF in body oil for pregnant women. RCR values are for the highest measured concentration of BHT and propylparaben in body oil for pregnant women. The RCR for D4 is based on the detection limit of the analyses, set at 30 mg/kg (0.003%). All figures are in internal doses and in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold**.

Product: Body oil	**Concentration (%)**	**Exposure** (µg/kg bw/d)	**$DNEL_T$** (µg/kg bw/d)	**$DMEL_T$** µg/kg bw/d	**$DNEL_{EAS}$** (µg/kg bw/d)	**$DMEL_{EAS}$** (µg/kg bw/d)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF*** ** $DNEL_T$	**RCR w. MAF*** ** $DMEL_T$	**RCR w. MAF*** ** $DNEL_{EAS}$	**RCR w. MAF*** ** $DMEL_{EAS}$
BHA	-	-	1000	100	100	10	-	-	-	-	-	-	-	-
BHT (NEU-K 181)	0.023	0.12	250	25	Not relevant	Not relevant	0.0005	0.0048	-	-	0.005	0.048	-	-
Butylparaben	-	-	Not relevant	Not relevant	20	2	-	-	-	-	-	-	-	-
Propylparaben (NEU-K 181)	0.098	4.7	Not relevant	Not relevant	20	2	-	-	0.24	**2.4**	-	-	**2.4**	**24**
D4	0.003*	0.020**	Not relevant	Not relevant	36	3.6	-	-	0.0006	0.006	-	-	0.006	0.06

"-": no calculation
* D4: The detection limit is set at 30 mg/kg for the D4 analyses
** D4: (7.82 g/d x 106 x 0.00003/60 kg = 3.91 µg/kg/d x 0.5%/dermal absorption rate) = 0.020 µg/kg bw/d)
*** RCR values using MAF of 10 when setting DNEL values

No risk of BHT has been identified (RCR <1) in body oil for pregnant women based on the highest measured concentration of BHT and propylparaben. For propylparaben a risk has not identified (RCR <1) using DNEL (threshold approach) without the use of MAF. When using DMEL (non-threshold approach) with and without the use of MAF, a risk has been identified (RCR> 1). No risk of D4 has been identified based on the detection limit of the analyses.

12.3.2.5 Sunscreen (children under 3 years)

TABLE 36. DNELs and DMELs for endocrine disrupting effects for T modality ($DNEL_T$ and $DMEL_T$) or EAS modalities ($DNEL_{EAS}$ and $DMEL_{EAS}$) as well as RCR values in sunscreen for children under 3 years of age. RCR values are the highest measured concentration of BHT and propylparaben in sunscreen for children under 3 years of age. The RCR of D4 is based on the detection limit of the analyses, set at 30 mg/kg (0.003%). All figures are in internal doses and in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold**.

Product: Sunscreen	**Exposure** (%)	**Exposure** (µg/kg bw/d)	**$DNEL_T$** (µg/kg bw/d)	**$DMEL_T$** µg/kg bw/d	**$DNEL_{EAS}$** (µg/kg bw/d)	**$DMEL_{EAS}$** (µg/kg bw/d)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF*** ** $DNEL_T$	**RCR w. MAF*** ** $DMEL_T$	**RCR w. MAF*** ** $DNEL_{EAS}$	**RCR w. MAF*** ** $DMEL_{EAS}$
BHA	-	-	1000	100	100	10	-	-	-	-	-	-	-	-
BHT **(NEU-K 193)**	0.047	0.9	250	25	Not relevant	Not relevant	0.0036	0.036	-		0.036	0.36	-	-
Butylparaben	-	-	Not relevant	Not relevant	20	2	-	-	-	-	-	-	-	-
Propylpara-ben **(NEU-K 193)**	0.17	30.2	Not relevant	Not relevant	20	2	-	-	**1.51**	**15.1**	-	-	**15.1**	**151**
D4	0.003*	0.072**	Not relevant	Not relevant	36	3.6	-	-	0.002	0.02	-	-	0.02	0.2

"-": no calculation
* The detection limit is set at 30 mg/kg for the D4 analyses
** (18 g/d x 106 x 0.00003/60 kg = 9 µg/kg/d x 0.5%/dermal absorption) = 0.045) x 1.6 = 0.072 µg/kg bw/d
*** RCR values using MAF of 10 when setting DNEL values

No risk of BHT has been identified (RCR <1) in sunscreen for children under 3 years of age based on the highest measured concentration of BHT and propylparaben. For propylparaben, a risk (RCR> 1) has been identified using DNEL (threshold approach) and DMEL (non-threshold approach) with and without the use of MAF. No risk of D4 has been identified based on the detection limit of the analyses.

The RCR value of propylparaben in sunscreen for children under 3 years of age is above 1 (1.51), which indicates a risk when using the RCR risk assessment method. This value is based on a DNEL approach which is still normal practice in risk assessment of ED substances. Using the DMEL approach (without threshold) and using the MAF increases the risk. The corresponding MoS value used in risk assessment of ingredients in cosmetic products is 110 (Appendix 9), which indicates that there is no risk in use. In the exposure scenario for this calculation, a lower amount of use has been applied than the health and environmental authorities recommend to achieve optimal protection. It is therefore not considered relevant to refine the RCR calculation.

12.4 RCR - Textiles, plastic and silicone products, single fabric

In the calculations below RCR values are derived to illustrate the degree of risk for the individual exposure scenarios. For all calculations, worst case exposure estimates (described in Chapter 5) with the relevant DNELs or DMEL values for the substances (set out in Chapter 9) have been used.

The migration analyses are based on the exposure scenarios, and thus the following formula can be used to calculate the daily exposure:

Daily exposure: Exposure (µg/kg bw/d) = (product $area_{contact}$ (cm^2) x $migration_{measured}$ (µg/cm^2) x absorption fraction)/kg bw

RCR values based on LOD or LOQ are included to assess whether the analysis method has been sufficiently sensitive. However, these RCR values cannot be considered as a real exposure potential. In cases where the RCR value is above 1, and where the exposure is calculated on the basis of LOQ or LOD, this means that the analysis method has not been sensitive enough to be able to clear the products of risk regarding the concerned substances. In other words, a more sensitive method of analysis will be needed to assess the risk of the products.

12.4.1 BPA from textile and plastic products and propylparaben in textile products

The results of the migration analyses performed for BPA in textile and plastic products are given in TABLE 18 (Chapter 8).

The absorption of BPA is stated by EFSA (2015): Oral intake 100%, dermal intake 10% (thermal paper) and 50% (cosmetics). As stated in Chapter 12.2.4 a dermal absorption of 10% is used in this report.

For BPA, the detection limit (LOD) of the method was 2 ng/cm^2, while the quantification limit (LOQ) was 6 ng/cm^2. For the migration measurements <LOD or <LOQ and worst case migration values of 5.9 µg/cm^2 and 1.9 µg/cm^2, respectively, are used to set up worst case exposure estimates.

TABLE 37. Exposure estimates for BPA (Bisphenol A) from textile and plastic products

Product	Product no.	Migration* (µg/cm²)	Area (cm²)	Exposure, external (µg/d)	Target group	Exposure route	Absorption (%)	Internal dose (µg/d)	Body weight (kg)	Exposure (µg/kg bw/d)
Socks	DK-T 122	0.0059 ** (<LOQ)	204	1.2	Children 3 years	Dermal	10	0.12	14	0.0086
Tights	DK-T 136	0.0019 (<LOD)	1947	3.7	Children under 3 years	Dermal	10	0.37	8.9	0.042
Socks	NEU-T 116	0.0029 *** (<LOQ)	154	0.45	Children 3 years	Dermal	10	0.045	14	0.0031
Pacifier shield	EU-P 3	0.0119 **** (<LOQ)	10.3	0.12	Children under 3 years	Oral	100	0.12	8.9	0.014
Mobile cover	DK-P 35	0.0019 (<LOD)	108.8	0.21	Pregnant women	Dermal	10	0.021	60	0.00034

* <LOD indicates that the migration concentration has been below the detection limit. <LOQ indicates that the migration concentration has been below the quantification limit.
** BPA is determined in the migration fluid above the detection limit (LOD), but below the quantification limit (LOQ). A worst case value of 5.9 µg/cm² has therefore been used.
*** The migration analysis was performed on 20 cm² of fabric instead of 10 cm², which is why LOQ (3µg/cm²) and LOD are lower. As the migration measurement is stated to be higher than LOD and lower than LOQ, 2.9 µg/cm² is used.
**** A larger volume had to be used to cover the curved pacifier shield with migration fluid. LOQ and LOD are therefore higher. A content of BPA is determined above the detection limit (LOD), but below the quantification limit (LOQ) in one of the two measurements.

Calculation example:

Daily exposure (BPA, DK-T 122)$_{\text{children 3 years}}$ = (product area$_{\text{contact}}$ (cm²) x migration$_{\text{measured}}$ (µg/cm²) x absorption)/kg bw
= (204 cm² x 0.0059 µg/cm²* x 10%)/14 kg = 0.0086 µg/kg bw/d

TABLE 38. DNELs and DMELs for BPA, as well as RCR values for BPA in textile and plastic products. All figures are in internal doses and in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold.**

Product no.	**Prod-uct type**	**Target group**	**Daily internal dose** (µg/kg bw/d)	**$DNEL_T$** ($DNEL_T$) (µg/kg/d)	**$DMEL_T$** ($DMEL_T$) (µg/kg/d)	**$DNEL_{EAS}$** ($DNEL_{EAS}$) (µg/kg/d)	**$DMEL_{EAS}$** ($DMEL_{EAS}$) (µg/kg/d)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
DK-T 122	Socks	Children 3 years	0.009	Not relevant	Not relevant	0.24	0.024	-	-	0.036	0.36	-	-	0.36	**3.6**
DK-T 136	Tights	Children under 3 years	0.042	Not relevant	Not relevant	0.24	0.024	-	-	0.17	**1.7**	-	-	**1.7**	**17**
NEU-T 116	Socks	Children 3 years	0.0032	Not relevant	Not relevant	0.24	0.024	-	-	0.013	0.13	-	-	0.1	**1.3**
EU-P 3	Pacifier shield	Children under 3 years	0.014	Not relevant	Not relevant	0.24	0.024	-	-	0.057	0.57	-	-	0.57	**5.7**
DK-P 35	Mobile cover	Pregnant women	0.0003	Not relevant	Not relevant	0.24	0.024	-	-	0.0013	0.013	-	-	0.013	0.13

"-": No calculation
*** A larger volume had to be used to cover the curved pacifier shield with migration fluid. LOQ and LOD are therefore higher. A content of BPA is determined above the detection limit (LOD), but below the quantification limit (LOQ) in one of the two measurements.

Calculations based on LOD will not be used further in the risk assessment of exposure sources and combined exposure, as the RCR value only relates to the analysis setup and not a real exposure possibility. This applies to DK-T 136 and DK-P 35. In cases where the RCR value is above 1, and where the exposure is calculated on the basis of LOQ or LOD, this means that the analysis method has not been sensitive enough to be able to clear the products of risk regarding the concerned substance(s). In other words, a more sensitive analysis method will be needed to risk assess the products. In the table above, this is not the case for some of the calculated RCR values using $DNEL_{EAS}$ without MAF.

Some of the RCR values are above 1 for DMEL and using MAF. It can therefore be concluded that the analysis is sufficiently sensitive for risk assessment with DNEL, but not for risk assessment with DMEL or MAF (both DNEL and DMEL).

12.4.2 Propylparaben from textiles and plastic products

The results of the migration analyses performed for propylparaben in textile and plastic products are given in TABLE 18 (Chapter 8).

For propylparaben, the detection limit (LOD) of the method was 1 ng/cm^2, while the quantification limit (LOQ) is 2 ng/cm^2. For the migration measurements <LOD or <LOQ worst case migration values of 0.9 µg/cm^2 and 1.9 µg/cm^2, respectively, are used to set up the worst case exposure estimates.

Dermal absorption rate of propylparaben is stated as in SCCS (2021b): dermal uptake 3.7%. In the calculations, an absorption by oral ingestion is assumed to be 100%.

TABLE 39. Exposure estimates for propylparaben from textile and plastic products

Product	**Product no.**	**Migration** (µg/cm^2)	**Area** (cm^2)	**Exposure, external** (µg/d)	**Target group**	**Exposure route**	**Absorption** (%)	**Internal dose** (µg/d)	**Body weight** (kg)	**Exposure** (µg/kg bw/d)
Socks	DK-T 122	0.003	204	0.61	Children 3 years	Dermal	3.7	0.023	14	0.0016
Tights	DK-T 136	0.014	1947	27.26	Children under 3 years	Dermal	3.7	1.01	8.9	0.11
Socks	NEU-T 116	0.0009 (<LOD)	154	0.14	Children 3 years	Dermal	3.7	0.005	14	0.00037
Pacifier shield	EU-P 3	0.0039* (< LOQ)	10.3	0.04	Children under 3 years	Oral	100	0.04	8.9	0.0045
Mobile cover	DK-P 35	0.0009 (<LOD)	108.8	0.098	Pregnant women	Dermal	3.7	0.004	60	0.00006

<LOD indicates that the migration concentration has been below the detection limit. <LOQ indicates that the migration concentration has been below the quantification limit
* A larger volume had to be used to cover the curved pacifier shield with migration fluid. LOQ and LOD are therefore higher. A content of BPA is determined above the detection limit (LOD), but below the quantification limit (LOQ) in one of the two measurements.

TABLE 40. DNELs and DMELs for propylparaben, as well as RCR values for propyl in textile and plastic products. All figures are in internal doses and in µg/kg bw/d (from Chapter 9).

Product no.	Product type	Target group	Internal dose (µg/kg bw/d)	$DNEL_T$ (µg/kg/d)	$DMEL_T$ (µg/kg/d)	$DNEL_{EAS}$ (µg/kg/d)	$DMEL_{EAS}$ (µg/kg/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
DK-T 122	Socks	Children 3 years	0.0016	Not relevant	Not relevant	20	2	-	-	0.000081	0.00081	-	-	0.00081	0.0081
DK-T 136	Tights	Children under 3 years	0.11	Not relevant	Not relevant	20	2	-	-	0.0057	0.054	-	-	0.057	0.57
NEU-T 116	Socks	Children 3 years	0.00037	Not relevant	Not relevant	20	2	-	-	0.000018	0.00018	-	-	0.00018	0.0018
EU-P 3	Pacifier shield	Children under 3 years	0.0045	Not relevant	Not relevant	20	2	-	-	0.00023	0.0023	-	-	0.0023	0.023
DK-P 35	Mobile cover	Pregnant women	0.00006	Not relevant	Not relevant	20	2	-	-	0.0000030	0.000030	-	-	0.000030	0.00030

"-": No calculation

Calculations based on LOD will not be used further in the risk assessment with exposure sources and combined exposure, as the RCR values only relate to the analysis setup and not a real exposure possibility. This applies to product no. NEU-T 116, EU-P 3 and DK-P 35.

In the present project, two measured migrations have been quantified by analysis that are considered useful in the further calculations. This applies to DK-T 122 and DK-T 136.BHT in plastic products

The results of the migration analyses for BHT in the two plastic products are given in TABLE 19 (Chapter 8). The detection limit (LOD) of the method is 30 ng/cm^2, while the quantification limit (LOQ) is 80 ng/cm^2 for BHT.

The absorption rate of BHT is stated in SCCS (2021c) to be 0.4% for dermal uptake and 100% for oral ingestion.

TABLE 41. Exposure estimates for BHT in plastic products

Product	Product no.	Migration* ($\mu g/cm^2$)	Area (cm^2)	Exposure, external (µg/d)	Target group	Exposure route	Absorption (%)	Internal dose (µg/d)	Body weight (kg)	Exposure (µg/kg bw/d)
Mobile cover	DK-P 34	0.029* (<LOD)	110.2	3.1958	Pregnant women	Dermal	0.4	0.013	60	0.00021
Pop It, baby	DK-P 56	0.029 (<LOD)	62.7	1.8183	Children under 3 years	Oral	100	1.82	8.9	0.20

"<LOD" indicates that the migration concentration has been below the detection limit. "<LOQ" indicates that the migration concentration has been below the quantification limit

* The analysis indicated a content of BHT in the migration fluid below the detection limit (LOD).

TABLE 42. DNELs and DMELs for BHT, as well as RCR values for BHT in plastic products. All figures are in internal doses and in µg/kg bw/d (from Chapter 9).

Product no.	Product type	Target group	Internal dose (µg/kg bw/d)	$DNEL_T$ (µg/kg/d)	$DMEL_T$ (µg/kg/d)	$DNEL_{EAS}$ (µg/kg/d)	$DMEL_{EAS}$ (µg/kg/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
DK-P 34	Mobile cover	Pregnant women	0.00021	250	25	Not relevant	Not relevant	0.00	0.00	-	-	0.00	0.00	-	-
DK-P 56	Pop It, baby	Children under 3 years	0.20	250	25	Not relevant	Not relevant	0.00066	0.0066	-	-	0.0082	0.082	-	-

"-": No calculation

Since the migration analyses for product no. DK-P 34 indicate a migration of BHT below the detection limit, this value can be used in the further calculations as a worst case assumption. For product no. DK-P 56, this RCR value will not be used in the further calculations, as it is based solely on LOD and relates exclusively to the analysis setup and not a real exposure possibility.

12.4.3 D4 in silicone products

The results of the migration analyses performed for D4 in the 12 silicone products are given in TABLE 20 (Chapter 8). The results indicate that D4 was not found in the migration analyses of the selected products. To assess the application of a detection limit of 2 µg/cm^2 in the migration analyses, RCR values are calculated for a migration of 1.9 µg/cm^2 for selected products in the migration analyses.

TABLE 43. Exposure estimates for D4 in silicone products

Product	Product no.	Migration* (µg/cm^2)	Area (cm^2)	Exposure, external (µg/d)	Target group	Exposure route	Absorption (%)	Internal dose (µg/d)	Body weight (kg)	Exposure (µg/kg bw/d)
Pop It	DK-S 57	1.9 (<LOD)	118.8	226	Children 3 years	Dermal	0.5	1.1	14	0.081
Pop It	EU-S 53	1.9 (<LOD)	900	1710	Children 3 years	Dermal	0.5	8.6	14	0.61
Pop It, baby	DK-S 56	1.9 (<LOD)	62.7	119	Children under 3 years	Oral	52	62	8.9	7.0
Pop It, arm	DK-S 54	1.9 (<LOD)	37.4	71	Pregnant women	Dermal	0.5	0.36	60	0.0059
Watch strap	DK-S 201	1.9 (<LOD)	37.4	71	Pregnant women	Dermal	0.5	0.36	60	0.0059
Watch strap	DK-S 202	1.9 (<LOD)	40.8	78	Pregnant women	Dermal	0.5	0.39	60	0.0065
iPad/tablet	NEU-S 81	1.9 (<LOD)	478	908	Children 3 years	Dermal	0.5	4.5	14	0.32
iPad/tablet	EU-S 84	1.9 (<LOD)	513	975	Children 3 years	Dermal	0.5	4.9	14	0.35
iPad/tablet	DK-S 89	1.9 (<LOD)	360	684	Children 3 years	Dermal	0.5	3.4	14	0.24
Teething ring	EU-S 71	3.9** (<LOD)	45	176	Children under 3 years	Oral	52	91	8.9	10
Teething ring	NEU-S 66	1.9 (<LOD)	39.2	74	Children under 3 years	Oral	52	39	8.9	4.4
Teething ring	DK-S 74	3.9** (<LOD)	57.8	225	Children under 3 years	Oral	52	117	8.9	13

* "<LOD" indicates that the migration concentration has been below the detection limit. "<LOQ" indicates that the migration concentration has been below the quantification limit

** Twice the amount of migration liquid has been used, which is why the migration value used is twice as large as for the other products.

Calculation example:

Daily exposure (D4, DK-S 57)$_{\text{children 3 years}}$ = (product area$_{\text{contact}}$ (cm^2) x migration$_{\text{measured}}$ (µg/cm^2) x absorption)/kg bw
= (118.8 cm^2 x 1.9 µg/cm^2 x 0.5%)/14 kg = 0.0081 µg/kg bw/d

TABLE 44. DNELs and DMELs for D4, as well as RCR values for D4 in silicone products. All figures are in internal doses and in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold**.

Product no.	Product type	Target group	Internal dose (µg/kg bw/d)	$DNEL_T$ (µg/kg/d)	$DMEL_T$ (µg/kg/d)	$DNEL_{EAS}$ (µg/kg/d)	$DMEL_{EAS}$ (µg/kg/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
DK-S 57	Pop It	Children 3 years	0.081	Not relevant	Not relevant	36	3.6	-	-	0.0022	0.022	-	-	0.022	0.22
EU-S 53	Pop It	Children 3 years (dermal)	0.61	Not relevant	Not relevant	36	3.6	-	-	0.017	0.17	-	-	0.17	**1.7**
DK-S 56	Pop It (baby)	Children under 3 years (oral)	7.0	Not relevant	Not relevant	36	3.6	-	-	0.19	**1.93**	-	-	**1.93**	**19.33**
DK-S 54	Pop It, arm	Pregnant women	0.0059	Not relevant	Not relevant	36	3.6	-	-	0.00016	0.0016	-	-	0.0016	0.016
DK-S 201	Watch strap	Pregnant women	0.0059	Not relevant	Not relevant	36	3.6	-	-	0.00016	0.0016	-	-	0.0016	0.016
DK-S 202	Watch strap	Pregnant women	0.0065	Not relevant	Not relevant	36	3.6	-	-	0.00018	0.0018	-	-	0.0018	0.018
NEU-S 81	iPad/tablet	Children 3 years	0.32	Not relevant	Not relevant	36	3.6	-	-	0.009	0.09	-	-	0.09	0.90
EU-S 84	iPad/tablet	Children 3 years	0.35	Not relevant	Not relevant	36	3.6	-	-	0.010	0.10	-	-	0.10	0.97

Product no.	Product type	Target group	Internal dose (µg/kg bw/d)	$DNEL_T$ (µg/kg/d)	$DMEL_T$ (µg/kg/d)	$DNEL_{EAS}$ (µg/kg/d)	$DMEL_{EAS}$ (µg/kg/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
DK-S 89	iPad/tablet	Children 3 years	0.24	Not relevant	Not relevant	36	3.6	-	-	0.007	0.07	-	-	0.07	0.68
EU-S 71	Teething ring	Children under 3 years	10.25	Not relevant	Not relevant	36	3.6	-	-	0.28	**2.9**	-	-	**2.9**	**29**
NEU-S 66	Teething ring	Children under 3 years	4.35	Not relevant	Not relevant	36	3.6	-	-	0.12	**1.2**	-	-	**1.2**	**12**
DK-S 74	Teething ring	Children under 3 years	13.17	Not relevant	Not relevant	36	3.6	-	-	0.37	**3.7**	-	-	**3.7**	**37**

"-": No calculation

From the table above, none of the calculations will be used further in the risk assessment as they are based on LOD. Thus, the RCR values relate solely to the analysis setup and not to a real exposure scenario. In cases where the RCR value is above 1, and where the exposure is calculated on the basis of LOQ or LOD, this means that the analysis method has not been sensitive enough to be able to clear the products of risk regarding the concerned substances. In other words, a more sensitive method of analysis will be needed to assess the risk of the products. In the table above, all RCR values calculated using $DNEL_{EAS}$ without MAF are all below 1 and the analysis method has therefore been sufficiently sensitive. It should be noted, however, that these calculations are made as worst case, i.e. the total area has been used for all products and not just the area that children (babies) actually put in their mouths (teething rings) or hold in their hands. Thus, the actual exposure is assessed to be able to be significantly lower.

12.4.4 Summary of risk assessment of migration analyses for selected products

TABLE 45 below summarizes RCR values based on migration measurements> LOD. However, a single measurement is included with a migration measurement <LOD, as this analysis indicated a content of BHT in the migration fluid. These values will be included in the further risk calculations.

TABLE 45. Overview of the risk calculations with migration measurement> LOD. Summary of risk assessment for selected products. DNELs and DMELs for measured focus substances, as well as RCR values for the focus substances in the selected products. All figures are in internal doses and in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold**.

Substance	Product no.	Prod-uct type	Target group	Daily internal dose (µg/kg bw/d)*	$DNEL_T$ (µg/kg/d)	$DMEL_T$ (µg/kg/d)	$DNEL_{EAS}$ (µg/kg/d)	$DMEL_{EAS}$ (µg/kg/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
BPA	DK-T 122	Socks	Children 3 years	0.009 (v. LOQ)	Not relevant	Not relevant	0.24	0.024	-	-	0.036	0.36	-	-	0.36	**3.6**
BPA	NEU-T 116	Socks	Children 3 years	0.0032 (v. LOQ)	Not relevant	Not relevant	0.24	0.024	-	-	0.01	0.1	-	-	0.1	**1.3**
BPA	EU-P 3	Pacifier shield	Children 3 years	0.011 (v. LOQ)	Not relevant	Not relevant	0.24	0.024	-	-	0.057	0.57	-	-	0.57	**5.7**
Propyl-paraben	DK-T 122	Socks	Children 3 years	0.0016 (measurement > LOQ)	Not relevant	Not relevant	20	2	-	-	0.000081	0.00081	-	-	0.00081	0.0081
Propyl-paraben	DK-T 136	Tights	Children under 3 years	0.092 (measurement > LOQ)	Not relevant	Not relevant	20	2	-	-	0.0057	0.057	-	-	0.057	0.57
BHT	DK-P 34	Mobile cover	Pregnant women	0.00021 (v.LOD)	250	25	Not relevant	Not relevant	0.00	0.00	-	-	0.00	0.00	-	-

"-": No calculation. "*" <LOD "indicates that the calculation is based on an assumed/theoretical worst case migration concentration below the detection limit. "<LOQ" indicates that the calculation is based on an assumed/theoretical worst case migration concentration below the quantification limit.

The above RCR values are calculated on worst case assumptions regarding exposure time and area. Therefore, the three calculations that resulted in RCR values above 1 should be refined (all for BPA). It is estimated that the following parameters can be refined in the three relevant calculations:

DK-T 122 and NEU-T 116 (socks, children 3 years): Area of product cannot be refined. The exposure time can be adjusted from worst case 14 hours to a realistic worst case average of 12 hours. The migration measurement for DK-T 122 was equal to 0.0059 µg/cm^2 for 14 hours. This migration can be converted to 12 hours by assuming a constant migration:

Migration (DK-T 122)$_{\text{refined time, 12 hours}}$ = (0.0059 µg/cm^2/14) x12 = 0.0051 µg/cm^2.

EU-P 3 (pacifier shield, children under 3 years): Area of product can be refined from 10.3 cm^2. In addition, the time for exposure can be adjusted from 7.7 hours (worst case)

Area (EU-P 3)$_{\text{refined area}}$ = 5 cm^2 (the product is not a “typical” pacifier shield, but a pacifier shield with less contact than a typical pacifier shields)

Time (EU-P 3)$_{\text{refined time}}$ = 3.6 hours (high average - see chapter 5.5)

Using the above refinement, the following RCR values are obtained:

TABLE 46. Refined use scenarios for individual products with RCR> 1. DNELs and DMELs for measured focus substances, as well as RCR values for the focus substances in the selected products. All figures are in internal doses and in µg/kg bw/d (from Chapter 9). RCR values> 1 are marked in **bold**.

Sub-stance	Product no.	Product type	Target group	Daily internal dose (µg/kg bw/d)*	$DNEL_T$ (µg/kg/d)	$DMEL_T$ (µg/kg/d)	$DNEL_{EAS}$ (µg/kg/d)	$DMEL_{EAS}$ (µg/kg/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
BPA	DK-T 122	Socks	Children 3 years	0.0073 (v. LOQ)	Not relevant	Not relevant	0.24	0.024	-	-	0.031	0.31	-	-	0.31	**3.1**
BPA	NEU-T 116	Socks	Children 3 years	0.0027 (v. LOQ)	Not relevant	Not relevant	0.24	0.024	-	-	0.011	0.11	-	-	0.11	**1.1**
BPA	EU-P 3	Pacifier shield	Children under 3 years	0.067 (v. LOQ)	Not relevant	Not relevant	0.24	0.024	-	-	0.028	0.28	-	-	0.28	**2.8**

"-": No calculation

A refinement of the use scenarios from worst case to realistic worst case average has resulted in slightly lower RCR values, but all three calculations are still larger than 1 and thus indicate a risk of endocrine disrupting effects in established exposure scenarios using the DMEL approach with the use of MAF. It should be noted, however, that the exposure used here is calculated on the basis of the quantification limit. Thus, it cannot really be assessed whether the product poses a risk or not.

12.5 RCR for selected sources of exposure (food, FCM and medicinal products)

In the three tables below, RCR values are given for the selected sources of exposure, food, FCM and medicinal products, for each of the six focus substances (calculated on the basis of exposure data from Chapter 10).

Overview of the calculations and tables:

- RCR values for the individual focus substance from the individual exposure source
  - Foods - TABLE 47
  - Food contact material (FCM) - TABLE 48
  - Medicinal products - TABLE 49

- RCR values for the total exposure from all three sources of exposure to focus substances with the same mode of action -TABLE 50.
  - The six focus substances are added according to their mode of action.
  - Sources of exposure - EAS mode of action includes D4, BHA, BPA, butylparaben and propylparaben.
  - Sources of exposure - T mode of action includes BHA and BHT.

The risk assessment includes contributions from several similar acting substances. Therefore, the RCR values in the tables below are intended for an average exposure and not a worst case, as a worst case consideration for all substances at once is not considered realistic. Furthermore, a worst case consideration for one substance from several sources of exposure is not considered realistic. In the RCR calculations, however, data for worst case exposure have been used when other data have not been available (an overview of the data used for the exposure sources can be found in Chapter 10).

This shows the risk of endocrine disrupting effects for the individual exposure sources food, FCM and medicinal products. It thus evident whether the sum of exposure from several substances with a similar acting effect from the three sources can lead to endocrine disrupting effects.

RCR values> 1 indicate a risk and are marked in **bold**.

TABLE 47. RCR for the six focus substances with food as source of exposure. Data on exposure from food are given in Chapter 10. Exposure contributions and DNELs/DMELs are given as internal doses. RCR values> 1 indicate a risk and are marked in **bold**.

Food	$DNEL_T$ (µg/kg bw/d)	$DMEL_T$ (µg/kg bw/d)	$DNEL_{EAS}$ (µg/kg bw/d)	$DMEL_{EAS}$ (µg/kg bw/d)	Target group	Exposure (µg/kg bw/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
BHA*	1000	100	100	10	Pregnant woman	30	0.03	0.3	0.3	**3**	0.3	**3**	**3**	**30**
					Child	40	0.04	0.4	0.4	**4**	0.4	**4**	**4**	**40**
BHT**	250	25	Not relevant	Not relevant	Pregnant woman	2.5	0.01	0.1	-	-	0.1	1	-	-
					Child	10	0.04	0.4	-	-	0.4	**4**	-	-
Butyl paraben	Not relevant	Not relevant	20	2	Pregnant woman	Not allowed	-	-	-	-	-	-	-	-
					Child		-	-	-	-	-	-	-	-
Propyl paraben	Not relevant	Not relevant	20	2	Pregnant woman	No data	-	-	-	-	-	-	-	-
					Child	No data	-	-	-	-	-	-	-	-
D4	Not relevant	Not relevant	36	3.6	Pregnant woman	No data	-	-	-	-	-	-	-	-
					Child	No data	-	-	-	-	-	-	-	-
BPA*** (incl. FCM)	Not relevant	Not relevant	0.24	0.024	Pregnant woman	0.159	-	-	0.7	**6.6**	-	-	**6.6**	**66**
					Child	0.375	-	-	**1.6**	**16**	-	-	**16**	**156**

"-": No calculation. FCM: food contact materials.

* Food (adult) - exposure 0.03 mg/kg bw/d (oral) corresponding to 30 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion); Food (child ≥ 3) - exposure 0.04 mg/kg bw/d (oral) corresponding to 40 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion) - Data from EFSA 2021b

Food	$DNEL_T$ (µg/kg bw/d)	$DMEL_T$ (µg/kg bw/d)	$DNEL_{EAS}$ (µg/kg bw/d)	$DMEL_{EAS}$ (µg/kg bw/d)	Target group	Exposure (µg/kg bw/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
** Food (adult) - exposure 2.5 µg/kg bw/d internal dose (assumes 100% uptake by oral intake) - Data from Husøy et al. (2019) (average estimate). Food, child - exposure 10/g/kg bw/d - Data from EFSA 2012b. *** Includes both food and FCM. Food (adult) - exposure 0.159 ng/kg bw/d internal dose corresponding to 0.159 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion); Food (child) - exposure 0.375 µg/kg bw/d internal dose (assumes 100% uptake by oral intake) - Data from EFSA 2015 (average data).														

In the table above, exposure to BHA, BHT and BPA is indicated for food, the latter being a total value for food and FCM. In the present project, no data have been identified for propylparaben and D4, and butylparaben is not permitted in foods.

The calculations for BHA and $BHT_{children}$ are based on data that reflect regulation (highest permitted concentrations) and are thus not based on measurements that reflect a current exposure (see more about this in Chapter 10). The use of exposure data for BHA and $BHT_{children}$ from food is thus subject to a great deal of uncertainty (Bredsdorff et al. 2020).

The RCR values for BHA exposure from food do not indicate a risk when using DNEL without MAF for either the T or EAS mode of action. For the EAS mode of action, however, the exposure from food results in relatively high RCR values above 1 when using MAF. However, it should be noted when reading the RCR values that the data for the BHA exposure from food reflect a theoretical exposure determined on the basis of the highest permitted content (Chapter 10). Despite a great deal of uncertainty, the exposure from food to $BHT_{children}$ does not entail a risk when using $DNEL_{without\ MAF}$, only when using DMEL and MAF.

Exposure data are based on content of both BHT and BPA. However, the BPA contributions via food and FCM are at least 6 years old (from EFSA 2015). There may be uncertainty about the data for BPA, but data are still considered relevant. For BPA, it is worth noting that food exposure to BPA poses a risk to children when using DNELs without MAF. In other words, exposure to BPA via food and FCM alone can be a risk.

The BHT contributions via food are from a recent reference and are considered very relevant.

