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Survey and risk assessment of teeth-whitening products for personal use

Survey of chemical substances in consumer products No. 186

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Preface

This report presents the results of a survey on teeth-whitening products for personal use that can be purchased on the internet from distributors in Denmark and abroad. Initially, a market screening was carried out, including a screening of the active substances used in teeth-whitening products, supplemented with existing knowledge in this field. Thereafter, selected products were purchased to be analysed for prioritized chemical substances and physico-chemical parameters. Lastly, it was assessed if the products may be harmful to health, or if these products, moreover, comply with the existing legislation for this type of products.

The survey was carried out from April to November 2020 for the Danish Environmental Protection Agency (EPA) by the Danish Technological Institute with DHI as a sub-contractor. The Danish EPA has contributed with elements of the report described in section 4.2.2 on compliance to a number of legal requirements, except the element on review of declaration of ingredients. Furthermore, a special thank you to Ulla Pallesen, Senior Dentist, at Department of Odontology, University of Copenhagen, for guidance regarding relevant literature and providing answers to follow-up questions.

The project was followed by:

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Summary and conclusion

The Danish Environmental Protection Agency wanted to acquire further knowledge on teeth-whitening products for personal use, specifically focusing on active whitening substances used and a risk assessment of these products. The active whitening substances used in teeth-whitening products for personal use can be, for example, peroxide compounds. In 2012, the EU implemented legal restrictions on hydrogen peroxide meaning that a product may contain/release no more than 0.1% hydrogen peroxide. Since then, several other active whitening substances have been observed in teeth-whitening products on the market, and therefore, more knowledge on the products as well as on the active whitening substances and on their health effects is requested.

The main aim of the project was to generate knowledge on teeth-whitening products that can be purchased for personal use. The project includes a survey of the market for teeth-whitening products in Denmark and abroad, as well as a survey on active substances with (assumed) whitening properties used in these products. The survey involved an analysis of products for content or release of hydrogen peroxide and other selected active substances. For products where the country of origin of the distributor is Denmark, the labelling, registration in the European Commission's cosmetic database, the Cosmetic Product Notification Portal (CPNP), and documentation for their assumed whitening effect was reviewed. Finally, it was assessed whether the usage of teeth-whitening products for personal use poses a threat to consumers.

The project focused on teeth-whitening products for personal use in the sense that teeth-whitening products included in this project may be purchased in physical shops or on the internet for use at home.

The market for teeth-whitening products

In this project, a market screening was carried out for teeth-whitening products that can be purchased by the Danish consumer in Denmark and via e-commerce from other EU countries and outside the EU. The screening was supplemented with existing knowledge on products, active whitening substances used and their mode of action from scientific literature and an expert in odontology. In the screening, mechanical whitening products that function as mechanical abrasives on the tooth surface were identified, and product types based on chemical whitening: teeth-whitening trays, pens, and strips, whitening toothpaste, and mouthwash. The occurrence of different product types, when consumers carry out an online search, was estimated, and it was found that particularly teeth-whitening trays occur frequently. Teeth-whitening pens, whitening toothpaste, and teeth-whitening powder/paste also occur rather frequently, but with a variation in single product types depending on whether the search is in Danish (primarily Danish distributors), or in English (distributors in or outside the EU). Declared substances that are known, claimed or assumed to have a chemical whitening effect on teeth, were registered in the screening:

- Hydrogen peroxide and substances producing hydrogen peroxide such as carbamide peroxide and phthalimidoperoxycaproic acid (PAP)
- Chlorite and chlorite-producing compounds (e.g., hypochlorite, hypochlorous acid and chlorine dioxide)
- Sodium borate (boron compounds are illegal in the products)
- Sodium bicarbonate
- Organic acids such as citric acid and inorganic acids such as phosphoric acid

According to the screening and existing knowledge on active substances and whitening properties, specific products were selected for analysis. The main parameters for selecting products for purchase and analysis consisted of:

- Delimitation to products with (expected) chemical whitening effect.
- Products of the most frequently occurring product types: teeth-whitening trays, pens, and strips.
- Products purchased from distributors in Denmark, other countries in the EU and outside the EU, as it was assumed that the number of purchased products of trays, pens and strips reflects the estimated occurrence of each product type on the respective market.
- Products that met the above criteria and occur early in an expected product search carried out by a private consumer.

