National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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Exposure to parabens in cosmetics in children as a case study

RIVM Letter Report 320015005/20111
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Abstract

Aggregate exposure assessment of chemicals in consumer products
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Consumers are exposed daily to chemicals from non-food consumer products. The level of exposure has to be assessed to evaluate the consequences of exposure to a substance for public health. A risk is calculated by comparing the exposure to a substance with the hazardous effect. Considering that a substance may be contained in several consumer products, the contribution of these products to the total exposure will have to be added up to determine the aggregate exposure. This includes summation of the different routes: dermal, inhalation, and oral.

More realistic exposure estimation with use data
In a case study, RIVM has coupled a model for aggregate exposure to use data of products; how often are they used and how much is used. Four parabens are chosen, which are present in personal care products for young children such as shampoo, baby wipes and hair lotion. It is common practice to use maximal defaults for frequency and amount in exposure estimations. A more realistic exposure estimation can be made using use data, which are gathered with a small survey.

Effectivity exposure estimation tested
Exposure estimations are performed step-by-step, using so-called tiers.An exposure estimation is at first calculated using (maximal) deterministic values. When risks cannot be excluded, the calculations can be performed in more detail. In this case study, a method for a higher tier is tested. This tier provides information on uncertainties in the exposure estimation as well as which sources contribute the most to the total exposure. Besides, insight is obtained on the distribution of exposure over the population. All this information is relevant for risk assessors and risk managers.

Keywords:
Aggregate exposure, case study, parabens

Rapport in het kort

Geaggregeerde blootstelling van chemische stoffen in consumentenproducten. Blootstelling aan parabenen in verzorgingsproducten voor kinderen als case studie

Consumenten staan dagelijks bloot aan chemische stoffen die zijn verwerkt in verschillende non-food-producten. Om de gevolgen voor de volksgezondheid te kunnen beoordelen, moet de blootstelling aan deze stoffen bekend zijn. Een risico wordt namelijk berekend door de blootstelling van een stof te vergelijken met het effect ervan. Om zicht te krijgen op de totale blootstelling aan één stof vanuit verschillende consumentenproducten wordt een zogeheten geaggregeerde blootstelling uitgevoerd. Hierin zijn ook de verschillende 'routes' verwerkt waardoor mensen een stof binnen kunnen krijgen: via de huid, via inademing, of via de mond.

Realistischere blootstellingschatting met gebruiksgegevens
Het RIVM heeft in een casestudie een model voor geaggregeerde blootstelling gekoppeld aan gebruiksgegevens van producten: hoe vaak worden ze gebruikt en in welke hoeveelheid. Gekozen is voor vier parabenen die in verzorgingsproducten voor jonge kinderen zitten, zoals shampoo, billendoekjes en haarlotion. Bij gewone blootstellingschattingen wordt doorgaans uitgegaan van de maximale frequentie en hoeveelheid. Met de gebruiksgegevens kan een realistischere inschatting van de blootstelling, en daarmee van het risico worden gemaakt. De gebruiksgegevens zijn met behulp van een kleinschalige enquête vergaard.

Effectiviteit blootstellingschatting getoetst
Blootstellingschattingen worden trapsgewijs uitgevoerd, in zogenoemde tiers. Dat betekent dat eerst een blootstelling uitgerekend wordt met (maximale) waarden. De berekeningen worden steeds gedetailleerder uitgewerkt naarmate risico's als gevolg van blootstelling niet kunnen worden uitgesloten. In de casestudie is de gebruiksinformatie gebruikt om de methode van de laatste testfase (de hoogste tier) te testen. Deze tier levert informatie op over onzekerheden in de blootstellingschatting en over welke bronnen de hoogste bijdrage leveren aan de blootstellingschatting. Daarnaast wordt inzicht verkregen welk deel van de bevolking aan hoge, respectievelijk lagere, concentraties blootstaan. Al deze informatie is relevant voor risicobeoordelaars en risicomanagers.

Trefwoorden:
Geaggregeerde blootstelling, case studie, parabenen

Contents

Summary

Aggregate exposure is the total exposure to a chemical that arises from multiple sources and via multiple exposure pathways. For risk assessment, it is important to estimate the total exposure to a chemical to avoid an underestimation of the risk. A general introduction to the concept of aggregate exposure is provided. The goal of the report is to obtain more insight in difference between methods for performing aggregate exposure assessments. This is done in two different ways, described in this report.
At first, an overview of several aggregate exposure assessments performed in the past is provided. From this overview, it can be concluded that several steps (tiers) are sometimes needed, especially when a risk could not be excluded when using a simple first tier calculation. When higher tier models were used, the reason was more to get insight in the drivers of the exposure assessment and to obtain information on the uncertainties.
Secondly, a case study is set up, to assess the differences between a deterministic worst-case (tier 1) approach and a more detailed, probabilistic (tier 2) approach using a case-study. A set of parabens that are present in personal care products has been chosen for the case study.

The aggregate exposure assessment for methyl-, ethyl-, propyl- and butylparaben will be performed per paraben. Denmark declared a ban in March 2011 on the use of propyl- and butylparaben in personal care products for children and the adverse effects of parabens are caused by estrogenic activity found in young animals. Therefore, the aggregate exposure is performed for a subpopulation of children between 0-3 yrs old.

In the tier 1 approach, default exposure parameters resulting in a realistic worst case exposure estimate are used. These include: 1). Default use amount of personal care products from the RIVM Cosmetic Factsheet, in some cases adjusted for the body surface area of a child, 2). Frequency of use based on RIVM Cosmetic Factsheet, 3). Maximum amount of paraben used in personal care products based on measurements by the nVWA in 2006. As a common refinement, retention factors are included to account for differences in rinse-off and leave-on products. The assumption is made of a maximal use of all products containing parabens. To go from external exposure to internal exposure, a paraben specific dermal absorption has been applied. Oral absorption is assumed to be 100 %. Using this worst-case approach, there is no reason for concern for methyl- and ethylparaben. For propyl- and butylparaben, the Margin of Safety is around 10 and thus below the safety factors of 100, giving reason for concern.

In the tier 2 approach, a person-oriented probabilistic assessment is performed. The term person-oriented refers to the fact that the exposed person in a population is taken as the central point in the assessment. Key element is the performance of a survey, in which more detailed information on personal care product amounts and use frequency by children as reported by their parents has been obtained. Probabilistic means that this method uses distributions of exposure estimates as input data rather than single values. Following this approach, there is no reason for concern for methyl- and ethylparaben. However, for propyl- and butylparaben, there is still a chance that some children in the population would be exposed to significant levels of propyl-and butylparaben. In order to make a quantitative statement to what fraction of the population this accounts, a detailed uncertainty analysis needs to be performed.

A tier 1 approach can be performed using simple equations and default point estimates, and serves as a starting point for an aggregated exposure assessment. If there is concern or a more detailed assessment is warranted, the

person-oriented probabilistic approach can be used. This approach is data demanding, but the detailed information can be used to analyze the uncertainty and drivers of the exposure assessment. For example, baby wipes have been identified as a product type that has a relatively high contribution to the exposure, but also has a large uncertainty in the exposure estimates.

Overall, relevance of a tier 2 approach of an aggregate exposure assessment for risk assessors and risk managers is evident, since more insight is provided in drivers of exposure and uncertainty on specific exposure parameters (where more information might be obtained). However, the data demand, together with the high demand in time might be reason to develop a "model in between" that is not as conservative as a tier 1 model, but not so complex and time demanding as a tier 2 model.

Samenvatting

Geaggregeerde blootstelling is de totale blootstelling aan één stof vanuit meerdere bronnen en via verschillende blootstellingsroutes. Voor een risicobeoordeling is het belangrijk de totale blootstelling aan een chemische stof te bepalen ten einde een onderschatting van het risico te voorkomen. Het rapport bevat een algemene introductie van een geaggregeerde blootstellingsberekening. Het doel van het rapport is om meer inzicht te krijgen in methoden om een geaggregeerde blootstellingsberekening uit te voeren. Dit wordt op twee verschillende manieren aangepakt.

Als eerste wordt in hoofdstuk 2 een overzicht gegeven van verscheidene geaggregeerde blootstellingsberekeningen die eerder uitgevoerd zijn. Vanuit dit overzicht kan geconcludeerd worden dat verschillende stappen ("tiers") in de modellen soms nodig zijn, met name wanneer in een simpele "first tier" berekening een risico wordt geconstateerd. Wanneer hogere tier modellen gebruikt worden, is dit meer om inzicht te krijgen in welke parameter belangrijk is in de blootstellingschatting, en waar de grootste onzekerheden in de berekeningen zitten.

Als tweede is een case studie opgezet, om de verschillen te bekijken tussen een deterministische conservatieve (tier 1) aanpak en een meer gedetailleerde probabilistische (tier 2) aanpak. Als stof voor de case studie is een reeks parabenen gekozen, die gebruikt worden in verzorgingsproducten.
De geaggregeerde blootstellingsschatting is apart uitgevoerd voor methyl-, ethyl-, propyl- en butylparabeen. Vanwege effecten veroorzaakt door estrogene activiteit in jonge dieren, en vanwege een verbod in Denemarken in maart 2011 op het gebruik van propyl- en butylparabeen in verzorgingsproducten voor kinderen, is een geaggregeerde blootstellingschatting uitgevoerd voor de subpopulatie kinderen tussen 0 en 3 jaar oud.

In de tier 1 aanpak worden standaard blootstellingsparameters gebruikt zodat de blootstellingschatting conservatief uitkomt. Dit zijn: 1). een standaard hoeveelheid gebruikt product uit de RIVM Cosmetica Factsheet, in sommige gevallen aangepast voor het lichaamsoppervlak van een kind, 2). de frequentie van gebruik gebaseerd op de RIVM Cosmetica Factsheet, 3). de maximum hoeveelheid van de parabeen gebruikt in verzorgingsproducten zoals gemeten door de VWA in 2006. Als een algemene verfijning zijn retentiefactoren gebruikt om rekening te houden met verschillen in blootstelling bij gebruik van zogenaamde "rinse-off" en "leave-on" producten. Er wordt uitgegaan van een maximaal gebruik van alle producten waarin parabenen aanwezig zijn. Voor de omzetting van externe naar interne blootstelling is gebruik gemaakt van een parabeen specifieke huidabsorptie. Voor de orale absorptie is 100% genomen. Met deze worstcase aanpak wordt geen risico gevonden voor methyl- en ethylparabeen. Voor propyl- en butylparabeen is de veiligheidsmarge ongeveer 10, lager dan de veiligheidsfactoren van 100, en dus een mogelijk risico.

In de tier 2 aanpak is een persoon-geörienteerde probabilistische aanpak uitgevoerd. De term persoon-geörienteerd slaat op het feit dat de blootgestelde persoon in de populatie gekozen is als centraal punt in de beoordeling. Er is een vragenlijst ontwikkeld om meer gedetailleerde informatie te verkrijgen over productgebruik en gebruikersfrequentie door kinderen, gerapporteerd door hun ouders. Probabilistisch betekent dat deze methode verdelingen van blootstellingschattingen als input data gebruikt, in plaats van een vast getal. Met deze aanpak wordt er ook geen risico voor methyl- en ethylparabeen gevonden.

Voor propyl- en butylparabeen echter wordt er een kans gevonden dat een aantal kinderen in de populatie blootgesteld zouden kunnen worden aan significante hoeveelheden van propyl- en butylparabeen. Om een kwantitatieve uitspraak te doen over de grootte van het deel van de populatie dat dit betreft, zou er een gedetailleerde onzekerheidsanalyse uitgevoerd moeten worden.

Een tier 1 aanpak kan uitgevoerd worden met simpele vergelijkingen en standaard puntschattingen, en kan dienen als een startpunt voor een meer gedetailleerde geaggregeerde blootstellingschatting. Wanneer er een risico wordt geconstateerd, dan kan een dergelijke uitgebreidere probabilistische blootstellingsbeoordeling uitgevoerd worden. Deze beoordeling vereist veel data, kost meer tijd en energie, maar zal meer inzicht geven in de onzekerheden en de bron(nen) met de hoogste bijdrage. In dit voorbeeld is aangetoond dat de babydoekjes de bron is met een hoge bijdrage aan de totale blootstelling, maar ook met een grote onzekerheid in de blootstellingschatting.

Tenslotte, de relevantie van een tier 2 aanpak voor risicobeoordelaars en risicomanagers zit in het feit dat meer inzicht wordt verkregen in de bronnen die het meest bijdragen aan de totale blootstelling. Inzicht in onzekerheden voor specifieke blootstellingsparameters kan richting geven aan nieuw relevant onderzoek. Er wordt echter ook geconstateerd dat het uitvoeren van het tier 2 model veel specifieke data vraagt en veel tijd en energie kost. Dat brengt de gedachte op de ontwikkeling van een aanpak er tussen in (tier 1.5?) die niet zo conservatief is als een tier 1 aanpak, maar minder complex and tijdsrovend dan een tier 2 aanpak.

Abbreviations

HIA	Health Impact Assessment
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MoS	Margin of Safety
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
nVWA	Dutch Food and Product Safety Authority
PHBA	Para-hydroxybenzoic acid
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCCP	Scientific Committee on Consumer Products
SCCS	Scientific Committees on Consumer Safety
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products
WHO/IPCS	World Health Organisation/International Programme on Chemical Safety

1 Introduction

Aggregate exposure is the total exposure to a single chemical that arises from multiple sources (e.g. different consumer products) and multiple exposure pathways (oral, dermal, inhalation). Aggregate exposure differs from cumulative exposure which is defined here as the total exposure to substances sharing the same mechanism of action; e.g. several phthalates present in multiple product types are known to lead to reproductive toxicity. In the WHO/IPCS framework [1], terminology has been developed to describe exposure as precisely descriptive as possible. Aggregate exposure is summarized by the WHO as 'single chemical, all routes'.

In the majority of risk assessments, the focus is on one substance that is present in one product. In many situations, people are exposed to the same substance via multiple sources and depending on the use of the product, exposure can occur via multiple pathways. For example, Carvone is a flavouring and fragrance agent that can be found in food, personal care products and pesticides and exposure can occur via the dermal and oral route [2]. This makes aggregate exposure assessment highly relevant for a risk assessment.

In several regulatory frameworks, aggregate exposure is mentioned in the Directives or Regulation, e.g., for REACH (guidance Chapter R.15). However, there is no specific guidance document present on how to perform the aggregate exposure assessment [3]. Under REACH, aggregation for multiple routes is mentioned, but it remains to be seen how Industries responsible for the risk assessment of a substance present in multiple sources will take the aggregate exposure assessment into account. For cosmetics and food contact materials, aggregate exposure is not mentioned in the Directive or Regulation. However, for food contact materials, aggregate exposure is considered for the food route only within the regulatory Framework (EC 1935/2004) itself. Within the Cosmetics framework, aggregate exposure assessment is usually considered and has been mentioned in two SCCP opinions. For Triclosan, a preservative that is present in multiple personal care products, an aggregate exposure assessment has been performed [4]. When taking Triclosan concentrations in 8 different personal product types into account, the maximum allowed concentration would not be considered safe. In a SCCP opinion on silver citrate, is has been mentioned that non-cosmetic uses should be considered when determining the exposure [5].

In conclusion, up until now aggregation of exposure is not common practice in risk assessment as risks are most often assessed separately for different exposure pathways and sources, especially when the products that form these sources fall under different chemical regulations. Most regulatory frameworks do aggregate exposure over different routes, but do not look at different contributing sources. In doing so, it may lead to an underestimation of the risk of a chemical substance.

1.1 Approaches for aggregate exposure assessment

Different methods and tools have been proposed to perform an aggregate exposure assessment [6]. Generally a tiered approach is taken, subdivided into a least complex method (tier 0), a deterministic approach (tier 1) and a most complex probabilistic method (further on called tier 2). The level of detail at which aggregation should be done is depending on the scope and the goal of the assessment. In some cases a rough idea of the order of magnitude of the maximal level of exposure for a population can be sufficient (tier 0). In case of a risk assessment for authorization or screening of a substance, a deterministic approach with (conservative) worst-case assumptions is accepted as the

practical standard (tier 1). In case a more realistic exposure assessment is needed e.g. for a Health Impact Assessment (HIA) or more refinement is needed after excessive risk has been identified following the conservative estimates in tier 1, a tier 2 approach is recommended [1, 6].

A description of the different tiers is given below.
Tier 0
Involves a rough estimation (order of magnitude) of the exposure based e.g. on production volume, general energy requirements in the case of food additives or market share information divided by the total number of people in a certain population. This leads to an estimation based on scarce data and a number of assumptions that can be used e.g. for ranking. It can be combined with physical-chemical data of a substance to determine for example whether inhalation of a substance is a likely route of exposure based on its volatility. Usually no information is included on exposure of certain subpopulations (e.g. high-end user) or any specification on exposure route or product types, but when available this can be done. If the estimate of the exposure is likely to represent the upper bound on the exposure that occurs in reality and this is lower than a threshold, the conclusion can be that there is no concern for this substance.