TABLE 48. RCR for the six focus substances with FCM as source of exposure. Data for the exposure from FCM are given in Chapter 10. Exposure contributions and DNELs/DMELs are given as internal doses.

FCM	$DNEL_T$ (µg/kg bw/d)	$DMEL_T$ (µg/kg bw/d)	$DNEL_{EAS}$ (µg/kg bw/d)	$DMEL_{EAS}$ (µg/kg bw/d)	Target group	Exposure (µg/kg bw/d)	RCR $DNEL_T$	RCR $DMEL_T$	RCR $DNEL_{EAS}$	RCR $DMEL_{EAS}$	RCR w. MAF $DNEL_T$	RCR w. MAF $DMEL_T$	RCR w. MAF $DNEL_{EAS}$	RCR w. MAF $DMEL_{EAS}$
BHA	1000	100	100	10	Pregnant woman	Data not used *	-	-	-	-	-	-	-	-
					Child	Data not used *	-	-	-	-	-	-	-	-
BHT**	250	25	Not relevant	Not relevant	Pregnant woman	50	0.2	**2**	-	-	**2**	**20**	-	-
					Child	200	0.8	**8**	-	-	**8**	**80**	-	-
Butyl-paraben	Not relevant	Not relevant	20	2	Pregnant woman	Not allowed	-	-	-	-	-	-	-	-
					Child		-	-	-	-	-	-	-	-
Propylparaben	Not relevant	Not relevant	20	2	Pregnant woman	No data	-	-	-	-	-	-	-	-
					Child	No data	-	-	-	-	-	-	-	-
D4	Not relevant	Not relevant	36	3.6	Pregnant woman	No data	-	-	-	-	-	-	-	-
					Child	No data	-	-	-	-	-	-	-	-
BPA	Not relevant	Not relevant	0.24	0.024	Pregnant woman	0.159	Exposure to BPA via FCM is included in the contributions from foods (see TABLE 47)							
					Child	0.375								

"-": No calculation

* Bredsdorff et al. (2020) assess that migration of BHA and BHT from FCM determined by EFSA (2012a) is unrealistic and too conservative/too cautious. Therefore, no data are available that reflect a realistic exposure to BHA via FCM.
** FCM (adult) - exposure 0.05 mg/kg bw/d (oral) corresponding to 50 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion); Food (child) - exposure 0.2 mg/kg bw/d (oral) corresponding to 200 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion) - Data from EFSA 2012b. Must be considered as worst case exposure.
*** Food (adult) - exposure 159 ng/kg bw/d internal dose corresponding to 0.159 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion); Food (child) - exposure 0.375 µg/kg bw/d internal dose (assumes 100% uptake by oral intake) – data from EFSA 2015 (mean data);

The table above lists risk calculations for exposure to BHT and BPA. In the present project, there has been no data for propylparaben and D4, and butylparaben is not allowed in FCM. The exposure to BPA from FCM is included in the food estimate and is thereby included in the risk calculation. The calculations for BHT are based on data that reflect regulation (maximum permissible concentration) and are thus not based on measurements that reflect a realistic exposure. The use of BHT exposure in food can thus be subject to great uncertainty.

TABLE 49. RCR for the six focus substances with medicinal products as source of exposure. Data for exposure from medicinal products are given in Chapter 10. Exposure contributions and DNELs/DMELs are given in µg/kg/d (internal dose).

Medicinal products	**$DNEL_T$** (µg/kg bw/d)	**$DMEL_T$** (µg/kg bw/d)	**$DNEL_{EAS}$** (µg/kg bw/d)	**$DMEL_{EAS}$** (µg/kg bw/d)	**Target group**	**Exposure** (µg/kg bw/d)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BHA*	1000	100	100	10	Pregnant woman	17	0.02	0.17	0.17	**1.7**	0.17	**1.7**	**1.7**	**17**
					Child	0.0003	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
BHT**	250	25	Not relevant	Not relevant	Pregnant woman	40	0.16	**1.6**	**-**	**-**	**1.6**	**16**	-	-
					Child	0.0003	0.00	0.00	-	-	0.00	0.00	-	-
Butyl-paraben	Not relevant	Not relevant	20	2	Pregnant woman	Not used	-	-	-	-	-	-	-	-
					Child		-	-	-	-	-	-	-	-
Propyl-	Not relevant	Not relevant	20	2	Pregnant woman	130	-	-	**6.5**	**65**	-	-	**65**	**650**

Medicinal products	**$DNEL_T$** (µg/kg bw/d)	**$DMEL_T$** (µg/kg bw/d)	**$DNEL_{EAS}$** (µg/kg bw/d)	**$DMEL_{EAS}$** (µg/kg bw/d)	**Target group**	**Exposure** (µg/kg bw/d)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
paraben***			20	2	Child	140	-	-	**7**	**70**	-	-	**70**	**700**
D4	Not relevant	Not relevant	36	3.6	Pregnant woman	Not used	-	-	-	-	-	-	-	-
					Child		-	-	-	-	-	-	-	-
BPA	Not assessed	Not assessed	0.24	0.024	Pregnant woman	Not used	-	-	-	-	-	-	-	-
					Child		-	-	-	-	-	-	-	-

"-": No calculation
* Determined on the basis of generic exposure estimates - adult exposure: 0.017mg/kg bw/d (oral) corresponding to 17 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion). Exposure to children was an estimated worst case exposure to BHA via medicinal products estimated at 0.07 mg/kg bw/d dermal. With a dermal absorption of 0.4%, this corresponds to 0.0003 mg/kg bw/d.
** Determined on the basis of generic exposure estimates - adult exposure: 0.04 mg/kg bw/d (oral) corresponding to 40 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion). Dermal exposure of child 0.07 mg/kg bw/d corresponds to 0.0003 mg/kg bw/d (dermal absorption equals 0.4%).
*** For example in medicine for acid reflux (adults) - exposure 0.13 mg/kg bw/d (oral) corresponding to 130 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion); medicinal product against acid regurgitation (child) - exposure 0.14 mg/kg bw/d (oral) corresponding to 140 µg/kg bw/d internal dose (assumes 100% uptake by oral ingestion). Values for adults are used to calculate RCR values.

The exposure estimates from medicinal products for BHA, BHT and propylparaben are calculated in Chapter 10. Butylparaben, D4 and BPA are not used in medicinal products. The exposure calculations are based on typical content concentrations stated by the Danish Medicines Agency. It is assessed that the target groups included in this report (pregnant women/unborn children, children 3 years of age and children under 3 years of age) cannot be expected to take medication on a daily basis. Therefore, exposure data of the three relevant focus substances must be considered to be based on a worst case assumption for medicinal products - which is considered to be realistic.

In the table above, the exposure of propylparaben gives a very high RCR value for both pregnant women and children. In all calculation methods this indicates a risk, i.e. that exposure to propylparaben from medicinal products alone may represent a risk.

The table below summarizes the exposure estimates of the six focus substances for the three selected sources of exposure, food, FCM and medicinal products. MAF is not included in the risk calculations for the total exposure of focus substances with the same mode of action from the three sources, as MAF deals with exposure to other similar acting substances and should only be used in the calculations for individual substances.

TABLE 50. Total RCR values for exposure ($RCR_{exposure\ sources,\ tot}$) from food, food contact materials (FCM) and medicinal products for single acting mode of action with and without the use of MAF.

		$RCR_{exposure\ source}$ $DNEL_T$	$RCR_{exposure\ source}$ $DMEL_T$	$RCR_{exposure\ source}$ $DNEL_{EAS}$	$RCR_{exposure\ source}$ $DMEL_{EAS}$	$RCR_{exposure\ source}$ **w. MAF** $DNEL_T$	$RCR_{exposure\ source}$ **w. MAF.** $DMEL_T$	$RCR_{exposure\ source}$ **w. MAF** $DNEL_{EAS}$	$RCR_{exposure\ source}$ **w. MAF** $DMEL_{EAS}$
BHA	Pregnant	0.05	0.47	0.47	4.7	0.47	**4.7**	**4.7**	**47**
	Child	0.04	0.4	0.4	**4.0**	0.40	**4.0**	**4.0**	**40**
BHT	Pregnant	0.37	**3.7**	-	-	**3.7**	**37**	-	-
	Child	0.84	**8.4**	-	-	**8.4**	**84**	-	-
Butyl-paraben	Pregnant	-	-	-	-	-	-	-	-
	Child	-	-	-	-	-	-	-	-
Propyl-paraben	Pregnant	-	-	**6.5**	**65**	-	-	**65**	**650**
	Child	-	-	**7.0**	**70**	-	-	**70**	**700**
D4	Pregnant	-	-	-	-	-	-	-	-
	Child	-	-	-	-	-	-	-	-
BPA	Pregnant	-	-	0.66	**6.6**	-	-	**6.6**	**66**
	Child	-	-	**1.6**	**16**	-	-	**16**	**156**
Added up	Pregnant	0.42	4.2	**7.6**	**76**	-	-	-	-
	Child	0.88	**8.8**	**9.0**	**90**	-	-	-	-

"-": No calculation

12.6 RCR for products and sources of exposure

The table below summarizes the exposure estimates of the six focus substances for the three selected sources of exposure, food, FCM and medicinal products. MAF is not included in the risk calculations for the total exposure of focus substances with the same mode of action from the three sources, as MAF deals with exposure to other similar acting substances and should only be used in the calculations for individual substances.

The total RCR values for exposure from food, FCM and medicinal products, as described in TABLE 50, are used in the following tables.

For each product, RCR values have been calculated, which add up analysis results for focus substances with the same mode of action with the total exposure contribution from the selected exposure sources, as well as RCR values for single substances with MAF added up with the exposure source contribution for the specific substance.

To calculate RCR values without MAF, the following formula has been used to include the selected sources of exposure in the risk assessment:

RCR (substance A) =

(product exposure (substance A)/DN(M)EL (substance A) +
(exposure from sources of exposure (substance A)/DN(M)EL (substance A)) +
(sum of RCR values for selected sources of exposure to other focus substances with the same mode of action calculated with DN(M)EL values for these substances).

For RCR values with MAF, the following formula is used:

RCR (substance A) =

(product exposure (substance A)/DN(M)EL (substance A)$_{w.\ MAF}$) +
(exposure from exposure sources (substance A)/DN(M)EL (substance A)$_{w.\ MAF}$)

As the content of several similar acting focus substances has been found in several of the cosmetic products, RCR values have been added up for these products. For each product, RCR values have been calculated, which add up analysis results for focus substances with the same behaviour with the total exposure contribution from the selected exposure sources.

12.6.1 RCR for cosmetic products - single substance (highest concentrations)

The following tables list RCR values for sunscreen, body lotion, aftersun and body oil for an adult and sunscreen for a child for the highest measured concentrations of propylparaben, butylparaben, BHA and BHT in specific products added up with the RCR values for the exposure sources (foods, FCM and medicinal products) with and without the use of MAF regarding similar acting mode of action. As no exposure has been identified for butylparaben, RCR values for butylparaben are not included in the tables below.

For D4, no further calculations have been made as exposure from food, FCM and medicinal products have not been identified (see Chapter 10 Exposure Assessment). The calculated RCR values for D4 from other consumer products did not give rise to RCR values> 1, based on the specific measured values.

By using the highest measured concentrations for the focus substances in the cosmetic products, the highest possible RCR value is obtained for the individual product types.

Calculations are divided so that they are calculated with DNEL or DMEL with and without MAF, respectively. As an example of the approach, the calculations for propylparaben in product EU-K 195 (sunscreen, adult) are specified below in the table. Corresponding calculations are used in the following tables.

A total value is not calculated for the three selected sources of exposure when using MAF, as MAF includes contributions from substances with the same mode of action in other products.

TABLE 51. Risk assessment of sunscreen (pregnant women) regarding the highest content of propylparaben with total contribution from the three sources of exposure (food, FCM and medicinal products) and specific exposure contribution from the three sources of exposure (propylparaben with and without the use of MAF).

Sunscreen Adult (EU-K 195)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben highest conc.	-	-	0.95	9.5	-	-	**9.5**	**95**
Propylparaben exposure sources	-	-			-	-	**65**	**650**
EAS exposure sources	-	-	**7.6**	**76**	-	-	-	-
$RCR_{high\ conc.}$ + RCR_{EAS}	-	-	**8.6**	**86**	-	-	-	-
$RCR_{high\ conc.}$ + $RCR_{propylparaben,\ exposure\ sources}$	-	-	-	-	-	-	**75**	**745**

"-": No calculation.

Propylparaben:

Risk assessment with DNELs and DMELs without the use of MAF:

$RCR_{DNEL\ (propylparaben)}$

= product exposure (substance A)/DNEL (substance A)) + (estimated contribution from selected sources of exposure from other sources (substance A)/DNEL (substance A)) + (sum of RCR values for sources of exposure for other focus substances with the same mode of action calculated by DNELs for these substances)

= RCR (DNEL, product exposure) + RCR (DNEL, estimated exposure from similar acting focus substances including propylparaben (EAS))

Propylparaben highest concentration ($DNEL_{EAS}$) + EAS exposure sources ($DNEL_{EAS}$)

= 0.95 + 7.6 = **8.6**

$RCR_{DMEL\ (propylparaben)}$

= product exposure (substance A)/DMEL (substance A)) + (estimated contribution from selected sources of exposure from other sources (substance A)/DMEL (substance A)) + (sum of RCR values for estimated contribution from selected sources of exposure for other focus substances with the same mode of action calculated with DMEL for these substances)

= RCR (DMEL, product exposure) + RCR (DMEL, estimated contribution from selected exposure sources from similar acting focus substances including propylparaben (EAS))

= Propylparaben highest concentration ($DMEL_{EAS}$) + EAS exposure sources ($DMEL_{EAS}$)

= 9.5 + 76 = **86**

Risk assessment with DNELs and DMELs using MAF:

$RCR_{DNEL\ (propylparaben)}$

= product exposure (substance A)/DNEL (substance A)) + estimated contribution from selected sources of exposure from other sources (substance A)/DNEL (substance a)

= RCR (DNEL, product exposure, substance A) + RCR (substance A estimated contribution from selected exposure sources)

= RCR (DNEL, product exposure, Propylparaben) + RCR (Propylparaben, estimated contribution from selected sources of exposure)

Propylparaben highest concentration ($DNEL_{EAS}$ with MAF) + Propylparaben exposure sources ($DNEL_{EAS}$ w. MAF)

= 9.5 + 65 = **75**

$RCR_{DMEL\ (propylparaben)}$

= product exposure (substance A)/DMEL (substance A)) + estimated contribution from selected sources of exposure from other sources (substance A)/DMEL (substance a)

= RCR (DMEL, product exposure, substance A) + RCR (substance A estimated contribution from selected sources of exposure)

= RCR (DMEL, product exposure, Propylparaben + RCR (Propylparaben, estimated contribution from selected sources of exposure)

Propylparaben highest concentration ($DMEL_{EAS}$) + Propylparaben exposure sources ($DMEL_{EAS}$ w. MAF)

= 95 + 650 = **745**

In sunscreen (pregnant women), a risk concerning propylparaben is very close to be identified in the threshold-based approach (RCR = 0.95). For the threshold value approach with MAF and for the DMEL approach without threshold with and without MAF, a risk of content in the

product has been identified. However, the selected sources of exposure (food, FCM and medicinal products) are seen to pose a significantly higher risk than the product itself.

TABLE 52. Risk assessment of sunscreen (pregnant women) regarding the highest content of BHA with total estimated contribution from selected exposure sources and specific exposure source contribution (BHA) with and without the use of MAF.

Sunscreen Adult (EU-K 196)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
$BHA_{exposure\ sources}$	0.0001	0.001	0.001	0.01	0.001	0.01	0.01	0.1
BHA exposure sources	-	-	-	-	0.47	**4.7**	**4.7**	**47**
EAS or T exposure sources	0.4	**4.2**	**7.6**	**76**	-	-	-	-
$RCR_{high\ conc.}$ + RCR_{EAS} or RCR_T	0.4	**4.2**	**7.6**	**76**	-	-	-	-
$RCR_{high\ conc.}$ + $RCR_{BHA,\ exposure\ sources}$	-	-	-	-	0.47	**4.7**	**4.7**	**47**

"-": No calculation

<u>BHA</u>
Risk assessment with DNELs and DMELs without the use of MAF:

$RCR_{DNEL\ (BHA)}$ = 0.0001 + 0.4 = 0.4 (T mode of action)
$RCR_{DMEL\ (BHA)}$) = 0.001 + 4.2 = **4.2** (T mode of action)
$RCR_{DNEL\ (BHA)}$ = 0.001 + 7.6 = **7.6** (EAS mode of action)
$RCR_{DMEL\ (BHA)}$ = 0.01 + 76.3 = **76** (EAS mode of action)

Risk assessment with DNELs and DMELs using MAF:

$RCR_{DNEL\ (BHA)}$ = 0.001 + 0.47 = 0.47 (T mode of action)
$RCR_{DMEL\ (BHA)}$ = 0.01 + 4.7 = **4.7** (T mode of action)
$RCR_{DNEL\ (BHA)}$ = 0.01 + 4.7 = **4.7** (EAS mode of action)
$RCR_{DMEL\ (BHA)}$ = 0.1 + 47 = **47** (EAS mode of action)

In sunscreen (pregnant women) with the highest content of BHA, no risk has been identified in a threshold-based approach with and without the use of MAF, including estimated contribution from selected sources of exposure (RCR <1). A risk has been identified in a non-threshold-based approach with and without MAF, where estimated contribution from selected sources of exposure is by far the largest source of the overall risk (RCR> 1).

TABLE 53. Risk assessment of sunscreen (pregnant women) regarding the highest content of BHT with total estimated contribution from selected exposure sources and specific exposure source contribution (BHT) with and without the use of MAF.

Sunscreen Adult (DK-K 198)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BHT highest conc.	0.0004	0.004	-	-	0.004	0.04	-	-

Sunscreen Adult (DK-K 198)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BHT expo-sure sources	-	-	-	-	**3.7**	**37**	-	-
T exposure sources	0.4	**4.2**	-	-	-	-	-	-
$RCR_{high\ conc.} + RCR_T$	0.40	**4.2**	-	--	-	-	-	-
$RCR_{high.conc.} + RCR_{BHT,\ exposure\ sources}$	-	-	-	-	**3.7**	**37**	-	-

"-": No calculation

BHT

Risk assessment with DNELs and DMELs without the use of MAF:

$RCR_{DNEL\ (BHT)} = 0.0004 + 0.4 = 0.4$
$RCR_{DMEL\ (BHT)} = 0.004 + 4.2 = \mathbf{4.2}$

Risk assessment with DNELs and DMELs using MAF:

$RCR_{DNEL\ (BPA)} = 0.004 + 3.7 = \mathbf{3.7}$
$RCR_{DMEL\ (BPA)} = 0.04 + 37 = \mathbf{37}$

In sunscreen (pregnant women) with the highest content of BHT, no risk has been identified in a threshold-based approach (DNEL) and a non-threshold-based approach (DMEL) with and without the use of MAF, including estimated contribution from selected sources of exposure (RCR <1). A risk has been identified in a non-threshold-based approach with and without MAF, where the exposure source contribution is by far the largest source of the overall risk (RCR> 1).

TABLE 54. Risk assessment of body lotion (pregnant women) regarding the highest content of BHT with total estimated contribution from selected exposure sources and specific exposure source contribution (BHT) with and without the use of MAF.

Body lotion Adult (NEU-K 171)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BHT highest conc.	0.0012	0.012	-	-	0.012	0.12	-	-
BHT exposure sources			-	-	**3.7**	**37**	-	-
T exposure sources	0.4	**4**	-	-	-	-	-	-
$RCR_{high.conc.} + RCR_T$	0.40	**4.0**	-	-	-	-	-	-
$RCR_{high.\ conc.} + RCR_{BHT,\ exposure\ sources}$	-	-	-	-	**3.7**	**37**	-	-

"-": No calculation

In body lotions (pregnant women) with the highest content of BHT, no risk has been identified in a threshold-based approach (DNEL) and a non-threshold-based approach (DMEL) with and without the use of MAF, including estimated contribution from selected sources of exposure (RCR <1). A risk has been identified in a non-threshold-based approach with and without MAF, where the exposure source contribution is by far the largest source of the overall risk (RCR> 1).

TABLE 55. Risk assessment of body lotion (pregnant women) regarding the highest content of propylparaben with a total estimated contribution from selected exposure sources and specific exposure source contribution (propylparaben) with and without the use of MAF.

Body lotion Adult (EU-K 183)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben highest conc.	-	-	0.24	**2.4**	-	-	**2.4**	**24**
Propylparaben exposure sources	-	-	-	-	-	-	**65**	**650**
EAS exposure sources	-	-	**7.6**	**76**	-	-	-	-
$RCR_{high.conc.}$ + RCR_{EAS}	-	-	**7.8**	**78**	-	-	-	-
$RCR_{high\ conc.}$ + $RCR_{propylparaben,\ exposure\ sources}$	-	-	-	-	-	-	**67**	**673**

"-": No calculation.

In body lotion (pregnant women) with the highest content of propylparaben, no risk has been identified in a threshold-based approach (DNEL) without the use of MAF (RCR <1), whereas there is a risk with the use of MAF (RCR> 1). A risk has been identified in a non-threshold-based approach with and without MAF, where estimated contribution from selected sources of exposure is by far the largest source of the overall risk (RCR> 1).

TABLE 56. Risk assessment of body oil (pregnant women) regarding the highest content of propylparaben with a total estimated contribution from selected exposure sources and specific exposure source contribution (Propylparaben) with and without the use of MAF.

Body oil Adult (NEU-K 181)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben highest conc.	-	-	0.24	**2.4**	-	-	**2.4**	**24**
Propylparaben exposure source contribution	-	-			-	-	**65**	**650**
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-
$RCR_{high\ conc.}$ + RCR_{EAS}	-	-	**7.8**	**78**	-	-	-	-

Body oil Adult (NEU-K 181)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
$RCR_{high\ conc.}$ + $RCR_{propylparaben,\ exposure\ source\ contribution}$	-	-	-	-	-	-	**67**	**674**

"-": No calculation. PrP: propylparaben

In body oil (pregnant women) with the highest propylparaben content, a risk has not been identified in a threshold-based approach (DNEL) without the use of MAF (RCR <1), whereas there is a risk with the use of MAF (RCR> 1). A risk has been identified in a non-threshold-based approach with and without MAF, where estimated contribution from selected sources of exposure is by far the largest source of the overall risk (RCR> 1), which overall provides a significant risk.

TABLE 57. Risk assessment of body oil (pregnant women) regarding the highest content of BHT with total estimated contribution from selected exposure sources and specific exposure source contribution (BHT) with and without the use of MAF.

Body oil Adult (NEU-K 181)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BHT highest conc.	0.0005	0.005	-	-	0.005	0.05	-	-
BHT exposure sources			-	-	**3.7**	**37**	-	-
T exposure sources	0.4	**4.2**	-	-	**-**	**-**	**-**	**-**
$RCR_{high\ conc.}$ + RCR_T	0.40	**4.2**	-	-	**-**	**-**	**-**	**-**
$RCR_{high\ conc.}$ + $RCR_{BHT,\ exposure\ source\ contribution}$	-	-	-	-	**3.7**	**37**	-	-

"-": No calculation

In body oil (pregnant women) with the highest content of BHT, no risk has been identified in a threshold-based approach (DNEL) and a non-threshold-based approach (DMEL) with and without the use of MAF (RCR <1). When adding an estimated contribution from selected exposure sources, a risk has been identified (RCR> 1), but not regarding DNEL without the use of MAF. The estimated contribution from selected sources of exposure is generally by far the largest source of the overall risk (RCR> 1).

TABLE 58. Risk assessment of aftersun (pregnant women) regarding the highest content of propylparaben with a total estimated contribution from selected exposure sources and specific exposure source contribution (propylparaben) with and without the use of MAF.

Aftersun Adult (NEU-K 192)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben highest conc.	-	-	0.36	**3.6**	-	-	**3.6**	**36**

Aftersun Adult (NEU-K 192)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben exposure sources	-	-			-	-	**65**	**650**
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-
$RCR_{high\ conc.}$ + RCR_{EAS}	-	-	**8.0**	**80**	-	-	-	-
$RCR_{high\ conc.}$ + $RCR_{propylparaben,\ exposure\ source\ contribution}$	-	-	-	-	-	-	**69**	**686**

"-": No calculation.

In aftersun (pregnant women) with the highest propylparaben content, no risk has been identified in a threshold-based approach (DNEL), without the use of MAF (RCR <1). For a non-threshold-based approach (DMEL) with and without the use of MAF, a risk has been identified (RCR <1). Contributions from the selected sources of exposure are generally by far the largest source of the overall risk (RCR> 1).

TABLE 59. Risk assessment of sunscreen (child) regarding the highest content of BHT with total estimated contribution from selected exposure sources and specific exposure source contribution (BHT) with and without the use of MAF.

Sunscreen Child (NEU-K 193)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BHT highest conc.	0.00	0.04	-	-	0.04	0.36	-	-
BHT exposure source contribution			-	-	**8.4**	**84**	-	-
T exposure source contribution	0.88	**8.8**	-	-	-	-	-	-
$RCR_{high\ conc.}$ + RCR_T	0.88	**8.8**	-	-	-	-	-	-
$RCR_{high\ conc.}$ + $RCR_{BHT,\ exposure\ source\ contribution}$	-	-	-	-	**8.4**	**84**	-	-

"-": No calculation

In sunscreen (child) with the highest content of BHT, no risk has been identified with a threshold-based approach (DNEL) and a non-threshold-based approach (DMEL), with and without the use of MAF (RCR <1). When adding estimated contributions from selected exposure sources, a significant risk has been identified (RCR> 1). The exposure source contribution from the selected sources is generally by far the largest source of the overall risk (RCR> 1).

TABLE 60. Risk assessment of sunscreen (child) regarding the highest content of propylparaben with total estimated contribution from selected exposure sources and specific exposure source contribution (propylparaben) with and without the use of MAF.

Sunscreen Child (NEU-K 193)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben highest conc.	-	-	**1.5**	**15**	-	-	**15**	**151**
Propylparaben exposure source contribution	-	-			-	-	**70**	**700**
EAS exposure source contribution	-	-	**9.0**	**90**	-	-	-	-
$RCR_{high\ conc.}$ + RCR_{EAS}	-	-	**11**	**105**	-	-	-	-
$RCR_{high\ conc.}$ + $RCR_{propylparaben,\ exposure\ source\ contribution}$	-	-	-	-	-	-	**85**	**851**

"-": No calculation.

In sunscreen (child) with the highest propylparaben content, a risk has been identified with a threshold-based approach (DNEL) and a non-threshold-based approach (DMEL) with and without the use of MAF (RCR> 1). By adding estimated contributions from selected exposure sources, a significant risk has been identified (RCR> 1). The exposure source contribution from the selected sources is generally by far the largest source of the overall risk.

Summary

In relation to the calculated RCR values with and without MAF based on a threshold (DNEL) or non-threshold (DMEL) value-based approach, the following summary table can be generated based on the highest measured concentrations for the focus substances across the individual cosmetic product groups:

TABLE 61. RCR values with and without MAF for cosmetic products (highest concentration measured). RCR values above 1 are indicated in **bold**.

Product	Target group	Sub-stance	Exposure source	RCR_{DNEL} without MAF	RCR_{D-MEL} without MAF	RCR_{DNEL} w. MAF	RCR_{DMEL} w. MAF
Sunscreen (EU-K 195)	Pregnant woman	Propyl-para-ben (EAS)	product	0.95	**9.5**	**9.5**	**95**
			Product + expo-sure sources.	**8.5**	**85**	**74**	**745**
Sunscreen (EU-K 196)	Pregnant woman	BHA (T)	product	0.00	0.00	0.00	0.01
			Product + expo-sure sources.	0.4	**4.2**	0.47	**4.7**
		BHA (EAS)	product	0.00	0.01	0.01	0.1
			Product + expo-sure sources.	**7.7**	**76**	**4.7**	**47**
Sunscreen (DK-K 198)	Pregnant woman	BHT (T)	product	0.0004	0.004	0.004	0.04
			Product + expo-sure sources	0.4	**4.2**	**3.7**	**37**
Body oil (NEU-K 181)	Pregnant woman	Propyl-para-ben (EAS)	product	0.24	**2.4**	**2.4**	**3.5**
			Product + expo-sure sources.	**7.8**	**78**	**67**	**653**
Body oil (NEU-K 181)	Pregnant woman	BHT (T)	product	0.001	0.01	0.01	0.1
			Product + expo-sure sources.	0.4	**4.2**	**3.7**	**37**
Body lotion (NEU-K 171)	Pregnant woman	BHT (T)	product	0.00	0.01	0.01	0.05
			Product + expo-sure sources.	0.4	**4.2**	**3.7**	**37**
Body lotion (EU-K 183)	Pregnant woman	Propyl-para-ben (EAS)	product	0.24	**2.4**	**2.4**	**3.5**
			Product + expo-sure sources.	**7.8**	**78**	**67**	**654**
Aftersun (NEU-K 192)	Pregnant woman	Propyl-para-ben (EAS)	Product	0.36	**3.6**	**3.6**	**36**
			Product + expo-sure sources.	**7.4**	**80**	**69**	**686**
Sunscreen (NEU-K 193)	Child	BHT (T)	product	0.00	0.04	0.04	0.36
			Product + expo-sure sources.	0.90	**8.8**	**8.4**	**84**
Sunscreen (NEU-K 193)	Child	Propyl-para-ben (EAS)	Product	**1.5**	**15**	**15**	**151**
			Product + expo-sure sources.	**11**	**105**	**85**	**851**

Based on the above summary table, an overall risk (RCR> 1) has been identified for all scenarios when including RCR contributions from selected exposure sources, both with and without the use of MAF.

For RCR values based on a DNEL approach without MAF, a risk has been identified in sunscreen for children under 3 years regarding the content of propylparaben (RCR> 1). For pregnant women, there is a very close risk (RCR = 0.95). For other cosmetic products, no risk (RCR> 1) is indicated for a DNEL approach without MAF.

In the calculations, it is clear that contributions from selected exposure sources dominate the overall RCR value and that the value is driven by data from the exposure sources.

12.6.2 RCR for cosmetic products with several focus substances with the same mode of action

For the cosmetic products where several focus substances have been found with the same mode of action, contributions have been added for the individual substances in connection with the overall risk assessment. This is primarily in selected body lotions for pregnant women where concentrations of propylparaben and butylparaben have been measured (product numbers: EU-K 183; EU-K 182; NEU-K 172; NEU-K 180), both of which have an EAS based mode of action. In addition, BHA and propylparaben have been found in sunscreen for pregnant women (product number: EU-K 196), both of which have an EAS based mode of action.

In sunscreen for children under 3 years of age, content of propylparaben (0.17%) and BHT (0.047%) were found with an EAS and a T based mode of action (product number NEU-K 193), respectively. Therefore, total RCR values have not been calculated for this product as the different modes of action are not considered to be additive. The same applies to body oil for pregnant women (product number NEU-K 181) where propylparaben (0.098%) and BHT (0.023%) were found.

In the following tables, total RCR values have been calculated for the specific cosmetic products where the content of two focus substances with the same mode of action has been found, in this case the EAS mode of action. The individual RCR values for each focus substance are calculated as previously described on the basis of the exposure calculations (internal dose) as well as the relevant DNEL and DMEL values for specific modes of action.

TABLE 62. Risk assessment of body lotion (pregnant women) (product number EU-K 183) regarding the highest content of propylparaben (0.099%) and content of butylparaben (0.025%) with total estimated contribution from selected exposure sources and specifically the source of exposure.

Body lotion Adult (EU-K 183)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben (0.099%).	-	-	0.24	**2.4**	-	-	**2.4**	**24**
Propylparaben exposure source contribution	-	-	-	-	-	-	**65**	**650**
Butylparaben (0.025%)	-	-	0.061	0.61	-	-	**0.61**	**6.1**
Butylparaben exposure source contribution	-	-	-	-	-	-	-	-

Body lotion Adult (EU-K 183)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-
$RCR_{high.conc.\ propylparaben}$ + $RCR_{conc\ butylparaben}$ + RCR_{EAS}	-	-	**7.9**	**79**	-	-	-	-
$RCR_{high.conc\ propylparaben}$ + $RCR_{conc\ butylparaben}$ + RCR propylparaben, exposure source contribution	-	-	-	-	-	-	**68**	**677**

"-": No calculation.

In body lotion (adult) containing both propylparaben and butylparaben (EU-K 183), for the highest propylparaben content no risk has been identified with a threshold-based approach (DNEL), while with a non-threshold-based approach (DMEL), using MAF (RCR> 1). For butylparaben, a risk has only been identified by a non-threshold approach (DMEL) using MAF. When adding estimated contributions from selected sources of exposure, a significant risk has been identified (RCR> 1). The exposure source contribution is generally by far the largest cause of the overall risk. Overall, in this body lotion product (adult) an overall risk has been identified with regard to the content of focus substances (propylparaben and butylparaben) with the same mode of action (EAS) with contributions from the selected sources of exposure. Without contributions from the selected sources of exposure, no risk has been identified in a threshold-based approach (DNEL) when adding RCR contributions for the two focus substances.

TABLE 63. Risk assessment of body lotion (pregnant women) (product number EU-K 182) regarding propylparaben content (0.095%) and butylparaben content (0.021%) with total contribution from the selected exposure sources and specific exposure source contribution (propylparaben), with and without use of MAF.

Body lotion Adult (EU-K 182)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben (0.095%)	-	-	0.23	**2.3**	-	-	**2.3**	**23**
Propylparaben exposure source contribution	-	-	-	-	-	-	**65**	**650**
Butylparaben (0.021%)	-	-	0.051	0.51	-	-	0.51	**5.1**
Butylparaben exposure source contribution	-	-	-	-	-	-	-	-

Body lotion Adult (EU-K 182)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-
$RCR_{conc.\ propylparaben}$ + $RCR_{conc\ butylparaben}$ + RCR_{EAS}	-	-	**7.9**	**79**	-	-	-	-
$RCR_{conc\ propylparaben}$ + $RCR_{conc\ butylparaben}$ + RCR-propylparaben, exposure source contribution	-	-	-	-	-	-	**68**	**678**

"-": No calculation.