Overall, 35 products were purchased out of which 15 were from Danish distributors, 7 from distributors from other countries in the EU and 13 from distributors outside the EU. Not all products were received within the time frame of this project, and in total, 25 products were included in the subsequent analysis.

Examination of purchased teeth-whitening products

As a part of this project, teeth-whitening products were examined closer as follows:

- The product declaration was reviewed focusing on whether substances were added that are regulated by legislation for cosmetic products.
- Physico-chemical parameters were measured with the aim to assess the products' whitening properties and perform risk assessment of products.
- Chemical analyses were performed with an aim to determine the content of substances with whitening properties and to investigate if the products contained forbidden substances.
- For products from Danish distributors, a review was carried out to see if selected requirements in the cosmetic legislation were met.

The oxidation potential was measured as a parameter for the possible whitening effect of the product. The results were compared with the analysis results of the active substances with whitening properties and with the declared active substance. The aim was to investigate whether the measurements can be used to assess which active substances the products contain and estimate their concentration. In this connection, no definite links were found between the measured oxidation potential and the declared active substance. However, products with a high oxidation potential have been selected with a view to determine the content of free chlorine. The pH value of the products was determined to investigate the acid/base properties. The products with either very high or very low pH values were selected for risk assessment.

In total, analyses of three different active substances with a whitening effect were carried out: hydrogen peroxide, chlorite, and hypochlorite. Analyses were carried out for products regardless of the product being declared with the respective active substance or not. Furthermore, the selected products were analysed for boron content, as some products were declared with boron-containing substances, and according to the Cosmetics Regulation they are forbidden in teeth-whitening products. The analysis results were compared to the declared substances of these products.

Among the examined products, several discrepancies between the product declaration and analysis results were identified. In other cases, deviations from the restrictions in the Cosmetics Regulation[1] were detected. Products with these deviations are listed in TABLE 1

TABLE 1 with an explanation of the observation.

[1] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (cosmetics regulation).

TABLE 1. Observations of examined products.

Observations	Product No.	Country of origin of distributor
Concentration of hydrogen peroxide determined by analysis is above the legal threshold value of 0.1% (content or released)*	12, 20, 22	Outside the EU
Chlorite identified by analysis, but no chlorite-containing substances declared	3	Denmark
	15	Other EU country
Boron identified by analysis or boron-containing substance declared**	7, 33	Denmark
	10	Outside the EU
Hydrogen peroxide or a hydrogen peroxide-releasing substance declared, but not identified by analysis	1, 3, 5, 14, 32	Denmark
	15, 16	Other EU country
	25	Outside the EU
A chlorite-containing substance is declared, but not identified by analysis	8	Other EU country

* According to cosmetics regulation, Annex III, reference no. 12
** Boron-containing substances must not be used in cosmetic products according to the Cosmetics Regulation, Annex II (several reference numbers relevant, incl. reference no. 1395)

Products for which Denmark was the country of origin of the distributor were analysed to see if a range of requirements in the Cosmetics Regulation were met, e.g., if products are registered in the European Commission's cosmetic database, the Cosmetic Product Notification Portal (CPNP). In the project, it was found that 4 out of 12 products are not registered in the database. It was also examined if the alleged effect of the products could be appropriately documented. For 6 out of 12 products, the distributor did not provide documentation within the project timeframe despite a request from the control unit of the Danish Environmental Protection Agency, the Chemical Inspection Service. For the 6 products where documentation was received it was evaluated that the documentation of 4 of the products was sufficient, whereas the documentation for two products was insufficient. Product packaging was reviewed according to the requirements in the cosmetics regulation and the cosmetics government order.[2] For 10 out of 12 products, one or more deviations from the labelling requirements were observed.

Risk assessment

Background

In the chemical analyses, hydrogen peroxide was detected in the interval 0.04-10.8% for 5 of the purchased teeth-whitening products. For 2 of these products, based on content declaration, hydrogen peroxide was detected to originate from content of sodium percarbonate and PAP, respectively. In addition, sodium chlorite was found in two of the remaining products with a content of 0.07-0.09%.