Tier 1
In tier 1, an inventory of the different exposure routes and sources representing an upper bound of the exposure in the population is made. Deterministic exposure estimates are added together following worst-case assumptions. All calculations are based on simple equations. If the exposure is below the Margin of Safety, than it is assumed that there is reason for concern. The Margin of Safety is the NOAEL in mg/kg bw/day divided by the exposure to a substance in mg/kg bw/day. For non-carcinogenic substances, the minimal MoS is usually set to 100. This consists of assessment factors for intra- and interspecies differences (10x10).
If a risk cannot be excluded, a differentiation into subgroups in the population or products/ exposure scenarios can be made for which the exposure is sufficiently low that they can be excluded from further assessment. The most important criterion is that the evaluated exposure is guaranteed to be conservative.

Tier 2
In tier 2, the goal is to obtain a more realistic exposure assessment and a more detailed insight in the distribution of exposure of different subpopulations. Daily averaged acute or longer term exposures are estimated and relative contributions of different sources, pathways and routes can be analysed. This can also help to determine where exposure management could take place.
Using person-oriented probabilistic methods, a probabilistic statement can be made on the lìkelihood that effects might occur or which fraction of a population is likely to be exposed to levels leading to adverse health effects. This method uses distributions of exposure estimates as input data rather than single values. The term person-oriented refers to the fact that the exposed person in a population is taken as the central point in the assessment. Only exposures from different consumer products should be added when a person is likely to use two or more products within a certain relevant timeframe. For instance it is not to be expected that one individual uses both aftersun lotion and bodylotion on the same day, but use of toothpaste and bodylotion is possible.

1.2 Goal of the project

The goal of this project is to provide more insight in performing aggregation of exposure following two approaches.
In Chapter 2 an overview is given of several aggregate exposure and/or risk assessments performed in the past. The case studies are divided in the above described different tiers.
In Chapter 3 the results of a case study on parabens are given. A deterministic approach will be applied that gives a rough summation of all exposure of multiple routes and sources by adding up exposure estimates from worst-case scenarios (tier 1) versus a person-oriented probabilistic approach (tier 2). The differences in data requirements and interpretation of the outcome will be investigated.
By systematically applying a tier 1 and a tier 2 approach for a case-study substance, the advantages and disadvantages of both approaches can be mapped and the added value of increasing refinement in the exposure assessment can be indicated. A suitable substance for a case study to complete both a tier 1 and a tier 2 approach has been selected. Parabens in consumer products have been chosen as a case-study, with a focus on the use of personal care products by children. Aggregate exposure for methyl-, ethyl-, propyl- and butylparaben will be considered separately.

2 Overview of aggregate exposure assessments for chemicals

In the following tables, for each tier a few examples of substances are presented. Substances included are primarily present in consumer products. This is therefore not an exhaustive overview. A pesticide like carbaryl [7] that might also be present in consumer products was not included, and three substances present mainly in food or for which the major route of exposure is food (besides possible presence in consumer products) like coumarin [8], bisphenol A [9] and calcium [2] have been excluded, since the focus here is on chemicals in consumer products.

In table 1, an example of a tier 0 approach is presented. Global daily exposure values for methenamine in cosmetic products have been roughly calculated by the Scientific Committee on Cosmetic Products and Non-food products (SCCNFP). In a worst-case scenario, one person may apply 17.79 grams daily on the skin. With a weight fraction of 0.15% and body weight of 60 kg, external exposure is 445 µg/kg bw/d [10]. In this case, this did not result in a concern for repeated dose toxicity. Therefore, a more in-depth aggregate exposure assessment was not needed.

For a tier 1 approach, far more examples have been found in literature as summarized in table 2. For Triclosan, it was shown that separate exposure assessments could result in a conclusion of no risk (the use of toothpaste alone). However, when adding exposure estimates resulting from the use of more products, the margin of safety is decreasing. For Triclosan however, adding up all products in an aggregate exposure assessment would lead to an unrealistic exposure assessment, when using the assumption that all products in which Triclosan is allowed are actually containing Triclosan and all used by the same person. In the Netherlands, the use of Triclosan is probably limited. Therefore, in another approach, four products have been chosen to be added up, without any consumer use information specific for the Dutch population. Following this calculation, it’s use in skin and sun care products still raises concern [2]. The comparison of three different exposure assessments for Triclosan also shows the importance of different choices for exposure parameters (such as product amount, frequency and dermal absorption percentage).

There are two examples given for the tier 2 approach in table 3. This concerns in both cases a probabilistic exposure assessment of phthalates. In the first example, this approach has been chosen to identify which parameters contribute most to the risk.

In conclusion
For a tier 1 approach, the most examples have been found. This can be due to the fact that a tier 0 approach only gives a very crude answer and this is often not satisfactory for a risk assessment. The tier one example included showed no risk, and for that reason, a higher tier was not needed.
Within the examples of the tier 1 approach, there is not one common approach to tackle the aggregate exposure assessment. The decision on which exposure route to take into account or what products to aggregate for are made specifically per assessment.
For a tier 2 approach a lot of specific data is needed that is usually lacking. So only for certain chemicals like phthalates, this approach could have been

followed. The reason to undertake this assessment is to obtain more insight in drivers of exposure and levels of uncertainty for specific exposure parameters.

Table 1 Example of a Tier 0 approach

substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw/day	Population	Route (absorption)	
Methenamine [10] and [11]	Hardening component, carpets,/upholstery cleaners, solid fuels, limestone removers and cosmetics	- (human) 57 mg/kg bw/day based on urological abnormalities - Skin and possible respiratory sensitizer effects.	445 µg/kg bw/day external / dermal	Global, no specification	Dermal absorption: assumed 50%	- repeated dose toxicity: no concern (MoS* = 253) - concern for skin sensitization (no quantitative RA possible)

*MoS = Margin of safety. Margin between the NOAEL and the exposure estimate. Depending on the starting point for the NOAEL (duration and type of animal study), the minimal MoS can differ. In many cases, 100 (10 for interspecies, 10 for intraspecies) is accepted to be enough.

Table 2 Examples of a Tier 1 approach

Substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw/day)	Population	Route (absorption)	
Triclosan [2]	Perfuming/ conservation: Cosmetics and oral hygiene products, textiles and plastics, food contact materials	Developmental toxicity mice (liver tox in dams and reduced weight and delayed ossification in fetuses): 25 mg/kg/day	sun care products, body lotion, mouth wash and bath foam. Breast feeding	Adult, child (2.5 yrs old), infant	Oral (100%) and dermal (25%), no hand to mouth transfer taken into account	Deterministic reasonable worst–case estimates, assuming all products contain Triclosan. Adult sun care product: MoS = 66, Adult: body lotion, + mouth wash and bath foam MoS = 32 Child sun care product: MoS = 42, Child baby oil: MoS = 20,

Substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw/day)	Population	Route (absorption)	
						combinations might end up lower. Infant: milk MoS >13000 Conclusion; based on conservative exposure risk cannot be excluded. Worthwhile to reconsider use of triclosan in oral hygiene products (mouth wash), in skin care (body lotion) and sun care cosmetics. To get a better estimate of this risk, additional exposure data (e.g. on the actual in-use level of triclosan in the various products) are needed.
Triclosan [4]		haematoxicity and decreased absolute and relative spleen weights in 2 yr rat study: 12 mg/kg/day	toothpaste, hand soap, soap/shower gel, deodorant stick, mouthwash, body lotion, face powder, blemish concealer) using maximum allowed concentration 0.15-0.3%	General population or adults (based on listed products frequency and use)	Oral (100%) and dermal (7-12%),	Industry info on which products contain triclosan and %. Several options are calculated, for example: - Toothpaste alone 0.0234 mg/kg bw/day; MoS=513 - Toothpaste, deodorant stick, and hand soap 0.0315 mg/kg bw/day; MoS=381 - Common-Use Products 0.3% triclosan (toothpaste, hand soap, body soap /shower gel, deodorant stick) 0.0583 mg/kg bw/day; MoS = 206 - All Products 0.15 – 0.3% triclosan (toothpaste, hand soap, body soap /shower gel, deodorant stick, mouthwash, body lotion, face powder, blemish concealer) 0.2449 mg/kg

Substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw/day)	Population	Route (absorption)	
						bw/day; MoS =49 - All Products 0.3% triclosan (toothpaste, hand soap, body soap /shower gel, deodorant stick, mouthwash, body lotion, face powder, blemish concealer) 0.3795 mg/kg bw/day; MoS = 32 Note: MoS based on rat NOAEL much lower than based on plasma levels humans. Conclusion: no safe use when considering aggregate exposure. Safe use for "common products"
Triclosan [12]		Oral chronic toxicity study in baboons: 30 mg/kg/day	Population based monitoring data using spot urine measurements.	all age groups; ages 6-11; ages 12-19; ages 20-59; ages ≥ 60; males; females, Mexican-American; White, non-Hispanic; and Black, non-Hispanic. Separate assessment for 6-12 months old	All possible routes. Infants: nursing, object-to-mouth, and hand-to mouth	Biological monitoring data (spot urine data) are used. MoEs* ranging from 4700 to 19000. At the 99th percentile the MOEs range from 260 to 1700

Substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw/day)	Population	Route (absorption)	
Permethrin [2]	Synthetic pyrethroid Residues in food: oral Preservative: oral, dermal , inhalation	Low acute toxic. 2 yr rat study and 1 yr dog study clinical signs, changes in body and organ weight and blood biochemistry: 5 mg/kg bw/day resulting ADI 0.05 mg/kg bw/day (cis:trans ration 25:75 to 40:60) AEL = 0.03 mg/kg bw/day (based on 60% oral absorption)	Food: Daily intake and residues from pesticides and veterinary medicine (2 methods: TMDI (theoretical maximum daily intake and monitoring data) Non-food: residual use as pesticide, pet care product, textile, carpets, mosquito nets, textile impregnation spray, lice control, wood preservative (8 products; summed).	Adult, Children	Oral for food. Oral, dermal and inhalation for non-food.	Food (comparison with ADI) Adults: 45% Children: 118.6% Monitoring, adults: < 0.01% Monitoring, children: < 0.09% non-food products (comparison with AEL) Adults: 23% Children: 76% No concern: aggregated exposure estimates are based on assumption that adults/children are simultaneously exposed to permethrin from a variety of sources, often using 90 percentiles of exposure data Since worst case aggregate exposure estimate no health concern, refinement of exposure estimates is considered not necessary
Carvone [2]	Flavor and fragrance, Food (natural and	No acute tox, 90 day gavage: increased liver and kidney weights	Natural occurrence 0.0004	General population EU habitants,	Oral, dermal	Based on deterministic reasonable worst case Aggregate exposure (0.053 mg/kg

Substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw/day)	Population	Route (absorption)	
	flavouring agent), pesticide, personal care products	ADI 0.025 mg/kg bw/day	Food additive 0.04 Pesticide residual 0.012 Pers. care 0.0006	Non-workers.		bw/day) exceeds ADI by 212%.. a reevaluation of carvone (d/l) as food additive is advised.
AHTN [10] + [13]	Fragrance/preservative, polycyclic musk	NOAEL based on haematological findings (90 day oral): 5 mg/kg bw/day	Cosmetics, 10 different products summed: 0.34 mg/kg/day household detergents: hand washed laundry: 0.0017 or 0.0019 pre-treatment of clothes: 0.028 hand dishwashing: 0.001 µg/kg/bw/day	General population	Dermal Absorption (human) 4.1% (Oral 50% assumed)	Worst-case exposure estimate, 97.5 percentile use levels. AHTN RA (EU-RAR): 2.5 / 0.014 dermal + 0.0046 inhalation = 0.019 mg/kg bw/day internal exposure / = 132. minMOS = 200, but worst case character exposure estimate, thus no concern
Parabens [14]	Preservative in cosmetic, personal care, pharmaceutical and food products.	Endocrine disrupting effects ADI 10 mg/kg bw/day for methyl- and ethylparaben	Cosmetic and personal care products more often used than once every 3 days	Adult females	Dermal Negligible oral exposure (1-4%)	Methyl: 0.79 mg/kg bw, ethyl: 0.13 mg/kg bw Propyl: 0.34 mg/kg bw butylparabens:0.0016 mg/kg bw. Cumulative: 1.26 mg/kg bw. Compared

Substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw/day)	Population	Route (absorption)	
			(metabolism).			to ADI of 10 mg/kg bw/day for methyl- and ethylparaben.
Kathon [10] + [15]	Preservative in cosmetics	- NOAEL = 8 mg/kg bw/day on acute toxicity of is ataxia and serious stomach irritation - skin sensitization	6 personal care products: 0.000041 to 0.0060 mg/kg bw/day (no summing performed)	Children 3 years old	Dermal Absorption assumed to be 100%	Deterministic worst-case exposure assessment - MOSses > 1300, no concern (minMOS = 100) - no RA for sensitization performed
8 phthalates DEHP, DMP, DEP, DINP, DIDP, BBzP, DnBP, and DiBP [16]	Beauty, automotive, industrial/agriculture, food packaging, building home, consumer, medical, pharmaceutical. 90% of global plasticizer production 10% is used in adhesives, caulks, skin creams, detergents, electrical capacitors, hairsprays, inks,	DEHP, DINP, DIDP, BBzP, DnBP, and DiBP are reproductive toxicants affecting mainly the male reproductive system. Shortened duration of pregnancy, disrupting endocrine system, decreased sperm quality.	mouthing of and dermal contact with toys, contact with textiles, se of personal care products, dermal contact with gloves, paints, inhalation of hair sprays and spray paints, consumption f food contaminated with phthalates, house dust and soil, inhalation of indoor and ambient	7 groups, (men and women different ages). Infants (0-12 months), toddlers (1-3 yrs), children (4-10 yrs yrs), female adolescents (11-18 yrs), male adolescents (11-18 yrs), female adults (18-80), male adults (18-80).	Oral, dermal, inhalation (15 pathways)	Realistic scenario based: Goal to identify main sources of exposure in Europeans - especially kids are highly exposed - largest source is food - (to cover all relevant pathways, data from a variety of sources of different quality had to be used. For most input parameters, minimum, mean, and maximum values or 5th, median, and 95th percentile values are determined, depending on the quality of available data. For a few parameters only point estimates are used.)

Substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw/day)	Population	Route (absorption)	
	solvents, lubricating oils, lotions, nail polish, paints, fragrances, and pharmaceuticals.		air. Medication is not considered.			
5 phthalates DEHP, DBP, DINP DIDP BBP [17]	Plasticizer	Endocrine disrupting effects	Toys, baby food, indoor air and dust inhalation, plastic gloves paints, adhesives and nail polish.	Adults, children (6-12 month), children (1-6 years), children (7-14 years)	Oral, inhalation, dermal	Using EUSES to calculate point estimates of exposure via food and air. Basic scenarios to simulate product related exposures. Used to identify most important route of exposure.

* MoE = Margin of Exposure. Margin between the exposure estimate and the exposure resulting in an adverse effect

Table 3 Examples of a tier 2 approach

substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw /day)	Population	Route (absorption)	
DEHP Di(2-ethylhexyl)phthalate [18]	Plasticizer in polymers (building materials, flexible toys, car interiors,	NOAEL of 4.9 mg/kg bw/day based on 3 generation continuous breeding study in rats,	Food, indoor air, toys	Sensitive human: adults and children	Oral, inhalation	More info on parameters that contribute most to risk. Modeled variability in exposure between persons, not uncertainties in exposure assessment.

substance	Used as	NOAEL based on	Exposure assessment			Risk assessment
			Sources and levels (mg/kg bw /day)	Population	Route (absorption)	
	clothing, medical equipment) and non-polymers (adhesives, fillers, printing ink, lacquers and paints)	administration via diet. Testis damage as critical effect [19].				Presentation of a method to integrate the entire distributions from probabilistic hazard characterization and exposure assessment into one risk characterization plot. The result of this probabilistic risk assessment (single plot) containing two pieces of information: the confidence in concluding there is no risk, and the fraction of the population this conclusion applies to.
5 phthalates DMP, DEP, DBP, BBP and DEHP [20]			Indoor and outdoor air , ingestion of drinking water, incidental ingestion of soil, ingestion of dust (indoors), and ingestion of food Exposure to phthalate esters contained in children's products or other consumer products is not evaluated.			Modeling exposure from several media. Probabilistic, median estimated daily intake. Compared with back-calculate phthalate ester intake from urinary metabolite data. Overestimation for DEHP, BBP, and DBP due to changes in food processing over time.