In body lotions (pregnant women) containing both propylparaben and butylparaben (EU-K 182), no risk of a threshold-based approach (DNEL) has been identified for the content of propylparaben. Using DMEL (non-threshold approach), with and without the use of MAF, a risk has been identified (RCR> 1).

For butylparaben, a risk has only been identified with a non-threshold approach (DMEL) using MAF. When adding contributions from selected sources of exposure, a significant risk has been identified (RCR> 1). The exposure source contribution from the selected sources is generally by far the largest cause of the overall risk. In this body lotion (adult) an overall risk has been identified with regard to the content of focus substances (propylparaben and butylparaben) with the same mode of action (EAS) with contributions from selected sources of exposure. Without exposure source contributions, no risk has been identified for a threshold based approach (DNEL) by adding RCR contributions for the two focus substances.

TABLE 64. Risk assessment of body lotion (pregnant women) (product number NEU-K 172)) regarding content of propylparaben (0.090%) and content of butylparaben (0.036%) with total contribution from selected sources of exposure and specific source of exposure (propylparaben), with and without the use of MAF.

Body lotion Adult (NEU-K 172)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben (0.09%)	-	-	0.22	**2.2**	-	-	**2.2**	**22**
Propylparaben exposure source contribution	-	-	-	-	-	-	**65**	**650**
Butylparaben (0.036%)	-	-	0.087	0.87	-	-	0.87	**8.7**
Butylparaben exposure source contribution	-	-	-	-	-	-	-	-

Body lotion Adult (NEU-K 172)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-
$RCR_{conc.\ propylparaben}$ + $RCR_{conc\ butylparaben}$ + RCR_{EAS}	-	-	**7.9**	**79**	-	-	-	-
$RCR_{conc\ propylparaben}$ + $RCR_{conc\ butylparaben}$ + RCR-propylparaben, exposure source contribution	-	-	-	-	-	-	**68**	**681**

"-": No calculation.

In body lotions (pregnant women) containing both propylparaben and butylparaben (NEU-K 172), no risk has been identified for propylparaben content with a threshold-based approach (DNEL), while a risk has been calculated for a non-threshold-based approach (DMEL) as well as for DNEL and DMEL approaches using MAF (RCR> 1). For butylparaben, a risk has only been identified by a non-threshold approach (DMEL) using MAF. When adding up exposure source contributions, a significant risk has been identified (RCR> 1). The exposure source contribution from the selected sources is generally by far the largest source of the overall risk. Altogether in this body lotion product (adult), an overall risk has been identified regarding the content of focus substances (propylparaben and butylparaben) with the same mode of action (EAS) with contributions from the selected sources of exposure. Without contributions from the selected sources of exposure, no risk has been identified in a threshold-based approach (DNEL) when adding RCR contributions for the 2 focus substances.

TABLE 65. Risk assessment of body lotion (adult) (product number NEU-K 180) with regard to the highest content of butylparaben (0.045%) and content of propylparaben (0.021%) with total contribution from the selected exposure sources and specific exposure source contribution (propylparaben), with and without the use of MAF.

Body lotion Adult (NEU-K 180))	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Butylparaben (0.045%)	-	-	0.11	**1.1**	-	-	**1.1**	**11**
Butylparaben exposure source contribution	-	-	-	-	-	-	-	-
Propylparaben (0.021%)	-	-	0.051	0.51	-	-	0.51	5.1
Propylparaben exposure source contribution	-	-	-	-	-	-	65	650
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-

Body lotion Adult (NEU-K 180))	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
$RCR_{conc.\ butylparaben}$ + $RCR_{conc\ propylparaben}$ + RCR_{EAS}	-	-	**7.8**	**78**	-	-	-	-
$RCR_{high.conc.\ butylparaben}$ $RCR_{conc.\ propylparaben}$ + $RCR_{propylparaben,\ exposure\ source\ contribution}$	-	-	-	-	-	-	**67**	**666**

"-": No calculation.

In body lotion (adult) containing both propylparaben and butylparaben (NEU-K 180), no risk has been identified for the highest content of butylparaben with a threshold-based approach (DNEL). A non-threshold-based approach (DMEL), with and without the use of MAF (RCR> 1), results in RCR values above 1. For propylparaben, only a risk with the use of MAF has been identified. When adding up exposure contributions from the selected sources, a significant risk has been identified (RCR> 1). Contributions from the selected sources of exposure are generally by far the largest source of the overall risk. Altogether in this body lotiotn product (adult), an overall risk has been identified with regard to the content of focus substances (propylparaben and butylparaben) with the same mode of action (EAS) with contributions from the selected sources of exposure. Without contributions from the selected sources of exposure, no risk has been identified in a threshold-based approach (DNEL) when adding RCR contributions for the 2 focus substances.

TABLE 66. Risk assessment of sunscreen (adult) (product number EU-K 196) regarding propylparaben content (0.046%) and BHA content (0.008%) with total contribution from selected exposure sources and specific contribution from the selected exposure sources (propylparabens), with and without the use of MAF.

Sunscreen Adult (EU-K 196)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben (0.046%).	-	-	0.26	**2.6**			**2.6**	**26**
Propylparaben exposure source contribution	-	-	-	-	-	-	**65**	**650**
BHA (0.008%)	-	-	0.001	0.01	-	-	0.01	0.1
BHA exposure source contribution	-	-	0.47	4.7	-	-	4.7	47
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-
$RCR_{conc\ propylparaben}$ + $RCR_{conc\ BHA}$ + RCR_{EAS}	-	-	**8.3**	**83**	-	-	-	-

Sunscreen Adult (EU-K 196)	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
$RCR_{conc\ propylparaben}$ + $RCR_{conc\ BHA}$ + $RCR_{propylparaben,\ exposure\ source\ contribution}$ + $RCR_{BHA,\ exposure\ source\ contribution}$	-	-	-	-	-	-	**72**	**723**

"-": No calculation.

In sunscreen (adult) containing both propylparaben and BHA (EU-K 196), no risk has been identified for propylparaben content with a threshold-based approach (DNEL), while risk has been identified with a non-threshold-based approach (DMEL), with and without the use of MAF (RCR> 1). For BHA, no risk has been identified. When adding up exposure contributions from the selected sources, a significant risk has been identified (RCR> 1). Contributions from the selected sources of exposure are generally by far the largest source of the overall risk. Altogether, in this sunscreen product (adult) an overall risk has been identified with regard to the content of focus substances (propylparaben and butylparaben) with the same mode of action (EAS) with and without exposure source contribution regarding a non-threshold-based approach (DMEL). Without contributions from the selected sources of exposure, no risk has been identified in a threshold-based approach (DNEL) when adding RCR contributions for the 2 focus substances.

Summary

The following table summarizes the total RCR values in body lotion for pregnant women for the specific products (single products) where concentrations of both butylparaben and butylparaben have been measured, as well as in sunscreen for pregnant women containing propylparaben and BHA. Calculations have been made for products with the highest concentration of propylparaben (EU-K 183) plus contribution of butylparaben and for the highest concentration of butylparaben (NEU-K 180) plus contribution of propylparaben. For comparison, the total RCR values for body lotion for pregnant women in similar products containing propylparaben and butylparaben are given (product numbers EU-K 182 and NEU-K 172).

Furthermore, RCR values have been summarized for sunscreen for pregnant women in which both BHA and propylparaben have been found (EU-K 196).

TABLE 67. RCR values with and without MAF for specific cosmetic products containing two focus substances with the same mode of action. RCR values for the two focus substances are added ups. RCR values above 1 are indicated in **bold**.

Product	**Target group**	**Substance**	**Exposure source**	**RCR_{D-NEL}** without MAF	**RCR_{D-MEL}** without MAF	**RCR_{D-NEL}** w MAF	**RCR_{D-MEL}** w MAF
Body lotion (EU-K 183)	Pregnant woman	Propylparaben (EAS) – highest concentration	Product	0.24	**2.4**	**2.6**	**23**
		Butylparaben (EAS) - conc	Product	0.061	0.61	0.61	**6.1**
		Propylparaben + Butylparaben + exposure source contribution (EAS)	Product + exposure source contribution	**7.861**	**78.61**		

Product	Target group	Substance	Exposure source	RCR_{D-NEL} without MAF	RCR_{D-MEL} without MAF	RCR_{D-NEL} w MAF	RCR_{D-MEL} w MAF
		Propylparaben + Butylparaben + Propylparaben exposure source contribution (EAS)	Product + exposure source contribution			**67.1**	**677.1**
Body lotion (NEU-K 180)	Pregnant woman	Butylparaben (EAS) – highest concentration	Product	0.105	**1.05**	**1.05**	**10.5**
		Propylparaben (EAS) - conc	Product	0.0505	0.505	0.505	**5.05**
		Butylparaben + Propylparaben + exposure source contribution (EAS)	Product + exposure source contribution	**7.756**	**77.56**		
		Butylparaben + Propylparaben + Propylparaben exposure source contribution (EAS)	Product + exposure source contribution			**66.56**	**665.6**
Sunscreen (EU-K 196)	Pregnant woman	Propylparaben (EAS) – conc	Product	0.255	**2.55**	**2.55**	**25.5**
		BHA (EAS) - conc	Product	0.001	0.01	0.01	0.1
		Propylparaben + BHA + exposure source contribution (EAS)	Product + exposure source contribution	**8.326**	**83.26**		
		Propylparaben + BHA + Propylparaben exposure source contribution (EAS) + BHA exposure source contribution (EAS)	Product + exposure source contribution			**72.26**	**722.6**
Body lotion (EU-K 182)	Pregnant woman	Propylparaben (EAS) – conc.	Product	0.23	**2.3**	**2.3**	**23**
		Butylparaben (EAS) – conc.	Product	0.051	0.51	0.51	**5.1**
		Propylparaben + Butylparaben + exposure source contribution (EAS)	Product + exposure source contribution	**7.881**	**78.81**		
		Propylparaben + Butylparaben + Propylparaben exposure source contribution (EAS)	Product + exposure source contribution			**67.81**	**678.1**
Body lotion (NEU-K 172)	Pregnant woman	Propylparaben (EAS) – conc.	Product	0.22	**2.2**	**2.2**	**22**
		Butylparaben (EAS) – conc.	Product	0.087	0.87	0.87	**8.7**
		Propylparaben + Butylparaben + exposure source contribution (EAS)	Product + exposure source contribution	**7.907**	**79.07**		
		Propylparaben + Butylparaben + Propylparaben exposure source contribution (EAS)	Product + exposure source contribution			**68.07**	**680.7**

As can be seen from the table the total risk of exposure to two focus substances with the same mode of action in the same cosmetics product, in this case body lotion for pregnant women, increases approx. a factor 1.22 - 1.45 compared to exposure to the highest concentration of a

single focus substance in the same product. In sunscreen containing propylparaben and BHA, it is the content of propylparaben that makes up the overall risk.

12.6.3 RCR for textiles, plastics and silicone products - contributions from selected sources of exposure

Products selected for migration analyses with useful and relevant analysis results for calculation of RCR values with contributions from selected exposure sources are shown in TABLE 45.

Below, four RCR values are calculated for each relevant measurement from the migration measurements. Calculations are organised into calculations with DNEL or DMEL with and without MAF, respectively. As an example, the calculations for propylparaben in product DK-T-122 (sock, children 3 years) are specified.

DK-T 122, sock, 3-year-old

TABLE 68. RCR values for propylparaben and BPA in stocking (DK-T 122) and contributions from food, FCM and medicinal products. The table contains RCR values for the migration measurements from the product (propylparaben product (0.009 µg/cm^2); BPA product (0.0059µg/cm2 *)), contributions from selected exposure sources of the relevant focus substances (propylparaben exposure source contribution; BPA exposure source contribution) and the total contribution from selected exposure sources of similar acting substances (EAS exposure source contributions).

DK-T-122, sock **Target group: Children** **3 years.**	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben product (0.009 µg/cm^2)	-	-	0.00	0.00	-	-	0.00	0.01
BPA product (0.0059µg/cm^2 *)	-	-	0.04*	0.40*	-	-	0.40*	**4.0***
Propylparaben exposure source contribution	-	-	-	-	-	-	**70**	**700**
BPA exposure source contribution	-	-	-	-	-	-	**16**	**156**
EAS exposure source contribution	-	-	**9**	**90**				
Propylparaben $RCR_{product}$ + $RCR_{EAS,\ exposure\ source\ contribution}$	-	-	**9**	**90**	-	-	-	-
BPA $RCR_{product}$ + $RCR_{EAS,\ exposure\ source\ contribution}$	-	-	**9**	**90**	-	-	-	-
Propylparaben $RCR_{product}$ + $RCR_{propylparaben\ exposure\ source\ contribution}$	-	-	-	-	-	-	**70**	**700**
BPA $RCR_{product}$ + $RCR_{BPA,\ exposure\ source\ contribution}$	-	-	-	-	-	-	**16**	**160**

"-": No calculation.

* The migration measurement showed a concentration above the detection limit, but below the quantification limit. The RCR value for the product is calculated with a worst case assumption of a migration concentration just below the quantification limit.

Propylparaben:

Risk assessment with DNELs and DMELs without the use of MAF:

$RCR_{DNEL(propylparaben)}$

= product exposure (substance A)/DNEL (substance A)) + (contribution from selected sources of exposure (substance A)/DNEL (substance A)) + (sum of RCR values for contributions from selected sources of exposure of other focus substances with the same mode of action calculated by DNELs for these substances)

= RCR (DNEL, product exposure) + RCR (DNEL, estimated contribution from selected exposure sources from similar acting focus substances including propylparaben (EAS))

= Propylparaben product ($DNEL_{EAS}$) + EAS exposure source contribution ($DNEL_{EAS}$)

= 0.00 + 9 = **9.0**

$RCR_{DMEL(propylparaben)}$

= product exposure (substance A)/DMEL (substance A)) + (estimated contribution from selected exposure sources (substance A)/DMEL (substance A)) + (sum of RCR values for exposure contribution of other focus substances with the same mode of action calculated with DMEL for these substances)

= RCR (DMEL, product exposure) + RCR (DMEL, estimated contribution from selected exposure sources from similar acting focus substances including propylparaben (EAS))

= Propylparaben product ($DMEL_{EAS}$) + EAS exposure source contribution ($DMEL_{EAS}$)

= 0.00 + 90 = **90**

Risk assessment with DNELs and DMELs using MAF:

$RCR_{DNEL(propylparaben)}$

= product exposure (substance A)/DNEL (substance A)) + contributions from selected sources of exposure of other sources (substance A)/DNEL (substance a)

= RCR (DNEL, product exposure, substance A) + RCR (substance A contribution from selected sources of exposure)

= RCR (DNEL, product exposure, propylparaben) + RCR (propylparaben, contributions from selected exposure sources)

= Propylparaben product ($DNEL_{EAS}$ with MAF) + propylparaben exposure source contribution ($DNEL_{EAS}$ with MAF)

= 0.00 + 70 = **70.00**

$RCR_{DMEL(propylparaben)}$

= product exposure (substance A)/DMEL (substance A)) + estimated contribution from selected sources of exposure (substance A)/DMEL (substance a)

= RCR (DMEL, product exposure, substance A) + RCR (substance A contribution from selected sources of exposure)

= RCR (DMEL, product exposure, propylparaben) + RCR (propylparaben, contributions from selected exposure sources)

= Propylparaben product ($DMEL_{EAS}$ with MAF) + propylparaben exposure source contribution ($DMEL_{EAS}$ with MAF)

= 0.01 + 700 = **700**

Calculations show that the exposure to propylparaben and BPA, from the product alone, gives an RCR value > 1 using DMEL and MAF. However, this value (RCR = 4.0) does not indicate a real risk, as the calculations for BPA are based on a worst case assumption for migration, as the migration concentration was too low to be quantified.

In the RCR calculations, which include exposure from the product and contributions from the selected exposure sources, all calculated RCR values are larger than 1. The highest value is calculated at 160. In the calculations, contributions from the selected exposure sources dominate the total RCR value and the value is therefore determined by data on the selected exposure sources.

NEU-T 116, sock, 3-year-old

TABLE 69. RCR values for sock (NEU-T 166) including contributions from selected sources of exposure. The table contains RCR values for the migration measurements of the product (BPA migration-on (0.0029µg/cm2 *)), estimates for exposure from selected sources of the relevant focus substance (BPA exposure source contribution) and the total contribution from selected exposure sources of similar acting substances (EAS exposure source contribution).

NEU-T 116, sock Target group: Children 3 years.	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BPA migration (0.0029µg/cm^2 *)	-	-	0.01*	0.13*	-	-	0.13*	**1.3***
BPA exposure source contribution	-	-	-	-	-	-	**15**	**156**
EAS exposure source contribution	-	-	**9**	**90**	-	-	-	-
$RCR_{product}$ + $RCR_{EAS,\ exposure\ source\ contribution}$	-	-	**9.0**	**90**	-	-	-	-
$RCR_{product}$ + $RCR_{EAS,\ exposure\ source\ contribution}$	-	-	**-**	**-**	-	-	**16**	**157**

"-": No calculation
* The migration measurement showed a concentration above the detection limit, but below the quantification limit. The RCR value of the product is calculated with a worst case assumption of a migration concentration just below the quantification limit.

Calculations show that the exposure to BPA from the product only gives a single RCR value greater larger than 1. This is for the BPA measurements using DMEL and MAF. However, this value (RCR = 1.3) does not indicate a real risk, as because the calculations for BPA are based

on a worst case assumption for migration, as the migration concentration was too low to be quantified.

In the RCR calculations, which include exposure from the product and the exposure source contribution, all calculated RCR values are larger than 1. The largest is calculated at 157. In the calculations, contributions from the selected exposure sources dominate the total RCR value and, the value is therefore determined by data on contributions from the selected sources of exposure.

EU-P 3, pacifier shield, children under 3 years

TABLE 70. RCR values for pacifier shields (EU-P 3) include contributions from selected sources of exposure. The table contains RCR values for the migration measurements of the product (BPA product (0.0119µg/cm^2), exposure source contribution of the relevant focus substance (BPA exposure source contribution) and the total contribution from selected exposure sources of similar acting substances (EAS exposure source contribution).

EU-P 3, pacifier shield **Target group: Children 3 years.**	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BPA migration (0.0119µg/cm^2)	-	-	0.06*	0.57*	-	-	0.57*	**5.7***
BPA exposure source contribution	-	-	-	-	-	-	**16**	**156**
EAS exposure source contribution	-	-	**9**	**90**	-	-	-	-
$RCR_{product}$ + $RCR_{EAS,\ exposure\ source\ contribution}$	-	-	**9.1**	**90**	-	-	-	-
$RCR_{product}$ + $RCR_{BPA,\ exposure\ source\ contribution}$	-	-	-	-	-	-	**16**	**162**

"-": No calculation
* The migration measurement showed a concentration above the detection limit, but below the quantification limit. The RCR value of the product is calculated with a worst case assumption of a migration concentration just below the quantification limit.

Calculations show that exposure to BPA from the product alone gives a single RCR value larger than 1. This is for the BPA measurements using DMEL and MAF. However, this value (RCR = 5.7) does not indicate a real risk, as the calculations for BPA are based on a assumption of migration. Migration of BPA from pacifier shields could not be quantified and therefore it was assumed that the migration was just below the LOQ. However, the migration could just as well be slightly higher than LOD and thus significantly lower than assumed in the above risk assessment.

In the RCR calculations, which include exposure from the product and contributions from the selected exposure sources, all calculated RCR values are larger than 1. The largest RCR is calculated at 162. In the calculations, contributions from the selected exposure sources dominate the total RCR value and the value is therefore determined by on data on contributions from the selected sources of exposure.

DK-T 136, tights, children under 3 years

TABLE 71. RCR values for tights (DK-T 136) include contributions from selected sources of exposure. The table contains RCR values for the migration measurements of the product (propylparaben product (0.0019 µg/cm2), contributions from selected exposure sources of the relevant focus substance (propylparaben exposure source contribution) and the total contribution from selected exposure sources of similar acting substances (EAS exposure source contribution).

DK-T 136, tights Target group: Children 3 years.	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben migration (0.0019 µg/cm^2)	-	-	0.01	0.06	-	-	0.06	0.57
Propylparaben exposure source contribution	-	-	**-**	**-**	-	-	**70**	**700**
EAS exposure source contribution	**-**	-	**9.0**	90	-	-	-	-
$RCR_{product}$ + $RCR_{EAS, exposure source contribution}$	**-**	-	**9.1**	90	-	-	-	-
$RCR_{product}$ + $RCR_{propylparaben exposure source contribution}$	**-**	-	**-**	-	-	-	**70**	**701**

"-": No calculation.

Calculations show that exposure to propylparaben from the product alone does not give an RCR value larger than 1 and thus the use of the product does not pose a risk.

In the RCR calculations which include exposure from the product and contributions from the selected exposure sources, all calculated RCR values are larger than 1. The largest is calculated at ~ 700. In the calculations, contributions from the selected exposure sources dominates the total RCR value and the value is therefore determined by data on these contributions.

DK-P 31, mobile cover, pregnant

TABLE 72. RCR values for mobile cover (DK-P 31) include contributions from selected sources of exposure. The table contains RCR values for the migration measurements of the product (BHT product (0.029µg/cm^2*), exposure source contribution of the relevant focus substance (BHT exposure source contribution) and the relevant total contribution from selected exposure sources of similar acting substances (T exposure source contribution).

DK-P 31, mobile cover Target group: Pregnant women	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
BHT migration 0.029µg/cm^2*	0.00	0.00	-	-	0.00	0.00	-	-
BHT exposure source contribution			-	-	**8.4**	**84**	-	-
T exposure source contribution	0.88	**8.8**	-	-	-	-	-	-
$RCR_{product}$ + $RCR_{T,\ exposure\ source\ contribution}$	0.88	**8.8**	-	-	-	-	-	-
$RCR_{product}$ + $RCR_{BHT,\ exposure\ source\ contribution}$	-	-	-	-	**8.4**	**84**	-	-

"-": No calculation
* The migration measurement showed a concentration above the detection limit, but below the quantification limit. The RCR value of the product is calculated with a worst case assumption of a migration concentration just below the quantification limit.

Calculations show that the exposure to BHA from the product alone gives RCR values lower than 1. These values are based on a worst case assumption for migration, as the migration concentration was too low to be quantified. Thus, the results show that the use of the product does not pose a risk.

In the RCR calculations which include exposure from the product and the total contribution from the selected exposure sources, three out of four calculated RCR values are larger than 1. The largest RCR is calculated at 84. In the calculations, contribution from the selected exposure sources dominates the total RCR value and the value is therefore determined by data on these.

For the textile, plastic and silicone products, RCR values with the same behaviour will not be added up, as migration concentrations have not been measured above LOQ for two focus substances in any of the products.

Summary
In the migration analyses, quantifiable migrations were measured only for one focus substance, propylparaben in two products (DK-T 122, sock, target group children 3 years and DK-T 136, tights, target group under 3 years). The other migration measurements did not demonstrate migrations above the quantification limit.

The migrations from DK-T 122 (socks, target group children 3 years) and DK-T 136 (tights, target group under 3 years) were shown to be 0.0016 µg/kg bw/d and 0.092 µg/kg bw/d, respectively. In the risk assessment of the two textiles, a dermal absorption of 3.7% was used to calculate the systemic exposure.

The calculated RCR values for the two products DK-T 122 and DK-T 136 were all <1 (stated in TABLE 73), and exposure to propylparaben from the two products does not pose a risk to the consumer.

TABLE 73. RCR values for products with measured migration concentration (> LOQ). RCR values are stated on the basis of the individual product as well as product (migration) + exposure source contribution and are calculated with and without MAF.

Product	Target group	Substance	Exposure source	RCR_{DNEL} without MAF	RCR_{DMEL} without MAF	RCR_{DNEL} w MAF	RCR_{DMEL} w MAF
DK-T 122 (sock)	Children 3 years	Propylparaben (EAS)	Product (migration)	0.00	0.00	0.00	0.00
			Product (migration) + exposure sources.	**9**	**90**	**70**	**700**
DK-T 136 (tights)	Children under 3 years	Propylparaben (EAS)	Product (migration)	0.01	0.06	0.6	0
			Product (migration) + exposure sources.	**9**	**89.9**	**70**	**700**

However, when contributions from selected sources of exposure to propylparaben and/or other focus substances with the same mode of action are included in the risk assessment, a completely different picture emerges. By including contributions from selected sources of exposure to propylparaben based solely on exposure to medicinal products, the risk assessment shows that both products pose a risk. However, this risk is driven solely by the risk calculated for propylparaben via medicinal products.

In general, data for on contributions from selected sources of exposure to propylparaben are based on a worst case assumption for medicinal products, which, however, is considered to be realistic.

12.7 RCR for combined exposure of each target group

For each of the three target groups, a combined RCR value is calculated below, where RCR is calculated for exposure to several products simultaneously.

Children under 3 years:
In this target group, several concentrations have been measured for EAS behaviour that can be combined (no further concentrations have been found for T behaviour for this target group). In cosmetic products, one relevant finding has been made in sunscreen, NEU-K 193. For the plastic, textile and silicone products, a single measurement has been quantified in the product tights, DK-T 136.

TABLE 74. Combined risk calculation (RCR) of the target group children under 3 years including food, FCM and medicinal products. The table contains RCR values for tights DK-T 136 (propylparaben tights), sunscreen NEU-K193 (propylparaben sunscreen), and the total contribution for selected exposure sources of similar acting substances (EAS exposure source contribution).

Combined target group: Children under 3 years.	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben tights	-	-	0.01	0.06	-	-	0.06	0.57
Propylparaben sunscreen	-	-	**1.5**	**15**	**-**	**-**	**15**	**151**
Propylparaben exposure source contribution	-	-	**-**	**-**	-	-	**70**	**700**
EAS exposure source contribution	**-**	-	**9**	**90**	-	-	-	-
$RCR_{products}$ + $RCR_{EAS,\ exposure\ source\ contribution}$	**-**	-	**1.5**	**105**	-	-	-	-
$RCR_{products}$ + $RCR_{propylparaben\ exposure\ source\ contribution}$	**-**	-	**-**	-	-	-	**95**	**851**
"-": No calculation								

It is clear that the combined RCR value is dominated by the EAS exposure sources (food, FCM and medicinal products), as well as the RCR value of the sunscreen. The RCR value of the tights contributes only marginally to the overall risk.

Children 3 years

In this target group, several concentrations have been measured for EAS behaviour that can be combined (no further concentrations have been found for T behaviour for this target group). In cosmetic products, one relevant finding has been made in sunscreen (NEU-K 193). For the plastic, textile and silicone products, a single measurement has been quantified in the product tights, DK-T 122.

TABLE 75. Combined risk calculation (RCR) of the target group children aged 3 years including food, FCM and medicinal products. The table contains RCR values for stocking DK-T 122 (propylparaben stocking; BPA stocking), sunscreen NEU-K193 (propylparaben sunscreen), and the total contribution for selected exposure sources of similar acting substances (EAS exposure source contribution).

Combined target group: Children 3 years.	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben sock	-	-	0.00	0.00	-	-	0.00	0.01
BPA sock	-	-	0.04*	0.40*	-	-	0.40*	**4.0***

Combined target group: Children 3 years.	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben sunscreen	-	-	**1.5**	**15**	-	-	**15**	**151**
Propylparaben exposure source contribution	-	-	-	-	-	-	**70**	**700**
BPA exposure source contribution	-	-	-	-	-	-	**16**	**156**
EAS exposure source contribution	-	-	**9**	**90**				
$RCR_{products}$ + $RCR_{EAS, exposure source contribution}$	-	-	**11**	**105**	-	-	-	-
Propylparaben $RCR_{products}$ + $RCR_{propylparaben exposure source contribution}$	-	-	-	-	-	-	**85**	**851**
BPA* $RCR_{products}$ + $RCR_{BPA, exposure source contribution}$	-	-	-	-	-	-	**16***	**160***

"-": No calculation.

* The migration measurement showed a concentration above the detection limit, but below the quantification limit. The RCR value for the product is calculated with a worst case assumption of a migration concentration just below the quantification limit.

As in the combined risk assessment of children under 3 years, the RCR value is dominated by the sunscreen and by the selected sources of exposure (food, FCM and medicinal products). The RCR value of the sock contributes only marginally.

Pregnant women/unborn children

In this target group, several concentrations for EAS mode of action have been measured, which can be combined (no further concentrations for T mode of action have been found for this target group). It is estimated that a pregnant woman uses sunscreen and aftersun during the summer period (defined as a summer scenario). For sunscreen is used the product with the highest total RCR value (product number EU-K 196) with propylparaben content (0.046%) and BHA content (0.008%). For aftersun, there is only one product (product number NEU-K 192) with RCR value based on propylparaben content (0.15%).

TABLE 76. Combined risk calculation (RCR) of the target group pregnant women/unborn children for a summer scenario. The table contains RCR values for sunscreen (EU-K 196) with propylparaben content (0.046%) and BHA content (0.008%) and RCR value for aftersun (NEU-K 192) based on propylparaben content (0, 15%). RCR values for the individual sub-

stances are stated as well as a combined RCR value of the total contribution from selected exposure sources of similar acting substances (EAS exposure source contribution) and specific exposure contributions for the substances (MAF approach).

Combined target group: Pregnant women/unborn children	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben (sunscreen)	-	-	0.26	2.6	-	-	**2.6**	**26**
BHA (sunscreen)	-	-	0.001	0.01	-	-	0.01	0.1
Propylparaben (aftersun)	-	-	0.36	**3.6**	-	-	**3.6**	**36**
Propylparaben exposure source contribution	-	-	-	-	-	-	**65**	**650**
BHA exposure source contribution	-	-	-	-	-	-	**4.7**	**47**
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-
$RCR_{products}$ + $RCR_{EAS, exposure source contribution}$	-	-	**8.2**	**82**	-	-	-	-
$RCR_{products}$ + $RCR_{propylparaben,}$ + $RCR_{BHA, exposure source contribution}$	-	-	-	-	-	-	**76**	**759**

"-": No calculation.

For the combined exposure using sunscreen and aftersun containing several similar acting substances, propylparaben dominates the RCR contribution in sunscreen and aftersun without the EAS exposure sources (food, FCM and medicinal products).

In the overall RCR calculation of the combined exposure, it is clear that the EAS exposure sources (food, FCM and medicinal products) make the largest RCR contribution. It is also seen that when using the threshold value approach (DNEL), the total RCR value without the EAS exposure sources will be <1. When using DMEL (non-threshold value approach) with and without MAF, the total RCR value will be> 1.

In this target group, several concentrations for EAS mode of action have been measured, which can be combined (no further concentrations for T mode of action have been found for this target group). As a thought example of the period outside the summer months (defined as a winter scenario), it is estimated that a pregnant woman uses body lotion and body oil as sun products are not normally used during this period. For body lotion is used the product (product number EU-K 183) with the highest content of propylparaben (0.099%) and content of butylparaben (0.025%). For body oil, there is only one product (product number NEU-K 181) containing propylparaben (0.098%) and BHT (0.058%). However, the contribution of BHT is not added as BHT has a T mode of action.

TABLE 77. Combined risk calculation (RCR) for the target group pregnant women/unborn children regarding a winter scenario. The table contains RCR values for body lotion (EU-K 183) with content of propylparaben (0.099%) and content of butylparaben (0.025%) and for body oil (NEU-K 181) with RCR value based on propylparaben content (0.098%) and BHT (0.058). RCR values for the individual substances are stated as well as a combined RCR value of the total contribution from selected exposure sources of similar acting substances (EAS exposure source contribution) and specific exposure contribution of the substances (MAF approach)

Combined target group: Pregnant women/unborn children	**RCR** $DNEL_T$	**RCR** $DMEL_T$	**RCR** $DNEL_{EAS}$	**RCR** $DMEL_{EAS}$	**RCR w. MAF** $DNEL_T$	**RCR w. MAF** $DMEL_T$	**RCR w. MAF** $DNEL_{EAS}$	**RCR w. MAF** $DMEL_{EAS}$
Propylparaben (body lotion)	-	-	0.24	**2.4**	-	-	**2.4**	**24**
Butylparaben (body lotion)	-	-	0.061	0.61	-	-	0.61	**6.1**
Propylparaben (body oil)	-	-	0.24	**2.4**	-	-	**2.4**	**24**
Propylparaben exposure source contribution	-	-	-	-	-	-	**65**	**650**
Butylparaben exposure source contribution	-	-	-	-	-	-	-	-
EAS exposure source contribution	-	-	**7.6**	**76**	-	-	-	-
$RCR_{products}$ + $RCR_{EAS,\ exposure\ source\ contribution}$	-	-	**8.1**	**81**	-	-	-	-
$RCR_{products}$ + $RCR_{propylparaben,}$ + $RCR_{BHA,\ exposure\ source\ contribution}$	-	-	-	-	-	-	**70**	**704**

"-": No calculation.

The content of propylparaben in each of the two products causes RCR > 1 in all assessment methods except when using DNEL without MAF. In other words, the propylparaben content dominates the RCR contribution in body lotion and body oil without the other EAS exposure sources (food, FCM and medicinal products). In the overall RCR calculation of the combined exposure, the EAS exposure sources (food, FCM and medicinal products) make the largest RCR contribution. It is also seen that when using the threshold value approach (DNEL), the total RCR value without the EAS exposure sources will be > 1.

12.8 Discussion

In this report, the aim of the risk calculations has been to assess whether exposure of children and pregnant women to the six selected focus substances, from selected products with and without contributions from selected sources of exposure, entails a risk (calculated as RCR> 1). The purpose of including calculations for a pregnant woman has been to assess the possible

risk to the unborn child through the indirect exposure via the mother, as the unborn baby in particular is considered to be very vulnerable to endocrine disruptors.

Contributions from the three selected sources of exposure (food, FCM and medicinal products), risk calculations for the three selected sources of exposure and the selected consumer products, as well as DNEL/DMEL and MAF are discussed below.