Furthermore, measurements of pH values and the oxidation potential of all teeth-whitening products were available as possible support to the risk assessment.

Hazard assessment

A literature search was carried out on the identified active teeth-whitening substances with the aim to collect existing knowledge/assessments regarding the usage of these substances in teeth-whitening products, and toxicological data was collected on the substances.

From all mentioned substances, the widest experience was found in the usage of hydrogen peroxide in teeth-whitening products. In 2007, the EU Scientific Committee of Consumer

[2] Government order No. 803 of June 21, 2013 on cosmetic products (cosmetics regulation).

Safety (SCCS) published a highly detailed risk assessment of products containing hydrogen peroxide. The risk assessment only describes the data of products with a hydrogen peroxide content above 3.3%, as the tests regarding professional whitening of teeth typically were performed on products with hydrogen peroxide concentrations in the interval of 3.3 - 35%.

Based on this assessment and other literature on teeth whitening, the following effects are typically indicated regarding the whitening of teeth:

- Increased tooth sensitivity/toothache
- Roughness, demineralization, reduced hardness, and tooth enamel erosion
- Gum irritation/corrosion, inflamed gums

Focusing on these local effects in oral cavity and teeth and based on the assessment of the systemic effects of the active substances after absorption in the body, the exposure levels, as shown in TABLE 22, could be identified as POD exposure levels (*Point of Departure*). POD values are effect-based exposure measurements estimated from NOAEL or LOAEL values for each substance, which then form the foundation of the risk assessment, where the POD value is compared to the actual exposure from the product.

TABLE 2. POD values for use in risk assessment of whitening substances.

Substance **CAS No.**	**POD** **Local effects, mucous membranes/gums**	**POD** **Systemic effects**	**POD** **Effect on teeth**
Hydrogen peroxide 7722-84-1	2% (H) Irritation/inflammation in mucous membranes and gums.	20 mg/kg bw/day (D) Effect on enzyme activity in plasma	1.1% (H) Increased tooth sensitivity
Sodium percarbonate 15630-89-4	Assessed based on the amount of released hydrogen peroxide	Assessed based on the amount of released hydrogen peroxide	Assessed based on the amount of released hydrogen peroxide
Phthalimidoperoxycaproic acid (PAP) 128275-31-0	Assessed based on the amount of released hydrogen peroxide (no data available for PAP)	30 mg/kg bw/day (D) Effects on fertility	Harmful effect on tooth enamel No data available for determination of POD
Sodium chlorite 7758-19-2	1% (D) Mucosal irritation	2.9 mg/kg bw/day (D) Effects on liver and nervous system	Harmful effect on tooth enamel in presence of citric acid in product No data available for determination of POD

(H): based on human data (D): based on animal test data

Considering the pH values measured in the products, it is found that early harmful effects on tooth enamel can be described as originating at pH values below 5.5, whereas more severe corrosive effects on mucous membranes are considered possible at pH values ≤ 2 or pH ≥ 11.5.

No data are available on the impact of the oxidation potential on harmful effects, and therefore it was not possible to include this parameter in the risk assessment.

Exposure assessment

To assess the local effects in oral cavity (mucous membranes, gums, and teeth), the percentage of active substance content is considered to be the most relevant exposure parameter, as the effect assessment is based on this.

The basis for calculations of systemic exposure in mg/kg bw/day is the usage of the teeth-whitening product in one day of treatment and possible repetition of the treatment over several consecutive days, e.g., up to 14 days. The exposure was measured based on the amount of applied teeth-whitening product per day multiplied by the measured concentration of the active substance in the product. The applied amount of teeth-whitening product is estimated based on the packaging size and the user instruction of the product, where the most intense treatment is used as the basis of the calculation.

Furthermore, it is assumed that 100% of the content of the active teeth-whitening substance is absorbed unmodified in the body. This is a very conservative consideration, as the reactive substances to a great extent will react and break down in the oral cavity. In the exposure calculation, the body weight of a consumer is set to 60 kg, which is generally used for risk assessment of cosmetic products for adults. However, the value is also assessed to be valid for, e.g., 16 to 17-year-olds, who are considered to be the youngest users of teeth-whitening products.