3 Parabens as a case-study

3.1 Introduction

In this chapter, the paraben case study is described. A deterministic approach will be applied that gives a rough summation of all exposure of multiple routes and sources by adding up exposure estimates from worst-case scenarios (tier 1) versus a person-oriented probabilistic approach (tier 2). The differences in data requirements and interpretation of the outcome will be investigated.
By systematically applying a tier 1 and a tier 2 approach for a case-study substance, the advantages and disadvantages of both approaches can be mapped and the added value of increasing refinement in the exposure assessment can be indicated.
A suitable substance for a case study to complete both a tier 1 and a tier 2 approach has been selected according to the following criteria:

1. The substance needs to be present in consumer products with significant risk for exposure.
2. The substance is present in multiple consumer products.
3. The toxicological endpoint should be suitable for aggregation and is preferably a systemic endpoint. Aggregation for all routes of exposure can be performed relatively easy when the toxic effect is related to the systemic dose.
4. The background exposure levels are known and can be quantified.
5. There are (specific) details on product use available, preferably more information than is present in RIVM ConsExpo Factsheets [21].
6. The amount of the substance used in the product is known.
7. Preferably, some information on absorption, distribution, metabolism and excretion is known to derive internal concentrations.
8. Exposure to the substance can preferably take place via multiple routes.
9. The aggregate exposure assessment has not been performed by others following a tier 1 and a tier 2 approach.

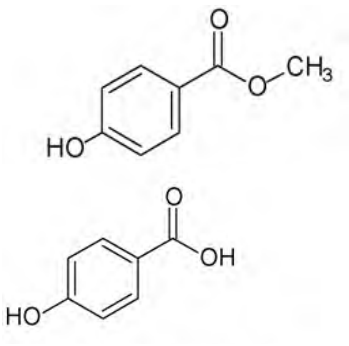
Following these criteria, parabens in consumer products have been chosen as a case-study, with a focus on the use of personal care products by children. Aggregate exposure for methyl-, ethyl-, propyl- and butylparaben will be considered separately.

3.2 Use and properties

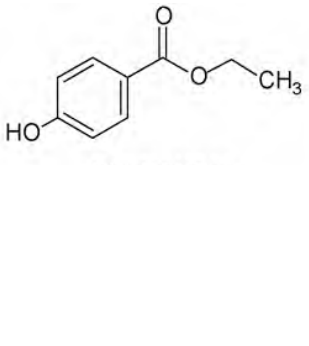
Parabens are currently widely used as preservatives in a wide variety of products. They are effective against fungi and bacteria at low concentrations, with more effectiveness against fungi compared to bacteria [22]. Parabens are found in cosmetics and personal care products, in consumer products such as dog shampoo, in pharmaceutical products such as antibiotics [23] and as food additives [24], all leading to exposure. According to Soni et al., personal care products are the main source of paraben exposure. From a total exposure of 76 mg/kg bw/day, personal care product contribution has been estimated at 50 mg/kg bw/day, while pharmaceutical products contribute for 25 mg/kg bw/day and exposure via food is only 1 mg/kg bw day [25].

Since personal care products are the main source of exposure, this will be the focus in the present document. There are 4 parabens that are mostly used in personal care products, namely the linear paraben esters methyl-, ethyl-, propyl- and butylparaben (figure 1). There are also branched paraben esters (isopropyl- and isobutylparaben) and benzylparaben, but these are not often

used in consumer products. The major metabolite is para-hydroxybenzoic acid (PHBA).

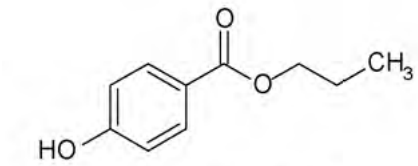


methylparaben

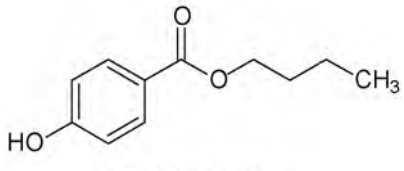


ethylparaben

para-hydroxybenzoic



propylparaben



butylparaben

Figure 1 Chemical structure of four most used parabens and the major metabolite

Parabens are solids that melt between 70 and 130°C. Further heating will make them decompose. The vapour pressure of all 4 parabens is very low, so they will not evaporate [26]. In addition, no applications of parabens in spray cans (e.g. like deodorant) have been found. Therefore, inhalatory exposure of parabens is unlikely. The main exposure route is via the skin after application of personal care products and orally for pharmaceuticals and food or accidental ingestion of personal care products.

The physical-chemical properties of 4 parabens are summarized in table 4 [25].

Table 4 Physical-chemical properties of parabens

Characteristics	Methyl	Ethyl	Propyl	Butyl
Chemical formula	C8H8O3	C9H10O3	C10H12O3	C11H14O3
Molecular weight (g/mol)	152.2	166.2	180.2	194.2
Melting point (°C)	131	116-118	194	68-69
Boiling point (°C)	270-280	297-298	-	-
pKa*	8.17	8.22	8.35	8.37
CAS-no	99-76-3	120-47-8	94-13-3	94-26-8
Characteristics	Methyl	Ethyl	Propyl	Butyl
Chemical formula	C8H8O3	C9H10O3	C10H12O3	C11H14O3

* pKa is acid dissociation constant

3.2.1 General uptake and metabolism

Parabens are absorbed from the gastrointestinal tract and metabolized by esterases in the liver, intestine [27] and the kidney in rats, rabbits, dogs, cats and humans [28]. In addition to urinary excretion, there is some excretion via the bile and faeces. The major metabolite is p-hydroxybenzoic acid (PHBA) (phase I metabolism) and minor metabolites are the glycine, glucuronic acid and sulphuric acid conjugates of p-hydroxybenzoic acid and the parent compound (phase II metabolism). The latter are only detected in humans, not in rats [25]. The half-life of all parabens after oral administration is determined in different species. In rabbits 86% is cleared within 24 hours [29-31], in rats 67-75% of the total paraben dose was excreted as p-hydroxybenzoic acid and 8-9% as glucuronylderivatives within 90 minutes [32], in cats within 72 hours both propyl and ethyl were completely excreted [33]. For the half-life after dermal application, no data has been found.

3.2.2 Dermal uptake

Following dermal application, paraben skin penetration decreases with increasing side chain length, while lipid solubilisers reduce percutaneous absorption and penetration enhancers increase penetration [34]. Hagedorn-Leweke et al. have determined the flux of butylparaben in human volunteers exposed to a saturated solution with a maximum of 40 µg cm^{-2} h^{-1} and a mean of 32 µg cm^{-2} h^{-1}. The amount of butylparaben that had penetrated into the skin was derived indirectly from the concentration decrease in the vehicle [35]. The more lipophilic the paraben, the less penetration was observed in human surgical skin studies with butylparaben < propylparaben < ethylparaben < methylparaben [35]. It has been shown that after a month of daily application of methylparaben by human volunteers, it persisted slightly and remained unmetabolised in the stratum corneum [36].

3.2.3 Dermal metabolism

In rat skin, paraben esters are said to be nearly completely hydrolyzed into PHBA after dermal application [37]. In general, hydrolysis by metabolic enzymes in the skin and liver has been found to decrease with increasing side chain length. The hydrolysis in human skin is much smaller compared to human liver, rat skin and rat liver, leaving a greater portion available for internal exposure. The hydrolysis rate in human skin is more than a 1000-fold lower for all parabens compared to human liver and rat liver/skin [38]. After application of parabens to human skin, there is a possibility that glucuronyl as well as sulphate conjugates are found in serum and urine [39, 40]. Butylsulphate has been found in human liver and skin cytosols [41].

In biomonotoring studies, free and/or conjugated parabens have been detected in serum [42] and urine [40, 43-46]. In addition, in children at age 4 (2005-2006) and woman in the third trimester of pregnancy, spot urine samples indicated presence of methyl-, ethyl, propyl-, and butylparaben as the parent compound. In 4 year-old children, the levels were respectively, 150.0, 8.1, 21.5 en 1.2 ng/ml urine. This indicates that in humans parabens are not completely hydrolysed to the main metabolite.

The differences in paraben metabolism in rat and humans are summarized in figure 2.

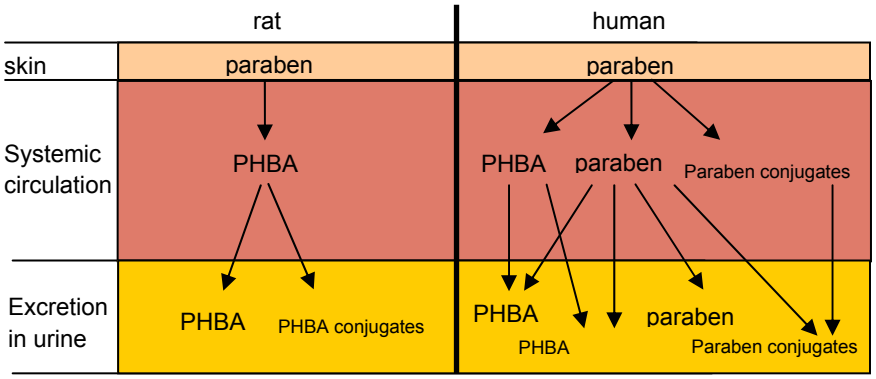


Figure 2 Comparison of rat and human skin and liver metabolites

3.2.4 Internal exposure

The estrogenic activity of parabens is expected to take place when a certain concentration of the parent compound interacts at the molecular level at the organ of relevance. Therefore, it is believed that the internal exposure to the parent compound will predict the toxicity. For the major metabolite PHBA, no endocrine modifying effects have been observed *in vitro* (human and rat cell lines) [41, 47, 48]. *In vivo* results are more contradictory. Most uterotrophic assays give a negative results [49, 50], while there is one study that reports uterotrophic effects at 5 mg/kg bw/day [51]. The estrogenic properties of the paraben conjugates are not known. To go from external to internal exposure, the absorption of parabens for the relevant routes of exposure needs to be determined. No data on oral absorption is found, but is assumed here to be 100%, although there is substantial metabolism by the liver.

There is a great deal of uncertainty with respect to the extent of dermal metabolism and absorption, mainly due to the lack of a well conducted human dermal absorption study. A single study has been conducted in which a mixture of 2% of butylparaben, 2% of diethyl phthalate and 2% of dibutyl phthalate was administered. Maximum serum levels were reached within 3 hours [42], followed by excretion in urine [39]. This study has been criticized, since simultaneous application of phthalates and parabens in high concentrations may have saturated skin esterases and may lead to higher serum levels of the parent compound. The lowest reported number for dermal absorption of unmetabolised paraben is 1% [52].

Metabolism of parabens in humans seems not to be complete or frequent regular dermal exposure can exceed the metabolic rate, since detectable concentrations of parabens in the serum, urine or seminal fluid have been measured in adults [40, 45], indicating internal exposure to parabens. However, biomonitoring studies cannot discriminate between paraben exposure from oral uptake or dermal application, nor between the sources of exposure, so a quantitative level of dermal absorption cannot be derived from these studies.

The SCCP has derived a dermal absorption of 3.7% for the parent compound butylparaben based on *in vitro* dermal absorption studies (with human and pig skin) in absence of appropriate human dermal absorption studies via a pragmatic approach [53]. Fasano et al. measured 37% dermal absorption for butylparaben and 50% for methylparaben in split-thickness skin or dermatomed skin [54], using a correction factor of 10 to account for skin metabolism in full thickness skin experiments [55]. Actual metabolism was more extensive indicated by butylparaben concentrations in the receptor fluid being 65 to 150 times lower than the metabolite (PHBA) concentration. Therefore, this is a conservative estimate.

Dermal uptake and especially dermal metabolism are very different in the rat skin compared to humans [56]. In addition, for rabbit skin no information is available on esterase activity on parabens compared to humans. For this reason, only studies using human skin are taken into account to derive a dermal absorption percentage (table 2).

Table 5 Dermal absorption in relevant skin models

Reference	Paraben	Model	Dermal absorption
Janjua 2007	butyl	Human skin in vivo	0.12% total paraben in serum at 4 hrs after application. Total absorption is the area under the curve and is much larger
Cross 2000	Methyl Ethyl Propyl Butyl	Human epidermis abdominal skin in vitro (worst-case, occluded, ethanol as vehicle, time 10 hrs)	36% 55% 28% 42%
Jewell 2007	Methyl Ethyl Propyl Butyl	Human skin in vitro	33% 44% 37% 17%

In the study by Jewell et al. the epidermis and a minimal thickness of upper dermis of human breast skin (350 µm) was used. This was chosen to obtain the highest concentration of esterases, as these are predominantly located at the basal layer of the epidermis [57] and in subcutaneous fat tissue [41] (figure 3).

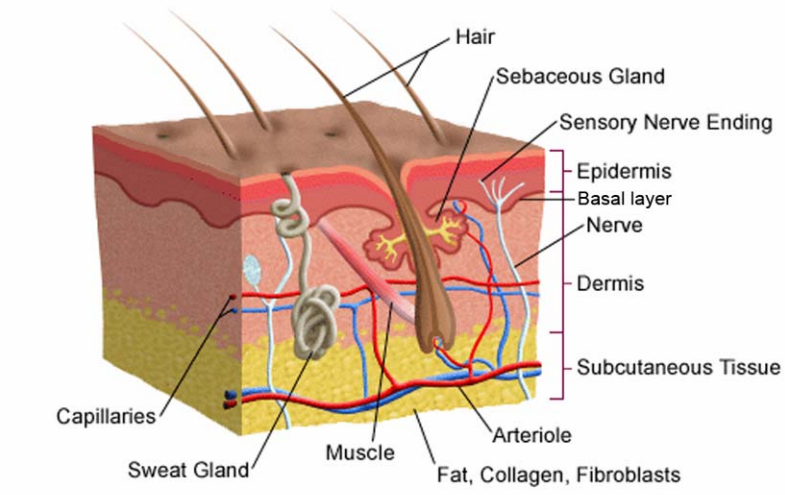


Figure 3 Schematic representation of the different layers of skin, including the layers that contain most esterase activity

In personal care products, parabens are most of the time used in combinations to increase antimicrobial potential. Interestingly, according to Caon et al., certain combinations have lower skin penetration than others. When methylparaben is combined with ethylparaben or propylparaben, the permeation flux values were significantly reduced, probably due to high retention in the

epidermis and dermis for methyl- and propylparaben but not for ethylparaben [58]. For the internal exposure calculation further down in this document, the exposure is considered "as to the single chemical substance". For some personal care products this is the case, but most products contain more than one paraben. Dermal absorption data for the different combinations is not available, only the flux.

In conclusion, for the internal exposure assessment of parabens in tier 1, conservative worst-case estimates for dermal absorption are used. These are based on human skin models (table 6) and correspond to 36%, 55%, 37% and 42 % for methyl-, ethyl-, propyl-, and butylparaben respectively. For the tier 2 approach, a distribution from 1-55% is included. These are the lowest and highest number for dermal absorption that has been reported.

3.3 Paraben toxicity

3.3.1 Acute toxicity

Low acute toxicity has been found for methyl-, propyl-, ethyl-and butylparaben in rodents after oral administration. The acute toxicity seems to decrease as the alkyl chain length increase [59]. Since these results are generated in studies as early as the 1930s and are summarized in a review from 1984 [22], LD50 values (median Lethal Dose for 50% of the animals) have been derived, but no NOAEL or LOAEL values for more specific toxic endpoints [25]. For the oral route the LD50 values lie between 1500 and 8000 mg/kg for methyl, propyl and ethyl paraben. For butylparaben, the LD50 lies around 13000 mg/kg [60]. For other routes besides the oral route, for example subcutaneous [61] and intra-peritoneal [60] administration, the LD50 values are around 10 times lower. No dermal irritation or sensitization has been detected in rodent assays [25]. In humans, daily application of parabens in skin patch testing resulted in essentially no irritation to moderate irritation. In some dermatitis patients, paraben application led to sensitization [22].

3.3.2 Subchronic and chronic toxicity

For butyl paraben given orally via the diet to 8 week old mice (female and male ICR/Jcl mice), a NOEL of 9000 mg/kg bw/day for subchronic toxicity based on significant atrophy of lymphoid tissue in organs and multifocal degeneration and necrosis of the liver parenchyma has been derived [62]. In male Wistar rats, a NOEL of 2000 mg/kg bw/day is derived after a 12 week diet based on reduced growth rate, decreased body weight and motor activity, and myocardial depression (in females) [60]. There has been no mutagenicity, carcinogenicity or teratogenicity reported for either paraben [63].

3.3.3 Reproductive toxicity

In vitro toxicity studies have shown that parabens have estrogenic activity and this activity increases with increasing chain length and branching of the alkyl chain. The suggested mechanism of action is that parabens mimic estrogen action with a lower binding affinity to the estrogen receptor (ER) than estrogen itself [53]. Another possible mechanism is interference with metabolic enzymes dedicated to synthesis of physiological estrogens of by modification of their free unconjugated form by inhibiting sulphotransferases [41]. Therefore, there is a possibility for estrogenic hazard or endocrine disrupting effects. According to the Weybridge definition (1997), "An endocrine disrupter is an exogenous substance

that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function."

Clinical observations like the presence of parabens in breast tumour tissue [64] together with the estrogenic potential in vitro could suggest that parabens may contribute to the incidence of breast cancer. Further clinical data that supports this hypothesis has not been found. The SCCP has published that there are insufficient data to establish a clear link between the use of underarm personal care products and breast cancer in their extended opinion of 2005 [65].