Contributions from selected sources of exposure
In the project contributions from the selected sources of exposure for the six focus substances, in addition to the analysed consumer products, have included three categories: food, FCM and medicinal products. Several of the available exposure data for food and FCM have been subject to uncertainty. The uncertainties include the actual procedures for determining contributions in the references used: older data (unknown whether these are representative of current exposure) and origin of data (data from countries outside the EU are not necessarily representative of the European population including Denmark). The method includes, as far as possible, data which are assessed to represent a realistic exposure. However, in several cases overestimation has been used due to exposure source estimates based on maximum permissible content concentrations or very conservative worst case considerations due to lack of reliable data. Consequently, the uncertainty of contributions from selected sources of exposure will be reviewed and discussed in the following sections.

Exposure contributions from food
Data on food exposure contribution are given in Chapter 10.

For BHA, BHT and BPA, contributions have been calculated by summing up contributions from food and FCM.

The exposure to BHA from food should be considered with caution as the calculations are theoretically based on maximum permitted concentrations in food. That is, data are not based on actual measurements but on the upper regulatory limit, and the exposure must be considered overestimated. The exposure to BHT from food, on the other hand, is derived from the Norwegian Scientific Committee for Food and Environment and is based on more recent measured content concentrations found in food (1787 samples).

The exposure to BPA is from an EFSA Opinion from 2015, which is very thorough and based on measurements. Therefore, the exposure to both BHT and BPA is considered reasonably representative and reliable.

No exposure has been established for butylparaben as the substance is not approved for use in food. For propylparaben, only data derived from food intake in the United States in the 1980s were available. The data were assessed not to represent intake of propylparaben from food in the EU/Denmark in 2021 and are therefore not included.

D4 is bioaccumulative and is found in fish among others (Greve et al., 2014), and exposure to the substance via food must therefore be expected. However, no useful data have been found so a potential contribution from food is not included, which may be an underestimation.

Overall, exposure data from food can be both overestimated and underestimated.

Exposure contribution from FCM
Data for exposure contribution from FCM are given in the tables in Chapter 10. Exposure from FCM is included for BHT and BPA (summed up contribution for food and FCM).

The exposure to BHT via FCM is based on theoretical data (maximum permissible concentrations). That is, data are not based on actual measurements, so exposure to BHT must be considered overestimated.

Data for BHA are not included, as the available data from EFSA (2012a) have been assessed as unrealistic (overestimated) by the DTU National Food Institute (Bredsdorff et al. 2020). Furthermore, migration of BHA from FCM has been assessed not to occur in a previous project (Larsen et al. 2017). The use of butylparaben in FCM is not permitted and thus it is not relevant to include exposure to this.

No exposure data from FCM were found for propylparaben and D4.

Exposure contributions from medicinal products
Data for exposure contribution from medicinal products are given in the tables in Chapter 10, and a realistic worst case exposure is calculated for specific concentrations of BHA, BHT and propylparaben in medicinal products using relevant databases and information from the Danish Medicines Agency.

Butylparaben, D4 and BPA are not used in medicinal products and are therefore not included in this exposure.

Total exposure contribution from the above selected sources
Data on exposure contributions for the three selected sources are given in the tables in Chapter 10. Thus, only the four substances BHA, BHT, propylparaben and BPA are included in the total exposure from the selected sources comprising food, FCM and medicinal products. It has not been possible to include the exposure to butylparaben and D4 from these sources, which may be an underestimation. However, this is not further covered in this project.

For propylparaben in medicinal products and BPA in food and FCM, usable data were only available from one source (summed up in the data source used).

Risk assessment of exposure from the selected sources
RCR values for the exposure sources are given in the tables in Chapter 12.5. Exposure data for selected sources are for BHA based on data from food and medicinal products. Data have not been included for FCM, as Danish data indicate that there is no migration of BHA from FCM and exposure data from EFSA have been assessed by the DTU National Food Institute to be very overestimated. RCR values calculated for BHA exposure of pregnant women are dominated primarily by data from food exposure (about 2/3) but also by medicinal products (about 1/3). For children, BHA exposure is primarily from food. The exposure to BHA from medicinal products is calculated for dermal exposure and is intended for a very low systemic exposure using a skin absorption of 0.4%. Exposure data for BHA from food are based on maximum permitted levels (MPLs) and are considered very conservative/cautious (overestimated).

Exposure data for BHT have been included for all three sources: food, FCM and medicinal products. Overall, the accumulated RCR value for the three BHT exposure sources is driven by FCM and medicinal products. For children, it is almost exclusively exposure from FCM that drives the RCR value. The exposure estimates for BHT from FCM have been calculated using maximum permitted migration limits assuming a daily intake of 1 kg of food, and they are considered very conservative/cautious (overestimated).

RCR values for BHA and BHT are dominated by data that overestimates an actual exposure to the two focus substances, and the total exposure to both substances is therefore not assessed as realistic. The risk assessment must therefore be considered very uncertain.

Overall, it is considered worth noting from TABLE 50 that the total exposure from the selected sources for each of the focus substances with estimated exposure values results in RCR values well above 1 in cases where MAF is used. The DMEL based approach without MAF also results in RCR values above 1 for all substances, while the DNEL based approach without MAF only results in RCR values above 1 for propylparaben and BPA.

Risk assessment of cosmetic products, content analyses

In the current project, risk calculations have been made based on the quantitative analyses in relation to a hormone-disrupting mode of action (either T or EAS). The risk calculations have been performed in accordance with the Notes of Guidance method according to SCCS with MoS calculations, where MoS values of 100 and above are typically not considered to pose a risk in relation to the content of a cosmetic product (see Appendix 9). In addition, risk assessments have been carried out based on the methods used in accordance with ECHA guidance R.8, i.e. with derivation of DNEL values and calculation of RCR values in relation to a T or EAS mode of operation. As an alternative method, an approach with discharge of DMEL has been used, assuming that there is no threshold value for the hormone-disrupting effect(s). From the table in Appendix 9, in which MoS values are calculated for each individual substance identified in the quantitative analyses above the detection limit (BHA, BHT, propylparaben, butylparaben), it appears that all MoS values are above 100 for cosmetic products for pregnant women, which does not indicate any risk when using the cosmetic products. The lowest MoS value found for pregnant women is 105 based on the content of propylparaben in sunscreen, which is close to constituting a risk.

In sunscreen for children under 3 years of age, a risk has been identified regarding the content of propylparaben as a MoS value of 67 has been calculated.

It is noted that the same conclusion is reached when the risk assessment is performed with RCR values based on DNEL approach without MAF. In sunscreen for children under 3 years of age, a risk (RCR of 1.5) has been identified due to the content of propylparaben, and for pregnant women an RCR value close to a risk has been calculated (RCR of 0.95). For the other cosmetic products, no risk (RCR> 1) was found in a DNEL approach without MAF, corresponding to what was found in the risk assessment using the MoS method.

In sunscreen, a user amount of 18 g of sunscreen for pregnant women has been applied, which is in accordance with the SCCS Notes of Guidance (SCCS, 2021a). However, this quantity is a subject of debate, as the health and environmental authorities state that a significantly higher user amount must be applied to achieve the desired protection factor. From the Ministry of the Environment, an amount four times higher has been proposed, i.e. 72 g. Assuming a quadruple amount of sunscreen, the corresponding MoS values will be a factor 4 x times lower. This will entail a risk concerning sunscreen products for pregnant women, as the MoS value will then be reduced from 105 to 26.

However, the conclusions are different when the methods with DNEL with MAF or DMEL with. and without MAF are used, as well as when contributions from selected exposure sources are included in the risk assessment. Here, risk has been identified for all scenarios, i.e. RCR> 1, when RCR contributions from the other selected exposure sources are included in the assessment (see summary table (TABLE 61), which indicates calculated RCR values based on the highest concentrations of the focus substances in the cosmetic products).

In the calculations, it is clear that contributions from the selected sources of exposure dominate the overall RCR value, and the risk value is therefore primarily driven by the contribution from these sources of exposure and to a lesser extent from the contribution from cosmetics.

Furthermore, using the RCR method, an overall risk has been calculated for the individual cosmetic products with content of two focus substances with the same mode of action, in this case EAS effects (body lotions EU-K 183; NEU-K 180; EU-K 182; NEU- K 172 and the sunscreen product EU-K 196). As can be seen from the summary table (TABLE 67), the total risk increases when exposed to two focus substances with the same mode of action in the same cosmetic product, in this case body lotion for pregnant women containing propyl- and butylparaben, approx. a factor of 1.22 - 1.45 compared to exposure to a single focus substance of the highest concentration in the same product. In these body lotions, propylparaben makes up the largest contribution, however, it is butylparaben in product NEU-K 180 that makes up the largest contribution without contribution from the exposure sources.

In sunscreen containing propylparaben and BHA (product EU-K 196), it is the content of propylparaben that makes up the overall risk without the contribution from the exposure sources. From these calculations, however, it is also clear that contributions from the selected sources of exposure dominate the overall RCR value, and risk is therefore driven by contributions from the selected sources of exposure and to a lesser extent by the contribution from cosmetics.

Risk assessment of textile, plastic and silicone products, migration analyses
In the current project, risk calculations have been made based on migration analyses. For products where no migration was detected (measured migration concentrations <LOD in the migration fluid), RCR values for worst case migration (a migration concentration just below LOD) were calculated. In this way, it can be assessed whether the analysis method used was sufficiently sensitive to be able to clear the products of a risk from the substance(s) in question.

For migration results in the interval LOD <analysis result> LOQ, a worst case migration was assumed (i.e. a migration concentration just below LOQ). As these calculations must be regarded as theoretical worst cases, they cannot be considered useful in assessing whether the products currently pose a risk. If the migration analyses with a measured value in the interval LOD <analysis result> LOQ are to be used to make a usable risk assessment of the products, it is recommended that in future calculations are made of the smallest value in the concentration interval. Using a minimum migration concentration, an actual risk assessment can be calculated (although less accurate than for quantified measurements).

In the migration analyses, only quantifiable migrations were measured for one focus substance, propylparaben, in two products (DK-T 122, socks, target group children 3 years, and DK-T 136, tights, target group children under 3 years). The other migration measurements showed no migrations above the quantification limit. The migrations from DK-T 122 (socks, target group children 3 years) and DK-T 136 (tights, target group children under 3 years) were 0.0016 µg/kg bw/d and 0.092 µg/kg bw/d, respectively.
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The calculated RCR values for socks and tights (DK-T 122 and DK-T 136) were all <1 and the exposure to propylparaben from the two products does not pose a risk to the consumer. However, when contributions from the selected sources of exposure to propylparaben and/or other focus substances with the same mode of action are included in the risk assessment of the two products, a completely different picture emerges. By including contributions from the selected sources of exposure to propylparaben, based solely on exposure to medicinal products, the risk assessment shows that both products pose a risk. However, this risk is driven solely by the risk calculated for propylparaben via medicinal products.

In general, data for contributions from selected sources of propylparaben exposure are based on worst case, but with a realistic content in medicinal products.

Overall, there are several relevant contributions from the selected sources of exposure to propylparaben. In addition to medicinal products, exposure from other sources such as food must also be expected. However, it has not been possible in this report to map this exposure to propylparaben.

Risk assessment of combined exposure from several products and selected sources of exposure

For each of the three target groups, children under 3 years of age, children 3 years of age and unborn children/pregnant women, a combined RCR value has been calculated. This combined value adds up exposure to the focus substances with the same behaviour from several of the analysed products, as well as exposure contributions from the three selected exposure sources.

For children under the age of 3 years, the analysis results showed a potential exposure from several products: BHT and propylparaben from a sunscreen (NEU-K 193) and propylparaben from a pair of tights (DK-T 136). When determining a total combined exposure, the exposures from several analysed products are added up for substances that have the same mode of action. As a single exposure has only been measured for a focus substance with a T mode of action, no calculations can be made for a combined exposure for substances with this mode of action.

For the EAS mode of action, there are measurements from two products, both for propylparaben. In cosmetic products, propylparaben has been found in a sunscreen (NEU-K 193). In plastic, textile and silicone products, one migration measurement has been quantified in a pair of tights (DK-T 136).

By adding the two RCR values for the two products (TABLE 74), an RCR value of 11 was calculated using DNEL without MAF. This combined value is primarily dominated by the EAS exposure source contribution (from food, FCM and medicinal products) with an RCR value of 9. The RCR value for sunscreen alone was 1.5. The exposure of the propylparaben from tights contributes only marginally (RCR equal to 0.01) to the combined value.

For children aged 3 years, the analysis results showed a potential exposure from several products with the focus substances, all with the EAS mode of action. The analyses showed a single exposure to a focus substance with the T mode of action, BHT in sunscreen (same as mentioned above for children under the age of 3). A combined exposure is therefore not calculated for focus substances with T mode of action.

For the EAS mode of action, measurements from two products can be combined. In cosmetic products, propylparaben has been found in a sunscreen (NEU-K 193). For plastic, textile and silicone products, one measurement has been quantified in a sock, also propylparaben (DK-T 122).

By adding the RCR values for the two products, an RCR value of 11 was calculated using DNEL without MAF (TABLE 75). As in the previous case, this value is also primarily dominated by the overall exposure estimate for the three selected sources of exposure (food, FCM and medicinal products), which is equal to 9. The contribution of propylparaben from the sunscreen is equal to 1.5. Exposure to propylparaben from the socks (RCR = 0.00) does not contribute to the combined value.

For pregnant women/unborn children, the results of the RCR calculations for combined exposure from cosmetic products (TABLE 76 and TABLE 77), regarding focus substances (propylparaben, butylparaben, BHA) with the same mode of action (EAS), show the same

trend as for the combined risk assessment of a single product containing two focus substances. This is seen in a thought example where a pregnant woman uses sunscreen and aftersun during the summer period. For sunscreen, the product with the highest total RCR value (product number EU-K 196) with propylparaben content (0.046%) and BHA content (0.008%) is used. For aftersun only one product (product number NEU-K 192) has an RCR value based on propylparaben content (0.15%).

It is seen that the content of propylparaben in each of the two products causes RCR> 1 in all assessment methods except the use of DNEL without MAF. In other words, the propylparaben content dominates the RCR contribution in body lotion and body oil without the selected EAS exposure sources (food, FCM and medicinal products). In the overall RCR calculation of the combined exposure, it is clear that the EAS exposure sources (food, FCM and medicinal products) give the largest RCR contribution. It is also seen that applying threshold access (DNEL), the total RCR value without the EAS exposure sources will be> 1.

As a realistic example for the period outside the summer months, it is estimated that a pregnant woman uses body lotion and body oil on the same day. For body lotion, product number EU-K 183 with the highest content of propylparaben (0.099%) and content of butylparaben (0.025%) is used. For body oil, only one product, product number NEU-K 181, contains propylparaben (0.098%) and BHT (0.058%). However, the BHT contribution is not added up, as BHT has a T mode of action.

It is seen that the content of propylparaben in each of the two products causes RCR> 1 in all assessment methods except the use of DNEL without MAF. In other words, the content of propylparaben dominates the RCR contribution in body lotion and body oil without the involvement of the EAS exposure sources (food, FCM and medicinal products). In the overall RCR calculation for the combined exposure, it is clear that the EAS exposure sources (food, FCM and medicinal products) give the largest RCR contribution. It is also seen that applying the threshold value approach (DNEL), the total RCR value without the EAS exposure sources will be > 1. If the RCR calculations for propylparaben alternatively are made without the use of read across from data on butylparaben but are based only on the more limited data on propylparaben, 50 times higher DNEL and DMEL as proposed by EMA (2015) (i.e., 1000 µg / kg bw / d instead of 20 µg / kg bw / d and 100 µg / kg bw / d instead of 2 µg / kg bw / d). In this scenario, RCR without threshold (DMEL) and RCR using MAF would still be > 1 (see Tables 49, 76 and 77).

It should be noted that the risk assessment for the preservative propylparaben in medicinal products has been performed according to the same principles as for the environmental and dietary exposure, in order to be able to relate the calculated risk of potential endocrine disruptive effects of the selected chemicals from other sources.

The Danish Medicines Agency notes that in 2015, the European Medicines Agency has evaluated and defined an acceptable daily intake of propylparaben as an excipient in orally administered medicinal products, on the basis of available studies and data. The Danish Medicines Agency would like to stress that when treatment during pregnancy is indicated, use of the medicinal product is still recommended irrespective of the possible propylparaben content. It is generally recommended that any medicinal product used during pregnancy should be administered for the shortest possible duration and at the lowest efficacious dose and only on indication and in agreement with the prescribing physician.

DNEL/DMEL and MAF

The established DNELs and DMELs (Chapter 9) used in the risk assessments show that the non-threshold-based approach (DMEL) results in factor 10 higher RCR values compared to a threshold-based approach (DNEL). This means that there is a risk of endocrine disruptors for

many more exposure scenarios when using a DMEL approach. This factor 10 derives from an extra AF of 10 in the DMEL determination, as the large assessment factor approach has been used in this project. This difference between DNEL and DMEL could be both smaller and larger if BMDL10 had been used as well as an AF of 10 at the time of the DMEL determination (Chapter 9).

It should be mentioned that the DMEL values set for endocrine disrupting effects do not express a specific level of risk, as is the case with DMEL values calculated for carcinogens. The present project has not aimed to decide whether to use DNELs or DMELs, that is whether the risk assessment is carried out on the basis of a threshold-based or non-threshold-based approach. This report applied both approaches to illustrate the consequences it entails in the conclusions of the risk assessments.

As another alternative approach, a Mixture Assessment Factor (MAF) has been included in the risk calculations. In the EU, the use of such an uncertainty factor and its size in terms of combination effects are discussed. This is intended to be included in risk assessments to take into account combination effects of contributions from other substances with the same mode of action. The use of a MAF is thus considered relevant, as the extent of similar acting substances and contributions from different sources are often unknown. In the present project, quantification of contributions from selected sources of exposure for all six focus substances has proved to be very challenging and subject to great uncertainty (see previous discussions on contributions from selected sources of exposure).

Calculating a realistic estimate of contributions from selected sources of exposure of similar acting substances would require identification of potentially similar acting substances and updated data on the content of such substances from a number of different sources. As this is very difficult to achieve, use of a MAF may be an alternative to compensate for these unknown contributions.

It should be emphasised that it will differ from substance to substance whether such a MAF is relevant depending on the mode of action and the effects of the substance. For example, a MAF for a substance with local irritant effects as the critical effect may be less relevant than a MAF for systemic effects.

If it is assessed that there is a significant contribution to the risk of simultaneous exposure to substances with the same mode of action or effect, a MAF of for instance10 can contribute to ensuring a better level of protection. If there is no significant contribution to the risk of simultaneous exposure to substances with the same mode action or effect, the use of a MAF of for instance 10 will undoubtedly lead to an overestimation of the risk. Both the use and the size of the MAF are currently under discussion in the EU. It will be an administrative decision whether a MAF should be used in future risk assessments and how large this should be, that is whether possible contributions from other substances with the same mode of action should be taken into account.

Conclusion

For the cosmetic products used by pregnant women, the risk assessment of the found content of four of the focus substances (BHA, BHT, propylparaben, butylparaben) has not demonstrated a risk using the DNEL method used under REACH. For children under 3 years of age, however, a risk of endocrine disrupting effects was identified with respect to the content of propylparaben in sunscreen (the same conclusion for the cosmetic products was obtained by the current risk assessment method for cosmetics (SCCS Notes of Guidance (SCCS 2021a)).

However, the conclusions are different when the methods with DNEL with MAF and DMEL with and without MAF are applied, and when contributions from selected sources of exposure

(food, FCM and medicinal products) are included in the risk assessment. Here it is clear that exposure contributions from the focus substances with the same behaviour from the selected exposure sources dominate the overall RCR value, and the value is therefore very dependent on data from contributions from the selected exposure sources.

For risk calculation of products other than the cosmetic products, only quantifiable migrations for one focus substance, propylparaben, were measured in the migration analyses of two products ("DK-T 122, socks, target group children 3 years" and "DK-T 136, tights, target group children under 3 years"). The other migration measurements showed no migration of the focus substances above the quantification limit. The risk assessment of the two products showed that the exposure to propylparaben from the two products does not pose a risk to the consumer. However, when contributions from the selected sources of exposure to propylparaben are included in the risk assessment, a completely different picture emerges. By including the exposure to propylparaben from the selected sources, which is based solely on exposure from medicinal products, the risk assessment shows that both products pose a risk.

In this project, both a threshold-based (DNEL) approach and a non-threshold-based (DMEL) approach have been used in the risk assessment. For the six focus substances assessed in this project, neither the absence nor the presence of a threshold has been identified, and as a result a DMEL approach to the risk assessment can be used for the six focus substances.

It is considered relevant to use MAF in the present project, as the extent of similar acting substances and contributions from these are not known. Quantification of contributions from the selected sources of exposure for all six focus substances (BHA, BHT, propylparaben, butylparaben, BPA, D4) has also proved to be very challenging. Calculating a realistic estimate of contributions from the selected sources of exposure of similar acting substances would require identification of all potentially similar acting substances as well as updated data on contributions of these substances from a number of different sources. Overall, it is concluded that today there is a lack of updated data on contributions from selected exposure sources for the endocrine disruptors, especially from food and FCM where the exposure is often highest, to be able to assess the real risk.

As such extensive and up-to-date knowledge is very difficult/impossible to obtain, a risk management alternative may be to incorporate a MAF to compensate for the unknown contributions from similar acting substances.

Although contributions from selected sources of exposure are of older date and probably overestimated, other contributions are probably underestimated. Based on the results of this report, it can be concluded that the individual product does not necessarily pose a risk, but the sum of exposure of young children (children under 3 years), 3-year-olds and pregnant women/unborn children can pose a problem - regardless of the approach used in the risk assessment.

Overall, the project indicates that reducing exposure to endocrine disruptors, especially through food and medicinal products, will be necessary to ensure the protection of children and pregnant women from endocrine disrupting effects. This applies whether an assessment method is used with or without a threshold value for the endocrine disrupting mode of action, or whether a MAF or not is used for with the two methods.

13. Conclusion

In this project, a large number of chemical analyses were carried out with focus on products of plastic, silicone and textiles and cosmetic products presuming that the six focus substances would occur. All six focus substances were identified in one or more of the products. Some substances (D4, propylparaben, BHT and BPA) are more predominant than others (butylparaben and BHA). Although several of the six focus substances are identified in the analysed consumer products, migration of the substances from the products under the applied migration conditions was limited.

In the analysed plastic, silicone and textile products, the migration analyses only measured quantifiable migrations from one focus substance, propylparaben, which was found in two products (in a pair of socks for children aged 3 and in a pair of tights for children under 3 years). The risk assessment of the two products showed that the exposure to propylparaben from the two products does not pose a risk to the consumer.

However, by including the exposure to selected sources of propylparaben (in this case medicinal products) in addition to the contribution from each of the two products, the risk assessment shows that the combined exposure poses a risk - but contribution from the products on their own is marginal (contributions from the medicinal products, which is based on a calculation of a realistic worst case, pose a risk).

In the cosmetic products used by pregnant women, the risk assessment of the found content of four of the focus substances (BHA, BHT, propylparaben, butylparaben) has not demonstrated a risk using the current risk assessment method for cosmetics (SCCS Notes of Guidance (SCCS 2021a)). However, for children under 3 years of age, a risk of endocrine disrupting effects regarding propylparaben content in sunscreen was identified. The same conclusion for the cosmetic products was obtained with the DNEL approach used according to the REACH method.

However, different conclusions are reached when the approaches with DNEL with MAF and DMEL with and without MAF are applied, and when contributions from selected sources of exposure (food, FCM and medicinal products) are included in the risk assessment. Here, it is evident that exposure contributions from the focus substances with the same behaviour from the selected exposure sources dominate the overall RCR value, and the value is therefore very dependent on data on contributions from the selected exposure sources.

In the present project, quantification of contributions from the selected sources of exposure (food, FCM and medicinal products) of all six focus substances (BHA, BHT, propylparaben, butylparaben, BPA, D4) has proved to be very challenging due to uncertainty about the data.

However, the available data show that if the risk contributions for similar acting focus substances are added together, it increases the overall risk significantly, which means that several known as well as unknown sources of exposure to similar acting endocrine disruptors must be considered when assessing the total risk to consumers.

The results of the project thus support the use of a MAF to ensure the protection of consumers against endocrine disrupting effects due to exposure to similar acting endocrine disruptors from diverse sources.

Based on the results of this report, it can be concluded that regardless of the assessment method there is a risk of endocrine disrupting effects in children and pregnant women. This is mainly due to exposure to the endocrine disrupting focus substances through food and medicinal products, whereas risk contributions from the selected consumer products seem relatively limited (apart from possible contributions from sunscreen).

To obtain protection against endocrine disrupting effects, it will therefore be necessary to reduce the exposure, especially from food and medicinal products, as even the least conservative (careful) risk assessment method with DNEL without MAF has shown a risk of endocrine disrupting effects in children and pregnant women.

Based on the individual findings and the available data, it has not been possible to assess whether a possible risk differ from products purchased from Denmark, the EU or outside the EU.

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Xue et al., 2017. Bisphenols, Benzophenones, and Bisphenol A Diglycidyl Ethers in Textiles and Infant Clothing. Xue J, Liu W, Kannan K. Environ. Sci. Technol. 2017, 51, 5279−5286.

Appendix 1. Legislation on plastic for food contact

For the investigated substances in this project, BPA, propylparaben, BHA and BHT are permitted to be used in plastic material for food contact (EU regulation no. 10, 2011). Specific migration limit values have been set for these substances, which must be complied with when producing plastic products for food contact (see TABLE 25). However, there is no specific migration limit value for propylparaben. Concerning butylparaben, it is not permitted for use in plastic for food contact.

TABLE 78. Permitted substances for the production of plastic for food contact (according to EU regulation no. 10, 2011)

Substance	CAS no.	Allowed	Restrictions	Specific migration limit for the substance
BPA	80-05-7	Yes May be used as a monomer Are allowed to be used in surface treatment agents for e.g. packaging of metals	Not to be used as an additive or a polymerisation aid. Not to be used for the manufacture of polycarbonate infant feeding bottles. Not to be used for the manufacture of polycarbonate drinking cups or bottles which, due to their spill-proof characteristics, are intended for infants and young children. Are not allowed to migrate from surface treated material etc. to food for babies or toddlers.	0.05 mg/kg
Propylparaben	94-13-3	Yes	Approved for use as an additive or polymerisation aid.	None
BHA	25013-16-5	Yes	Approved for use as an additive or polymerisation aid.	30 mg/kg
BHT	128-37-0	Yes	Approved for use as an additive or polymerisation aid.	3 mg/kg

Appendix 2. Additives for food

BHA and BHT are the only substances studied in this project that, according to the EU Regulation on food additives are allowed to be used as food additives (listed in the EU's database of permitted food additives[13]). The foods where BHA and BHT may be added, as well as the maximum permitted amounts are stated in TABLE 26 below.

TABLE 79. Foods where BHA and BHT are allowed for use as additives

Type of food	BHA (Maximum permitted quantity)	BHT (Maximum permitted quantity)
Dehydrated milk	200 mg/kg Only milk powder for vending machines	*Not permitted*
Fats and oils essentially free from water (excluding anhydrous milkfat)	200 mg/kg Only fats and oils for the professional manufacture of heat-treated foods; frying oil and frying fat (excluding olive pomace oil) and lard, fish oil, beef, poultry, and sheep fat	100 mg/kg Only fats and oils for the professional manufacture of heat-treated foods; frying oil and frying fat (excluding olive pomace oil) and lard, fish oil, beef, poultry, and sheep fat
Other fat and oil emulsions including spreads and liquid emulsions	200 mg/kg Only frying fat	100 mg/kg Only frying fat
Nut butters and nut spreads	200 mg/kg Only processed nuts	*Not permitted*
Processed potato products	25 mg/kg Only dehydrated potatoes	*Not permitted*
Chewing gum	400 mg/kg	400 mg/kg
Breakfast cereals	200 mg/kg Only pre-cooked cereals	*Not permitted*
Pre-cooked or processed cereals	200 mg/kg Only pre-cooked cereals	*Not permitted*
Fine bakery wares	200 mg/kg Only cake mixes	*Not permitted*
Non-heat-treated processed meat	200 mg/kg Only dehydrated meat	*Not permitted*
Seasoning and condiments	200 mg/kg	200 mg/kg
Soups and broths	200 mg/kg Only dehydrated soups and broths	*Not permitted*
Sauces	200 mg/kg	*Not permitted*
Potato-, cereal-, flour- or starch-based snacks	200 mg/kg Only cereal-based snack foods	*Not permitted*
Processed nuts	200 mg/kg	*Not permitted*

[13] https://webgate.ec.europa.eu/foods_system/main/?sector=FAD&auth=SANCAS

Type of food	BHA (Maximum permitted quantity)	BHT (Maximum permitted quantity)
Food supplements supplied in solid form including capsules and tablets and similar forms, excluding chewable forms. Excluding food supplements for infants and young children.	400 mg/kg	400 mg/kg
Food supplements supplied in liquid form. Excluding food supplements for infants and young children.	400 mg/kg	400 mg/kg

Appendix 3. D4

Octamethylcyclotetrasiloxane, Cyclotetrasiloxane, D4, CAS no. 556-67-2

Appendix 3.1 Data availability and literature search

Previous reports	ED list report, (Hass et al. 2018), reviewed many existing lists of chemicals, in total contain more than 7,000 suspected substances. Based on these lists, a priority list of 172 substances was compiled containing substances where data indicate that they have an endocrine disrupting effect and where there is a strong likelihood that humans and the environment will be exposed to them. The report includes a hazard identification of different substances but not a full risk assessment. 13 substances, including D4, were carefully evaluated based on the EU's new criteria for biocides and pesticides. This project concluded that D4 fulfils the WHO definition of an EDC. This was based on strong evidence of Estrogenic MoA (Mode of Action) both in vivo and in vitro. The adverse effects are as described in the ED list report: Reduced fertility, disturbed estrous cycles, reduced ovulations, increased uterus weights with endometrial hyperplasia, vaginal mucification and ovarian atrophy and a strong link between MoA and these adverse effects. SVHC documentation by ECHA: D4 is concluded to be an SVHC by ECHA member state committee due to PBT (persistent, bioaccumulative, toxic) and vPvB (very persistent, very bioaccumulative) properties and (ECHA, 2016 and ECHA, 2021). CLH documentation: D4 is classified for reproductive toxicity as a substance suspected of damaging fertility or the unborn child (Cat. Repr. 2) (ECHA, 2017). SCCS opinion 2010 concluding no risk for human health and noting classification (Cat. 2) of D4 as reprotoxic substance. NOAEL for risk assessment by SCCS for systemic toxicity (150 ppm in inhalation studies corresponding to 17.8 mg/kg bw/day) also covers reproductive toxicity (SCCS, 2010). MST project "Exposure of pregnant consumers to suspected endocrine disrupters", (Andersen et al. 2012). A DNEL (195 µg/kg bw/d) for estrogenic effects was determined and applied for risk assessment. MST project "Exposure of children and unborn children to selected chemical substances", (Larsen et al. 2017). A DNEL (195 µg/kg bw/d) for estrogenic effects was determined and applied for risk assessment.
New search	For update of ED evaluation after the literature review in ED list 2018 (Hass et al. 2018), we performed an update for the period 2017-2021. This also enabled update of DNEL determination after the latest DNEL selection in Larsen et al. 2017. We carried out searches in PubMed 19/4 2021. The search strategy was based on the description in ECHA/EFSA guidance 2018 and focused on ED effects (page 130): #1 (Octamethylcyclotetrasiloxane OR Cyclotetrasiloxane OR 556-67-2) AND (rats OR mice OR human OR toxicity) AND (endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*) – 16 results #2 A relatively broad search using the search string: "(Octamethylcyclotetrasiloxane OR Cyclotetrasiloxane OR 556-67-2) AND (rats OR mice OR human OR toxicity or endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*)– 105 results #2 limited to 2017-2021 – 35 results

	Limitation to the period 2017 to 2021 (period after previous literature search from ED list project) identified 35 hits, which were included in the screening process. The screening process constitutes 3 steps as described in ECHA/EFSA guidance (2018): 1) Screening of titles 2) Screening of abstracts 3) Screening of full text 1. Title screen: 35 studies after 2017 not included in ED list project (report published 2018) was screened for relevance for this project: 2. Abstract screen: After exclusion of e.g. human exposure studies (e.g. Helm et al. 2019), 10 studies were considered potentially relevant. 3. Screening of full text: the updated literature search did not result in more experimental studies on D4 for the period 2017-2021. But below in the MoA table (under b), references are made to the findings in several of the papers also included in the ED list project.
Review of the ECHA dissemination site for D4	Performed in May 2021. A preliminary review of the data available at the ECHA dissemination site led to the conclusion that the results from the many studies performed by the registrant have been disseminated both in REACH dossiers and subsequently in peer reviewed publications. A thorough review of all available information on the ECHA dissemination site and a thorough comparison to all of the published data will be necessary in the next phase of this project to be absolutely certain that all available information is included in the published papers. Our preliminary review of the ECHA dissemination site resulted in the identification of one additional inhalation study relevant for ED assessment (McKim et al 2001b), but a more thorough review may be necessary for further establishment of the evidence base.
Data applied for ED evaluation	The ED assessment is based on the data presented in ED list 2018 report. No further experimental studies relevant for ED assessment were identified in the update for the period 2017-2021. Reviews by Franzen et al 2017 and Dekant et al 2017 are considered with respect to human relevance information (see below).
Data applied for DNEL determination	The DK EPA report entitled “Exposure of pregnant consumers to suspected endocrine disruptors” (Andersen et al. 2012) derived a DNEL of 195 µg/kg bw/d on estrogenic effects. The DNEL determination in the current project included data from Andersen et al. 2012 as well as more recent studies. The study by Jean and Plotzke (2017) revealed findings relevant for adjusting the DNEL, see section c) below.

Appendix 3.2 ED assessment overview

T-mediated endocrine effects

Evidence for endocrine activity in vitro (T-mediated): no studies
Evidence for endocrine activity in vivo (T-mediated): no studies
Evidence for adverse effect (T-mediated) [weak] In an inhalation study only one dose of D4 (700 ppm) was tested, and the effects were compared to the effects of the positive control compound for liver-mediated thyroid toxicity – phenobarbital (McKim et al 2001b). The authors found increased thyroid gland weights, hyperplasia and increased proliferation in thyroid glands after 6 and 13 days of inhalation exposure in the D4 group. Thyroid weight were also increased after 27 days of exposure, whereas the increased proliferation was no longer seen at this tie point.