Besides estrogenic effects *in vitro*, developmental and reproductive effects have been observed in rodents. As endpoints, hormone secretion, semen quality and reproduction in immature male rats have been studied and have been used to derive a NOAEL for human risk assessment. In females, uterotrophic effects, hormone levels as well as development of reproductive organs have been evaluated. In appendix 1, table 7, an overview of the NO(A)ELs for endpoints determined in rodents is presented. The NO(A)ELs that will be used for risk assessment are highlighted in bold.

For methylparaben, a NOAEL of 1000 mg/kg bw/day is derived by EFSA based on a study by Oishi et al. [66]. This does not take the possible spermatogenic effects into account found by Hoberman et al. [67] or a delay in the date of vaginal opening in prepubertal rats and a decrease in length of the estrous cycle with a NOAEL of 250 mg/kg bw/day [68]. The NOAEL for uterotrophic effects is much lower than the NOAEL for male reproductive effects or female reproductive organ development, namely 5.5 mg/kg bw/day. For ethylparaben, a NOAEL of 250 mg/kg bw/day could be derived on a reduction in estradiol levels in female prepubertal rats [68]. The lowest NOAEL has been observed for uterotrophic effects in an ovariectomized mouse model [50]. In an uterotrophic assay, effects of a substance with known estrogenic action like estradiol are compared to a test substance. Under influence of estrogen, the weight of the uterus will increase due to the absorption of fluid and cell proliferation. NOAELs from uterotrophic assays are not used here for human risk assessment as this data is regarded as only supportive of a mechanism of action. A response is not exclusively due to estrogenic chemicals, so it should be confirmed by corroborating information such as ER binding or transcriptional activation. For propylparaben, a NOAEL of 10 mg/kg bw/day is derived [69]. Although this is considered to be a no observed effect level, effects on sperm counts in the testis were detected. Boberg et al. concluded that this is a LOAEL and corrects with an assessment factor of 3 for the lack of a NOAEL [27]. For butylparaben a NOEL of 2 mg/kg bw/day has been derived from a juvenile rat study in which the paraben was administered subcutaneously [70]. As critical endpoint the development of the testis was investigated, especially the efferent ducts. These ducts are an important site for both fluid resorption and estrogen action within the male genital system [71]. Recent evidence suggests that exposure to non-physiological levels of estrogen can induce disturbances in normal fluid dynamics and may have consequences for male fertility [72].

Effects found after perinatal exposure are equivocal and therefore no NOAELs are derived. Kang et al. has found reduced sperm count in male offspring after subcutaneous exposure to 100 or 200 mg/kg bw/day of butylparaben *in utero* and during lactation [73], while Taxvig et al. found no effect on male foetuses (after subcutaneous exposure of pregnant rats (gestation day 7–21) to 200 and 400 mg/kg bw/day of butylparaben or ethylparaben) [74]. No effects on implantation have been found while being exposed during early gestation [75]. No developmental effects were found after administration of 10, 100 or 1000 mg/kg bw/day of butylparaben (oral gavage)

from gestation day 6 to 19, although maternal weight gain was reduced in the highest dose group [76].

Following toxicity studies in immature rats and mice, parabens can affect reproductive and endocrine endpoints both in females and males. Human exposure may lead to a risk of endocrine disruption in boys and girls. In theory, estrogenic effects in boys can affect the masculinisation process associated with a risk of decrease in sperm quality. For girls, there could be an increased risk of early puberty, premature mammary gland development and mammary cancer [27]. For the risk assessment described in this report, a NOAEL of 1000 mg/kg bw/day for methyl- and ethylparaben will be used based on reviewed reports by the SCCS [53] and EFSA [24]. For both propylparaben and butylparaben the SCCS has derived a NOEL of 2 mg/kg bw/day. For propylparaben, this NOEL will not be used further in this report as the studies that SCCS has used to derive the value have not administered propylparaben, but only butylparaben. For the risk assessment, a NOAEL of 3.3 mg/kg bw/day for propylparaben is taken based on the Oishi study on sperm counts [69]. For butylparaben, a NOAEL of 2 mg/kg bw/day will be used as based on the SCCS reviewed report [53] (summary in appendix 1, table 7).

3.4 Aggregate exposure assessment

3.4.1 Introduction

The assessment of paraben exposure from consumer products is used as a case-study to gain more insight into the process of performing an aggregate exposure assessment. A tier 1 approach as well as a tier 2 approach including person-oriented probabilistic modelling will be used to systematically perform the exposure assessment.

Parabens are preservatives that are used in a variety of cosmetic and personal care products, including products for babies and young children. Given the effects on reproductive toxicity endpoints found in immature rats and mice and the potential severity of the effects during early human child development, an aggregate exposure assessment for children between 0-3 years is performed. In addition, in March 2011, the Danish delegation of the Council of the European Union has announced a ban on propylparaben and butylparaben in personal care products for children under the age of three years. The ban was enforced in Denmark on 15 March 2011 after the outcome of a report of the Danish EPA by Tønning et al. on a study of 2-year old children and their exposure to endocrine disrupters [77]. These children were considered a particularly vulnerable group, since long-term effects of endocrine disruptors are not known. Following worst-case assumptions after use of bodylotion, sunscreens, shampoo and liquid soap, it was estimated that the children were exposed to 0.22 mg/kg bw/day propyl- and butylparaben. The Margin of Safety in the assessment is below 100 based on a NOAEL of 3.3 mg/kg bw/day for both propyl- and butylparaben [77].

Parabens can be used at maximum concentrations of 0.5% per paraben in personal care products due to their solubility [78]. The allowed concentration in personal care products in Europe is 0.4% per paraben and 0.8% for the total amount of parabens [79]. In 2010, the SCCS published an opinion in which the allowed concentration for methyl-and ethylparaben is suggested to remain unchanged. However, propyl- and butylparaben are considered to be safe for humans as long as the sum of their individual concentrations does not exceed 0.19% in the finished cosmetic product [53].

For adult females, an aggregate exposure assessment has been performed in 2009 for methyl-, ethyl-, propyl- and butylparaben following a tier 1 approach

using data on concentrations of paraben in actual products [14]. Refinements have been made including results from a consumer use survey on co-use and non-use patterns. The outcome of the assessment has been compared with the ADI of 10 mg/kg bw/day. However, this ADI is applicable for methyl-and ethylparaben only. When deriving a Margin of Safety for the four parabens, there is a concern for the aggregate exposure to propylparaben. The Margin of Safety (NOAEL of 3.3 divided by the total exposure to propylparaben of 0.34 mg/kg bw/day) is 10 [14, 27]. The aggregate exposure to butylparaben is low with no reason for concern based on the MoS due to low concentrations of butylparabens in very few products.

Given the general severity of adverse effects in reproductive endpoints with an irreversible character and the exposure of a vulnerable group (children under the age of 3 years), the aggregate exposure assessment for the 4 most common parabens is explored further. The outcome of the tier 1 approach can be directly compared with the assessment described by Tønning et al. By following a person-oriented probabilistic approach, more realistic exposure estimations can be made, meanwhile insight into the uncertainties and variability in the assessment can be obtained.

3.4.2 Methods

Tier 1: deterministic approach

In order to get a conservative estimate of external paraben exposure for a population of children between 0 and 3 years old according to a tier 1 approach, the following parameters are used:

1) The default amount of personal care product (in grams of product; appendix 3, table 10) [21].
2) The frequency of use (in times per day; appendix 3, table 10) [21].
3) The maximum amount of a paraben that is used in a product (in mg/kg product; appendix 2, table 10). Information on the amount of parabens in a series of personal care products for children between 0-3 years is based on measurements by the Dutch Food and Consumer Product Safety Authority (nVWA) in 2006 [80]. The level of butylparaben in some products for children can comprise of a certain amount of benzylparaben. During analysis, in some cases the HPLC peak of butyl- and benzylparaben coincided in the chromatogram.

The external exposure in mg/day is divided by the body weight of a 1.5 year old child for which 11,1 kilogram is assumed [81]. All the exposure parameters mentioned above are used in the following equation:

$$E_{ext} = (A_{prod}/1000) \times wf \times F / W_{body}$$

with:
E_{ext} : External exposure after the dermal and oral route [mg/kg bw/day]
A_{prod} : amount of product applied [g]
wf : weight fraction of the compound in the product [mg/kg]
F: Frequency of use [times/day]
W_{body} : body weight of the exposed child [kg bw]

A common refinement to tier 1 has been added to account for the fact that some products like shampoo and liquid soap are used in a diluted form or contact with the substance is only for a short time period. The option that has been chosen here is to use retention factors as proposed by the SCCS [82]. For all rinse-off products like shampoo, 2 in 1 shampoo, liquid soap, bath/shower soap and bath oil, a dilution factor is taken into account leading to a retention factor of 0.01

[82]. For leave-on products like sunscreen, after sun, body-lotion and baby salve it is assumed that all product applied to the body stays in contact with the skin for a sufficient amount of time for parabens to be absorbed. Hair lotion is a sort of hair conditioner for children and is not rinsed-off. It is estimated that skin contact takes place for 1/10 of the total amount. Therefore, a retention factor of 0.1 is used [82]. All retention factors that are used are summarized per product type in appendix 3, table 4. The equation with refinement is:

$$E_{ext} = (A_{prod}/1000) \times wf \times F \times Rf / W_{body}$$

Rf: retention factor

Most products are applied dermally (except for toothpaste) so these values are corrected for dermal absorption to go from external exposure to internal exposure. The equation for internal exposure is:

$$E_{int} = ((A_{prod}/1000) \times wf \times F \times Rf / W_{body}) * A_{dermal}$$

A_{dermal}: dermal absorption (%)

For toothpaste, the absorption is assumed to be 100%, so the internal exposure is the same as the external exposure.

Calculations can be done by hand according to the equations or an updated version of ConsExpo 5.0 beta can be used. In this case, part of the calculations made according to the equations have been checked by running them in ConsExpo 5.0 beta [83].

Tier 2: person-oriented probabilistic approach
For the second tier, a model under development in collaboration with ETH Zurich and the University Medical Center St Radboud Nijmegen is used [84]. To perform a person-oriented probabilistic approach, more detailed data on daily contact profiles of personal care products for children between 0-3 years old is needed. An electronic survey in Dutch has been developed (by using FormDesk) and distributed (appendix 4). The survey consists of 2 parts. The first part contains general questions on: 1). the age of the child, 2). whether it is a boy or a girl, 3). the body length in centimetres and 4). the weight of the child in kilograms. The second part has specific questions on: 1). the type of personal care product used out of a list of 12 products, 2). the amount of product used, 3). the frequency of use within the last 6 months or in case of sunscreen and aftersun in the last year, 4). On which part of the body it was used in case of bodylotion, sunscreen and aftersun, 5) whether the product was a spray, lotion or cream in case of sunscreen and aftersun to determine whether there was a chance for inhalatory exposure next to the dermal route.
With the anonymous response of 28 parents, an Access database has been created with the (co)use patterns, product amounts and frequency of use. The information on which part of the body the product was used has not been used in the database. The amount of the product is estimated by the participants by viewing 3 photographs with an increasing amount of a product (Figure 4).

Figure 4 Example of photographs from the survey to estimate amount of shampoo used

An example of a question in the survey is: Do you estimate that for shampoo you use for your child a) less than the amount shown in photograph A, b) the amount shown in photograph A, c) more than the amount shown photograph A but less than in photograph B, d) the amount shown in photograph B, e) more than the amount shown in photograph B but less than in photograph C or f) the amount shown in photograph C. Photograph A corresponds to 2.72 grams of shampoo, B to 7.72 grams and C to 12.39 grams. If the reported amount corresponds to the amount shown in a single photograph, this number is taken as a point estimate. If a range is reported, e.g. an amount between photograph A and B, a uniform distribution is assumed and this is used as input for the database. Similar questions were asked for the frequency of use and the answers are also converted to a point estimate or a uniform distribution. To account for imprecision in the answers of the survey, in the probabilistic calculations a random value is selected from the reported distributions every time a value of the parameter is needed; a process called Monte Carlo sampling.

Detailed information on the weight fraction of parabens in 12 personal care product types is obtained from measurements by the nVWA in 2006 [80]. Only those product types have been included in the survey and in the database for which the nVWA has reported at least one product that contains either methyl-, ethyl-, propyl-, and/or butylparaben, since there is a chance that use of this product contributes to the aggregate exposure. Raw data of the measurements have been included in the database. When a certain product within a product group contains no parabens, 0 mg/kg is used.

Using this data, a daily contact profile is generated for an individual in the model population by appointing a specific product from the list of products in the database based on the product use in the survey. This is then repeated for a second individual up until a population of a 1000 individuals is simulated (figure 5). For each person, the actual number of products that has been reported is used to construct the profile. This is coupled to the reported variability in the amount of product used and the frequency of use as well as the weight fraction of the paraben in the product. Following this process, if a person from the survey is selected multiple times, the corresponding persons in the modelled population will exhibit a variation in their use frequency or reported amount, representing the reported variability of the individual in the survey. For example, for person 1 that uses between 1 and 2 grams of bodylotion three times a week, a random number between 1 and 2 grams, e.g. 1.2 gram is picked and this is multiplied by the weight fraction of methylparaben in a bodylotion. A second time person 1 from the survey is sampled, the amount that is randomly picked is 1.7 grams three times a week and this is multiplied by the weight fraction of methylparaben in another bodylotion or by chance by the same weight fraction.

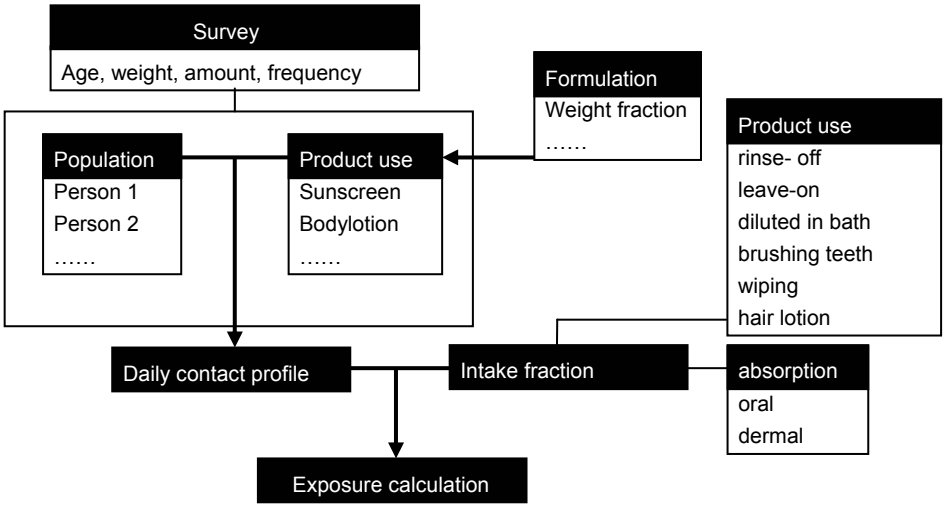


Figure 5 structure and coupling of input provided by the survey and product use scenarios

For the exposure calculation, the daily contact profile is linked to the intake fraction of a paraben that is determined by 2 parameters, namely the product use scenario, e.g. use of a rinse-off product and dermal absorption. The oral absorption is set to 100% and for the dermal absorption a distribution of 1-55% is used. The latter is based on uncertainty in dermal absorption with the lowest reported number of unmetabolised paraben of 1 % [52] and the highest for ethylparaben from *in vitro* absorption studies with human skin [85]. The time period for which the aggregate exposure assessment is performed is 28 and 56 days assuming that this period takes place in summer and sunscreen and aftersun products are used according to the survey. No large differences have been found between 28 and 56 days calculations, indicating that the simulation time of 56 days is sufficiently long to provide representative average exposure estimates. The 56 day calculations have been used to construct figures in the results section.
For all individuals for all days in the simulation the exposure is evaluated by combining the amount used of each product on every day with the intake fraction of a product. The result is a table with information on all 56 days in the simulated period for all 1000 individuals on the amount of exposure to all products this person uses. The aggregate exposure per day is determined by adding all exposures on the same day for 1 person and subsequently averaging the daily aggregate exposure for each individual. The calculations and Access data operations are done in R modelling software.

3.4.3 Results

Tier 1

The nVWA has measured paraben levels in different personal care products found in the stores for children between 0-3 years in 2006 [80]. A list of these personal care products is given in appendix 2, table 8. Not all products contained parabens, but 12 out of 17 products did. If a product contains one of the four most used parabens (methyl-, ethyl, propyl- or butylparaben), the percentage and absolute number of products is given. The maximum amount of paraben present per product type is given in appendix 2, table 9.

In most cases there are no specific default estimations for the amount of product used for children between 0-3 years old given in the RIVM Cosmetic Factsheet [21]. For personal care products in the categories that involve application on body surface area (sunscreen, aftersun, bodylotion, shower/bath

soap) a correction has been done for the smaller total body surface area in children, e.g. the amount of sunscreen applied by adults based on the Cosmetic Factsheet is corrected by a factor of 0.27 (4800 cm^2 for a child of 1.5 years old /17500 cm^2 for adult based on table 16 and table 12 in reference [81], respectively). This is under the assumption that indeed less product is used in children than in adult. For liquid soap that is mostly used to wash hands, a factor of 0.29 is used (247.2 cm^2 for children's hands of 1.5 years old/ 857.5 cm^2 for adult hands). For hair lotion, shampoo and 2 in1 shampoo, a factor of 0.66 is used (768 cm^2 for surface area head of a child of 1.5 years old/ 1155 cm^2 for adults).

Data on frequency of use and amount of baby wipes is scarce. The use frequency has been estimated to coincide with every change of a diaper resulting in 5 times a day 1 wipe. By weighing commercially available wipes, the average weight of 1 wipe turned out to be 5 g. Since contact with the skin is not permanent and does not necessarily involve the full surface of the wipe, a retention factor is used. According to van Engelen et al., 0.5 ml of liquid from a wipe deposits on the skin per event [86]. Taking the 5 grams of wipes/day and a retention factor of 0.1, this results in a total amount on the skin of 2.5 g/day. The RIFM reports an exposure to 4 mg/cm2/day of a substance via wiping. When considering the surface area of application of a 1.5 year old child of half the trunk (groin, buttocks and upper thighs: 1728 cm2), this results in an external exposure of 3 g of product/day [87], which is close to the 2.5 g/day that is used in the tier 1 calculation.
For the 12 product types, the total external exposure per paraben in mg/kg bw/day is estimated by multiplying the amount of product used, the frequency of use, the retention factor and the maximum concentration of paraben in a product divided by the body weight of a 1.5 year old child. The outcomes are summed up to obtain the total external exposure per paraben (Table 3). The worst-case scenario is that every person uses all 12 products and all 12 products contain parabens. The total amount of personal care products used then is 10.45 g/day (appendix 3, table 4). Using paraben specific dermal absorptions (as described in section 2.4, table 2) or an oral absorption of 100%, the internal exposure is calculated per product type and summed to obtain the internal exposure. By dividing the specific NOAELs per paraben by the internal exposures, the Margin of Safety (MoS) is obtained (Table 3). The NOAELs for methyl-, ethyl- and propylparaben are derived from studies following oral administration. The assumption is that there is 100% oral absorption in these studies. The NOAEL for butylparaben is derived after subcutaneous administration, also assuming 100% absorption.

Table 6 Output Tier 1: external and internal exposure to parabens and MoS

	Methyl	**Ethyl**	**Propyl**	**Butyl**
External exposure (mg/kg bw/day) based on maximum amount incl. retention factors	2.32	0.36	1.05	0.47
Dermal absorption	36%	55%	37%	42%
Internal exposure (mg/kg bw/day) based on maximum amount incl. retention factors and dermal absorption	1.01	0.20	0.41	0.20
NOAEL (external and internal)	1000	1000	3.3	2
MoS	**991**	**4966**	**8**	**10**

For methyl-and ethylparaben the MoS does not give rise to concern. The MoS is well above 100 that is derived from safety factors of 10x10 for intra- and interspecies differences. The NOAELs are based on exposures of several weeks, while higher NOAELs have been reported in studies with a longer duration of administration. The choice of these NOAELs was already conservative, so no additional safety factor for duration is applied, and repeated dose studies showed effects at much higher levels. This is stated by the SCCS as well [53]. However, for propylparaben using a NOAEL of 3.3 mg/kg bw/day based on adverse effects on hormone levels and male reproduction and butylparaben using a NOAEL of 2 mg/kg bw/day based on defects in testis development, the MoS is well below 100 and therefore giving rise to concern.

Tier 2

The probabilistic approach employed in tier 2 estimates a variation in the exposure of the population. This variation is due to both uncertainty (lack of knowledge) and natural variability in the input data. Contributions of uncertainty and variability to the overall variation have not been separated in this case. The resulting probability distribution P(E) may be interpreted as the probability of any person in the population to have an exposure E.

The aggregate exposure output from the person-oriented probabilistic approach can be visualized in histograms and cumulative probability plots. In the cumulative plot, on the y-axis the probability that a person in the population is exposed is presented and on the x-axis the corresponding exposure level in mg/kg bw/day is given on a log scale. The cumulative probability y at any exposure x gives the probability of any person in the population that he or she has an exposure lower or equal to x. In the histograms, the distribution of the exposure to a paraben per number of persons is plotted. In both plots, the outcome of the tier 1 approach is indicated as well as the level of the NOAEL/100, as a risk assessment comparative value.

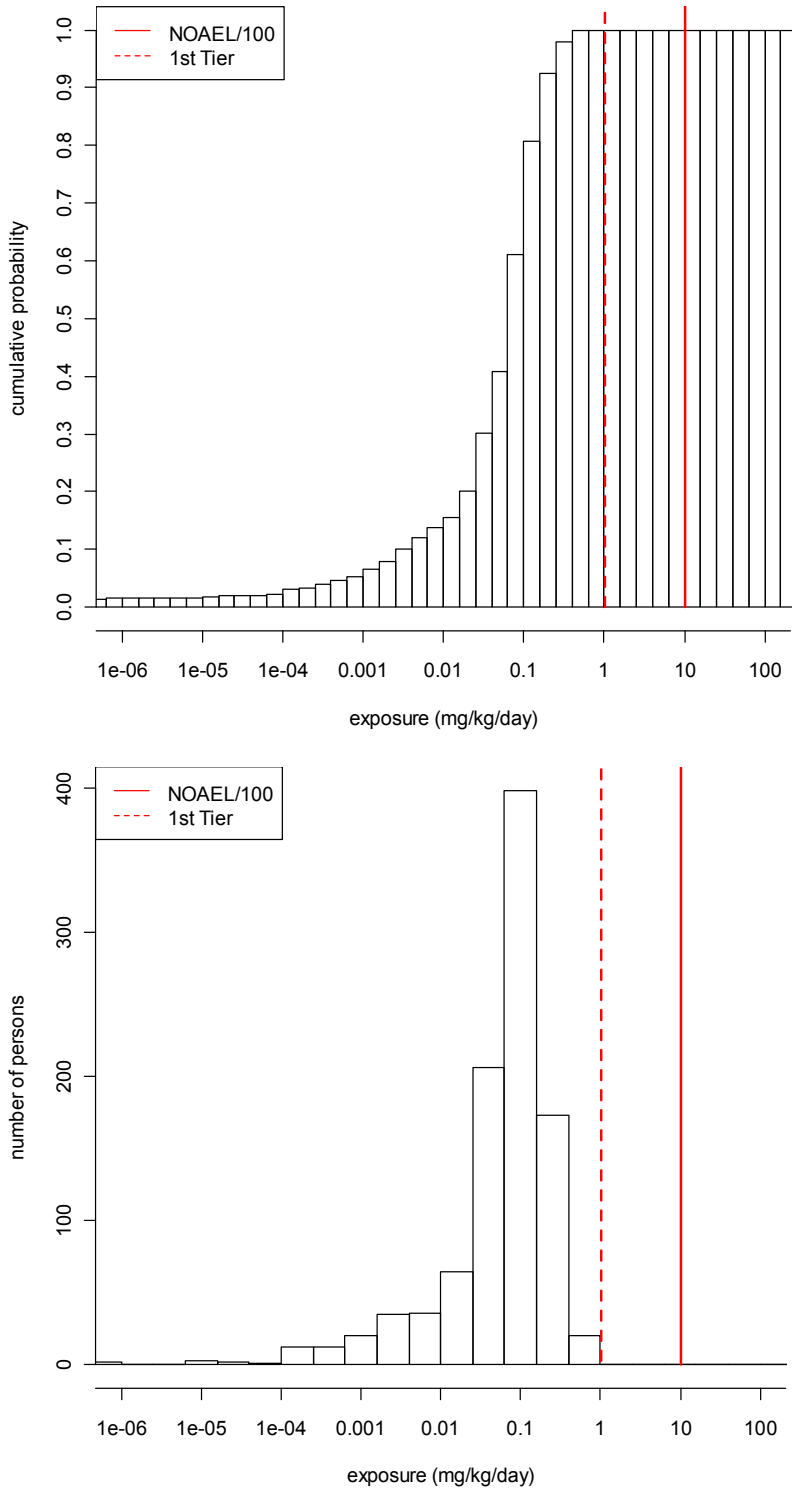


Figure 6 Cumulative plot and histogram for methylparaben

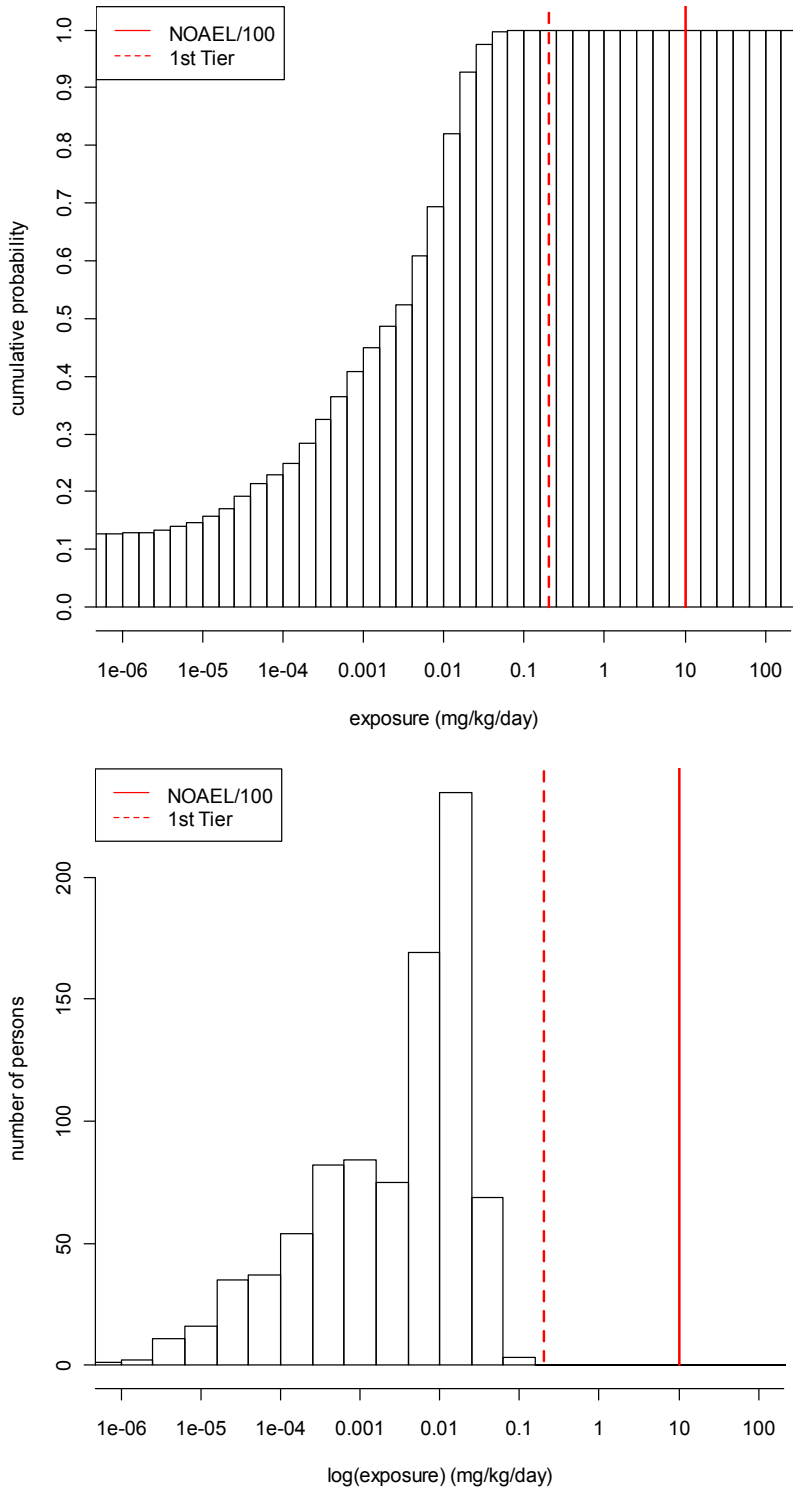


Figure 7 Cumulative plot and histogram for ethylparaben

For methyl- and ethylparaben (cumulative probability plots in figure 6 and 7, respectively) it can be seen that a 100% cumulative probability is reached at an exposure level that is below the exposure level estimated by the tier 1 approach. The probability of persons in the population of being exposed to a level

exceeding the MoS is estimated to be zero. In the second tier therefore, it is concluded that there is no risk.