The ED assessment is based on the data presented in ED list report (Hass et al. 2018), as no further experimental studies relevant for ED assessment were identified in the update for the period 2017-2021. In the literature search performed for the ED list report (2018), no studies investigating thyroid effects were identified. However, a review of the ECHA dissemination site

for D4 performed in May 2021 revealed that one relevant study has been performed and published (McKim et al 2001b). In this inhalation study only one dose of D4 (700 ppm) was tested, and the effects were compared to the effects of the positive control compound for liver-mediated thyroid toxicity – phenobarbital. The authors found increased thyroid gland weights, hyperplasia and increased proliferation in thyroid after 6 and 13 days of inhalation exposure in the D4 group. Thyroid weight were also increased after 27 days of exposure, whereas the increased proliferation was no longer seen at this time point. As only one dose of D4 was tested, a NOAEL could not be determined, whereas the LOAEL in this study for thyroid toxicity was 700 ppm (the only tested dose). More studies are needed to verify this LOAEL.

No studies have investigated endocrine activity of D4 (in vitro or in vivo) for the thyroid modality, and only one study has investigated the T-mediated adverse effect, leading to the conclusion that there is a moderate degree of evidence for adverse T-mediated effects. Despite the insufficient amount of data, a Mode of Action analysis has not been performed for thyroid hormone system as this analysis is not always required regarding EATS mediated adverse effects according to ECHA/EFSA 2018 (p.39-40). We have identified a large data gap regarding studies on thyroid effects in vivo and in vitro.

Conclusion – T modalities: There is not sufficient evidence to conclude that D4 is ED via T modality. Given the available data, the T modality is not sufficiently investigated, and D4 can be regarded as a suspected endocrine disrupter for T modality.

EAS-mediated effects

Evidence for endocrine activity in vitro (EAS-mediated): [STRONG]estrogenic
Evidence for endocrine activity in vivo (EAS-mediated): [STRONG] estrogenic
Evidence for adverse effect (EAS-mediated) [STRONG] The adverse effects are: Reduced female fertility, disturbed estrous cycles, reduced ovulations, increased uterus weights with endometrial hyperplasia, vaginal mucification and ovarian atrophy and a strong link between MoA and these adverse effects. In males, increased incidence of testicular interstitial cell hyperplasia was observed

Mode of action		
	Brief description of event	**Supporting evidence**
MIE	Molecular: Activation of estrogen receptor	Strong evidence in vitro: Quinn et al. 2007a: Weak binding of D4 to ERα was observed. D4 did not bind to ERβ, PRα or PRβ. Activation of the ERα reporter gene assay was seen, whereas no activation of the PRβ reporter gene assay was observed for D4. He et al. 2003: D4 bound competitively to ERα but not to ERβ in an ER binding assay.
KE1	Increased estrogen receptor signalling	Strong evidence in vitro: Lee et al. 2015: CaBP-9K (Calbindin-D9k) gene expression was increased in GH3 cells exposed to E2 or D4. CaBP-9k is a calcium binding protein expressed in mammalian intestine, uterus and placenta. It is believed to be involved in transepithelial calcium transport in intestine and placenta and regulation of cytosolic calcium concentration in uterus. Here it is used as an estrogenic biomarker. When cells were exposed to the estrogen receptor antagonist ICI 182-780 in combination with D4 or E2, the gene expression level of CaBP-9K was not affected. Protein expression of CaBP-

Mode of action		
	Brief description of event	**Supporting evidence**
		9K was slightly increased by E2 and D4 but not when ICI was administered simultaneously. Similarly, progesterone receptor (PR) gene- and protein expression levels were increased by D4 and E2, an effect that was blocked by ICI. Conversely, gene-and protein expressions of ERα were downregulated by E2 and D4 and ICI blocked the effect.
KE2	Organ: Increased response in estrogen sensitive tissue	Strong evidence in vivo: Lee et al. 2015: In the Uterotrophic assay, no effects on uterus weight were seen with s.c. administration of D4. Gene- and protein expression levels of CaBP-9K, an estrogenic biomarker, were increased in the uterus by EE and D4 and co-administration of ICI inhibited the effect. PR gene expression in the uterus was decreased by EE and the high D4 dose. ERα gene expression was reduced in the uterus by EE and D4. Gene expression of CYP2B1/2 (cytochrome P450 (CYP) subforms) in the livers was increased markedly compared to controls in the D4 dose-group in a dose-dependent manner. Quinn et al. 2007a: In the Uterotrophic assay with inhalation exposure to D4, uterine weight was increased, uterus was fluid filled and had increased luminal and epithelial cell height in both strains tested. D4 but not ICI 182,789 showed weak anti-estrogenic activity [In uterotrophic assay]. He et al. 2003: D4 induced increased uterine weight in the Uterotrophic assay and increased uterine peroxidase activity. Pre-treatment with ICI 182,780 blocked the D4-induced increase in uterine weight, indicating that the effects on uterus weight are ER-mediated. Additionally, the D4 induced increase in uterus weight was absent in exposed αERKO mice. McKim et al. 2001a: Body weight was decreased in the highest D4 dose-group. Uterus weight was significantly increased by 250, 500 and 1000 mg/kg/day of D4. Co-administration of D4 with EE attenuated the effect of EE on uterine weight suggesting an anti-estrogenic effect of D4. D4 inhibited the effect of EE on uterine weight. Uterine epithelial cell height was increased by EE and D4 in a dose-dependent manner.
KE3	Organ: Altered Prolactin and LH signalling	Strong evidence in vivo:Jean et al. 2017: Progesterone levels were elevated in exposed rats 2-10 weeks after start of treatment and estradiol was reduced over the total study period. As a consequence, lower estradiol:progesterone ratios compared to controls were found in D4 treated females. Corticosterone concentrations were increased in exposed animals during almost the entire study period. Quinn et al. 2007b: A decrease in plasma LH peak levels in female rats were related to the ovulatory status, i.e. lower mean levels of LH were related to a higher number of non-ovulators in the treatment groups. In ovulating females, prolactin levels were reduced. In the 900 ppm group. Plasma estrone and 17β-estradiol hormone levels were increased in both treatment groups (700 and 900 ppm). The ratio between estrone and 17β-estradiol was reduced in the 900 ppm group in non-ovulating females. FSH was decreased in both treatment groups. Progesterone was increased in the highest exposure group.

Mode of action		
	Brief description of event	**Supporting evidence**
Adverse Outcome (AO)1	Impaired female reproduction	Strong evidence in vivo: Reduced female fertility (Meeks et al. 2007) disturbed estrous cycles (Siddiqui et al. 2007), reduced ovulations (Quinn et al. 2007b), increased uterus weights (Quinn et al. 2007b) with endometrial hyperplasia (Jean and Plotzke 2017), vaginal mucification (Burns-Nass et al. 2002) and ovarian atrophy and increased uterine weights (Jean and Plotzke, 2017). An increased incidence of uterine cystic endometrial hyperplasia was found in high-dose females. Small but statistically significantly increased incidence of cervical squamous epithelial hyperplasia and/ or ovarian atrophy was observed. (Jean and Plotzke 2017)
Adverse Outcome (AO)2	Impaired male reproduction	Testis weights were increased in animals in the 700 ppm group exposed through inhalation for 24 months (Rats, n=60/sex/group);Similarly, a modest but significant increase in the incidence of testicular interstitial cell hyperplasia was observed after 24 months of exposure to 150 and 700 ppm D4 (Jean and Plotzke, 2017).

Biological plausibility of key event relationships

In agreement with the ED list report from 2018, we find strong evidence that D4 has EAS related adverse effects on the reproductive system. The ED list concluded that "There is strong evidence for an estrogenic mode of action of D4, and strong evidence for adverse effects on female reproductive system that can be related to this estrogenic mode of action of D4 together with an endocrine mode of action through LH (luteinizing hormone). However, changes in LH levels may be species specific. Changes in LH levels are probably responsible for some of the adverse effects observed, but D4 also had a strong estrogenic activity, and it is unclear which adverse effects can be linked to this mode of action alone. The male reproductive effects are likely related to an endocrine mode of action as well, but the few data available on androgen-related mode of action did not confirm an anti-androgenic mode of action of D4. It is possible that the estrogenic mode of action of D4 could be responsible for the testicular effects observed. The mode of action behind the effects observed on thyroid glands cannot be determined based on the available data."

It is noted that the Increase in Hyperplasia (Leydig cells) mentioned in Jean and Plotzke, 2017 is a Key event (https://aopwiki.org/events/744) involved in AOP (Adverse outcome pathway) no. 111 (Decrease in androgen receptor activity leading to Leydig cell tumours (in rat), https://aopwiki.org/aops/111) and in AOP 120 (Inhibition of 5α-reductase leading to Leydig cell tumours (in rat), https://aopwiki.org/aops/120). This strengthens the conclusion that adverse effects of D4 are likely to be EAS mediated.

The review by Franzen et al. 2017 (written by a consultancy agency funded by the Silicones Environmental, Health and Safety Center (SEHSC) does not support that D4 is an endocrine disruptor as they conclude:
"The reproductive effects reported in the female rats in the two generation reproductive study (Siddiqui et al., 2007) and the additional studies (Quinn et al., 2007a,b; He et al. 2003; Lee et al. 2015) conducted to assess the potential endocrine activity of D4 have suggested that D4 has very weak estrogenic and antiestrogenic activity. However, there are observations in the reproductive studies that don't support the direct effect of D4 as a weak estrogen and that are inconsistent with this activity (Siddiqui et al., 2007), thus indicating the very weak hormonal potency of D4. A more relevant explanation for the reproductive toxicity is induction of a delay of the LH surge necessary for optimal timing of ovulation (Quinn et al., 2007a,b). An insufficient or blocked pre-ovulatory LH surge fails to induce complete ovulation in the rat and results in

the reduced litter size observed following exposure. However, the current understanding of estrous cyclicity and neural/hormonal regulation of ovulation in humans suggests that the effects of D4 on fertility as observed in the rat are unlikely to be relevant to humans (Plant, 2012; Dekant et al., 2017)."

Likewise, a review by Dekant et al. 2017 (supported by the American Chemistry Council) does not support that D4 is an endocrine disruptor as they conclude:
"D4 possesses only very weak estrogenic and antiestrogenic activity in rats and has a low affinity for estrogen receptor-a (He et al., 2003). D4 had no estrogenic/antiestrogenic activity on pubertal timing in male or female rats in a two-generation study (Siddiqui et al., 2007). D4 does not have progestagenic, androgenic, or anti-androgenic activity (Quinn et al., 2007b). A direct hormonal effect of D4 on endometrial cells is unlikely as a mode of action for D4-associated endometrial hyperplasia and adenoma in the aging F344 rat."

DTU finds strong evidence for estrogenic effects in vitro and in vivo, and thus disagree with the views of these papers. In addition, we find that effects on LH signalling also serve as a relevant endocrine mode of action. In the absence of evidence for the opposite, effects are considered human relevant.

Conclusions on Mode of action analysis	
Biological plausibility of key event relationships	It is biologically plausible that adverse effects are due to the endocrine activity of D4.
Dose and temporal concordance	Females: Dose-dependent effects on reduced fertility, disturbed oestrous cycles, reduced ovulations, increased uterus weights with endometrial hyperplasia, vaginal mucification, reduced ovary weight and atrophy of ovaries. Males: Significant increase in the incidence of testicular interstitial cell hyperplasia was observed after 24 months of exposure to 150 and 700 ppm D4. In this study the effect was dose-dependent.
Essentiality, consistency, analogy and specificity	For determining essentiality it should be demonstrated whether or not downstream KEs and/or the adverse effect is prevented/decreased if an upstream event is experimentally blocked. Such studies were not performed for D4. The data on endocrine activity and adverse effects are consistent, specifically for estrogenic effects in vitro and in vivo. The observed adverse effects on female reproductive organs and reproductive function in rodents are considered specific and not resulting from non-endocrine modes of action. No alternative non-endocrine mode of action is demonstrated.
Human relevance	DTU finds that, relevance to humans is assumed by default in the absence of appropriate scientific data demonstrating non-relevance. The 2 reviews below finds that these endocrine modes of action are not relevant to humans. DTU disagree with the views of these papers and still find that there is human relevance. No epidemiological studies were found that examined the relationship between D4 exposure and effect on EAS relevant adverse effects. Franzen et al. 2017 mentions that: *the current understanding of estrous cyclicity and neural/hormonal regulation of ovulation in humans suggests that the effects of D4 on fertility as observed in the rat are unlikely to be relevant to humans*

Conclusions on Mode of action analysis	
	Dekant et al. 2017 writes: *In summary, the available information suggests that the induction of benign proliferative endometrial lesions in the rat after chronic D4 inhalation has no relevance for human risk characterization. Due to the absence of genotoxicity of D4 and absence of any appreciable direct hormonal activity of D4, the induction of cystic endometrial hyperplasia and the significant trend for an increased incidence of uterine endometrial adenoma observed across D4 dose levels in the two-year inhalation study are likely due to interferences of D4 with rat estrous cycle control that are only seen at doses that exceed the metabolic capacity of animals and not relevant to women.*
Identified uncertainties	Changes in LH levels may be species specific. Changes in LH levels are probably responsible for some of the adverse effects observed, but D4 also had a strong estrogenic activity and it is unclear which adverse effects can be linked to this mode of action alone. The male reproductive effects are likely related to an endocrine mode of action as well, but the few data available on androgen-related mode of action did not confirm an anti-androgenic mode of action of D4. It is possible that the estrogenic mode of action of D4 could be responsible for the testicular effects observed.

The analysis leads to the conclusion that it is biologically plausible that estrogen receptor activation leads to adverse effects on the reproductive system, specifically adverse effects on female reproductive system that can be related to this estrogenic mode of action of D4 together with an endocrine mode of action through LH. However, changes in LH levels may be species specific. Changes in LH levels are probably responsible for some of the adverse effects observed, but D4 also had a strong estrogenic activity, and it is unclear which adverse effects can be linked to this mode of action alone. The male reproductive effects are likely related to an endocrine mode of action as well, but the few data available on androgen-related mode of action did not confirm an anti-androgenic mode of action of D4. It is possible that the estrogenic mode of action of D4 could be responsible for the testicular effects observed as well. The mode of action behind the effects observed on thyroid glands cannot be determined based on the available data. The mode of action for adverse reproductive effects of D4 is based on “EAS-mediated adversity”, and the substance is considered to be an endocrine disrupter. No alternative non-endocrine mode of action is demonstrated.

Conclusions on Mode of action analysis – EAS modality. There is sufficient evidence of endocrine activity (estrogenic mode of action of D4). There is strong evidence for adverse effects of D4 (on both female and male reproductive system). The literature update was made for the ED list in 2017. In the update for the period 2017-2021 we identified no further experimental studies relevant for ED assessment. Our re-evaluation withholds the conclusion from the ED list report that D4 fulfils the definition of an EDC. Whether it is enough evidence for the substance to be identified as a substance of very high concern exposure gives rise to an equivalent level of concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH), will be clarified in phase II of this project.

Appendix 3.3 DNEL and DMEL determination

The study by Jean and Plotzke (2017) revealed findings not described in the previous evaluation of the same study on the basis of information in the SCCS 2010 opinion for the Larsen et al. 2017 report. These findings were used for deriving a new, lower DNEL in the present project than presented by Larsen et al. (2017). The ED list report (Hass et al. 2018) and MoA analysis (above on EAS modalities) also mentioned several other studies such as Meeks et al. 2007 showing decreased fertility from 300ppm and increasing doses.

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
Jean and Plotzke 2017	Rats, 24-month combined chronic/ oncogenicity inhalation rat study Doses 0; 10; 30; 150 or 700 ppm n=60/sex/group	↑ incidence and severity of testes interstitial cell hyperplasia at 150 and 700 ppm (NOAEL 30 ppm)	3.6/17.8/- (30/150/- ppm) (male rats) (in SCCS opinion the NOAEL is 17.8 in the male rats)	DNEL: 10 (interspecies) *10 (intraspecies) =100 DMEL: 10 (interspecies) *10 (intraspecies) *10 (nature of endocrine disrupting properties) =1000	$DNEL_{eas}$: 36 $DMEL_{eas}$: 3.6	**$DNEL_{eas}$: 36** **$DMEL_{eas}$: 3.6**	NOAEL 150 ppm in inhalation study set by SCCS 2010. The NOAEL of 150 ppm was derived, based on non-neoplastic changes (increased liver weights and centrilobular hypertrophy of hepatocytes in male rats receiving 700 ppm D4 for 12 months (SCCS, 2010). The SCCS opinion did not mention the findings of the testicular interstitial cell hyperplasia. We however find that the NOAEL should be 30 ppm based on testicular effects and thereby 5 times lower than suggested in the SCCS opinion (2010). See table below
Siddiqui et al., 2007	Rats, 2. generation study, inhalation, (doses of 0, 70, 300, 500 or 700 ppm of D4 for 6 hours per day) (F0, 165 per sex) (F1, n=23-27 litters per group)	↓ fertility and ↓ litter size at doses above 150 ppm	19.5/32.5/- (female rats)	DNEL: 10 (interspecies) *10 (intraspecies) =100 DMEL: 10 (interspecies) *10 (intraspecies) *10 (nature of endocrine disrupting properties) =1000	$DNEL_{eas}$:195 $DMEL_{eas}$: 19.5	$DNEL_{eas}$:195 $DMEL_{eas}$: 19.5	NOAEL 150 ppm in inhalation study, conversion to internal dose was based on SCCS (2010) opinion (page 99). The NOAEL for systemic toxicity (150 ppm) used by SCCS also covers reprotoxic effects (NOAEL of 300 ppm from the Siddiqui et al. study)
Comments: A $DNEL_{eas}$ of 36 µg/kg bw/d and a $DMEL_{eas}$ of 3.6 µg/kg bw/d was derived in this project from a 24-month combined chronic/oncogenicity inhalation rat study (Jean, and Plotzke 2017). The adverse findings in the males (testes interstitial cell hyperplasia) were used for the revised NOAEL setting and the DNEL. This DNEL is lower than the DNEL of 195 µg/kg bw/d derived for the Larsen et al. 2017 report based on a two-generation study in rats (Siddiqui et al., 2007).							

Notes on study by Jean and Plotzke 2017:

The 30 ppm conversion to internal dose was based on SCCS 2010 opinion (p.99 and below):

NOAEL: 30 ppm (exposure 6 hours, 5 days per week)

Conversion factor: 1 ppm = 0.012 mg/l (D4)

Combined conversion factor: 1 ppm = 0.0135 mg/l

Converted NOAEL: 30 ppm = 0.0135 mg/l x 30 = 0.405 mg/l

(exposure 6 hours, 5 days per week)

Inhalation volume 1, male rat 20.5 l/h;

Weight male rat: 0.5 kg;

Exposure by inhalation, male rat:

[(0.405 x 20.5 x 6) x 5/7]/0.5 = 71.16 mg/kg bw/day

Absorption by inhalation, rat 5%

NOAEL male rats (71.16 x 0.05) = 3.6 mg/kg bw/day

This effect on the male reproductive system reflects a sensitive marker for ED mediated adverse effects. The effect is seen in adults after lifelong exposure, and such effects are not evaluated in 2-generation studies. Therefore, setting a DNEL for this endpoint serves as a cautious choice when performing risk assessment for not only adult men, but also children and pregnant women.

Therefore, DTU finds that an extra assessment factor is not needed to take into account that the effect is seen in adult animals and not developing animals. This is in line with principles described in the ED risk rapport (Hass et al. 2019).

Appendix 3.4 Notes on other effects of relevance for human health

The Siddiqui et al. (2007) study (2 gen study) observed some general toxicity in the offspring as evidenced by increased organ weights of liver, kidney and pituitary glands and histologically observed hypertrophy of hepatocytes, indicative of increased metabolising activity of the liver. Moreover, the F1 females (First generation female offspring) showed more signs of toxicity (increased organ weights and histological changes in livers indicating metabolising activity) compared to F0 females (Parental generation females) and this may explain why more marked effects on reproductive parameters such as gestation length and estrous cycle length were seen in the F1 females. Nevertheless, the study provides moderate evidence of adverse effects on female reproduction that could be explained by an endocrine disrupting mode of action.

Appendix 3.5 References for D4

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Appendix 4. BHA

Butylated hydroxyanisole, BHA, CAS no. 25013-16-5

Appendix 4.1 Data availability and literature search

Previous reports	EFSA opinions (EFSA 2011, 2012). The scientific panel noted potential endocrine effects of BHA. Acceptable daily intake (ADI) for BHA was set based on effects on growth retardation of pups, increased mortality and behavioural effects. CEHOS SIN list report (Hass et al. 2012). Evaluation of available data for BHA against the Danish criteria for identification of ED substances led to evaluation in Category 1, Endocrine Disruptor. MST project "Exposure of children and unborn children to selected chemical substances" (Larsen et al. 2017). A DNEL for thyroid hormone disrupting effects was determined and applied for risk assessment.
New search 2021	For update of DNEL determination and ED evaluation in this project, a search was conducted in PubMed on 12 April 2021. The search strategy was based on the description in ECHA/EFSA guidance (ECHA/EFSA 2018) (page 130). A relatively broad search using the search string: "(((butylated) AND (hydroxyanisole)) OR (25013-16-5)) AND (((rats) OR (mice)) OR (toxicity))" gave 1000 + hits covering all years. As focus is on ED effects we chose to instead use a targeted search strategy covering all years using the search string: "((((butylated) AND (hydroxyanisole)) OR (25013-16-5)) AND (((rats) OR (mice)) OR (toxicity))) AND ((((((endocrin*) OR (hormon*)) OR (androgen*)) OR (estrogen*)) OR (thyroid*)) OR (steroid*))". This resulted in the 95 hits, which were included in the screening process. The screening process constitutes 3 steps as described in ECHA/EFSA guidance (ECHA/EFSA 2018): 1) Screening of titles 2) Screening of abstracts 3) Screening of full text Overview screening process:

	Search string	Date of search	Number of hits in PubMed	Screen 1 (title)	Screen 2 (abstract)	Screen 3 (full text)	Relevant for ED assessment
BHA	((((butylated) AND (hydroxyanisole)) OR (25013-16-5)) AND (((rats) OR (mice)) OR (toxicity))) AND ((((((endocrin*) OR (hormon*)) OR (androgen*)) OR (estrogen*)) OR (thyroid*)) OR (steroid*))	12/4 - 2021	95	19 relevant + 13 maybe relevant	13 relevant + 5 maybe relevant	15 relevant (6 in vivo, 9 in vitro) + 3 maybe relevant	14 relevant (5 in vivo, 8 in vitro + 1 in vitro from the maybe list)

	After screen 3 (full text) 14 articles (5 in vivo, 9 in vitro) were considered relevant for inclusion in ED assessment. Furthermore, three in vitro studies from the CEHOS SIN list report (Hass et al. 2012) were included (Jobling et al. 1995; Soto et al. 1995; ter Veld et al. 2006).
Review of the ECHA dissemination site	BHA entries in ECHAs public dissemination site were investigated on 18/5-2021. This resulted in identification of six additional papers (public access), of which three in vivo studies were found to be relevant for ED assessment (Hansen and Meyer 1978; Pop et al. 2013; Liang et al. 2014). Additionally we identified 17 toxicity studies, where only confidential study report were available. Based on the provided study summaries we could not assess reliability or ED-relevance of these studies, and these studies have therefore not been included in the ED assessment or DNEL setting.
Data applied for ED evaluation	Experimental studies relevant for ED assessment were identified in literature search and investigation of ECHA dissemination site.
Data applied for DNEL determination	The DNEL determination in the current project included data from Larsen et al. (2017) as well as studies that are more recent. The DK EPA report entitled “Exposure of children and unborn children to suspected endocrine disruptors” (Larsen et al. 2017) derived a DNEL of 1000 µg/kg bw/d for thyroid disrupting effects. Reproductive effects were identified by Larsen et al. 2017, but were not applied for DNEL determination, as that report required effects to be categorized as either estrogenic or anti-androgenic, which could not be decided. The current project includes all EAS relevant effects, and is not limited to substances following patterns seen for clear anti-androgens or estrogens. Therefore, a DNELeas is derived in the current project (see section c)) on the basis of data included in Larsen et al. 2017.

Appendix 4.2 ED assessment overview

T-mediated endocrine activity

Evidence for endocrine activity in vitro (T-mediated): [WEAK] Few data investigating T-mediated effect in vitro. Two studies in zebra fish larvae has investigated effects on T-system; one showing decreased T3 and increased T4 and TSH after BHA exposure (Zhao et al. 2020) and the other showing altered expression of central genes regulating the HPT axis (Yang et al. 2018). One study using GH3.TRE-Luc gene reporter assay showed both agonism and antagonism of thyroid receptor (Klopčič and Sollner Dolenc 2017).
Evidence for endocrine activity in vivo (T-mediated): [WEAK] Few data investigating T-mediated activity in vivo. In Jeong et al. (2005), thyroid hormone levels in F0 and F1 generation in both females and males were reported; in adult females (F0 generation, exposure included gestation period) no effects were seen on T4 levels. In adult males (F0 generation) reduced T4 levels were seen. In offspring females (F1 generation, 13 weeks of age), decreased T4 levels were seen, whereas in offspring males (F1 generation, 13 weeks of age) no effects were seen. In castrated rats (Hershberger assay), no effect was seen on T4 levels (Kang et al. 2005).
Evidence for adverse effect (T-mediated) [MODERATE] Thyroid histopathology affected in male and female offspring exposed during gestation, lactation and up to 13 weeks of age (Jeong et al. 2005). Thyroid histopathology also affected in pigs exposed 3 weeks before conception and up to gestation day 110 (Hansen et al. 1982). Few effects were seen on thyroid weight in both adult and perinatally exposed animals (rat and pig).

The data from both in vitro and in vivo studies indicates endocrine disrupting effects after exposure to BHA. A MoA analysis was therefore carried out.

Mode of action		Interference with thyroid hormone system
Hypothesis		The molecular initiating event (MIE) is not characterized, and several possible MIEs could cause the observed changes in thyroid histology. Though only shown in some studies, the adverse effects on the thyroid glands were most likely mediated via changes in thyroid hormone levels. The affected thyroid histology is an adverse effect that may also affect human thyroid function.
	Brief description of event	**Supporting evidence**
MIE	Molecular: Binding to TR and /or a yet unidentified MIE	Not characterized
KE	Organ: Altered thyroid hormone concentrations	Weak evidence A study in zebra fish larvae showed decreased T3 and increased T4 and TSH after BHA exposure (Zhao et al. 2020). In rats, Jeong et al. (2005) report no effects on T4 levels in adult females, whereas a reduction was seen males. In the same study, 13 week old female offspring showed reduced T4 levels, whereas no effects were seen in males. A study in castrated males (Hershberger assay) report no effect on T4 levels after BHT exposure (Kang et al. 2005).
AO	Organism: Thyroid gland toxicity	Moderate evidence Thyroid histopathology was affected in 13 week old male and female offspring (Jeong et al. 2005), as well as in adult pigs exposed from 3 weeks before conception up to gestation day 110 (Hansen et al. 1982).

Conclusions on Mode of action analysis	
Biological plausibility of key event relationships	It is biologically plausible that the adverse effects registered are due to the endocrine activity of BHA
Dose and temporal concordance	Based on the studies conducted it seems as if developing organisms and offspring exposed during development may be more sensitive. More specific dose response effects are difficult to delineate on the data at hand, but it seems as if effect is seen at the higher doses.
Essentiality, consistency, analogy and specificity	For determining essentiality it should be demonstrated whether or not downstream KEs and/or the adverse effect is prevented/decreased if an upstream event is experimentally blocked. No such studies have been provided for BHA. However, the effects on thyroid gland histopathology are considered to be due to endocrine mode of action, as no alternative non-endocrine mode of action is demonstrated.
Human relevance	Even though thyroid hormone disruption may be quantitatively more sensitive in rats than in humans, human relevance should be assumed (ECHA/EFSA 2018), especially as effects were also seen in pigs.
Identified uncertainties	There is a lack of robust studies for investigations of both endocrine activity in vivo and vitro as the data at hand is scarce.

Conclusions on Mode of action analysis – T modality. There is weak evidence of endocrine activity and sufficient evidence adverse effects (histological changes in thyroid in rats and pigs) of BHA. BHA fulfils the WHO definition for being considered an endocrine disrupter via T modality.

EAS-mediated endocrine activity

Evidence for endocrine activity in vitro (EAS-mediated): [WEAK (estrogenic/anti-estrogenic) – STRONG (anti-androgenic)]

The data on androgenic and anti-androgenic activity shows a clear pattern of no androgen receptor agonism (Schrader and Cooke 2000; Pop et al. 2016), but clear anti-androgenic activity with antagonism of the androgen receptor (Schrader and Cooke 2000; Pop et al. 2016; Klopčič and Sollner Dolenc 2017). In one of these studies, the antagonistic activity of BHA was found to be more potent than that of the positive control (Klopčič and Sollner Dolenc 2017). BHA exposure also reduces androgen production in immature Leydig cells and reduces gene- and protein expression and activity of several enzymes central to androgen synthesis (Li et al. 2016).

The data for estrogenic activity shows a varied pattern in vitro. One transactivation assay shows no agonism (Pop et al. 2018), whereas another shows activation, though less than 20% of the positive control estradiol (Jobling et al. 1995). When looking at induction of proliferation both estrogenic (Pop et al. 2018; Jobling et al. 1995) and anti-estrogenic activity was seen (Pop et al. 2018). In assays investigating ERα and ERβ binding, BHAs response was 18.3 and 15.6% response of that of estradiol (ter Veld et al. 2006). In E-screen BHA was not very potent and likely a partial agonist (Soto et al. 1995) and in a study using rainbow trout liver cytosol to evaluate ER binding, it was found to reduce binding of estradiol, but it is not known if it was by direct competition (Jobling et al. 1995). In a study using liver cytosol from Xenopus laevis to investigate competitive displacement of radiolabeled E2 from ER, BHA had an IC50 value approximately 830 times bigger than that of E2. This shows some displacement capacity (Lutz & Kloas 1999).

Evidence for endocrine activity in vivo (EAS-mediated): [WEAK to MODERATE in males – STRONG in females]

In F0 males exposed for 7 weeks and F1 offspring exposed during gestation, lactation and up to 13 weeks of age, decreased testosterone levels were seen (Jeong et al. 2005). In a Hershberger assay, BHA did not affect testosterone levels after co-administration of Testosterone Propionate (nor alone, testosterone not affected in these castrated rats) (Kang et al. 2005).

In F0 females exposed for 10 weeks (including gestation) and F1 offspring exposed during gestation, lactation and up to 13 weeks of age, estradiol levels were not affected (Jeong et al. 2005). In a uterotrophic assay exposing to BHA for 18 days and hereafter to estradiol and estrone for 3 days, decrease in estradiol and estrone levels were seen (Zhu et al. 1997). In uterotrophic assay, decreased uterus weight was seen both with and without co-exposure of estradiol, but no effects were seen on uterus histopathology (Kang et al. 2005). Reduced response in uterine weight gain was also seen in an uterotrophic study in mice (Zhu et al. 1997).

Evidence for adverse effect (EAS-mediated): [MODERATE]

Males:

Statistically significantly, shorter Anogenital distance (AGD) on PND22 after perinatal exposure, but it was evaluated as not biologically significant according to the authors of the article. The AGD data are not depicted in the article and therefore not possible to evaluate. In the same study, no effect was seen on AGD at 13 weeks of age (Jeong et al. 2005). Delayed sexual maturation after perinatal exposure decreased prostate weight in males after 7 weeks of adult exposure (F0 generation) and perinatal exposure (F1 generation) (Jeong et al. 2005). Testis weight was only reported in the perinatal exposure study showing reduced weight after perinatal exposure in adult F1 offspring, but not in F0 males or in prepuberty (Jeong et al. 2005). Testis histopathology was only examined in F1 males and showed no effect of exposure.

Sperm parameters were affected in perinatally exposed males (F1) but not in adult exposed males (F0) (Jeong et al. 2005).

Females:

The only adverse outcome seen is delayed vaginal opening and changed estrous cycling after perinatal exposure (oral) in Jeong et al. (2005). No effects seen on ovary weight or histopathology.

The data from both in vitro and in vivo studies clearly indicates endocrine disrupting effects after exposure to BHA. A MoA analysis was therefore carried out.

Male reproductive system

Mode of action		Interference with male reproductive system
Hypothesis		The molecular initiating event (MIE) is antagonism of the androgen receptor (AR). Additionally, interference with the male reproductive system could also possibly be interference with an uncharacterized MIE leading to reduced androgen synthesis.
	Brief description of event	**Supporting evidence**
MIE	Molecular: antagonism of androgen receptor + possible uncharacterized MIE related to affected steroidogenesis	Strong evidence in vitro: Anti-androgenic activity with antagonism of the androgen receptor (Schrader and Cooke 2000; Pop et al. 2016; Klopčič and Sollner Dolenc 2017).
KE 1	Cell: reduced testosterone synthesis + effects on steroidogenic enzymes	Moderate evidence: Reduces androgen production in immature Leydig cells and reduced gene- and protein expression and activity of several enzymes central to androgen synthesis (Li et al. 2016).
KE 2	Organ: Altered testosterone levels	Weak to Moderate evidence: In F0 males exposed for 7 weeks and F1 offspring exposed during gestation, lactation and up to 13 weeks of age, decreased testosterone levels were seen (Jeong et al. 2005). In a Hershberger assay, BHA did not affect T levels after co-administration of TP (Kang et al. 2005). This lack of effect in Hershberger assay may be due to the timing of exposure, as an in vitro study show effects in immature Leydig cells (Li et al. 2016) and effects on testosterone is seen in rats exposed during gestation and lactation, hence immature Leydig cells were exposed (Jeong et al. 2005).
AO	Organism: affected male reproductive system	Moderate evidence There are several different endpoints affected; delayed sexual maturation, testis weight and sperm parameters after perinatal exposure and decreased prostate weight after adult exposure (Jeong et al. 2005) resulting in an overall picture of affected male reproductive system.