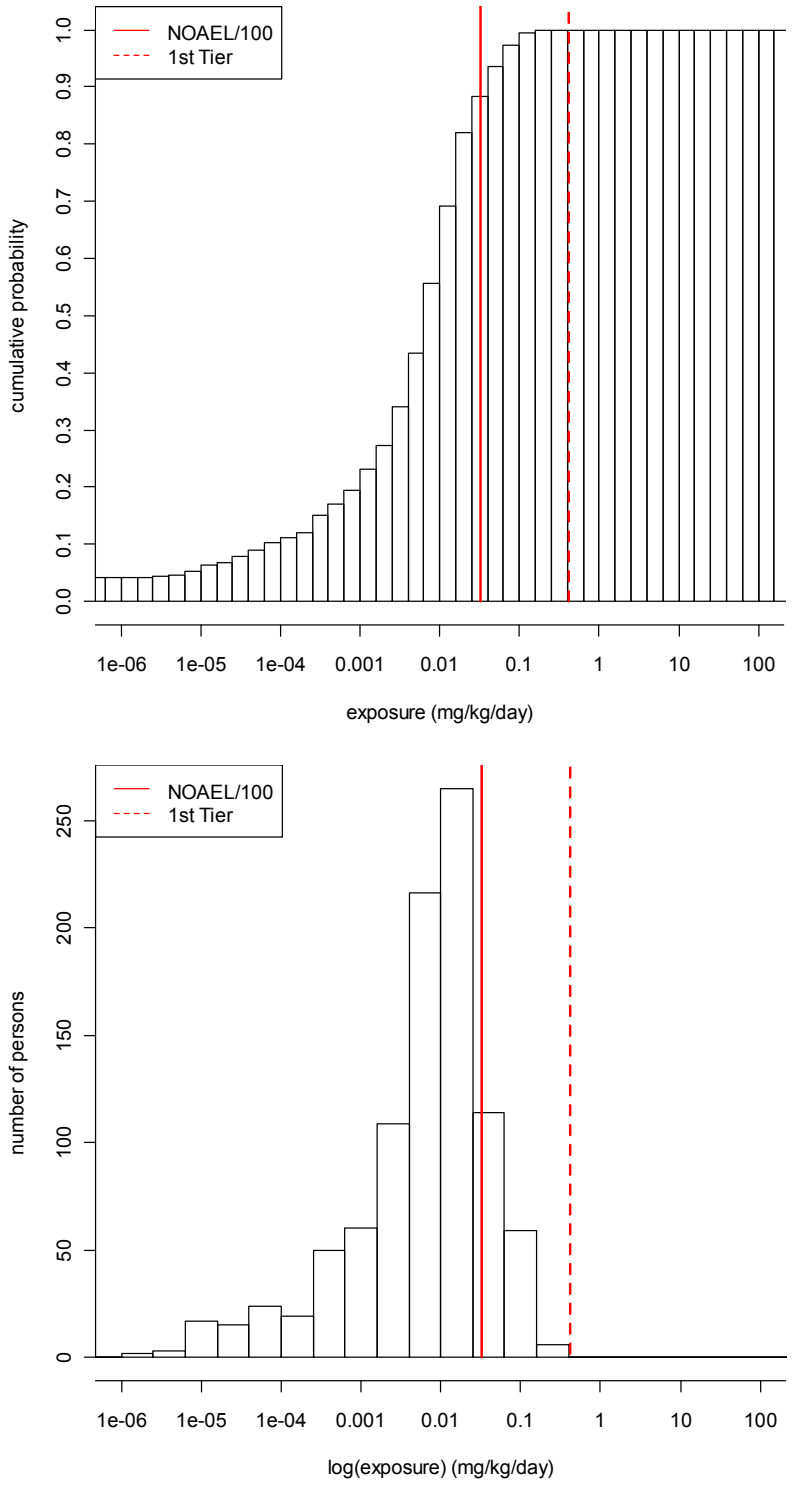


Figure 8 Cumulative plot and histogram for propylparaben

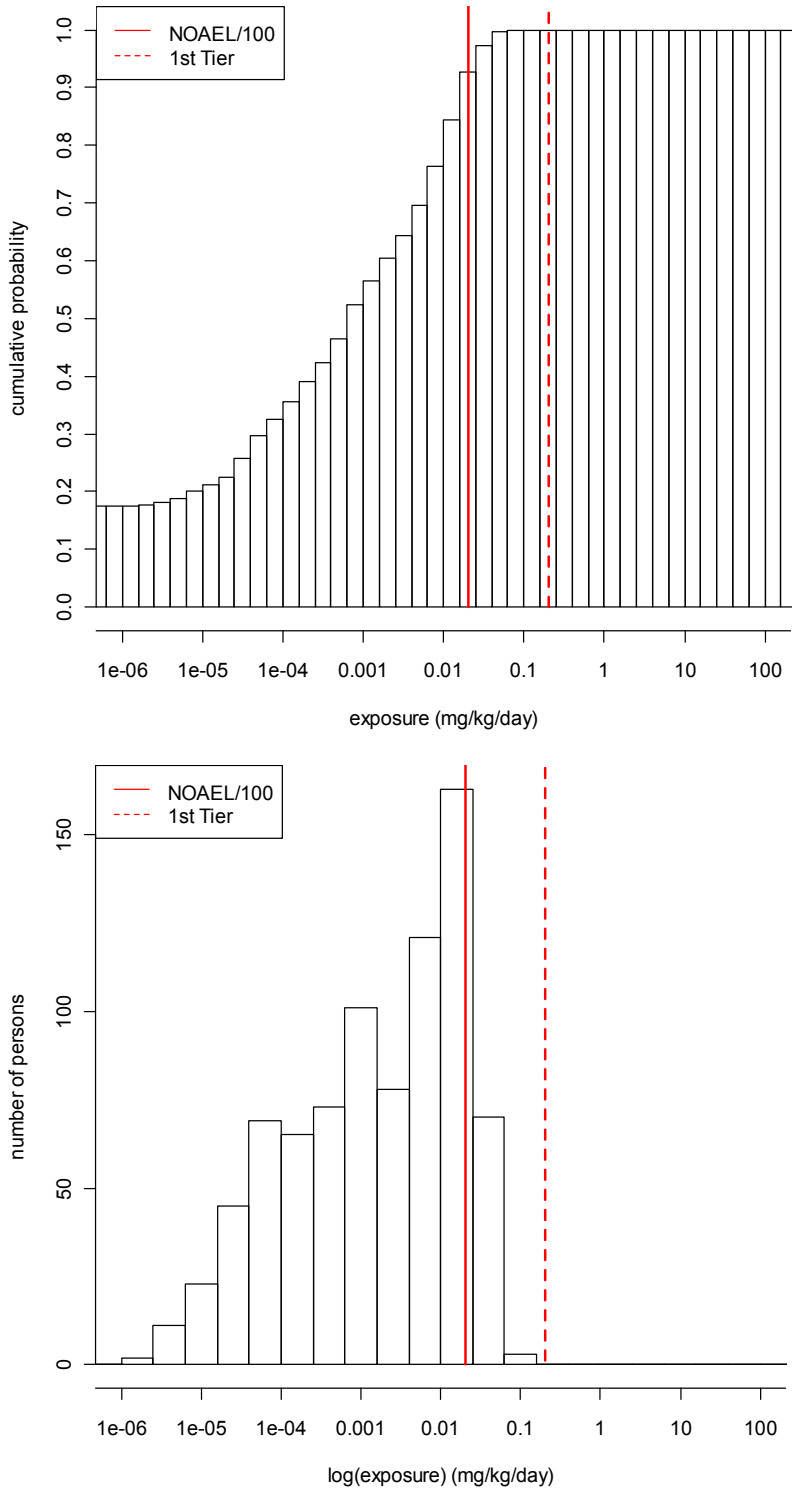


Figure 9 Cumulative plot and histogram for butylparaben

From the cumulative plots in figure 8 and 9 can be seen that the percentile of the population with a probability being below the NOAEL/100 is lower than 100%. This means that there is still a small chance of persons being exposed to a level above the MoS. Adverse effects can therefore not be excluded.

The relative contribution for a certain product type to the total aggregated exposure per paraben can be calculated by determining the total population exposure per product type. The contribution as a percentage to the total is given in figure 10 to 13.

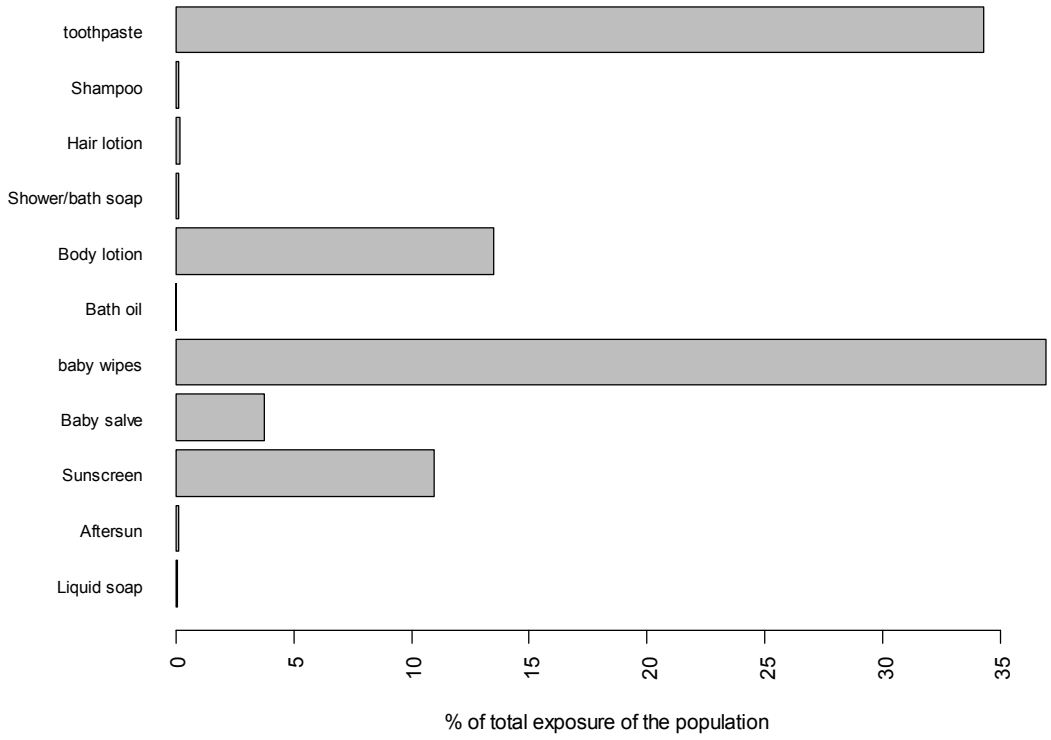


Figure 10 Relative contributions of different product types to the total exposure of the population for methylparaben

Toothpaste and baby wipes have the highest relative contribution to the total aggregate exposure for methylparaben. This can be explained by the high concentrations of methylparaben that have been measured in toothpaste and the assumption that there is a 100% oral absorption. For baby wipes, the high relative contribution can be assigned to a high total amount of product that is used. Bodylotion and sunscreen have the second highest and baby salve the third highest contribution. These are all leave-on products, contributing significantly due to the fact that the amount applied stays in contact with the skin. The other product types have either been reported to be hardly ever used or in very small amounts, or this product does not often contain this specific paraben.

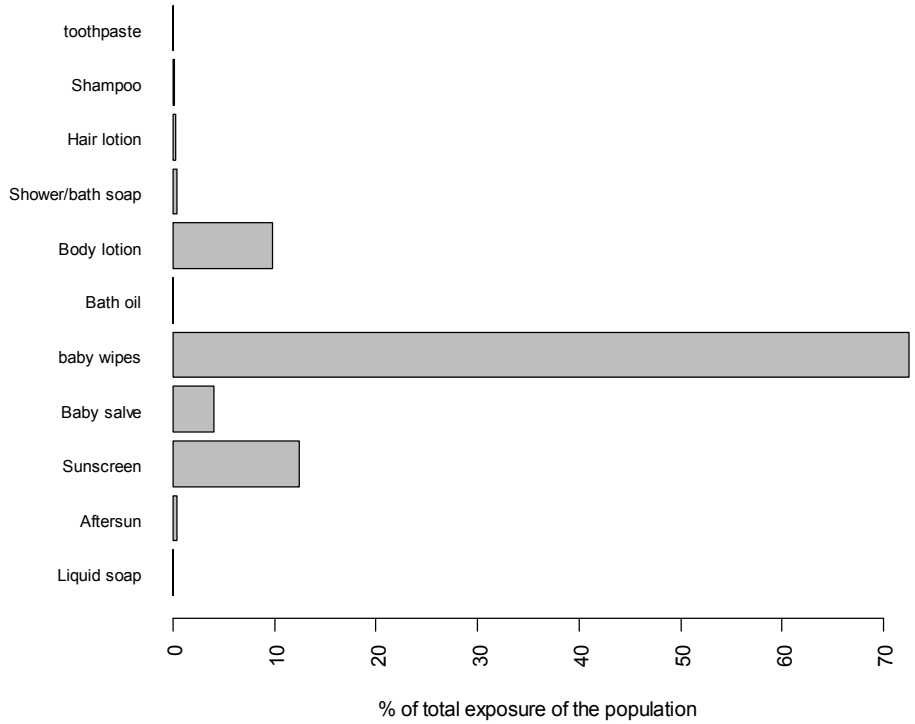


Figure 11 Relative contributions of different product types to the total exposure of the population for ethylparaben

For ethylparaben, the relative contribution by toothpaste is reduced to zero, since this paraben is not used as a preservative in toothpaste. Baby wipes have the highest relative contribution of more than 70%, which is (relatively) twice as much as seen for methylparaben. This is again due to a high total amount of product that is used and the absence of other product types that contribute to the total exposure to a high extent. Bodylotion and sunscreen have the second highest and baby salve the third highest contribution.

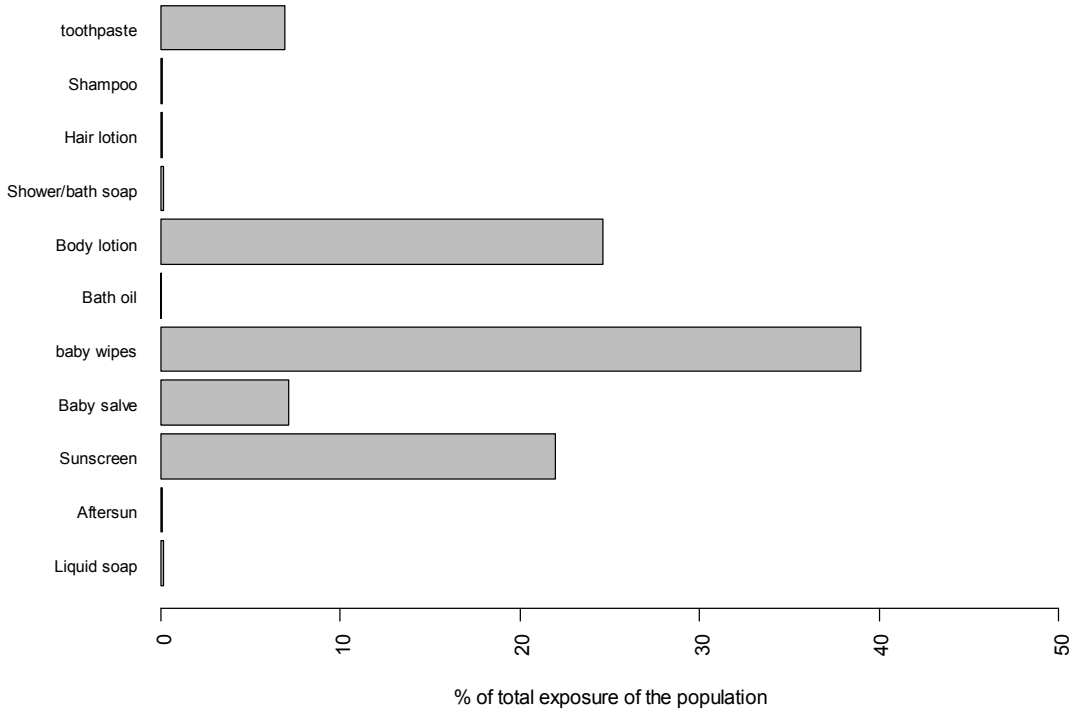


Figure 12 Relative contributions of different product types to the total exposure of the population for propylparaben

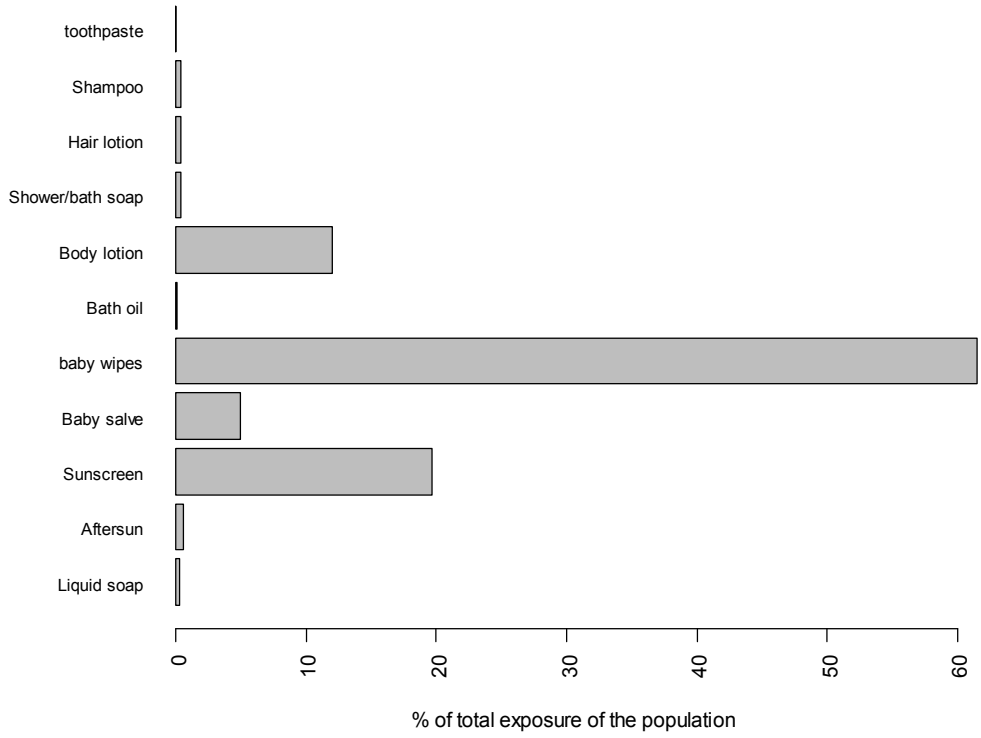


Figure 13 Relative contributions of different product types to the total exposure of the population for butylparaben

The relative contributions of product types for propyl-and butylparaben are similar to those for ethylparaben, with baby wipes as highest and leave-on products as second highest contributors. Butylparaben is not used in toothpaste, while propylparaben is.
By plotting the age dependent exposure per paraben (example is for butylparaben in figure 14, but similar results are obtained for all parabens), it can be seen that at age 14 months, there is a high-end user that drives the total exposure. By going back to the survey data, this has been attributed to the profile of a 14 months old girl for which use of a lot of different product types in high amounts has been reported.