Conclusions on Mode of action analysis, males	
Biological plausibility of key event relationships	It is biologically plausible that the adverse effects registered are due to the endocrine activity of BHA
Dose and temporal concordance	Based on the studies conducted, it seems as if developing organisms and offspring exposed during development may be more sensitive.
Essentiality	For determining essentiality it should be demonstrated whether or not downstream KEs and/or the adverse effect is prevented/decreased if an upstream event is experimentally blocked. No such studies have been provided for BHA. However, the effects on male reproductive endpoints are considered to be due to endocrine mode of action, as no alternative non-endocrine mode of action is demonstrated.
Human relevance	When effects on male reproductive system is seen in rats, especially on sperm parameters, the data are considered to have human relevance.
Identified uncertainties	There is a lack of robust studies for investigations of both endocrine activity in vivo and adverse outcome in vivo.

Female reproductive system

Mode of action		Interference with female reproductive system
Hypothesis		The molecular initiating event (MIE) is uncharacterized, but could be anti-estrogenic.
	Brief description of event	**Supporting evidence**
MIE	Molecular: Uncharacterized	No evidence
KE 1	Cell: reduced estrogenic response	Weak in vitro: Anti-estrogen effect in proliferation assay (Pop et al. 2018).
KE 2	Organ: Anti-estrogen effect	Strong evidence: Anti- estrogen effect was seen in three uterotrophic studies; exposure to BHA for 18 days and hereafter to estradiol and estrone for 3 days, decrease in estradiol and estrone levels (Zhu et al. 1997), decreased uterus weight was seen both with and with out co-exposure of estradiol (Kang et al. 2005), reduced response in uterine weight gain (Zhu et al. 1997).
AO	Organism: affected female reproductive system	Moderate evidence: Delayed vaginal opening and changed estrous cycling after perinatal exposure (Jeong et al. 2005).

Conclusions on Mode of action analysis, females	
Biological plausibility of key event relationships	It is biologically plausible that the adverse effects registered are due to the endocrine activity of BHA, especially as strong anti-estrogenic effects are seen in vivo.
Dose and temporal concordance	Based on the studies conducted it is not possible to evaluate the dose and temporal concordance.
Essentiality	For determining essentiality it should be demonstrated whether or not downstream KEs and/or the adverse effect is prevented/decreased if an upstream event is experimentally blocked. No such studies have been provided for BHA. However, the anti-estrogenic effects in vivo are considered to be due to endocrine mode of action, as no alternative non-endocrine mode of action is demonstrated.
Human relevance	It is not possible to determine human relevance.
Identified uncertainties	There is a lack of robust studies for investigations of both endocrine activity in vitro and adverse outcome in vivo.

Conclusions on Mode of action analysis – EAS modality. There is sufficient evidence of endocrine activity and adverse effects of BHA (for both female and male reproductive system). Our evaluation withholds the conclusion from the CEHOS SIN list report (Hass et al. 2012) that BHA fulfils the WHO definition for being considered an endocrine disrupter.

Appendix 4.3 DNEL and DMEL determination

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
Hansen et al., 1982	Pigs, young adult, dietary exposure 3 weeks before mating and 110 days into pregnancy to 0, 50, 200, 400 mg/kg bw/day of BHA (n = 9-13)	↑ absolute and relative thyroid (and liver) weight at all tested dose levels. Both absolute and relative thyroid weight was increased at lowest dose to 140% of controls. Relative thyroid weights increased further with increasing dose, whereas no increase was seen in absolute thyroid weight with increasing dose	Thyroid: -/50/-	DNEL: 10 (intraspecies) x2 (pig to human) x2.5 (remaining differences interspecies) x3 (lack of a NOAEL)=150 DMEL: 10 (intraspecies) x2 (pig to human) x2.5 (remaining differences interspecies) x3 (lack of a NOAEL) x10 (nature of endocrine disrupting properties) =1500	$DNEL_{thyr}$: 333 $DMEL_{thyr}$: 33	$DNEL_{thyr}$: 333 $DMEL_{thyr}$: 33	No effect on endpoints sensitive to disturbance of sex hormones. Allometric scaling factor 2 for pigs
Jeong et al., 2005	Rats, two generation study, non-guideline, exposure pregestation, gestation and lactation and offspring exposed until 13 weeks of age, 0, 10, 100, 500 mg/kg bw/day of BHA (n = 12)	High dose: ↑ relative thyroid weight in F0 to 119% of control (absolute thyroid weight NS increase to 112% of control). ↓ serum T4 in male F0 and female F1, altered thyroid histology in female F1 (epithelial cells being enlarged in cell height, vacuolated and exfoliated. Follicles decreased in size with sparse colloidal fluid) with no change in thyroid weight. ↓ testosterone in male F0 and F1, ↓ weight of testis (abs) and ventral prostate (absolute and relative) in F0 adults.	Thyroid: 100/500/- EAS: 10/100/-	DNEL: 10 (intraspecies) x4 (rat to human) x2.5 (remaining differences interspecies) =100 DMEL: 10 (intraspecies) x4 (rat to human) x2.5 (remaining differences interspecies) x10 (nature of endocrine disrupting properties) =1000	$DNEL_{thyr}$: 1000 $DMEL_{thyr}$: 100 $DNEL_{eas}$: 100 $DMEL_{eas}$: 10	$DNEL_{thyr}$: 1000 $DMEL_{thyr}$: 100 $DNEL_{eas}$: 100 $DMEL_{eas}$: 10	EFSA Panel 2011 considered that the study was not performed according to OECD guidelines and that effect sizes in general were too small (<10%) or with too large variation and could not be used to derive a point of departure for risk assessment. With regards to thyroid histology, the comment on effects size is not relevant, and the effect is considered relevant here. This study is considered more robust than the study by Hansen et al. 1982 and therefore used for $DNEL_{thyr}$ determination.

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
		Sperm parameters affected at all dose levels but most markedly at high dose. Delayed sexual maturation and irregular estrous cycling in F1 females. Middle dose: ↓ vaginal weight in adult F1.					
Kang et al., 2005	Uterotrophic: Immature 20 day old female rats, 3 days exposure to 50, 100, 250, 500 mg/kg bw/day of BHA (n = 11) Hershberger: 51-day old castrated male rats, 10 days exposure to 50, 100, 250, 500 mg/kg bw/day of BHA without TP co-administration or to 250 mg/kg bw/day with TP co-administration.	Uterotrophic: ↓ absolute and relative uterus weight at all doses; no effect on epithelial cell height. Also ↓ absolute and relative uterus weight when supplemented with ethinyl estradiol. Hershberger: no effect of BHA on weights of androgen-sensitive organs when administered alone, but BHA increased ventral prostate weight when co-administered with testosterone propionate (TP).	EAS Uterotrophic: Not determined/50/- Hershberger: no sign of anti-androgenic or androgenic effect	$DNEL_{eas}$: 10 (intra-species) x4 (rat to human) x2.5 (remaining differences interspecies) x3 (lack of NOAEL) =300 $DMEL_{eas}$: 10 (intra-species) x4 (rat to human) x2.5 (remaining differences interspecies) x3 (lack of NOAEL) x10 (nature of endocrine disrupting properties) =3000	$DNEL_{eas}$: 166 $DMEL_{eas}$: 17	$DNEL_{eas}$: 166 $DMEL_{eas}$: 17	No effect on thyroxine level or thyroid weight after 10 days in Hershberger study.
Comments: **$DNEL_{thyr}$ of 1000 µg/kg bw/d and a $DMEL_{thyr}$ of 100 µg/kg bw/d** derived from reproductive toxicity study by Jeong et al., 2005, was selected for cumulative risk assessment because the observed effects were observed following a relevant exposure period for the current project and the thyroid disrupting effect of BHA was confirmed in a pig study. A $DNEL_{eas}$ of 100 µg/kg bw/d and a $DMEL_{eas}$ of 10 µg/kg bw/d was set on the basis of the same study, as BHA showed mixed endocrine disrupting effects, although the patterns of anti-androgenic and anti-estrogenic modes of action were not similar to patterns seen for other well-described endocrine disrupters.							

Appendix 4.4 Notes on other effects of relevance for human health

No other effects noted of relevance for human health (not specifically addressed in the literature search).

Appendix 4.5 References for BHA

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Larsen, PB; Boberg J, Poulsen PB, Mørck TA, Boyd HB, Andersen DN, Axelstad M, Hass U (2017) Exposure of children and unborn children to selected chemical substances MST survey of chemical substances in consumer products no. 158 ISBN: 978-87-93529-84-7 https://mst.dk/service/publikationer/publikationsarkiv/2017/maj/exposure-of-children-and-unborn-children-to-selected-chemical-substances/

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Lutz I, Kloas W (1999) Amphibians as a model to study endocrine disruptors: I. Environmental pollution and estrogen receptor binding. Sci Total Environ 225:49–57. doi: 10.1016/S0048-9697(99)80016-3

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Appendix 5. Butylated hydroxytoluen (BHT)

2,6-di-tert-butyl-p-cresol, CAS 128-37-0

Appendix 5.1 Data availability and literature search

Previous reports	EFSA opinion (EFSA 2012). MST project "Exposure of children and unborn children to selected chemical substances" (Larsen et al. 2017). A DNEL was determined for endocrine disrupting properties.
New search 2021	For update of DNEL determination and ED evaluation in this project, a search was conducted in PubMed on 12 April 2021. The search strategy was based on the description in ECHA/EFSA (2018) (page 130). We used a targeted search strategy with focus on ED using the search string: "((((butylated) AND (hydroxytoluene)) OR (128-37-0)) AND (((rats) OR (mice)) OR (toxicity))) AND ((((((endocrin*) OR (hormon*)) OR (androgen*)) OR (estrogen*)) OR (thyroid*)) OR (steroid*))". This resulted in the 109 hits screened in this document. The screening process constitutes 3 steps as described in ECHA/EFSA (2018): 1) Screening of titles 2) Screening of abstracts 3) Screening of full text Overview screening process:

	Search string	Date of search	Number of hits in PubMed	Screen 1 (title)	Screen 2 (abstract)	Screen 3 (full text)	Relevant for ED assessment
BHT	((((butylated) AND (hydroxytoluene)) OR (128-37-0)) AND (((rats) OR (mice)) OR (toxicity))) AND ((((((endocrin*) OR (hormon*)) OR (androgen*)) OR (estrogen*)) OR (thyroid*)) OR (steroid*))	12/4-2021	109	13 relevant + 14 maybe relevant	9 relevant + 1 maybe relevant	9 relevant (2 in vivo + 7 in vitro)	9 relevant (2 in vivo + 7 in vitro)

After screen 3 (full text), 9 articles (2 in vivo and 7 in vitro) were considered relevant for inclusion in ED assessment.

Additionally, one in vivo study (Olsen et al. 1986) from the EFSA (2012) report was included. Information concerning thyroid effects from an unpublished study (Price 1994) referred to in EFSA (2012) and JECFA (1996) was also included. Two in vitro studies from the CEHOS SIN list report (Hass et al. 2012) were included (Jobling et al. 1995; Soto et al. 1995).

Data from ECHA database accessed May 2021	Compared to the rather limited number of identified toxicity studies on BHT found in the open literature, a surprisingly large number of toxicity studies are included on the ECHA dissemination site. Because of the large number of studies, we have not stated assessment of them, but here only summarize the identified number: 67 repeated dose oral studies, 4 repeated dose dermal studies, 59 carcinogenicity studies, 28 reproduction studies, 59 developmental toxicity studies, 3 epidemiology studies and 40 studies under specific investigation. Furthermore, under "additional toxicity studies" there are 20 hits, and each of them refers to 10 study references. Thus, approximately 200 more references that need to be reviewed for relevance.
Data applied for ED assessment	All accessible data were included, but limited data availablility/access is noted
Data applied for DNEL determination	All accessible data were included, but limited data availablility/access is noted

Appendix 5.2 ED assessment overview

T-mediated endocrine activity

Evidence for endocrine activity in vitro (T-mediated): [WEAK] One in vitro study using zebra fish larvae reports change in expression of central genes regulating the HPT axis (Yang et al. 2018).
Evidence for endocrine activity in vivo (T-mediated): [Not identified] No effect on T3 or T4 levels in blood after adult exposure (Søndergaard and Olsen 1982). Another study also reports no change in serum thyroxine (reference to unpublished study by Price (1994) in JECFA (1996); EFSA (2012).
Evidence for adverse effect (T-mediated): [MODERATE] Several effects on the thyroid gland have been reported after BHT exposure. In rats, iodine uptake in the thyroid gland was increased after BHT exposure, thyroid weight was increased and height of follicular thyroid cells was increased (with many secretory vacuoles) after different types of exposure regimes (Søndergaard and Olsen 1982). Another study reports reduced thyroid follicular size, reduced colloid, and increased number of follicular cells at middle and high dose (reference to unpublished study by Price (1994) in JECFA (1996); EFSA (2012).

The accessible data in open literature is sparse and does not constitute a solid fundament to conduct a mode of action analysis for T-mediated effects. However, there are adverse effects related to EATS mediated toxicity, and EFSA applies this adverse effect for ADI determination. Therefore, a MoA evaluation is included here.

Mode of action		**Interference with thyroid hormone system**
Hypothesis		The molecular initiating event (MIE) is not characterized, and several possible MIEs could cause the observed changes in thyroid histology and could be via changes in thyroid hormone levels. The affected thyroid histology is an adverse effect that may also affect human thyroid function.
	Brief description of event	**Supporting evidence**
MIE	Molecular: Binding to TR and /or a yet unidentified MIE	Not characterized
KE	Organ: Altered thyroid hormone concentrations	Not characterized

Mode of action		Interference with thyroid hormone system
AO	Organism: Thyroid gland toxicity	Moderate evidence In rats, iodine uptake in the thyroid gland was increased after BHT exposure, thyroid weight was increased and height of follicular thyroid cells was increased (with many secretory vacuoles) after different types of exposure regimes (Søndergaard and Olsen 1982). Another study reports reduced thyroid follicular size, reduced colloid, and increased number of follicular cells at mid and high dose (reference to unpublished study by Price (1994) in JECFA (1996); EFSA (2012).

Conclusions on Mode of action analysis	
Biological plausibility of key event relationships	It is biologically plausible that the adverse effects registered are due to the endocrine activity of BHT.
Dose and temporal concordance	Dose-response effects are difficult to delineate on the data at hand, but it seems as if effect is seen at the higher doses.
Essentiality	For determining essentiality it should be demonstrated whether or not downstream KEs and/or the adverse effect is prevented/decreased if an upstream event is experimentally blocked. No such studies have been provided for BHT. However, the effects on thyroid gland histopathology are considered to be due to endocrine mode of action, as no alternative non-endocrine mode of action is demonstrated.
Human relevance	Even though thyroid hormone disruption may be quantitatively more sensitive in rats than in humans, human relevance should be assumed (ECHA/EFSA 2018).
Uncertainties	There is a lack of robust studies for investigations of both endocrine activity in vivo and vitro as the data at hand is scarce.

Due to adverse effects related to EATS mediated toxicity, the WHO definition of endocrine disrupters is not fulfilled for effects via T modality. To fulfill the WHO definition, more clear findings would be necessary. BHT can be considered a suspected endocrine disrupter via T modality.

EAS-mediated

Evidence for endocrine activity in vitro (EAS-mediated): [WEAK] In reporter gene assay no estrogenic, but weak anti-estrogenic activity was registered (Pop et al. 2018). In a proliferation assay, weak estrogenic activity was reported, but no anti-estrogenic activity (Pop et al. 2018). No ER binding was seen in liver extract from rainbow trout containing ER biding sites, proliferation assay, nor on ER activity in reporter gene assay (Jobling et al. 1995). No estrogenic effect in E-screen (Soto et al. 1995).

No AR agonistic properties (Schrader and Cooke 2000; Pop et al. 2016), but anti-androgenic activity was significant (Schrader and Cooke 2000; Pop et al. 2016). In testicular cell homogenates, BHT interfere with Ca2+ signaling (inhibit Ca2+ ATPase activity), which may have effects on testicular function (Michelangeli et al. 1996; Hughes et al. 2000).

Additionally, BHT seems to increase progesterone secretion of corpora lutea in a dose dependent manner. Possibly, via stimulation of P450SCC as inhibition of this enzyme reduced progesterone secretion after exposure to BHT (Carlson et al. 1995).

Evidence for endocrine activity in vivo (EAS-mediated): [No data]

Evidence for adverse effect (EAS-mediated): [WEAK] Few data. In rats exposed 13 weeks before mating and during gestation, no effect on gestation rate was seen, but a decreased number of pups per litter was reported (Olsen et al. 1986). In mice exposed from gestation day 1 (GD 1) until GD5 and GD6, effect was seen on endometrial decidualization: reduction in number of implantation sites and uterine weight, increased abnormal embryo spacing, histological abnormalities of the endometrium as well as reduced gene and protein expression of critical marker in implantation sites were seen (Sun et al. 2021).

The accessible data on endocrine activity in vivo is lacking the open literature, however, there are data showing endocrine activity in vitro as well as adverse effect in vivo, indicating ED effects. No MoA assessment is carried out for EAS modalities due to weak evidence of adverse effect.

Appendix 5.3 DNEL and DMEL determinations

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
Unpublished study by Price (1994), referred to in (JECFA (1996); EFSA (2012).	Wistar rats, 13 weeks premating, exposure of offspring until 144 weeks of age, 0, 25, 108, 276 mg/kg bw/day in diet, N=40-60	Reduced thyroid follicular size, reduced colloid, and Increased number of follicular cells at mid and high dose. No change in serum thyroxine	25/108/-	DNEL: 10 (intraspecies) x4 (rat to human) x2.5 (remaining differences interspecies) =100 DMEL: 10 (intraspecies) x4 (rat to human) x2.5 (remaining differences interspecies) x10 (nature of endocrine disrupting properties) =1000	250 ($DNEL_{thyr}$) 25 ($DMEL_{thyr}$)	**250 ($DNEL_{thyr}$)** **25 ($DMEL_{thyr}$)**	Described as thyroid hyper-activity, not hypo-activity, but considered to be part of the same effect pattern as other thyroid disrupting compounds
Søndergaard and Olsen 1982	Rats, 28 days, 0, 25, 250 mg/kg bw/day in diet. Thyroid histology n = 6, T3 and T4 measurements n =8 (only control and high dose investigated for thyroid hormone levels)	Increased number of follicle cells at high dose. No change in T3 or T4. Increased uptake of iodine	25/250/-	DNEL: 10 (intraspecies) x4 (rat to human) x2.5 (remaining differences interspecies) =100 DMEL: 10 (intraspecies) x4 (rat to human) x2.5 (remaining differences interspecies) x10 (nature of endocrine disrupting properties) =1000	250 ($DNEL_{thyr}$) 25 ($DMEL_{thyr}$)	**250 ($DNEL_{thyr}$)** **25 ($DMEL_{thyr}$)**	JECFA 1996 used NOAEL to set ADI
Comments: **$DNEL_{thyr}$ of 250 µg/kg bw/d and $DMEL_{thyr}$ of 25 µg/kg bw/d** was derived from two rat studies by Søndergaard and Olsen (1982); Olsen et al. (1986). This evaluation is based on detailed data selection in a report by EFSA (2012) applying these data to set an ADI. According to EFSA (2012), possible behavioural effects have been seen in offspring and for details, please refer to that report.							

Appendix 5.4 Other effects of relevance for human health

No other effects are noted (not targeted in literature search). It is however noted that numerous carcinogenicity studies for BHT are included in the data available on the ECHA dissemination site pointing to a concern/previous concern for carcinogenicity. This is not further evaluated.

Appendix 5.5 References for BHT

Carlson JC, Sawada M, Boone DL, Stauffer JM (1995) Stimulation of progesterone secretion in dispersed cells of rat corpora lutea by antioxidants. Steroids 60:272–276. doi: 10.1016/0039-128X(94)00053-F

ECHA/EFSA (2018) ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC). Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 11. EFSA J 2018 16:5311, 135 pp. doi: https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN

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JECFA (1996) 833. Butylated hydroxytoluene. Toxicological evaluation of certain food additives and contaminants in food. Prepared by the forty-fourth meeting in the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series 35. http://www.inchem.org/documents/jecfa/jecmono/v35je02.htm

Jobling S, Reynolds T, White R, et al (1995) A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic. Environ Health Perspect 103:582–587. doi: 10.1289/ehp.95103582

Larsen, PB; Boberg J, Poulsen PB, Mørck TA, Boyd HB, Andersen DN, Axelstad M, Hass U (2017) Exposure of children and unborn children to selected chemical substances MST survey of chemical substances in consumer products no. 158 ISBN: 978-87-93529-84-7 https://mst.dk/service/publikationer/publikationsarkiv/2017/maj/exposure-of-children-and-unborn-children-to-selected-chemical-substances/

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Olsen P, Meyer O, Bille N, Würtzen G (1986) Carcinogenicity study on Butylated Hydroxytoluene (BHT) in Wistar rats exposed in utero. Fd Chem Toxic 24:1–12

Pop A, Drugan T, Gutleb AC, et al (2018) Estrogenic and anti-estrogenic activity of butylparaben, butylated hydroxyanisole, butylated hydroxytoluene and propyl gallate and their binary mixtures on two estrogen responsive cell lines (T47D-Kbluc, MCF-7). J Appl Toxicol 38:944–957. doi: 10.1002/jat.3601

Pop A, Drugan T, Gutleb AC, et al (2016) Individual and combined in vitro (anti)androgenic effects of certain food additives and cosmetic preservatives. Toxicol Vitr 32:269–277. doi: 10.1016/j.tiv.2016.01.012

Price SC (1994) The role of hepatocellular injury in the chronic toxicity of BHT: Two generation Wistar albino rat study. Robens Institute, U. of Surrey, Guildford, Surrey, U.K. Study No: 1/91/Tx. Final Report No: R193/TOX/0020. Vol. 1-8. Submitted to WHO by Robens Institute. Unpublished.

Schrader TJ, Cooke GM (2000) Examination of Selected Food Additives and Organochlorine Food Contaminants for Androgenic Activity in Vitro. Toxicol Sci 53:278–288. doi: 10.1093/toxsci/53.2.278

Søndergaard D, Olsen P (1982) The effect of butylated hydroxytoluene (BHT) on the rat thyroid. Toxicol Lett 10:239–244. doi: 10.1016/0378-4274(82)90081-9

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Sun Z, Gao R, Chen X, et al (2021) Exposure to butylated hydroxytoluene compromises endometrial decidualization during early pregnancy. Environ Sci Pollut Res Int April 1:(ahead of print). doi: 10.1007/s11356-021-13720-0

Yang X, Sun Z, Wang W, et al (2018) Developmental toxicity of synthetic phenolic antioxidants to the early life stage of zebrafish. Sci Total Environ 643:559–568. doi: 10.1016/j.scitotenv.2018.06.213

Appendix 6. Bisphenol A (BPA)

Phenol, 4,4′-(1-methylethylidene)bis-, CAS no. 80-05-7

Appendix 6.1 Data availability and literature search

Previous reports	ECHA (SVHC documentation, CLH documentation): - BPA has been identified as a substance of very high concern (SVHC) due to its endocrine disrupting properties for human health and the environment (ECHA, 2017). - BPA is a substance for which certain uses are Restricted under REACH at EU level - BPA is classified as being toxic to reproduction: Hazard class and category code(s): BPA is classified as toxic for reproduction (Repr. 1B) (ECHA 2017) EFSA evaluation 2015: *EFSA published a comprehensive re-evaluation of BPA exposure and toxicity in January 2015 and reduced the tolerable daily intake (TDI) for BPA from 50 to 4 µg/kg bw/day. The TDI was made temporary and EFSA committed to re-evaluate BPA toxicity again after a two-year study by the U.S. National Toxicology Program (CLARITY-BPA program)* (https://www.efsa.europa.eu/en/topics/topic/bisphenol) *In 2018 – a new EFSA working group of scientific experts starts evaluating recent toxicological data on BPA with an updated assessment scheduled for 2020.* *Status from EFSA (by mail from Team BPA, EFSA):* *"We are currently updating the project plan regarding the finalisation and publication of the BPA opinion, after which we will update the information on the website. We envisage finalisation and publication in Q4 2022".* At the end of 2021 EFSA published a draft opinion and proposes lowering the tolerable daily intake TDI of 0.04 nanograms per kilogram of body weight per day[14]. A final opinion have not been published (spring 2022). DTU opinion 2015 (https://www.food.dtu.dk/english/News/2015/02/National-Food-Institute-maintains-its-assessment-of-bisphenol-A): EFSA has in the 2015 evaluation included uncertainty evaluations of the likelihood for effects of BPA on the mammary gland, and the reproductive, neurobehavioural, immune and metabolic systems. The EFSA uncertainty evaluation is considered as insufficient by DTU. Thus, DTU does not support the extra factor of 6 chosen by EFSA leading to the use of 100 µg/kg bw/day as basis for deriving the new EFSA t-TDI of 4 µg/kg bw/day. DTU evaluates that 4 µg/kg bw/day is not sufficiently protective with regards to endocrine disrupting effects of BPA. DTU finds that a TDI for BPA has to be 0.7 µg/kg bw/day or lower to be sufficiently protective with regards to endocrine disrupting effects of BPA. Highly exposed humans incl. pregnant women and children can according to EFSA's exposure assessment be exposed to more than 0.7 µg/kg bw/day. DTU finds that this gives rise to concern with regards to risk for health effects of BPA for highly exposed persons.

[14] https://www.efsa.europa.eu/en/news/bisphenol-efsa-draft-opinion-proposes-lowering-tolerable-daily-intake

	MST project "Exposure of pregnant consumers to suspected endocrine disrupters" (Andersen et al. 2012). Two different DNELs for estrogenic effects was determined and applied for risk assessment. SCCS 2021. Refers to EFSA 2015 for point of departure selection.
New search 2021	1) EFSA evaluation 2015 (literature searches until end of 2012) 2) update 2013-2021 For update of DNEL and ED a search was conducted in PubMed 19/4 2021. The search strategy was based on the description in ECHA/EFSA guidance 2018 and focused on ED effects (page 130): Update search in PubMed 11/5 2021: #1 (Bisphenol A OR Phenol, 4,4′-(1-methylethylidene)bis- OR 80-05-7) AND (rats OR mice) AND (endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*) 1690 results. #2 (Bisphenol A OR Phenol, 4,4′-(1-methylethylidene)bis- OR 80-05-7) AND (rats OR mice OR endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*) – 6414 results. #3 (Bisphenol A OR Phenol, 4,4′-(1-methylethylidene)bis- OR 80-05-7) AND (rats OR mice) AND (endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*) AND (fetal OR development* OR prenatal OR pregnan*) – 936 results. #1 limited to 2013-2021 – 952 results #2 limited to 2013-2021 – 3983 results #3 limited to 2013-2021– 534 results Limitation to the period 2013 to 2021 (period after previous literature search from EFSA evaluation 2013) identified 534 hits, which were included in the screening process. The screening process constitutes 3 steps as described in ECHA/EFSA guidance (2018): 1) Screening of titles 2) Screening of abstracts for possible DNEL relevant effects 3) Screening of full text 1) Title screen: 534 studies after EFSA evaluation 2015 (literature searches in the EFSA evaluation was until end of 2012) was screened for relevance for this project with the focus of the DNEL determination. The title screen resulted in 42 papers, whereas 9 papers was considered relevant and 33 was considered maybe relevant 2) Abstract screen: After exclusion of not relevant studies all 42 studies from title screen were considered with DNEL relevance 3) Full text, in total 24 studies were considered if they were relevant for DNEL determination. Some was included in DNEL table under c) below.
Review of the ECHA dissemination site for BPA	Not relevant
Data applied for ED evaluation	SVHC documentation by ECHA 2017 serves as the main data source for conclusion on ED properties of BPA
Data applied for DNEL determination	The DK EPA report entitled "Exposure of pregnant consumers to suspected endocrine disruptors" (Andersen et al. 2012) derived two DNELs of 4 and 0.7 µg/kg bw/d on estrogenic effects. The lowest DNEL was derived in the DTU evaluation in 2015 whereas the other is based on the temporary TDI in EFSA opinion from 2015. The DNEL determination in the current project thereby included data from Andersen et al. 2012 as well as several new studies including some from DTU Food and CLARITY BPA in US, see section c) below.

Appendix 6.2 ED assessment overview

The ED assessment of BPA (including the MoA analysis) is not included below as ECHA identified BPA as an SVHC according to article 57(f) for probable serious effects on human health and the environment due to its endocrine disrupting properties for human health (ECHA, 2017).

Appendix 6.3 DNEL and DMEL determination

For the DNEL and DMEL determination EFSA 2015, DTU 2015 and published studies from 2015 until now have been included. In addition, some studies from CLARITY BPA from US is included.

Notes on CLARITY BPA studies:
The Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA), a research program between the National Institute of Environmental Health Sciences (NIEHS) and the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA), developed to bridge guideline-compliant research conducted at the FDA with hypothesis-based research investigations conducted by academia on the toxicity of BPA. The CLARITY-BPA research program has two components: 1) A “core” guideline-compliant chronic study conducted at NCTR according to FDA Good Laboratory Practice (GLP) regulations and 2) studies of various endpoints, conducted by NIEHS-funded researchers at academic institutions using animals born to the same exposed pregnant rats as the core GLP study. The purpose of this research program was to evaluate chronic exposure to BPA over a broad dose range using traditional and non-traditional endpoints. It aimed to determine if non-traditional endpoints reveal toxicity not detected by traditional guideline study endpoints and provide mechanistic support for observations made in the guideline study.

The NTP report (NTP, 2018) concluded:
In conclusion, in the CLARITY-BPA core study, statistical differences between BPA treatment groups, particularly below 25,000 µg/kg bw/day, and the vehicle control group detected by the low-stringency statistical tests applied to histopathology lesions, were not dose responsive, sometimes occurring in only one low or intermediate dose group, and did not demonstrate a clear pattern of consistent responses within or across organs within the stop- and continuous-dose arms and sacrifice times. In contrast, the high EE2-dose elicited several estrogenic effects in females in a clearly interpretable and biologically plausible manner. Several observations at 25,000 µg BPA/kg bw/day may be treatment related, including effects mentioned above in the female reproductive tract (ovary, uterus, and vagina) and in the male pituitary.

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
SCCS 2021, EFSA 2015 (Based on Tyl et al. 2008)	Rat, two-generation study	Extrapolation from BMDL for kidney effects to cover also reproductive effects (e.g. mammary gland effects)	-/-/8.960 for kidney effects (BMDL10) Human equivalent dose (HED): -/-/0.609 Extrapolation to cover uncertainty for other endpoints: -/-/0.1	DNEL: (10 for intraspecies, x2.5 for remaining differences in toxicodynamics and 1 for toxicokinetic, as toxicokinetic intraspecies differences were addressed using HED (Human equivalent dose) = 25 DMEL: (10 for intraspecies, 2.5 for remaining differences in toxicodynamics and 1 for toxicokinetic, as toxicokinetic intraspecies differences were addressed using HED (Human equivalent dose) x10 (nature of endocrine disrupting properties)) = 250	$DNEL_{eas}$: 4 (to be compared with external human dose) **($DNEL_{eas}$)** $DMEL_{eas}$: 0.4	$DNEL_{eas}$: 4 $DMEL_{eas}$: 0.4	EFSA TDI, covers effects on reproduction, mammary development and other effects. See reference for details. DNEL external is applied for comparison with external human exposure values. SCCS use the same data for dermal DNEL.
DTU evaluation (Based on Delclos et al., 2014) and WoE (Weight of Evidence) on the mammary gland development findings in Betancourt et al. 2010, Jenkins et al. 2009, Moral et al. 2008, Tharp et al. 2012 (3 rat studies and a study in monkeys)	Rat, exposed orally GD 6-PND 90	Mammary hyperplasia in adult females	0.025/0.080/- Conversion from rat to human using factor 0.72 (EFSA 2015): 18/57.6/-	DNEL: (10 for intraspecies, 2.5 for toxicodynamics and 1 for toxicokinetic, as toxicokinetic intraspecies differences were addressed using HED) = 25 DMEL: (10 for intraspecies, 2.5 for toxicodynamics, 1 for toxicokinetics (as	**$DNEL_{eas}$: 0.7 (or lower)** (to be compared with external human dose) $DMEL_{eas}$: 0.07	$DNEL_{eas}$: 0.7 $DMEL_{eas}$: 0.07	Based on study by Delclos et al., 2014, and use of assessment factors as in EFSA 2015. DNEL external is applied for comparison with external human exposure values.