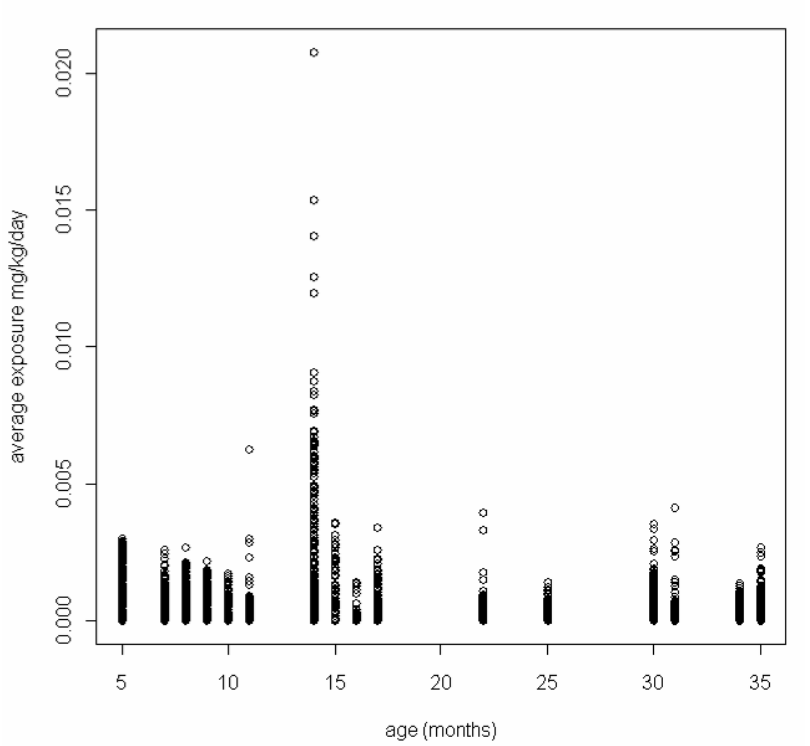


Figure 14 Age dependent exposure for butyl paraben

3.5 Discussion

In several regulatory frameworks, e.g. REACH, the Pesticide Directive and the Biocide Products Directive, consideration of aggregate exposure to a chemical from all known sources is mentioned. For consumer products, in "The SCCP's notes of guidance for the testing of personal care ingredients and their safety evaluation" no specific notes on aggregate exposure are described [82]. However, in the specific case of preservatives, the SCCNFP has proposed a global daily exposure value for all personal care products that one person may daily apply on the skin [88] of 17.4 g/day or 269 mg/kg bw/day. Apart from this, there is no further guidance on how to perform aggregate exposure assessment for consumer products.
Here, a two tiered approach for an aggregate exposure assessment has been examined using parabens as a case-study. In the tier 1 deterministic approach, the external and internal aggregate exposure is calculated by simple equations. The use of conservative estimates and assumptions for all parameters in these equations could ultimately lead to a too worst-case exposure scenario. The methods used in a first tier will not be able to evaluate the degree of conservatism, as the contribution of information on variability and uncertainty is

not explicitly accounted for. When summing the individual exposures for every product type that has been identified for children that contains either methyl-, ethyl-, propyl- or butylparaben, this could lead to an unrealistically high exposure. For example, it is highly unlikely that all 12 product types are used by one individual. In addition, not all products from the same product type contain paraben(s) to the same extent. The simple deterministic method is not suited to address these problems. Refinement is also difficult, since detailed data on the use of personal care products is unavailable and it is uncertain whether extrapolation from adult use is possible.

To overcome limitations of the deterministic tier 1 approach, a probabilistic method was used as tier 2. The result of the tier 2 approach is a probability distribution of paraben exposure in the population. It can be used for example to estimate the likelihood that a safe level of exposure is exceeded in a population. This likelihood is determined by both uncertainty and variability. To make estimates of the fraction of a population actually at risk, contributions of uncertainty and variability to the evaluated population exposure should be determined separately. In order to do this, parameters that contribute to the uncertainty and to the variability in the exposure must be discerned. In this assessment, parameters that contribute to the variability are body weight, age, the weight percentage of paraben in a product and the number of products used. Uncertainty is present in 1). the amount of product used, 2). the frequency of use, 3). the dermal absorption, 4). the concentration of butylparaben in a product and 5). the retention factors. For example, when a person reports to use less than 0.5 g of a product since this is the amount that was shown on the first picture in the questionnaire, it is not possible to set the lower bound. A similar problem arises for the reported use frequency, when someone reports to use a product less than 1 time per week. The lower bound is then unclear. By setting the dermal absorption to a fixed level, e.g. 50% and perform the calculation and then repeat this analysis with the dermal absorption set on 1% and on 80% as a maximum, the uncertainty can be quantified. In addition, there is a level of uncertainty in the measured butylparaben concentration in some products, since the peak in the chromatogram coincided with benzylparaben. Since benzylparaben is used far less in personal care products according to the product labels while butylparaben is reported more frequent as an ingredient, the worst-case assumption is made that the whole amount that is reported is butylparaben. In doing so, the level of butylparaben in products that has been reported by Rastogi et al. [89] of 0.07% is only exceeded three times out of 84 cases. Therefore, the influence of the uncertainty in this parameter is expected to be small. The retention factors as reported by the SCCS [82], lack support by profound scientific data and have an arbitrary character.

By plotting the exposure levels per person, it is seen that 1 person (girl of 14 months old) has a relatively high exposure compared to the other children implying that she may drive the high exposure levels seen in figure 13. A larger sample size would give more insight whether this high-end user profile occurs more often in the population or is a single observation. The observation may be caused by bad reporting by the person filling in the survey e.g. when a question has been misinterpreted or difficulties exist in estimating use of amount of product from photographs and could then be regarded as an outlier. On the other hand, this observation could represent a high-end user that actually exists in the population.

By comparing the relative contributions of products, it can be seen that the sources of exposure to parabens are not equal for each paraben. For example, toothpaste has a high contribution due to the high levels of methylparaben in the product. For propylparaben, a relatively high contribution is found for

sunscreen and bodylotion. For all parabens, the use of baby wipes is the highest contributor. This is also a product type for which a large uncertainty exists on the amount of product that actually is left on the skin after use. Hardly any data or estimations on exposure levels following the use of wipes were found. To refine the exposure and to reduce the uncertainty, the migration of parabens from wipes and what is left on the skin should be investigated closer.
Performing a consumer survey on the use of various types of products and amounts is a time-consuming effort. In addition, to obtain a larger sample size by distributing the survey amongst more people is a considerable task. In general, surveys on consumer product use have not been performed to the same extent as has already been done for e.g. food consumption. For example, EFSA has published a concise database on food consumption for several European countries with data from ~1000 persons per country in different age groups (from infants to adults of 75 years or older) and with information on 160 different food groups with both regular and high consumption patterns [90]. However, once established, the data from a consumer product survey can be used multiple times for different exposure assessments. The data can be used to refine the tier 1 and tier 2 approach, and may be used in the tier 2 approach to determine the effect on the outcome of the uncertainty and variability in the parameters.
The tier 1 approach can be refined by including co-use and non-use patterns that may lead to inclusion or exclusion of certain product types as has been done e.g. by Cowan-Ellsberry et al. for adult exposure [14]. On average, people use 6 products from the list of 12 with a range of 3-8 product types. In addition, a better estimation of the amount of product used on a child between 0-3 years old could be made with data from the survey. By expanding the survey to a larger sample size, this could even lead to the adaptation of the default values.

Risk assessment
Following the tier 1 approach, the aggregate exposure levels of propyl-and butylparaben of 0.41 and 0.20 mg/kg bw/day, respectively approximate the levels reported by the Danish EPA (0.22 mg/kg bw/day for both) [77]. Here 12 product types have been considered, while the Danish EPA aggregated exposure from four products. The Margin of Safety derived for propyl- and butylparaben gives rise for concern. This is obtained following worst-case conservative estimates and it is conceivable that when performing a more realistic exposure assessment, this might lead to less concern. The exposure assessment could be refined by correcting for co-use and non-use of certain products from the survey and for information on the percentage of personal care products actually containing parabens. For methyl- and ethylparaben, there is no reason for concern following the tier 1 approach. The same conclusion can be drawn for the tier 2 approach; it was estimated that was no chance on exposure levels above the outcome of tier 1 and the NOAEL/100. For propyl- and butylparaben, there is still a chance that some children in the population would be exposed to significant levels of propyl-and butylparaben. In order to make a quantitative statement on the possible fraction of the population at risk, a detailed uncertainty analysis needs to be performed (which is not done in this report).

Cumulative exposure
Adverse effects by estrogenic activity have been reported for all 4 parabens to a certain extent in *in vitro* and *in vivo* studies. Assuming a common mechanism of action, a cumulative exposure assessment might be more relevant for the risk assessment of parabens. Since the focus here is on aggregate exposure assessment and the evidence is limited that on a molecular level the 4 parabens indeed act via the same mechanism of action, this has not been applied here. To

perform a cumulative exposure assessment, relative potencies of the 4 parabens could be assigned. Also more detail on dermal absorption at simultaneous application of all parabens is needed, since they influence each other like described by Caon et al. [58]. Ultimately, co-exposure with other estrogenic compounds might have to be considered for the risk assessment if there are indications that other compounds like e.g. phthalates act by the same mechanism as well. To this end, an extended consumer product user survey could help to sketch the daily contact profile to multiple substances in many more consumer products to get a complete characterisation of the exposure.

3.6 Conclusions

In the case of butylparaben and propylparaben, the outcome of the risk assessment using the first tier exposure assessment resulted in a concern. The tier 2 approach resulted in more detailed information, and it could be concluded that there is a chance that some children in the population would still be at risk. For methyl- and ethylparaben, both approaches resulted in no concern.
The exposure assessment using tier 2 showed that the exposure was driven by baby wipes. However, the amount of paraben released and left on the skin is very uncertain. For methyl- and propylparaben exposure, there is a large contribution from toothpaste. Other important drivers are leave-on products like sunscreen, bodylotion and baby salve, with a note that uncertainty in the dermal absorption values is high with a range of 1 to 55%.

In general, where a tier 1 approach can be used to get a rough idea whether there is reason for concern following exposure to a substance from multiple routes and products, a tier 2 approach is more complex and will lead to a more realistic and much more informative exposure assessment. Since a tier 1 approach can be performed using simple equations and default point estimates, this approach can always serve as a starting point for an aggregated exposure assessment. If the outcome gives no reason for concern and there is no indication that e.g. for a certain subpopulation the risk might be different, the assessment is finished. If a more detailed assessment is warranted in case of a concern in a screening risk assessment, in case of a Health Impact Assessment or there is an interest to obtain more details on specific aspects of the exposure, the person-oriented approach following probabilistic modelling can be used. This approach is data demanding, but the detailed information will lead to a better idea of which fraction of the population is exposed to high levels that give rise to concern after analyzing the uncertainty in the exposure assessment.

3.7 Recommendations

Survey
The use of more detailed user data of consumer products could significantly reduce uncertainties in the exposure assessment for a tier 1 as well as a tier 2 approach. Therefore, extending the survey to more persons would be useful and would also decrease the uncertainty introduced by one high end user that has been identified here. By adapting the questions in the survey with respect to the frequency of use (by including open questions when reported use is less than 1 time per week) and include photographs with smaller amounts of product, the lower bounds of use frequency and amount can be determined. The survey has been taken anonymously, leaving no chance to go back and discuss the reported profile of a child with the parent. By keeping a link to the person that has filled in the questionnaire, it is possible to establish whether the girl of 14 months was actually a high end user or there was misinterpretation of the question or bad reporting. A consumer product survey as already exists for food consumption

would be worthwhile to construct. As a start, this first attempt could be extended to more children but also to adults. Personal care products as a category is a good start. Extension can be performed regarding other product categories, starting for example with household cleaning products, or textiles, or toys as of yet no survey database exists for these product types.

Parameters
A large uncertainty has been found in the exposure to parabens following use of baby wipes. Experimental research could be done to the migration of parabens (and/or other substances) from baby wipes, and the amount that would be left on the baby skin. Uncertainty in the dermal absorption could be reduced by performing a well designed absorption study in human volunteers. Now, oral absorption is assumed to be 100%, but given the rapid metabolism of parabens, the uptake of the parent compound in the circulation may be much less. This could be experimentally determined as well, like for dermal absorption.

Tier 1
Default amounts that are described in the tier 1 approach could be adjusted for the 75^{th} percentile of amounts used for children reported following a more comprehensive survey.

Tier 2
A detailed uncertainty analysis needs to be performed, in order to make a quantitative statement on the possible fraction of the population at risk.

4 Overall conclusion and policy implications

In most cases, the limitations of an aggregate risk assessment are restricted to the exposure assessment. With respect to aggregate exposure, sometimes simple worst case deterministic exposure assessments are sufficient to indicate the absence of concern. In that case no further actions are required. If concern cannot be excluded, refinement of the exposure assessment is the first priority. However, this refinement is often limited due to the absence of relevant exposure data. Therefore, additional measurements on specific substances and products or data on exposure parameters will be needed to improve the risk assessment. Such additional measurements can possibly be obtained from enforcement monitoring programs or should be separately addressed. More information is needed on the use pattern of products, including use frequency, used product amounts, co-use of products and the use of specific brands.
To be able to deal with the increasing regulatory demands for aggregate risk assessment, further development of exposure models will be necessary. A joint action between public and private parties may be the most efficient way forward. In this report, a tier 2 (or might be considered as tier 3) model under development [84] is used. In the case study with parabens, two different tier models are used to assess the aggregate exposure. For two parabens, the first tier model already resulted in a conclusion of no concern, which was confirmed in the assessment with the tier 2 model. For two other parabens, the aggregate risk assessment using the tier 1 model resulted in a conclusion of concern. The assessment with the tier 2 model making use of the performed survey on product amount and use frequency focussed on child personal care products, did not result in a definitive answer. It was concluded that a concern still could not be excluded for part of the childrens population. An uncertainty analysis needs to be performed which might give a more quantitative answer. However, the tier 2 model results gave more insight in the drivers of the exposure (being especially toothpaste and baby wipes). Furthermore, the highest uncertainty seems to be present in the frequency of use and the amount of parabens released from baby wipes. In the future, more information could be gathered specifically on those points.

This report is relevant for both risk assessors and risk managers. The tier 2 model is providing more insight in drivers of exposure and uncertain parameters as goal for further investigations. The need for that kind of information is also demonstrated for example in the recent restriction dossier under REACH on four phthalates with a proposed ban on the presence in many articles [91]. Exposure to the four selected phthalates results directly from these articles, but also indirectly via food, indoor air and dust. When assessing the effectiveness of the proposed ban, which is an obligation under REACH, information on drivers of the total exposure estimate, together with insight in the uncertainty around exposure parameters is urgently needed. However, a total detailed assessment for all articles included is highly data demanding and time and energy consuming. Therefore, it has been proposed to develop a kind of tier 1.5 model, not as conservative as a tier 1 model, but not so complex and time demanding as a tier 2 model. This could for example be done by using distributions for only a part of the exposure parameters (choice should be made case by case), and keeping single point values for other parameters.

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Appendix 1

Table 7 Overview NO(A)ELs for four parabens

	NO(A)EL (mg/kg bw/day)	Route of administration	Model	Critical effect
Methylparaben	**1000** [66]	Oral (8 weeks)	Wistar rats 25-27 days	Secretion sex hormones and male reproduction
	5.5# [50]	Subcutaneous (3 days)	CD1 mice 21 days	Uterotrophic assay: increased uterine weight
	250 [68]	Oral (19 days)	Sprague-Dawley 21 days	Development female reproductive organs: delay vaginal opening and decreased estrous cycles
Ethylparaben	**1000**$ [66]	Oral (8 weeks)	Wistar rats 25-27 days	Secretion sex hormones and male reproduction
	6# [50]	Subcutaneous (3 days)	Adult ovariectomized CD1 mice	Uterotrophic assay: increased uterine weight
	250 [68]	Oral (19 days)	Sprague-Dawley 21 days	Development female reproductive organs: reduced estradiol levels
Propylparaben	**3.3*** [69]	Oral (4 weeks)	Wistar rats 21 days	Secretion sex hormones and male reproduction
	6.5# [50]	Subcutaneous (3 days)	CD1 mice 21 days	Uterotrophic assay: increased uterine weight
Butylparaben	**2**# [70]	Subcutaneous (2 weeks)	Wistar rats 2-18 days	Testis development: efferent ducts
	3.3* [92]	Oral (8 weeks)	Wistar rats 21 days	Secretion sex hormones and male reproduction
	3.3* [93]	Oral (10 weeks)	CD1 mice 4 weeks	Secretion sex hormones and male reproduction
	0.7# [50]	Subcutaneous (3 days)	CD1 mice 21 days	Uterotrophic assay: increased uterine weight

The NO(A)ELs used for the risk assessment described in this report are highlighted in bold.

* based on a LOAEL of 10 mg/kg bw/day and a factor 3 to derive a NOAEL.

is NOEL instead of NOAEL

$ highest dose tested

Appendix 2

Table 8 Personal care products for children 0-3 years (number of products/total number of products and percentage of product containing a paraben). Information from VWA report (49).

Product categories	**Contains paraben?**
Baby oil	No
Baby powder	No
Massage oil	No
Ear cleaner	No
Anti-cradle cap product	No
Sunscreen	Yes (9/15, 60%)
Aftersun	Yes (3/5, 60%)
Shampoo	Yes (20/38, 53%)
Hair lotion	Yes (6/9, 67%)
2 in 1 shampoo	Yes (2/3, 67%)
Body lotion	Yes (16/21, 76%)
Shower/bath soap	Yes (18/56, 32%)
Bath Oil	Yes (2/14, 14%)
Liquid soap	Yes (10/30, 33%)
Toothpaste	Yes (14/24, 58%)
Baby wipes	Yes (25/38, 66%)
Baby salve	Yes (26/46, 57%)

Table 9 Maximum amount of parabens in personal care products (based on measurements by VWA (49)).

Product category	**methyl (mg/kg)**	**ethyl (mg/kg)**	**propyl (mg/kg)**	**butyl (mg/kg)**
Sunscreen	2030	398	988	463
Aftersun	1538	377	192	490
Shampoo	3185	402	470	1081
Hair lotion	1024	229	108	247
2 in 1 shampoo	1663	na	551	699
Liquid soap	4070	283	4091	1473
Shower/bath soap	3087	449	889	540
Bath oil	1026	222	111	314
Body lotion	3407	522	2053	577
Baby salve	3372	654	1742	684
baby wipes	1337	348	458	643
toothpaste	3017	na	247	na

Appendix 3

Table 10 Parameters per product used for the calculation of total exposure and exposure per paraben for children 0-3 years old, based on the Cosmetic Factsheet (8).