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
				toxicokinetic intraspecies differences were addressed using HED) x10 (nature of endocrine disrupting properties)) = 250			
Anses 2015/ ECHA 2015 (Moral et al., 2008)	Rats	Mammary gland development	0.025/0.080/-	(10 Interspecies x10 toxicokinetics/toxicodynamics x 3 uncertainty low dose and NMDR) = 300	0.083	0.0025 (3% absorption fraction)	The use of 300 as assessment factor is according to DTU too cautious.
DTU Studies (1: Christiansen et al. 2014; 2: Hass et al. 2016; 3: Mandrup et al. 2016; 4: Lejonklou et al. 2016)	Wistar rats n=18-21 Doses: 0.025, 0.25, 5, 50 mg/kg	At 0.025mg/kg effect on 1. Female AGD (males from 0.250 only) 2. Males: Decreased sperm count and females: altered spatial learning in a Morris water maze 3. Male offspring showed increased mammary outgrowth on pup day (PD) 22 4. altered femoral geometry in both male and female offspring.	0.025 is therefore considered a LOAEL -/0.025/- Conversion from rat to human using factor 0.72 (EFSA 2015): 0.025 x 0.72 =0.018	DNEL: (10 for intraspecies, 2.5 for toxicodynamics and 1 for toxicokinetic, as toxicokinetic intraspecies differences were addressed using HED) x3 (LOAEL to NOAEL): =75. DMEL: (10 for intraspecies, 2.5 for toxicodynamics and 1 for toxicokinetic, as toxicokinetic intraspecies differences were addressed using HED) x3 (LOAEL to NOAEL) x10 (nature of endocrine disrupting properties) =750.	**DNEL: 0.24** (to be compared with external human dose) **($DNEL_{eas}$)** $DMEL_{eas}$: 0.024	$DNEL_{eas}$: 0.24 $DMEL_{eas}$: 0.024	Supports the DTU evaluation above but considers 0.025 as a LOAEL instead of a NOAEL, and thus suggests even lower DNEL and DMEL
Uchtmann et al. 2020	CLARITY BPA studies	Male rat urogenital sinus (UGS) Low dose BPA (2.5 or 25 µg/kg/day induces changes in	0.025 or 0.0025				Not applied for DNEL determination as no adverse effect (changes in UGS urethral size)

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
		UGS urethral size and increase in body weight					
Prins et al. 2019 (Part of CLARITY BPA study, (Academic studies) (MiniReview) + Prins et al. 2018	CLARITY BPA studies (behavioural, molecular and cellular studies by academic laboratories focused on previously identified BPA-sensitive organ systems	Findings at 2.5 µg/kg BW: - alter ER expression in the brain - In BPA- or EE-treated females at PND21, cardiomyopathy incidence was increased compared to control females. Significant increase in severity was found for 2.5, 250 or 25,000 µg BPA/kg BW/day and both EE groups - Clear indicators of exposure-related cardiotoxicity in the 2.5 µg/kg/day BPA group resulting from increases in adverse vascular events - 2.5, 250 or 25000 µg BPA/kg BW showed significant increases in lateral prostate prostatic intraepithelial neoplasia (PIN) severity compared to vehicle controls at one year, shifting from low-grade PIN in controls to high-grade PIN in rats developmentally exposed to BPA with the highest PIN score observed at the 2.5 µg BPA/kg BW dose	<0.0025 is therefore considered a LOAEL -/0.0025/- Conversion from rat to human using factor 0.72 (EFSA 2015): 0-.0025 x 0.72 =0.0018	DNEL: (10 for intraspecies, 2.5 for toxicodynamics and 1 for toxicokinetic, as toxicokinetic intraspecies differences were addressed using HED) x3 (LOAEL to NOAEL): =75. DMEL: (10 for intraspecies, 2.5 for toxicodynamics and 1 for toxicokinetic, as toxicokinetic intraspecies differences were addressed using HED) x3 (LOAEL to NOAEL) x10 (nature of endocrine disrupting properties) =750.	DNEL: 0.024 (to be compared with external human dose) DMEL: 0.0024	-	Not applied for DNEL determination as adverse effect (increased PIN lesion severity) is observed in a hormone challenge study. The authors conclude: *These findings are clear indicators of exposure-related cardiotoxicity in the 2.5 µg/kg/day BPA group resulting from increases in adverse vascular events, findings that support a NOAEL of <2.5 µg/kg/day for effects in the heart.*
Silva et al. 2019	Wistar rat offspring BPA10 (10 µg/kg/day) and BPA50 (50 µg/kg/day) oral gavage	At weaning, BPA10 female pups: higher plasma cholesterol and triacylglycerol. BPA10 male pups: lower plasma T3. BPA10 pups both sexes: higher plasma progesterone, testosterone and estradiol.	**LOAEL 0.01 mg/kg** **NOAEL 0.0033** Conversion from rat to human using factor 0.72 (EFSA 2015): 2.4				Not applied for DNEL determination as no ED related adverse effect: higher plasma cholesterol)

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
		At adulthood, females of both BPA groups had lower food intake and higher insulinemia, whereas males had lower visceral fat, lower progesterone and testosterone concentrations. BPA10 females and males had lower T4 levels, while only males showed lower estradiol.					
Boudalia et al. 2014	Wistar rats 5 µg/kg/day oral gavage (GD 1) until the last day of lactation (LD 21), and then to F1 offspring from weaning (PND 21) to adulthood (PND 100)	BPA exposure: 1) decreased maternal behaviour in F1 dams, 2) caused developmental defects in both F1 and F2 offspring, with a noticeable decrease in anogenital distance in male rats, and 3) did not affect flavored solution intake in F1, but induced changes in sweet preference in F2 juveniles and in salt and fat solution intakes in F2 adults, and 4) induced a body weight increase in the F2 generation only, whereas food intake and water consumption did not change.	**LOAEL 0.005** mg/kg/day no NOAEL Divided by 3 0.0016 Conversion from rat to human using factor 0.72 (EFSA 2015): 1.2				Not applied for DNEL determination as only one dose included in the study
Arambula et al. 2017 (CLARITY study)	Sprague-Dawley rats were randomly assigned to 5 groups: BPA (2.5, 25, or 2500 µg/kg bw/day), a reference estrogen (0.5 µg Ethinyl estradiol (EE2)/kg bw/day), or vehicle. Exposure occurred by gavage to the dam from gestational day 6 until parturition, and then to	Perinatal exposure to 2.5 µg/kg bw/day BPA increased AVPV volume in females and exposure to 25 and 2500 µg BPA /kg bw/day increased volume in both males and females					Not applied for DNEL determination as no adverse effect was seen

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
	the offspring from birth through weaning.						
Patel et al. 2017	(CLARITY , female effects)	The results show that continuous exposure to BPA at 2.5 and 250 mg/kg bw/d decreases the number of primordial, primary, preantral, and total healthy follicle numbers present in the ovary at PND 21.					Not applied for DNEL determination as no adverse effect was seen
Camacho et al. 2019 (Part of CLARITY BPA, (Core study))	Rats, two-year toxicology study Dosing: GD6 to the start of parturition and then directly to pups from the day after birth until postnatal day 21 or continuously until termination at one or two years	Many endpoints including histopathology and mammary gland non-neoplastic lesions	-	-	-	-	The authors conclude that the core study (CLARITY) data **do not suggest a plausible hazard of BPA exposure in the lower end of the dose range tested** Doses: 2.5, 25, 250, 2,500, and 25,000 µg/kg body weight (bw)/day)
Badding et al. CLARITY-BPA Core Study (Exponent (INDUSTRY) authors)	Rats, two-year toxicology study Dosing: GD6 to the start of parturition and then directly to pups from the day after birth until postnatal day 21 or continuously until termination at one or two years	Focus on NMDR (Non monotone dose response)	-	-	-	-	This analysis found limited evidence for NMDR and suggest no lower NOAEL/reference dose.
Bansal R et al. 2019	CLARITY BPA	Thyroid functions and thyroid hormone action	-	-	-	-	Neither BPA nor EE affected serum thyroid hormones or thyroid hormone–sensitive end points in the developing brain at PND 15

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
Comments: Two different DNELs are listed for estrogenic effects of Bisphenol A. **$DNEL_{eas}$ of 4 µg/kg bw/d** corresponds to the EFSA TDI, and **$DNEL_{eas}$ of 0.7 µg/kg bw/d** or lower was derived by DTU from a reproductive dose response study (Sprague-Dawley rats exposed orally from GD 6 -PND 90 showing low-dose effects on mammary gland development (Delclos et al., 2014)) and others. Both values are listed in a report entitled "Exposure of pregnant consumers to suspected endocrine disruptors" (Andersen, 2012) and was carried forward to risk assessment in that project. The use of 300 as assessment factor in the ANSES report (based on study by Moral et al. 2008) is by DTU considered too cautious and the DNEL set on that base is not put forward for risk assessment. No data for effects on the thyroid hormone system was identified and therefore no $DNEL_{Thyr}$ was derived in this project. The CLARITY –BPA studies do not observe clear effects of BPA on thyroid system (Bansal R et al. 2019 and Heindel et al. 2020). The lower NOAEL and thereby **$DNEL_{eas}$ of 0.24 µg/kg bw/d** and DMEL of 0.024 suggested by DTU studies and supported by some of the CLARITY studies will be used in this work and put forward for risk assessment. Prins studies (2019, 2018) also support that the latter DNEL should be lower than the first mentioned DNEL proposals.							

Appendix 6.4 Notes on other effects of relevance for human health

Both the previous and updated EFSA TDIs are based on general toxicological effects in the liver and kidney and not on reproductive or endocrine-mediated effects.

Appendix 6.5 References for BPA

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Appendix 7. Butylparaben

Butylparaben, butyl p-hydroxybenzoate, ButPar, CAS no. 94-26-8

Appendix 7.1 Data availability and literature search

Previous reports	SHVC documentation, ECHA 2020. An assessment of endocrine disrupting properties was carried out in accordance with criteria developed for pesticide and biocides. Butylparaben was considered a SVHC due to its endocrine disruption properties via EAS modalities. MST project "Exposure of children and unborn children to selected chemical substances", Larsen et al. 2017. A DNEL was determined for endocrine disrupting properties (estrogenic mode of action), and this was based on data used in previous SCCS reports (SCCS 2011, 2013) and a previous MST project (Andersen et al. 2012). CEHOS SIN list (Hass et al. 2012). Evaluation of butylparaben data against the Danish criteria for identification of ED substances led to evaluation in Category 1, Endocrine Disruptor.
New search 2021	For update of ED evaluation after the literature review for the SVHC documentation in 2020, we performed an update for the period 2020-2021. This search together with information in the SVHC document also enabled update of DNEL determination after the latest DNEL selection in Larsen et al. 2017. We carried out searches in PubMed 27/4 2021: #1 (butylparaben OR 94-26-8 OR (butyl p-hydroxybenzoate)) AND (rats OR mice OR human OR toxicity) AND (endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*) – This resulted in 152 publications, and a limitation of this search to 2020-2021 (search #2) resulted in 34 publications. A broader search #3 was carried out (butylparaben OR 94-26-8 OR (butyl p-hydroxybenzoate)) AND ((rats OR mice OR human OR toxicity) OR (endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*)) leading to 286 results, and a limitation to the period 2020-2021 (search #4) – resulted in 56 publications. Title screen for Search #4 led to 39 papers potentially relevant to ED assessment or DNEL determination. Most studies were human epidemiological studies. Abstract screen: For the purpose of updating the ED assessment 15 studies were considered potentially relevant. For the purpose of revising DNEL from Larsen et al. 2017 seven studies were considered potentially relevant. As the SVHC documentation did not include an evaluation of T modality, a search was carried out for all years specifically targeted to thyroid toxicity: #5: (butylparaben OR 94-26-8 OR (butyl p-hydroxybenzoate)) AND thyroid*). This search resulted in 7 publications.
Review of ECHA dissemination site	ECHA dissemination site visited 31-5-2021. No repeated dose studies, carcinogenicity studies or reproductive toxicity studies included.
Data applied for ED evaluation	SVHC documentation by ECHA 2020 serves as the main data source for conclusion on ED properties of butylparaben. After the SVHC documentation 2020, a few new studies were identified investigating adverse effects related to the MoA proposed in the SVHC 2020, i.e. EAS related effects (Hubbard et al. 2020, Oliveira et al. 2020).

	Endocrine disruption via T modality was not examined specifically in SVHC document. Six studies investigating thyroid related endpoints were included for this evaluation (Gogoi and Kalita 2020, Li et al.2020, Taha et al. 2020, Vo et al. 2010, Taxvig et al. 2008, Janjua et al. 2007).
Data applied for DNEL determination	The data included for DNEL determination in the report by Larsen et al. 2017 serve as the main data source for setting $DNEL_{eas}$ in the current project. Revision included evaluation of studies published after that time. For the purpose of DNEL determination, no studies were identified showing EAS related effects at doses below the LOAEL applied for to set DNEL in the Larsen et al. 2017 report. Additionally all thyroid-relevant studies were evaluated to clarify the relevance of setting a $DNEL_{thyr}$.

Appendix 7.2 ED assessment overview

This evaluation refers to an evaluation in the SVHC document for butylparaben. In that evaluation perinatal exposure was found to induce adverse effects on male offspring exposed perinatally. The mode of action was EAS related endocrine activity leading to altered male reproductive function following perinatal exposure. The evidence was most clear for estrogenic mode of action, but also anti-androgenic activity and steroid synthesis inhibition was observed.

T-mediated endocrine effects

Evidence for endocrine activity in vitro (T-mediated): [moderate] Increased proliferation of the GH3 cells in the T-Screen assay, indicating weak thyroid hormone receptor agonism (Taxvig et al. 2008).
Evidence for endocrine activity in vivo (T-mediated): [moderate] Reduced T3 and T4 and increased TSH in rats, two studies. Reduced T3 and T4 and increased TSH in male rats after 60 days exposure to 50 mg/kg bw/d (NOAEL 10 mg/kg bw/d). No information on exposure route (Taha et al. 2020). Reduced free and total T3, reduced free and total T4, and increased TSH in female Wistar rats after 7 and 21 days exposure to 1 and 5 mg/kg/day. However, no effects were seen at 10 mg/kg bw/d (Gogoi and Kalita, 2020). The lack of clear dose-response relationship, limited the use of the results from this study. Butylparaben did not affect T3 or T4 levels in pregnant dams at GD 21 following s.c. exposure from GD 7 to 21 at doses of 200 and 400 mg/kg (Taxvig et al, 2008).
Evidence for adverse effect (T-mediated): [no effect or not sufficiently investigated] Vo et al. 2010 investigated thyroid weights and histology in rats exposed from PND 21 to 40 to three doses (62.5, 250, 1000 mg/kg bw/d) of butylparaben (and five other parabens). Of all parabens investigated, only the lowest dose of butylparaben increased thyroid weight at PD 41. No parabens affected thyroid histology.

Human studies with focus on thyroid hormone disruption have been performed by Li et al. 2020 and Janjua et al. 2007. In a birth cohort, Li et al. 2020 found that maternal urinary butylparaben concentrations were not associated with changes in cord serum T3 or thyroid peroxidase antibodies, - which were significantly associated with increased ethyl- and propylparaben concentration, respectively. Janjua et al. 2007 found no effects on serum T3, T4 or TSH levels after one week topical application of butylparaben in healthy adult men and women. As data for butylparaben do not reveal adverse effect on T-mediated endpoints, no MoA assessment was carried out. The WHO definition for identifying butylparaben as an endocrine disruptor via T modality is not fulfilled.

EAS-mediated effects

This evaluation refers to an evaluation in the SVHC document for butylparaben. In that evaluation perinatal exposure was found to induce adverse effects on male offspring exposed perinatally. Data on pubertal or adult exposure are not included here. After the publication of the SVHC report, a large rat study on butylparaben was published by Hubbard et al., 2020. A study by Oliveira et al., 2020, investigated antioxidant effects on testes of rats exposed prenatally. These studies are included below together with information from the SVHC report.

Mode of action		
Hypothesis		The molecular initiating event (MIE) is activation of the estrogen receptor(s). In developing males, increased estrogen receptor signaling results in altered testicular development in offspring and subsequently altered testicular function in adulthood. In turn, reduced sperm count and quality are observed in offspring.
	Brief description of event	**Supporting evidence**
MIE	Molecular: Activation of estrogen receptor	Strong evidence. Lines of evidence show sufficient evidence for endocrine activity related to estrogen receptor activation. Several studies show estrogen receptor agonistic response similar to estrogen (Gonzalez et al, 2018; Pop et al, 2018; Watanabe et al, 2013).
KE1	Increased estrogen receptor signaling	Strong evidence. Several studies show effects on growth of estrogen sensitive cells (Khanna & Darbre, 2013; Charles & Darbre, 2013; Gonzalez et al, 2018; Pop et al, 2018; Williams et al, 2019, van Meeuwen et al. 2008) or tissues (uterotropic assay in vivo; Routledge et al, 1998; Hossaini et al, 2000; Lemini et al, 2003; Lemini et al, 2004; Goswami & Kalita, 2016; Vo & Jeung, 2009).
KE2	Organ: Altered reproductive development of male offspring	Moderate evidence. Reduced AGD in males at PND 1 and 21 (Zhang et al, 2014; Boberg et al, 2016), but other studies showed no effect on AGD at PND 1 (Kang et al, 2002; Guerra et al, 2017) or in fetal males GD 21 (Taxvig et al, 2008). Inconsistency between studies on AGD may be due to different exposure periods, dose levels and measuring sensitivity. The two studies including doses of 400 mg/kg bw/day or above both showed reduced sperm counts at these doses (Zhang et al, 2014; Boberg et al, 2016). A dose of 100 mg/kg bw/day reduced AGD in one study (Boberg et al, 2016), but in other studies doses in the same range (10 to 200 mg/kg bw/day) did not affect AGD (Kang et al, 2002; Zhang et al, 2014; Guerra et al, 2017). Effects on testis weights were seen in some but not all studies. No changes in fetal testis histology (Boberg et al, 2016; Guerra et al, 2017). Signs of histological effects on seminiferous tubules of prepubertal testes in one study (Zhang et al, 2014).
KE3	Organ: Altered testicular and epididymal function of adult offspring	Moderate evidence. Altered serum levels of T, estradiol (E2) (and LH, FSH; increase or decrease depending on study design) (Zhang et al, 2014; Zhang et al, 2016; Guerra et al, 2017, Maske et al. 2020). Altered adult testicular histopathology (increased number of Leydig cells and possible change in spermatogenesis kinetics (Guerra et al, 2017), reduced number of round and elongated spermatids (Kang et al, 2002), degenerative changes in tubules and reduced spermatogenesis (Maske et al. 2020). Altered testicular expression of hormone receptors (altered expression of ERalpha and ERbeta mRNA (Kang et al, 2002); possibly reduced protein expression of ERalpha and AR in some cell types and spermatogenic stages (Guerra et al, 2017). No reports of change in epididymal histology.

Mode of action		
Adverse Outcome (AO)1	Organ: Reduced sperm count and quality of offspring's	Strong evidence. Several studies using perinatal exposure by subcutaneous or oral gavage caused altered sperm count and/or quality, though different parameters were affected in different studies. A large study using dietary exposure showed no effect on sperm numbers or motility (Hubbard et al. 2020). Reduced epididymal sperm count in four studies (50-75% of control; Kang et al, 2002; Boberg et al, 2016; Zhang et al. 2014; Maske et al, 2020) but no change in epididymal sperm count in another study (Guerra et al, 2017). Reduced sperm motility (60% of control; Kang et al, 2002) and at low but not high dose in another study (Maske et al, 2020). Reduced percentage of progressive motile sperm (low dose only, Guerra et al, 2017). Increased percentage of sperm with head abnormalities and reduced percentage of normal sperm (Guerra et al, 2017).
AO2	Organism: Impaired fertility of male offspring	Low evidence for effect in rodents, but high plausibility that impaired sperm count and quality in humans lead to impaired fertility (see Biological plausibility table below). No effect on fertility assessed by natural mating or artificial insemination (Guerra et al, 2017).

Conclusions on Mode of action analysis	
Mode of action	There is sufficient evidence of endocrine activity (estrogen receptor activation and possibly altered steroidogenesis and androgen receptor antagonism) and adverse effects (decreased sperm count and quality).
Biological plausibility of key event relationships	It is biologically plausible that adverse effects are due to the endocrine activity of butylparaben.
Dose and temporal concordance	In each study, indicators of key events related to endocrine activity are affected at the same doses causing adverse effects. Between studies, there are differences in effective doses. Key events are observed in the hypothesized order, i.e. in vivo indicators of endocrine activity are seen in developing animals, and adverse effects are seen in adulthood.
Essentiality, consistence, analogy, specificity	Essentiality has not been investigated. Consistency between studies is moderate, as four studies on perinatally exposed rats (gavage or subcutaneous exposure) show effect on sperm count/quality, whereas one large study using dietary exposure does not. It is possible that exposure route differences can explain the observed differences. Similar effects have been seen with structural analogues propylparaben and isobutylparaben.
Human relevance	Human relevance is assumed, as there are no data indicating that these endocrine modes of action are not relevant to humans.
Uncertainties	The uncertainty analysis highlights that the evidence base for butylparaben is relatively limited, yet there is consistency between different studies on both an endocrine mode of action and adverse effects.

There is sufficient evidence of endocrine activity and adverse effects, and it is biologically plausible that adverse effects are due to the endocrine activity of butylparaben. The WHO definition of an endocrine disruption is fulfilled. This is in agreement with SVHC (ECHA 2020) after re-evaluation in view of recent studies.

Appendix 7.3 DNEL and DMEL determinations

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
Boberg et al., 2016 (supported by other studies showing adverse effect at same or higher doses: Kang et al., 2002; Zhang et al. 2014; Maske et al, 2020; Guerra et al, 2017)	Rats; several studies on perinatal exposure to butylparaben; oral or s.c. exposure.	↓ semen quality at exposure in offspring of exposed pregnant rats	-/10/-	DNEL: 5 (NOAEL-to-LOAEL extrapolation for shallow slope) *4 (rat to human) * 2.5 (remaining toxicokinetic interspecies differences) *10 (intraspecies) =500 DMEL: 5 (NOAEL-to-LOAEL extrapolation for shallow slope) *4 (rat to human) * 2.5 (remaining toxicokinetic interspecies differences)*10 (intraspecies) * 10 (nature of endocrine disrupting properties) =5000	$DNEL_{eas}$: 20 $DMEL_{eas}$: 2	**$DNEL_{eas}$: 20** **$DMEL_{eas}$: 2**	SCCS 2013 notes that oral studies on butylparaben may be of limited relevance for risk assessment
SCCS 2011, SCCS 2013 (Fischer et al., 1999, was applied to set NOAEL while other rat studies report adverse effects, Kang et al. 2002, Lemini et al. 2003, 2004)	Rats, neonatal exposure, PD 2-18, s.c. exposure.	Lack of effect on testis weight, epididymis and histology in study by Fisher et al 1999 is used as a NOAEL by SCCS. Findings in other studies with other study designs are seen at higher doses	2/-/-	DNEL: 4 (rat to human) * 2.5 (remaining toxicokinetic interspecies differences) *10 (intraspecies) =100 DMEL: 4 (rat to human) * 2.5 (remaining toxicokinetic interspecies differences) *10 (intraspecies) *10 (nature of endocrine disrupting properties) =1000	$DNEL_{eas}$: 20 $DMEL_{eas}$: 2	$DNEL_{eas}$: 20 $DMEL_{eas}$: 2	SCCS uses the same NOEL for propyl- and butylparaben. Overall assessment of several studies considered by SCCS 2011 and 2013.

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
Hubbard et al. 2020, National Toxicology Program	Rats, Reproductive assessment by continuous breeding (RACB) study, feed (From F0 generation and continues through the F2 generation). Dose: 0, 5000, 15000, 40000 ppm, n = 22 (F0), 26-40(F1) /group. Doses correspond to 336-730, 991-2062, 3170-6117 mg/kg bw/d during gestation and lactation.	Body weight: ↓ dose-related and across generations. Weight-related delay in pubertal onset in males and females and reduced male reproductive organ weight at high dose. Fertility: No effects. Total litter size ↓ trend in F0&F1 pairings increasing. No effect on AGD/ Nipple retention, Sperm quality parameters, Estrous cyclicity. Liver weight and histological changes but no change in weights of adrenal glands, kidney, spleen, thymus, thyroid. Relative prostate weights: ↓ trend with increasing exposure.	336/991/- (5000 ppm/15000 ppm/-)	DNEL: 4 (rat to human) * 2.5 (remaining toxicokinetic interspecies differences)*10 (intraspecies) =100 DMEL: DNEL: 4 (rat to human) * 2.5 (remaining toxicokinetic interspecies differences)*10 (intraspecies) *10 (nature of endocrine disrupting properties) =1000	DNEL: 3360 DMEL: 336	DNEL: 3360 DMEL: 336	NOAEL is for effects on body weight changes, reduced prostate weight and delayed age at vaginal opening in middle and high dose group. Despite the lack of effects in this study, the findings in other studies concluding adverse effects on ED related endpoints are considered relevant to DNEL determination.
Comments: **$DNEL_{eas}$ of 20 µg/kg bw/d and $DMEL_{eas}$ of 2 µg/kg bw/d** was derived from a study on butylparaben showing reduced sperm count at 10 mg/kg bw/d. The same reference dose is reflected in the risk assessment by SCCS 2013 based on reproductive effects in rat offspring at 2 mg/kg bw/day. It is however noted that oral studies on butylparaben may be of limited relevance for risk assessment, according to SCCS 2013. No adverse effect on the thyroid gland weight or histopathology were seen in a high-dose study with repeated dose exposure. Therefore, no $DNEL_{thyr}$ was set.							

Appendix 7.4 Notes on other effects of relevance for human health

No other effects considered (not targeted in the literature search).

Appendix 7.5 References for butylparaben

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Appendix 8. Propylparaben

Propyl 4-hydroxybenzoate, Propylparaben, CAS no. 94-13-3

Appendix 8.1 Data availability and literature search

Previous reports	SCCS 2011 and 2013. SCCS uses a read-across approach to use the same data for butylparaben and propylparaben for risk assessment. Due to toxicokinetic issues, SCCS question the use and relevance of the oral rat model with regards to the risk assessment of propyl- and butylparaben. Specifically, "the oral rat model may be misleading when applied to human risk assessment; the available oral rat studies on potential endocrine/estrogenic effects cannot be used to demonstrate that dermal exposure to parabens does not pose a risk to humans" (p. 23). EMA 2015. In a *reflection paper* on the use of methyl- and propylparaben in medicinal products, the European Medicines Agency (EMA) has determined a NOAEL for propylparaben of 100 mg/kg bw/day. This is based on unpublished, confidential data from a GLP-compliant juvenile toxicity study, showing significant effects on the onset of female puberty (accelerated) and on the weight of uterus (increased) at 1000 mg/kg/day. SCCS 2021. An overview of studies on endocrine activity in vivo and in vitro are presented together with a summary of recent unpublished studies performed with dietary exposure to propylparaben in rats (a 90-day study, a prenatal developmental toxicity study, an extended one-generation reproductive toxicity study). The SCCS 2021 considered a NOAEL of 1000 mg/kg bw/day based on these studies showing no effects at the top dose and concluded that "although the available data on propylparaben provide some indications for potential endocrine effects, the current level of evidence is not sufficient to conclusively regard it as an endocrine disrupting substance or to derive a specific endocrine-related toxicological point of departure for use in safety assessment." (p.39). The concerns of SCCS 2013 regarding use of oral rat studies for risk assessment are no longer expressed in SCCS 2021. DTU evaluation of the preliminary SCCS opinion from 2020. The Danish Ministry of Environment asked DTU FOOD (DTU) to evaluate the draft of the latest SCCS opinion of propylparaben, during the public consultation period. In the resulting note (published on DTU webpage as Boberg et al. 2020) it is explained why DTU reaches a different conclusion regarding the endocrine disrupting properties and hazard assessment of propylparaben than the SCCS. DTU finds that it is not appropriate to use a dose of 1000 mg/kg bw/day as a NOAEL. This because several in vivo results indicate endocrine disrupting properties and reproductive toxicity effects of propylparaben, at 1000 mg/kg bw/day and lower dose levels. DTU has not yet had the possibility of evaluating the full data material (full study reports from all the relevant new in vivo studies) and therefore cannot conclude with certainty whether the identified effects should be viewed as adverse. In the current report, DTU is using a more cautious approach than the one suggested by SCCS and has therefore determined a NOAEL based on a read-across approach to data on the substance butylparaben, rather than concluding that a dose of 1000 mg/kg bw is safe, when there are indications that this may not be the case. Consequently, DTU also disagrees with the Margin of Safety (MoS) of> 12,000 calculated by the SCCS. MST risk assessment projects by Larsen et al. 2018 and Andersen et al. 2012. DNEL was determined for endocrine disrupting properties (estrogenic mode of action), and this was based on data used in previous SCCS reports (SCCS 2011, 2013).

	RIVM 2017, Brand et al. Exposure and toxicity of methyl-, ethyl- and propylparaben. In this report based on a literature review, the hormone-disrupting effects of methyl-, ethyl- and propylparaben and the NOAELs derived by previous studies were described and discussed in relation to the WHO definition of endocrine disruption. Seven in vitro studies evaluated estrogenic effect of propylparaben, four in vivo studies evaluated anti-androgenic effect of propylparaben, and three in vivo studies examined male or female reproductive effects. Clear endocrine mode of action and indications of ED-related in vivo effects were identified. Comparison with criteria for endocrine disrupters led to no clear conclusion but highlighted a need for more in vivo studies on adversity and potency. CEHOS SIN list 2012 (Hass et al. 2012). An evaluation of ED properties based on a literature review up to 2011 led to the conclusion that Propylparaben is a "suspected ED". Substances can be allocated to this category based on: 1) Adverse effects in vivo where an ED mode of action is suspected, 2) ED mode of action in vivo that is suspected to be linked to adverse effects in vivo, 3) ED mode of action in vitro combined with toxicokinetic in vivo data (and relevant non test information such as read across, chemical categorisation and QSAR predictions). For propylparaben, the evaluation is based on strong evidence for estrogenic effects in vitro.
New search 2021	Literature update 2021: To update the literature search from the SIN list project, a search was carried out in PubMed 27/4 2021: #1 (propylparaben OR 94-13-3 OR (propyl p-hydroxybenzoate)) AND (rats OR mice OR human OR toxicity) AND (endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*) – 135 results #2 (propylparaben OR 94-13-3 OR (propyl p-hydroxybenzoate)) AND ((rats OR mice OR human OR toxicity) OR (endocrin* OR hormon* OR androgen* OR estrogen* OR thyroid* OR steroid*)) – 383 results #3: search #1 limited to 2012-2021 – 103 results #4: search #2 limited to 2012-2021 – 243 results Title and abstract screen for Search #3 led to 46 papers potentially relevant to ED assessment and 9 papers potentially relevant to DNEL determination. Most studies were cell-based or human epidemiological studies. New studies were identified investigating adverse effects related to the MoAs proposed for butylparaben in the SVHC (ECHA 2020) (EAS modality). As previous evaluations did not include T modality, a search was carried out for all years specifically targeted to thyroid toxicity: #5: (propylparaben OR 94-13-3 OR (butyl p-hydroxybenzoate) AND thyroid*).
Review of ECHA dissemination site	ECHA dissemination site includes information from one 90-day study (report 2019/2020, unpublished), one dermal sub chronic study (1978-1981), one oral (feed) EOGRTS study (Clariant GmBH 2019 unpublished, oral, feed), one oral (gavage) prenatal developmental toxicity study in rats (2018 unpublished), one uterotrophic study in immature rats (unpublished). A summary section lists studies on estrogenic and thyroid hormone related endpoints.
Data applied for ED evaluation	[Read-across from data on butylparaben]
Data applied for DNEL determination	There is a substantial amount of uncertainty associated with the DNEL determination for propylparaben. Even though several regulatory in vivo studies have recently been performed, full study reports are not publicly available, and the results could therefore not be properly evaluated. A recent SCCS opinion (2021) concluded that a NOAEL of 1000 mg/kg bw/day was appropriate, while an earlier EMA report identified a dose of 100 mg/kg bw/day as the NOEL. Due to the uncertainties related to DNEL determination for propylparaben, and a high degree of overlap in both physical/chemicals properties, and endocrine activity between butylparaben and propylparaben, the authors of the present report have performed **read across from data on butylparaben** in the DNEL determination for propylparaben. Butylparaben data show a LOAEL of 10 mg/kg bw/day leading to

a NOAEL of 2 mg/kg bw/day. It is presently not possible to determine if the "true" NOAEL for propylparaben is closer to 2 or 100 mg/kg bw/day, only that the available data are encumbered with a high degree of uncertainty, and that because of this, a cautious approach was used in the DNEL determination in the present report.

Appendix 8.2 ED assessment overview

T-modality

Five studies investigating thyroid related endpoints were included for this evaluation (Li et al 2020, Carlsson et al 2019, Aker et al. 2019, Aker et al. 2018, Vo et al. 2010).

Evidence for endocrine activity in vitro (T-mediated): [no effect or not sufficiently investigated] In tadpoles, no indications of specific thyroid-disrupting effects were seen for propylparaben (Carlsson et al 2019).

Evidence for endocrine activity in vivo (T-mediated): [no effect or not sufficiently investigated] A decrease in T4 levels was seen at all doses of propylparaben in rats exposed from PND 21 to 40 (62.5, 250, 1000 mg/kg bw/d), but the effect was only statistically significant at the medium dose (Vo et al 2010). T4 levels at these doses were 78, 58 and 85% of control levels, respectively. For the other parabens, T4 levels were also slightly lower, but were only statistically significant for middle dose isopropylparaben and low dose isobutylparaben.

Evidence for adverse effect (T-mediated): [no effect or not sufficiently investigated] Vo et al. 2010 investigated thyroid weights and histology in rats exposed from PND 21 to 40 to three doses (62.5, 250, 1000 mg/kg bw/d) of propylparaben (and five other parabens). In propylparaben-exposed animals, thyroid weights were slightly but not significantly higher than controls (115% of controls). Of all six parabens investigated, only the highest dose of methyl paraben and the lowest dose of butylparaben significantly increased thyroid weight (to 122-150% of controls) at PD 41. No parabens affected thyroid histology.

Human studies with focus on thyroid hormone disruption have been performed by Li et al. 2020, Aker et al. 2019, and Aker et al. 2018. In a birth cohort, Li et al (2020) found that maternal urinary propylparaben concentrations were associated with changes in cord serum T3 or thyroid peroxidase antibodies – an association which was also seen for ethyl paraben, but not for butylparaben. Aker et al. 2018 detected a negative association between plasma free thyroxine (FT4) and urinary propylparaben in pregnant American women (n=439). The same authors, Aker et al. 2019, found no association with TSH, T3, free T3, T4 or free T4 levels in humans in pregnant Puerto Rican women (n=602). These human studies were not considered sufficient to conclude on potential thyroid-disrupting effects.

As data for propylparaben did not reveal adverse effect on T-mediated endpoints, no MoA assessment was carried out. The WHO definition for identifying propylparaben as an endocrine disruptor via T modality is not fulfilled.

EAS modality

For propylparaben, ED assessment by Belgium is ongoing for the purpose of SVHC assessment. That evaluation includes information on the studies included in the ECHA database; data that are not available as study reports to us. Therefore, we have not carried out a thorough ED assessment for propylparaben and await the results of the Belgian assessment.
In addition to studies on propylparaben, an evaluation of parabens may also include comparison to analogues butylparaben and isobutylparaben. Therefore, the current evaluation leans on the ED evaluation in the SVHC document for butylparaben (ECHA 2020), and we preliminarily propose that propylparaben is also an ED. In that evaluation, perinatal exposure to bu-

tylparaben by subcutaneous and oral route was found to induce adverse effects on male offspring exposed perinatally. The MoA was mainly estrogenic activity leading to altered male reproductive function following perinatal exposure. In addition, anti-androgenic activity and steroid synthesis inhibition may contribute. In that evaluation, perinatal exposure was found to induce adverse effects, whereas data on pubertal or adult exposure were not included. After the publication of the SVHC report, a large rat study on dietary exposure to butylparaben during development was published by Hubbard et al. 2020. This study did not detect adverse effects on a number of endocrine sensitive targets including sperm count of offspring. Nevertheless, butylparaben may be considered an endocrine disrupter due to the presence of several other studies showing consistent findings of adverse effects in male offspring exposed perinatally via gavage or subcutaneous injections (see ECHA 2020).

The following sections provides an overview of the available studies on propylparaben. This overview presents data included in the SIN list project (Hass et al. 2012) as well as new literature regarding adverse effects of propylparaben identified in the literature search. Human studies have indicated weak associations between increased paraben exposure and markers for human reproductive health, whereas other studies showed no effects. These findings are not sufficient to conclude on endocrine disruption and are not reviewed here.

Evidence for endocrine activity in vitro (EAS-mediated): strong for estrogenic effect, moderate for anti-androgenic effect]

Several types of in vitro assays investigating estrogenicity (ER binding, ER mediated proliferation, ER mediated gene expression as well as ER transactivational assays) all show effects of propylparaben (Routledge 1998, Miller 2001, Schultis and Metzger 2004, Morohoshi 2005, Okubo 2001, Byford 2002, Schultis and Metzger 2004, Vanapyris 2006, Blair 2000, Lemini 2003, Gomez 2005, Vo et al. 2010, Kim et al. 2011, Vo et al. 2011, Yang et al. 2011, Terasaki et al. 2009, Watanabe et al. 2013). For the group of parabens collectively, a pattern of increasing potency of the paraben with growing alkyl R-group is seen, and the response of propylparaben is similar to that of butylparaben in several of the studies conducted (see e.g. Boberg et al. 2010 review paper).

In androgen/anti-androgenic test assays, all of the parabens show a minimal or no effects (Sato 2005, Chen 2007, Kjaerstad et al. 2010, Kim et al. 2010). However, when an effect (AR antagonism) is present, the potency seems to increase with chain length, and effects of propylparaben are observed. Results from in vitro assays testing other ED related endpoints (PXR, CAR or PPARα transactivation) show slight differences between parabens, with propylparaben being more potent regarding effect on PPARα transactivation but less on PXR or CAR transactivation (Fujino et al. 2019, Watanabe et al. 2013).

See also SCCS 2021.

Evidence for endocrine activity in vivo (EAS-mediated): [moderate]

Estrogenic activity: Four studies on in vivo endocrine activity revealed uterotrophic effects of propylparaben (Lemini et al. 2003, 2004), whereas three studies did not (Sivaraman et al 2018, Hossaini et al 2000, Otha et al. 2012). In general, the potency appears to increase with growing alkyl R-group (i.e. lower LOELs with growing alkyl side chain).

Lee JH 2017 described changes in ovarian expression of genes related to steroidogenesis and ovary development after 5 weeks exposure of adult female rats, concomitantly with an increase in serum FSH.

In a toxicokinetic study, Pollock T et al. 2017 did not see changes in urinary estradiol levels of male and female CF1-mice exposed to a single s.c. dose of propylparaben, whereas an increased estradiol level was seen for butylparaben.

See also SCCS 2021.

Evidence for adverse effect (EAS-mediated): [weak/moderate – insufficient data available]

Males/females: A postnatal exposure study on propylparaben showed no effect on estrous cycle or mating performance, but no data on sperm analysis are presented (Sivaraman et al. 2018). In the same study, significantly earlier vaginal opening was seen in female rats at the high dose of 1000 mg/kg bw/day administered from PND 4 to 90 (n=10 for examination at PND 90, n=25 for pubertal onset and estrous cyclicity). At this age, no difference in body weight was present between groups. The authors consider this due to unusually late pubertal onset in some controls. However, this response corresponds well with an estrogenic mode of action of propylparaben. A lower body weight at vaginal opening was

observed and is likely due to the earlier vaginal opening. This strengthens the evaluation that early pubertal onset is an endocrine effect and not caused changes in body weight, as higher – not lower – body weight during puberty could be a relevant alternative non-endocrine cause of early pubertal onset.

Males: In young adult males, Oishi 2002 reported reduced epididymal sperm count in a dose-related manner, starting from 100 mg/kg bw/d. Serum testosterone levels were reduced in a dose-related manner in all dose groups, but was only statistically significant at 1000 mg/kg bw/day. Body weight was reduced at 1000 mg/kg bw/day. This indicates a lowest-observed adverse effect level (LOAEL) of 10 mg/kg bw/day for propylparaben, but the study has some shortcomings also noted by SCCS.

Gazin et al 2013 reported no effects in juvenile males on male reproductive organ weights, epididymal sperm parameters, histopathology or hormone levels. Propylparaben was orally administered by gavage to male Wistar rats at doses of 3, 10, 100, or 1000mg/kg/day for 8 weeks starting on PND21 (n=10 in cohort sacrificed at end of treatment and n=10 at end of recovery period). Only at the end of a recovery period – Collectively, studies in young males (Oishi 2002 and Gazin et al. 2013) only show relatively weak indications of adverse effects on male reproduction. However, these studies are generally not sufficient to determine robust NOAEL values for parabens, as studies with perinatal exposure and investigation of several endocrine-regulated endpoints are endpoints are necessary for determining a NOAEL with respect to endocrine disruptive effects.

Females: In adult female rats orally exposed to 100 mg/kg bw/d of propylparaben for 5 weeks, estrous cycle was affected (shorter estrous cycle and consistent di-estrous after a few cycles of exposure) and changes in ovarian expression of genes related to steroidogenesis and ovary development were altered (Lee et al. 2017). The same pattern of effects was seen for butylparaben but not methylparaben. Serum FSH was increased, and the number of secondary follicles and Graafian follicles were reduced. As reporting is unclear and a small n of 6 females in only one dose group was applied, it is unclear if the effects on ovary and estrous cycle can be considered valid.

In a pubertal assay, Vo et al 2010 investigated female rats orally gavaged with doses of 62.5, 250 and 1000 mg/kg/day of propylparaben (and five other parabens) from PND 21 to 40 (n=10). Propylparaben did not significantly affect pubertal onset, estrous cyclicity, reproductive organ weights or histology. An increase in uterus thickness was statistically significant.

Mogus et al. 2021 investigated the influence of propylparaben exposure on the morphology of mammary gland post-lactation (after involution). Indications of reduced gland density was seen but given that also pup numbers per litter was slightly reduced, the relevance of this finding may be questioned. The possible mode of action behind such potential effect is not clear.

Comments on the EOGRTS study: This study was referred by SCCS 2021 opinion. DTU does not agree with the conclusion made by SCCS that the extended one-generation reproductive toxicity (EOGRTS, OECD TG 443) study in rats (Clariant GMBH 2019) supports a NOAEL for reproductive endpoints to be 1000 mg/kg bw/day (top dose). DTU finds that the NOAEL should be lower due to the findings mentioned below. It should be noted, that the study report was not available to DTU at the time of evaluation (December 2020). This study included doses of 0, 100, 300 and 1000 mg/kg bw/day (n=20 in F1 and n=10 for some sub-cohort endpoints). Specifically, adverse effects are seen together with indications of endocrine activity:

- Statistically significant decrease of individual pup weight is considered an adverse finding relevant for NOAEL determination. This finding is considered robust, as it is seen at high dose in several cohorts of F1 offspring at birth and at several ages up to weaning PND 21. These findings warrant further examination of the study report, which was not available to DTU at the time.
- Changes in anogenital distance (AGD) and anogenital index was reported and warrants further examination of the study report.
- No effect on sperm count was reported, but indications of decreased sperm motility and increased number of abnormal sperm warrant further evaluation of the study report. Decrease of sperm motility and increase of abnormal sperm has also been seen in some studies on perinatal exposure to butylparaben

Conclusions on endocrine activity and adverse effects:

The in vivo studies available in the open literature for propylparaben provide indications of adverse effects on EAS related endpoints but are insufficient to determine a robust NOAEL. The unpublished EOGRTS study may provide additional data to clarify concerns regarding adversity. Possible changes in anogenital distance, nipple retention and prostate weight are indicated, but cannot be evaluated without access to the full study report. As this unpublished data is not available, a cautious approach was used where read-across to the structural and functional analogue butylparaben, (which is considered ED according to the SVHC evaluation (ECHA 2020)) was used.

Mode of action analysis	
Mode of action	There is sufficient evidence of endocrine activity for propylparaben, but not sufficient evidence for adverse effects. For the structural analogue butylparaben, there is sufficient evidence of endocrine activity (estrogen receptor activation and possibly altered steroidogenesis and androgen receptor antagonism) and adverse effects (decreased sperm count and quality).
Biological plausibility of key event relationships	For butylparaben, it is biologically plausible that adverse effects are due to the endocrine activity. For propylparaben, the same pattern of endocrine activity in vitro and in vivo is seen, and therefor similar adverse effects are suspected.
Dose and temporal concordance	In each study, indicators of key events related to endocrine activity are affected at the same doses causing adverse effects. Between studies, there are differences in effective doses. For butylparaben, key events are observed in the hypothesized order, i.e., in vivo indicators of endocrine activity are seen in developing animals, and adverse effects are seen in adulthood.
Essentiality, consistence, analogy, specificity	Essentiality has not been investigated. There is consistency in findings between studies using subcutaneous exposure or oral gavage with respect to endocrine activity of propylparaben. For butylparaben, studies on adverse effects are consistent for studies using subcutaneous exposure or oral gavage, whereas a large study using dietary exposure did not show effects.
Human relevance	Human relevance is assumed, as there are no data indicating that these endocrine modes of action are not relevant to humans.
Uncertainties	The uncertainty analysis highlights that the evidence base for both butylparaben and propylparaben is relatively limited. This uncertainty may be reduced when results of an EOGRTS study on propylparaben becomes available.

There is sufficient evidence of endocrine activity for propylparaben, and indications of adverse effect (reduced AGI in male), but may not be considered sufficient evidence for adverse effects. As the study report on the EOGRTS study is not available, there is not sufficient data to conclude on adverse effect of propylparaben. For the structural analogue butylparaben, there is sufficient evidence of endocrine activity and adverse effects, and it is biologically plausible that adverse effects are due to the endocrine activity of butylparaben.

In conclusion, the WHO definition for identification of butylparaben as an endocrine disrupter is fulfilled, and in the absence of sufficient data for propylparaben, the same is concluded for propylparaben.

Appendix 8.3 DNEL and DMEL determinations

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
SCCS 2011, SCCS 2013 (Fischer et al., 1999; Kang et al., 2002; Oishi 2002; Lemini et al., 2003; Lemini et al., 2004)	Rats, neonatal exposure, PD 2-18, s.c. exposure supported by several studies on perinatal exposure to **butylparaben**.	Lack of effect on testis weight, epididymis and histology with neonatal exposure; ↓ semen quality in offspring of exposed pregnant rats	2/10/-	DNEL: 10 (interspecies) *10 (intraspecies) =100 DMEL: 10 (interspecies) *10 (intraspecies) *10 (nature of endocrine disrupting properties) =1000=5000	$DNEL_{eas}$: 20 $DMEL_{eas}$: 2	**$DNEL_{eas}$:20** (not adjusted for oral absorption fraction in study on oral dosing) ($DNEL_{eas}$ by read across) **$DMEL_{eas}$: 2**	By read across, see appendix 7, butylparaben. SCCS uses the same NOEL for propyl- and butylparaben. Overall assessment of several studies considered by SCCS 2011 and 2013.
Boberg et al., 2016 (supported by other studies showing adverse effect at same or higher doses: Kang et al., 2002; Zhang et al. 2014; Maske et al, 2020; Guerra et al, 2017b)	Rats, **butylparaben**, several studies on perinatal exposure; oral or s.c. exposure	↓ semen quality in offspring of exposed pregnant rats	-/10/-	DNEL: 5 (NOAEL-to-LOAEL extrapolation for shallow slope) *10 (interspecies) *10 (intraspecies) =500 DMEL: 5 (NOAEL-to-LOAEL extrapolation for shallow slope) *10 (interspecies) *10 (intraspecies) * 10 (nature of endocrine disrupting properties)	**$DNEL_{eas}$: 20** **$DMEL_{eas}$: 2**	**$DNEL_{eas}$: 20** **$DMEL_{eas}$: 2**	See appendix 4, Butylparaben. SCCS 2013 notes that oral studies on butylparaben may not be optimal for risk assessment of dermal exposures.
EMA 2015: NOAEL based on unpublished study by Pouliot L (2013).	Propylparaben, three-month oral developmental study in juvenile rats.	Ealier puberty and increased uterine weight in females.	100/1000/-	DNEL: 10 (interspecies) *10 (intraspecies) =100 DMEL: 10 *10*10 (nature of endocrine disrupting properties)	**$DNEL_{eas}$: 1000** **$DMEL_{eas}$: 100**	**$DNEL_{eas}$: 1000** **$DMEL_{eas}$: 100**	EMA (2015) finds that based on results from a juvenile study, the NOEL for propylparaben should be 100 mg/kg bw/day

Reference	Study design (and exposure route)	Effect-parameter	NOAEL/ LOAEL/ BMDL (mg/kg bw/day)	Assessment factors	DNELexternal/DMELexternal (µg/kg bw/d)	DNELinternal / DMELinternal (µg/kg bw/d)	Notes
Unpublished, Clariant GMBH 2019 as reported in SCCS 2021 and ECHA vdatabase	Propylparaben, Extended one-generation reproductive toxicity study in rats. 0, 100, 300, 1000 mg/kg bw/d (diet).	Altered anogenital distance in male and female offspring, nipple retention in male offspring, prostate weight reduction in adults	300/1000/-	DNEL: 10 (interspecies) *10 (intraspecies) =100 DMEL: 10 (interspecies) *10 (intraspecies) * 10 (nature of endocrine disrupting properties)	$DNEL_{eas}$: 3000 $DMEL_{eas}$: 300	$DNEL_{eas}$: 3000 $DMEL_{eas}$: 300	
Comments: **$DNEL_{eas}$ of 20 µg/kg bw/d** and a **$DMEL_{eas}$ of 2 µg/kg bw/d** was derived from a study on butylparaben showing effects on sperm count in rats, and on another study showing absence of reproductive effects in rat offspring at 2 mg/kg bw/day (as evaluated by SCCS 2013). It is however noted that oral studies on butylparaben may not be optimal for risk assessment of dermal exposures, according to SCCS 2021. Data for Propylparaben, showing endocrine disruptive (estrogenic) effects is considered to be reliable, but the determination of DNEL is considered to be less robust, i.e., subject to some uncertainty (See Boberg et al. 2020) and therefore read across from data on butylparaben was used for DNEL determination of propylparaben. No evidence of effects on the thyroid hormone system was located, and no $DNEL_{thyr}$ was set.							

Appendix 8.4 Notes on other effects of relevance for human health

Appendix 8.5 References for propylparaben

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Appendix 9. Risk assessment of cosmetic products using the SCCS Notes of Guidance method

In the following table, the systemic internal dose (SED - µg/kg bw/d) has been calculated from the quantitative analyses based on the previously described use scenarios (see section 12.3.1 Exposure calculations) and identified systemic threshold value (PoD - mg/kg bw/dx 103 = µg/kg bw/d) and typical NOAEL or LOAEL values from repeated dose studies. For each substance (BHA, BHT, propylparaben, butylparaben), PoD is identified in the hazard assessment in Chapter 9. The same NOAEL/LOAEL values used for the derivation of DNEL/DMEL values are also used as PoD regarding calculation of MoS values.

When deriving DNEL/DMEL values for propylparaben and butylparaben, an assessment factor (AF) of 5 has been used in the hazard assessment in Chapter 9 to convert the LOAEL to NOAEL as well as uncertainty about identification of NOAEL, cf. REACH Guidance (ECHA 2012). When calculating PoD for use in the MoS calculation, an uncertainty factor of 3 (UF 3) is typically used to get from LOAEL to NOAEL in accordance with the SCCS Notes of Guidance from 2021. It is also stated that the value of this uncertainty factor can be increased when taking into account for example the severity of the effects or the slope of the dose-response curve. This is why a value of 5 as proposed in Chapter 9 is maintained, as the rationale here is that the dose-response curve is flat and therefore setting a zero-effect level based on a LOAEL value is more uncertain.

The internal systemic dose (SED) is calculated based on the following in accordance with the SCCS Notes of Guidance (2021):

$$SED = E_{product} \times C/100 \times DAp/100$$

Where Eproduct (mg/kg bw/day) is the estimated daily exposure, C (%) = the concentration of the substance and DAp (%) = dermal absorption.

Calculation of SED is reviewed in section 12.3.1 Exposure calculations, but in the following the calculation of SED for propylparaben in sunscreen for pregnant women and children under 3 years is shown:

- Propylparaben (sunscreen, pregnant women - Product Lab no. EU-K 195):
  According to SCCS (2021a), a daily consumption of 18 g/d is used in risk assessment of sunscreen. With a content of propylparaben of 0.17%, a woman of 60 kg will thus be exposed to:
- Exposure (external) = (18 g/d x 10^6 µg/g x 0.0017)/60 kg = 510 µg propylparaben/kg bw/d
- Internal dose (µg/kg bw/d) = 510 µg BHA/kg/d x 3.7% = 19 µg propylparaben/kg bw/d

- Propylparaben (Propylparaben (sunscreen, children under 3 years - Product Lab no. NEU-K 193):

  According to SCCS (2021a), the ratio between the surface area of the skin and body weight is 1.6 times larger in children aged 1 year compared to adults. This means that at the same exposure per. cm^2, the exposure will be 1.6 times higher per kg body weight for children of 1 year compared to adults. Based on this, and with a child of 1 year representing the group of children under 3 years, the following exposure can be calculated:

  According to SCCS (2021a), a daily consumption of 18 g/d is used in risk assessment of sunscreen. With a propylparaben content of 0.17%, a child under 3 years will thus be exposed to:

- Exposure (external) = (18 g/d x 10^6 µg/g x 0.0017)/60 kg x 1.6 = 816 µg propylparaben/kg bw/d

- Internal dose (µg/kg bw/d) = 816 µg propylparaben/kg/d x 3.7% = 30 µg propylparaben/kg/d

Based on SED and PoD, MoS values have been calculated in the following:

MoS = PoDsys/SED

In the quantitative analyses of content of D4 in cosmetic products, D4 was not identified in concentrations above the detection limit in any one of the 20 purchased cosmetic products. The detection limit in the quantitative analyses of D4 is identified as 30 mg/kg. In the following table, MoS values have been calculated based on the detection limit to examine whether the detection limit constitutes a problematic level regarding the MoS calculations.

In the table below, MoS values have been calculated for all ingredients above the detection limit as well as for D4, where the detection limit has been used.

The following are examples of calculations of the MoS value for pregnant women regarding content of BHA, BHT, propylparaben, butylparaben (indicated with product numbers) and D4 (not indicated with product number as the detection limit is used) based on the PoD values identified in the hazard assessment in Chapter 9 as well as the calculated SED values (see section 12.3.1 Exposure calculations). In addition, the MoS value of propylparaben in sunscreen for children under 3 years is calculated.

- Propylparaben (sunscreen, pregnant women - Product Lab no. EU-K 195):
  Rat; several studies with perinatal oral exposure.
  LOAEL: 10 mg/kg bw/d
  NOAEL: 10/5 = 2 as an uncertainty factor of 5 (UF 5) is used to get from LOAEL to NOAEL in accordance with SCCS Notes of Guidance (2021a) and the assessment in Chapter 9.
  PoD: 2 mg/kg bw/d (internal dose assuming an oral absorption of 100%)
  SED: 19 µg/kg bw/d (internal dose) = 0.019 mg/kg bw/d
  MoS: 2/0.019 = 105

- Propylparaben (sunscreen, children under 3 years - Product Lab no. NEU-K 193):
  Rat; several studies with perinatal oral exposure.
  LOAEL: 10 mg/kg bw/d

NOAEL: 10/5 = 2 as an uncertainty factor of 5 (UF 5) is used to get from LOAEL to NOAEL in accordance with SCCS Notes of Guidance (2021a) and the assessment in Chapter 9.
PoD: 2 mg/kg bw/d (internal dose assuming an oral absorption of 100%)
SED: 30 µg/kg bw/d (internal dose) = 0.030 mg/kg bw/d
MoS: 2/0.030 = 67

- BHA (sunscreen, pregnant women - Product Lab no. NEU-K 196)):
  Rat, oral two-generation study; 0, 10, 100, 500 mg/kg bw/d BHA
  NOAEL: 100 mg/kg bw/d (T); 10 mg/kg bw/d (EAS)
  PoD: T-mode 100; EAS mode of action 10 mg/kg bw/d (internal dose, assuming an oral absorption of 100%)
  SED: 0,096 µg/kg bw/d (intern dosis) = 0,000096 mg/kg bw/d
  MoS: 10/0,000096 = 104167

- BHT (sunscreen, pregnant women - Product Lab no. DK-K 198):
  13-week oral study, exposure of offspring, 0, 25, 108, 276 mg/kg bw/d BHT
  NOAEL: 25 mg/kg bw/d
  PoD: 25 mg/kg bw/d (internal dose, assuming an oral absorption of 100%)
  SED: 0.0966 µg/kg/d (internal dose) = 0.000096 mg/kg bw/d
  MoS: 25/0.0000966 = 260417

- Butylparaben (body lotion, pregnant women - Product Lab no. NEU-K 180):
  Rat; several studies with perinatal oral exposure.
  LOAEL: 10 mg/kg bw/d
  NOAEL: 10/5 = 2 as an uncertainty factor of 5 (UF 5) is used to get from LOAEL to NOAEL in accordance with SCCS Notes of Guidance (2021) and the assessment in Chapter 9.
  PoD: 2 mg/kg bw/d (internal dose assuming an oral absorption of 100%)
  SED: 2.2 µg/kg bw/d (internal dose) = 0.0022 mg/kg bw/d
  MoS: 2/0.0022 = 909

- D4 (sunscreen, pregnant women):
  Rat, 24-month chronic inhalation study 0; 10; 30; 150 or 700 ppm (6 hours/day, 5 days/week)
  NOAEL: 30 ppm; Modified NOAEL: 30 ppm = 0.0135 mg/l x 30 = 0.405 mg/l
  Inhalation volume: rat 20.5 l/h; weight rat: 0.5 kg.
  Exposure (inhalation): [(0.405 x 20.5 x 6) x 5/7] /0.5 = 71.16 mg/kg bw/d;
  Absorption (inhalation): 5% (0.05)
  PoD: 71.16 x 0.05 = 3.6 mg/kg bw/d (systemic dose)
  SED: 0.045 µg/kg/d (internal dose) = 0.000045 mg/kg bw/d
  MoS: 3.6/0.000045 = 80000

The table below shows that most MoS values for the content of BHA, BHT, propylparaben and butylparaben in cosmetic products for pregnant women are well over 100, indicating that no risk has been found. The lowest MoS value found is 105 for the content of propylparaben in sunscreen for pregnant women. There is no risk if a MoS value is 100 or above, and therefore no risk has been identified for the content of propylparaben in sunscreen for adults, even as a borderline case.

In sunscreen, a user amount of 18 g of sunscreen for pregnant women has been applied, which is in accordance with the SCCS Notes of Guidance (SCCS, 2021a). However, this quantity is a subject of debate, as the health and environmental authorities state that a significantly higher user amount must be applied to achieve the desired protection factor. From the

Ministry of Environment, an amount four times higher has been proposed, i.e. 72 g. Assuming a quadruple amount of sunscreen, the corresponding MoS values will be a factor 4 x times lower. This will entail a risk concerning sunscreen products for pregnant women, as the MoS value will then be reduced from 105 to 26.

MoS values for propylparaben in sunscreen, body lotion, body oil and aftersun for pregnant women and aftersun for pregnant women are all up to 1000. For content of butylparaben in body oil for pregnant women, all MoS values are well over 100, typically between 1000 - 2000. The remaining MoS values in terms of content of BHA and BHT are typically 5-6 digit values.

Overall, the risk assessment of the identified content of the focus substances in the various cosmetic products for adults does not shown a risk when the risk assessment method for cosmetics is used.

In sunscreen for children under 3 years, the risk assessment of propylparaben content has shown a risk, as the calculated MoS value was 67.

SCCS (2021b) assessment of PoD for propylparaben

The calculated MoS values are based on a systemic threshold value (PoD - mg/kg bw/d x 103 = µg/kg bw/d) and typical NOAEL or LOAEL values from repeated dose studies concerning endocrine disrupting effects. In this context, it should be mentioned that SCCS in their latest expert assessment of propylparaben from 2021 concluded that although there were indications of endocrine disrupting properties, propylparabens do not have endocrine disrupting properties and therefore a PoD based on endocrine disrupting effects could not be derived. Instead, a NOAEL of 1000 mg/kg bw/d was selected as the PoD value based on propylparaben data on reproduction, neurotoxicity and immunotoxicity. This value was used for MoS calculations in the SCCS expert assessment. Compared to the PoD used in this report (2 mg/kg bw/d for endocrine disrupting effects), there will be a difference of 500 compared to the PoD value used by SCCS (1000 mg/kg bw/d for non-endocrine disrupting effects).

If the PoD value from SCCS of 1000 mg/kg bw/d is used, the corresponding MoS values will be 500 times higher and thus not indicate a risk concerning sunscreen for children under 3 .

TABLE 80. MoS values for all ingredients above the detection limit found in the cosmetic products as well as for D4 where the detection limit has been used. MoS values are calculated based on the PoD values identified in the hazard assessment in Chapter 9 as well as the calculated SED values. MoS ≥ 100 indicates no risk.

Product Lab no.	Product type	Target group	BHA (%)	BHT (%)	Propylparaben (%)	Butylparaben (%)	D4 (%)	BHA (SED)*	BHT (SED)*	Propylparaben (SED)*	Butylparaben (SED)*	D4 (SED)*	BHA PoD**	BHT PoD**	Propylparaben PoD**	Butylparaben PoD**	D4 PoD**	BHA MoS	BHT MoS	Propylparaben MoS	Butylparaben MoS	D4 MoS
NEU-K 171	Body lotion	Preg. Wom.	≤ 0.004	0.058	No	No	-	-	0.3	-	-	-	-	$25x10^3$	-	-	-	-	83333	-	-	-
NEU-K 181	Body oil	Preg. Wom.	≤ 0.004	0.023	0.098	No	-	-	0.12	4.73	-	-	-	$25x10^3$	$2x10^3$	-	-	-	208333	423	-	-
EU-K 183	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0005	0.099	0.025	-	-	-	4.77	1.21	-	-	-	$2x10^3$	$2x10^3$	-	-	-	419	1653	-
EU-K 182	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0003	0.095	0.021	-	-	-	4.58	1.01	-	-	-	$2x10^3$	$2x10^3$	-	-	-	437	1980	-
DK-K 187	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0003	0.091	No	-	-	-	4.39	-	-	-	--	$2x10^3$		-	-	-	456	-	-
NEU-K 192	After sun	Preg. Wom.	≤ 0.004	≤ 0.0005	0.15	No	-	-	-	7.25	-	-	-	-	$2x10^3$	-	-	-	-	276	-	-
EU-K 168	Sunscreen	Preg. Wom.	≤ 0.004	≤ 0.0003	0.066	No	-	-	-	7.33	-	-	-	-	$2x10^3$	-	-	-	-	273	-	-

Product Lab no.	Product type	Target group	BHA (%)	BHT (%)	Propylparaben (%)	Butylparaben (%)	D4 (%)	BHA (SED)*	BHT (SED)*	Propylparaben (SED)*	Butylparaben (SED)*	D4 (SED)*	BHA PoD**	BHT PoD**	Propylparaben PoD**	Butylparaben PoD**	D4 PoD***	BHA MoS	BHT MoS	Propylparaben MoS	Butylparaben MoS	D4 MoS
EU-K 195	Sunscreen	Preg. Wom.	≤ 0.004	≤ 0.0005	0.17	No	-	-	-	19	-	-	-	-	$2x10^{33}$	-	-	-	-	105	-	-
EU-K 196	Sunscreen	Preg. Wom.	0.008	≤ 0.0003	0.046	No	-	0.096	-	5.11	-	-	$10x10^{3}$	-	$2x10^{3}$	-	-	104167	-	391	-	-
NEU-K 172	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0005	0.090	0.036	-	-	-	4.34	1.74	-	-	-	$2x10^{3}$	$2x10^{3}$	-	-	-	461	1149	-
NEU-K 180	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0005	0.021	0.045	-	-	-	1.01	2.17	-	-	-	$2x10^{3}$	$2x10^{3}$	-	-	-	1980	909	-
NEU-K 193	Sunscreen	Children under 3 years	≤ 0.004	0.047	0.17	No	-	-	0.9	30	-	-	-	$25x10^{3}$	$2x10^{3}$	-	-	-	-	27777	**67**	-	-
EU-K 173	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0003	0.054	No	-	-	-	2.60	-	-	-	-	$2x10^{3}$	-	-	-	-	769	-	-
DK-K 174	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0005	0.0002	No	-	-	-	0.0096	-	-	-	-	$2x10^{3}$	-	-	-	-	208333	-	-
DK-K 176	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0003	0.092	No	-	-	-	4.44	-	-	-	-	$2x10^{3}$	-	-	-	-	451	-	-

Product Lab no.	Product type	Target group	BHA (%)	BHT (%)	Propylparaben (%)	Butylparaben (%)	D4 (%)	BHA (SED)*	BHT (SED)*	Propyl-paraben (SED)*	Butylparaben (SED)*	D4 (SED)*	BHA PoD**	BHT PoD**	Propyl paraben PoD**	Butyl-paraben PoD**	D4 PoD***	BHA MoS	BHT MoS	Propyl paraben MoS	Butylparaben MoS	D4 MoS
DK-K 198	Sun-screen	Preg. Wom.	≤ 0.012	0.008	No	No	-	-	0.096	-	-	-	--	$25x10^3$	-	-	-	-	260417	-	-	-
EU-K 184	Body lotion	Preg. Wom.	≤ 0.012	0.048	No	No	-	-	0.25	-	-	-	-	$25x10^3$	-	--	-	-	100000	-	-	-
DK-K 185	Body lotion	Preg. Wom.	≤ 0.012	0.051	No	No	-	-	0.27	-	-	-	-	$25x10^3$	-	-	-	-	92593	-	-	-
DK-K 186	Body lotion	Preg. Wom.	≤ 0.004	≤ 0.0003	0.043	No	-	-	-	2.07	-	-	-	-	$2x10^3$	-	-	-		966		--
DK-K 197	Sun-screen	Preg. Wom.	≤ 0.004	0.003	No	No	-	-	0.036	-	-	-	-	$25x10^3$	-	-		--	694444	-	-	-
-****	Sun-screen	Preg. Wom.	-	-	-	-	0.003	-	-	-	-	0.045	-	-	-	-	$3.6x10^3$	-	-	-	-	80000
-****	Body lotion	Preg. Wom.	-	-	-	0.003		-	-	-	-	0.020	-	-	-	-	$3.6x10^3$	-	-	-	-	180000
-****	After-sun	Preg. Wom.	-	-	-	0.003		-	-	-	-	0.020	-	-	-	--	$3.6x10^3$	-	-	-	-	180000
-****	Body oil	Preg. Wom.	-	-	-	0.003		-	-	-	-	0.020	-	-	-		$3.6x10^3$	-	-	-	-	180000

Product Lab no.	Product type	Target group	BHA (%)	BHT (%)	Propylparaben (%)	Butylparaben (%)	D4 (%)	BHA (SED)*	BHT (SED)*	Propylparaben (SED)*	Butylparaben (SED)*	D4 (SED)*	BHA PoD**	BHT PoD**	Propylparaben PoD**	Butylparaben PoD**	D4 PoD***	BHA MoS	BHT MoS	Propylparaben MoS	Butylparaben MoS	D4 MoS
-****	Sunscreen	Children under 3 years					0.003					0.072					$3.6x10^3$					50000

* SED: internal systemic dose - µg/kg bw/d

** PoD: systemic threshold value (NOAEL/LOAEL) - mg/kg bw/d x 103 = µg/kg bw/d

*** D4: NOAEL male rats = 3.6 mg/kg bw/d (systemic dose) x 103 = µg/kg bw/d

**** For D4 no specific product Lab no is specified as the detection limit applies to all products

Analyses and risk assessment of endocrine disruptors in products for pregnant women and children

The aim of the project was to carry out chemical analyses, hazard-, exposure- and risk assessments substance-by substance and/or combined for selected endocrine disruptors and suspected endocrine disruptors in products for pregnant women and children.

The exposure scenarios were established for pregnant women (unborn child), toddlers under 3 years of age and children aged 3 years. In the risk assessments, the total exposure from both consumer products and other products such as food, food contact materials and pharmaceuticals is included. Furthermore, the assessments have been made both when it is assumed that a threshold can be set, DNEL, and when it is assumed that a safe threshold cannot be set, DMEL. In both cases, assessments have been made with and without the use of an additional safety assessment factor, MAF.

In total, 73 screening analyses, 40 quantitative analyses and 24 migration analyses have been carried out for products used by pregnant women and children. This includes analyses of toys, mobile covers, teethers, dummies, watch straps, textiles and leave-on cosmetic products. Control analyses have also been carried out for the migration of BPA from toys and the content of parabens in cosmetic products.

The result was, that all 6 substances (BHT, BHA, BPA, propylparaben, butylparaben and D4) have been evaluated as endocrine disruptors.

In one sunscreen for children a risk cannot be rejected, while other products do not individually present a risk of endocrine disrupting effects substance by assuming a lower threshold for the 6 substances.

When the added exposure is assessed or when MAF is included with a threshold or a safe threshold is assumed not to be assessed, with and without MAF, there may be a risk of endocrine disrupting effects

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