Product category	**Amount (g)**	**Frequency (x/day)**	**Retention factor**	**Corrected amount (g/day)**
Sunscreen	2.7*	0.21	1	0.55
Aftersun	2.7*	0.21	1	0.55
Shampoo	13.2*	0.71	0.01	0.09
Hair lotion	13.2*	0.71	0.1	0.94
2 in 1 shampoo	13.2*	0.71	0.01	0.09
Liquid soap	0.29*	5	0.01	0.01
Shower/bath soap	2.3*	0.90	0.01	0.02
Bath oil	9	0.28	0.01	0.03
Body lotion	2.16*	2	1	4.32
Baby salve	0.27	1	1	0.27
baby wipes	5	5	0.1	2.50
toothpaste	0.53	2	1	1.06

***** adjusted to total body or body part surface area for a child following the default values for adults from the Cosmetic Factsheet [21]

Appendix 4

Survey

Vragenlijst Persoonlijke Verzorgingsproducten

Door middel van deze vragenlijst willen wij een overzicht krijgen over het gebruik van persoonlijke verzorgingsproducten bij kinderen onder de 3 jaar. Persoonlijke verzorgingsproducten bevatten verschillende soorten stoffen. Sommige van deze stoffen kunnen de gezondheid beïnvloeden. Het is onbekend aan welke hoeveelheden stoffen kinderen worden blootgesteld. Het is daarom belangrijk om informatie te krijgen over de hoeveelheid, het type en de frequentie van persoonlijke verzorgingsproducten die gebruikt worden. Daarnaast zijn we ook geïnteresseerd in de plaats op het lichaam waar de producten worden aangebracht. De gegevens uit deze enquête worden geheel anoniem gehouden. U wordt dan ook niet gevraagd uw naam in te vullen.

Deze vragenlijst bestaat uit 2 onderdelen:
1. Algemene gegevens
2. Het gebruik van persoonlijke verzorgingsproducten

Het invullen van de vragenlijst zal ongeveer 10 minuten in beslag nemen.
Vult u alstublieft de vragenlijst zo precies mogelijk in!

Aanvullingen en opmerkingen kunnen genoteerd worden aan het eind van de vragenlijst.

Als u vragen heeft, kunt u contact opnemen met:
Ilse Gosens
Telefoonnummer: xxxxxxxxxxxxx
E-mail adres: ilse.gosens@rivm.nl

Algemene gegevens

1. Wat is de leeftijd van uw kind?
   ___ maanden

2. Is het een jongen of een meisje?
   _____

3. Wat is zijn/haar lengte?
   _____ cm

4. Wat is zijn/haar gewicht?
   _____ kg

Het gebruik van persoonlijke verzorgingsproducten

De volgende vragen gaan over het gebruik van persoonlijke verzorgingsproducten. We zijn onder andere geïnteresseerd in de hoeveelheden van de persoonlijke verzorgingsproducten die u gebruikt bij uw kind. Aan de hand van foto's worden deze hoeveelheden gemeten. Geef aan bij welke foto de hoeveelheid die u gebruikt bij uw kind het dichtst in de buurt komt. Alle vragen gaan over de afgelopen 6 maanden (tenzij anders vermeld).

We willen graag benadrukken de vragenlijst zo precies mogelijk in te vullen.

1. Welke van de onderstaande persoonlijke verzorgingsproducten gebruikte u bij uw kind tijdens de afgelopen 6 maanden?
☐ anti-zonnebrand crème/lotion/spray
☐ aftersun crème/lotion/spray
☐ shampoo
☐ haarlotion
☐ shampoo en conditioner in 1
☐ (vloeibare) zeep (bijvoorbeeld om handen te wassen)
☐ douche- of badschuim
☐ badolie
☐ bodylotion of bodymelk
☐ baby zalf (tegen luieruitslag)
☐ baby/billendoekjes
☐ tandpasta
☐ geen persoonlijke verzorgingsproducten

2. Welke soort anti-zonnebrand bij uw kind gebruikte u tijdens de afgelopen 6 maanden?
(meerdere antwoorden mogelijk)
☐ crème
☐ lotion
☐ spray

3. Hoe vaak gebruikte u anti-zonnebrand bij uw kind het afgelopen jaar?
☐ 1 dag
☐ 2-4 dagen
☐ 5-7 dagen
☐ 8-14 dagen
☐ 15-21 dagen
☐ 22-30 dagen
☐ 31-60 dagen
☐ 61-100 dagen
☐ meer dan 100 dagen, namelijk:

4. Hoeveel product gebruikte u per keer?
☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:…..

5. Waar op het lichaam gebruikte u het product in het afgelopen jaar?
(meerdere antwoorden mogelijk)
☐ hoofd
☐ nek
☐ schouders
☐ oksel
☐ bovenarmen
☐ onderarmen
☐ handen
☐ borst
☐ buik
☐ rug
☐ billen
☐ schaamstreek
☐ bovenbenen
☐ onderbenen
☐ voeten

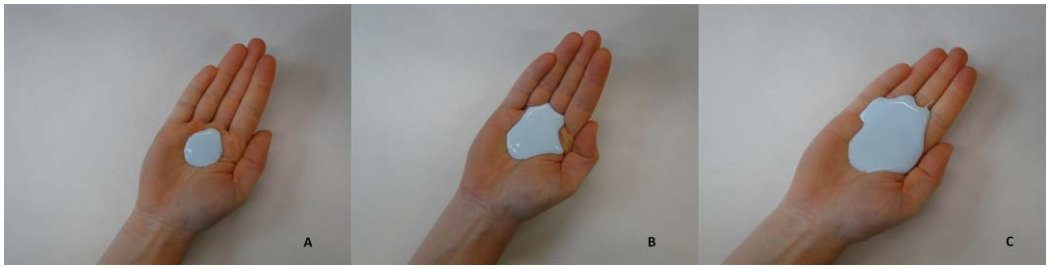
6. Welke soort aftersun bij uw kind gebruikte u tijdens de afgelopen het afgelopen jaar?
(meerdere antwoorden mogelijk)
☐ crème
☐ lotion
☐ spray

7. Hoe vaak gebruikte u aftersun bij uw kind in het afgelopen jaar?
☐ 1 dag
☐ 2-4 dagen
☐ 5-7 dagen
☐ 8-14 dagen
☐ 15-21 dagen
☐ 22-30 dagen
☐ 31-60 dagen
☐ 61-100 dagen
☐ meer dan 100 dagen, namelijk:

8. Hoeveel product gebruikte u per keer?
☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:…..

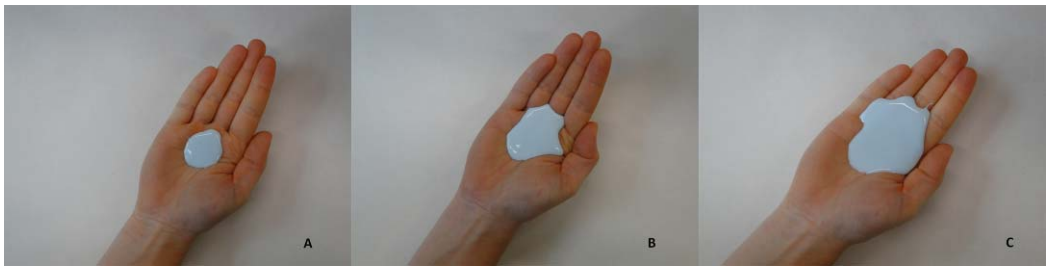
9 Waar op het lichaam gebruikte u het product in het afgelopen jaar? (meerdere antwoorden mogelijk)
☐ hoofd
☐ nek
☐ schouders
☐ oksel
☐ bovenarmen
☐ onderarmen
☐ handen
☐ borst
☐ buik
☐ rug
☐ billen
☐ schaamstreek
☐ bovenbenen
☐ onderbenen
☐ voeten

10. Hoe vaak gebruikte u shampoo bij uw kind in de afgelopen 6 maanden?
☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ meer dan 1 keer per dag, namelijk:



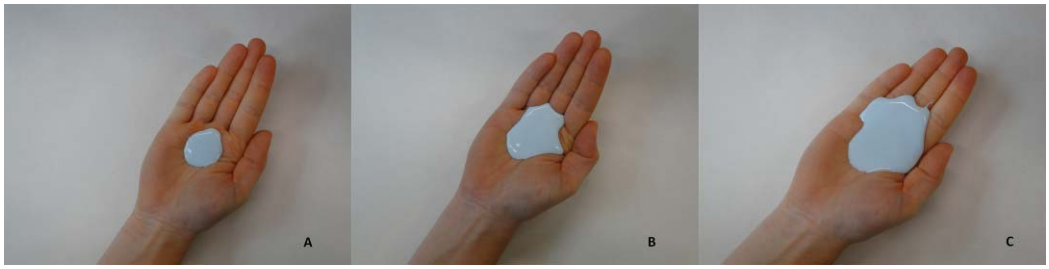
11. Hoeveel product gebruikte u per keer?
☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:

12. Hoe vaak gebruikte u haarlotion bij uw kind in de afgelopen 6 maanden?
☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ meer dan 1 keer per dag, namelijk:



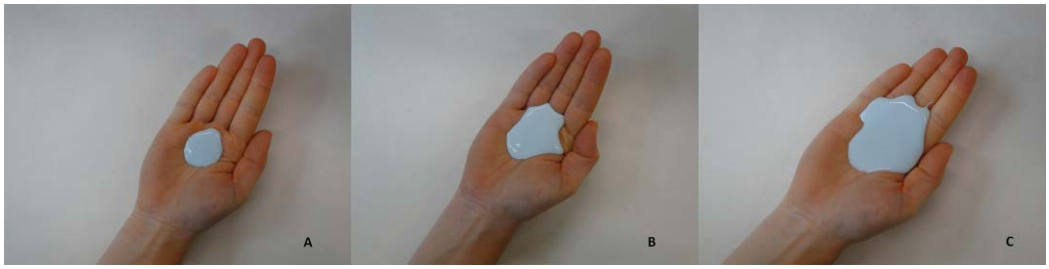
13. Hoeveel product gebruikte u per keer?
☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:

14. Hoe vaak gebruikte u shampoo en conditioner in 1 bij uw kind in de afgelopen 6 maanden?
☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ meer dan 1 keer per dag, namelijk:



15. Hoeveel product gebruikte u per keer?
☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:

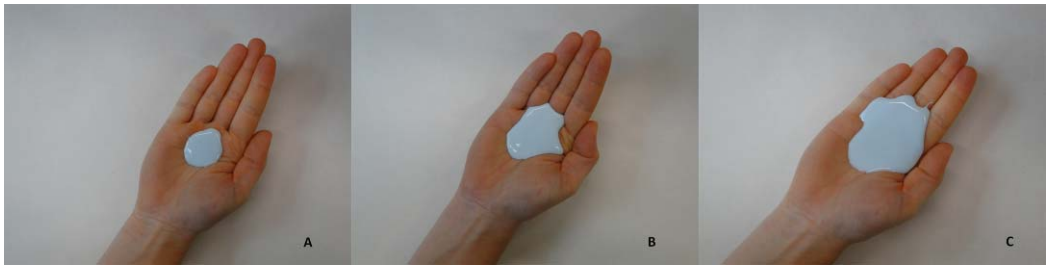
16. Hoe vaak gebruikte u (vloeibare) zeep bij uw kind in de afgelopen 6 maanden?
☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ 2-3 keer per dag
☐ meer dan 3 keer per dag, namelijk:



17. Hoeveel product gebruikte u per keer?
☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:

18. Hoe vaak gebruikte u douche- of badschuim bij uw kind in de afgelopen 6 maanden?

☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ 2-3 keer per dag
☐ meer dan 3 keer per dag, namelijk:

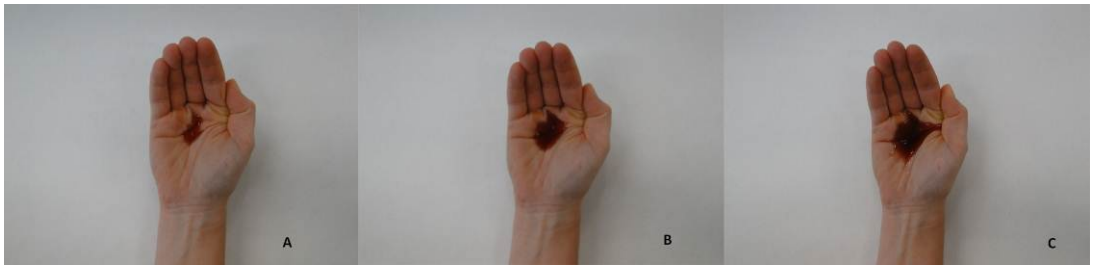


19. Hoeveel product gebruikte u per keer?

☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:

20. Hoe vaak gebruikte u badolie bij uw kind in de afgelopen 6 maanden?

☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ meer dan 1 keer per dag, namelijk:



21. Hoeveel product gebruikte u per keer?

☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:

22. Hoe vaak gebruikte u bodylotion of bodymelk bij uw kind in de afgelopen 6 maanden?

☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ meer dan 1 keer per dag, namelijk:

23. Hoeveel product gebruikte u per keer?

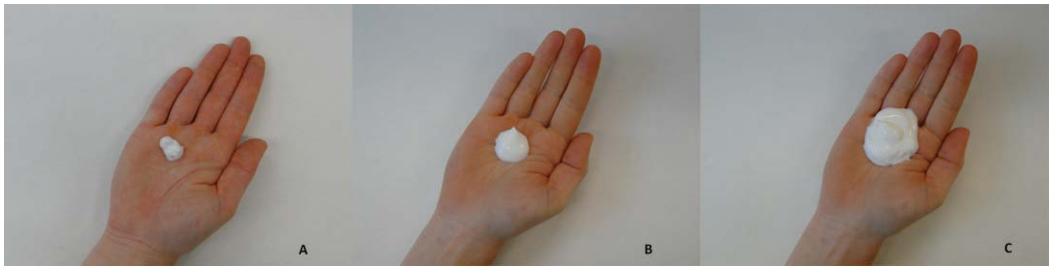
☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:

24. Waar op het lichaam gebruikte u bodylotion of bodymelk in de afgelopen 6 maanden? (meerdere antwoorden mogelijk)

☐ hoofd
☐ nek
☐ schouders
☐ boven armen
☐ onder armen
☐ handen
☐ borst
☐ buik
☐ rug
☐ billen
☐ boven armen
☐ onder armen
☐ voeten

25. Hoe vaak gebruikte u babyzalf bij uw kind tijdens de afgelopen 6 maanden?

☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ 2-3 keer per dag
☐ meer dan 3 keer per dag

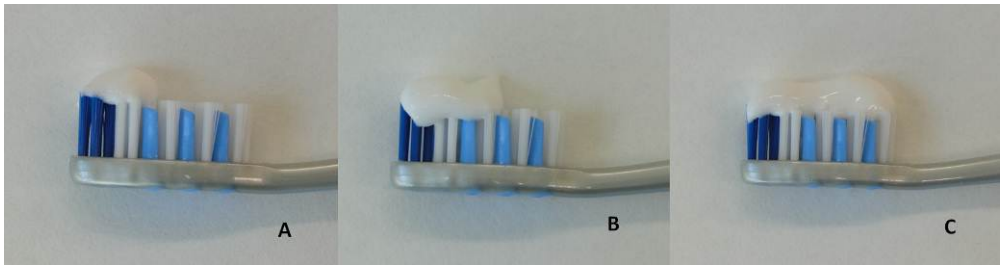


26. Hoeveel product gebruikte u per keer?
☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:…..

27. Hoe vaak gebruikte u baby/billendoekjes bij uw kind tijdens de afgelopen 6 maanden?
☐ minder dan 1 keer per week
☐ 1-2 keer per week
☐ 3-4 keer per week
☐ 5-6 keer per week
☐ 1 keer per dag
☐ 2-3 keer per dag
☐ meer dan 3 keer per dag

28. Hoeveel product gebruikte u per keer?
☐ 1 doekje per keer
☐ 2 doekjes per keer
☐ 3 doekjes per keer
☐ meer dan 3 doekjes per keer

29. Hoe vaak gebruikte u tandpasta bij uw kind in de afgelopen 6 maanden?
☐ minder dan 1 per dag
☐ 1 keer per dag
☐ 2 keer per dag
☐ 3 keer per dag
☐ meer dan 3 keer per dag, namelijk:



30. Hoeveel tandpasta gebruikte u per keer?

☐ minder dan op foto A
☐ ongeveer evenveel als op foto A
☐ meer dan op foto A, maar minder dan op foto B
☐ ongeveer evenveel als op foto B
☐ meer dan op foto B, maar minder dan op foto C
☐ ongeveer evenveel als op foto C
☐ meer dan op foto C, namelijk:

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