Risk assessment

In the risk assessment, Margin of Safety values (MoS) have been calculated for the usage of each product:

MoS = POD (mg/kg bw/day or %) / exposure (mg/kg bw/day or %)

For systemic effects, the MoS values above 100 are considered to indicate a safe application if the POD value is based on animal tests, whereas a MoS value above 10 typically is adequate if POD is based on human data. For local effects (e.g., effects due to simple tissue irritation of the mucous membrane), a MoS value of 10 is considered appropriate.

Risk assessment of effects in oral cavity/teeth

For three products (two products consisting of a teeth tray and one product consisting of a pen) with a measured content/release of hydrogen peroxide of 1.9-10.8%, the calculated MoS values in the interval 0.19-1.1 indicate that the usage of these products may constitute a risk for the consumer in terms of increased tooth sensitivity and minor effects on mucous membranes and gums (irritation and inflammation symptoms).

For the remaining two products (both teeth tray products) with measured content/release of hydrogen peroxide of 0.04 and 0.09%, respectively, the calculated MoS values (12-50) are considered to be sufficient to show that the usage of these products is safe in terms of local effects.

For the two products with sodium chlorite (0.09 and 0.12%), the calculated MoS values (8-11) are considered very low, and therefore using these products is believed to constitute a risk to the consumer in terms of effects on mucous membranes and gums (irritation and inflammation symptoms). For the product with a declared sodium chlorite content of 1.0% (but where this content could not be measured) a MoS value of 1 was calculated indicating a risk of effects on the mucous membranes and gums when using the product if it contains 1.0% sodium chlorite.

Risk assessment of systemic effects

For two of the products (two products consisting of a teeth tray) with a content/release of hydrogen peroxide measured as 3.1% and 10.8%, the MoS values of 22 and 38, respectively,

were calculated. Products with such low MoS values (calculated on the basis of animal test data) are generally not considered safe. However, it is difficult to provide a more precise conclusion on the basis of insufficient knowledge about the actual systemic absorption of hydrogen peroxide, as it must be assumed that part of the hydrogen peroxide is degraded on surfaces and in saliva in oral cavity. For all other products with hydrogen peroxide within the interval of 0.09-1.9%, the calculated MoS values of 222-400 were considered high enough to assess that the products are safe to use.

For a product with the content of PAP of 0.33% (calculated on the basis of the amount of released hydrogen peroxide) and for two products with sodium chlorite, the MoS values for all products were calculated to above 100. Therefore, these products do not constitute a risk of systemic effects.

Risk assessment of pH

For 10 out of all 25 products, the pH value was measured below pH 5.5, and therefore the products may potentially damage the tooth enamel. It is complicated to qualify the risk degree of these products, but especially the products with the lowest and highest pH values can be considered to constitute a risk to the consumer.

Two products with a pH value of 0 and 11.5, respectively, can also be considered to constitute a risk of corrosion effect on mucous membranes.

Overall assessment

If the products with identified risks are assessed in relation to the country of origin of the distributors, the overview shown in TABLE 3 is achieved.

TABLE 3. Products with identified risk distributed on the country of origin of the distributor.

Distributor country of origin	Risk to tooth enamel or mucous membranes (incl. effects from pH) Product number	Number of tested products
Denmark	2, 3, 5, 6, 27, 32, 33	12
Other EU countries	8, 15, 30	6
Outside the EU	10, 12, 20, 22	7
In total	14	25

It should be mentioned that the products 12, 20 and 22 were the only products exceeding the legal threshold value of 0.1% content or release of hydrogen peroxide given in the Cosmetics Regulation.

Overall, the risk assessment indicates that teeth-whitening products with a content or release of the highest allowable hydrogen peroxide concentration of 0.1% can be seen as safe in relation to local and systemic effects. For products with a content or release of more than 0.1% hydrogen peroxide, it has been assessed that there is a risk of temporary discomfort consisting of irritation of the gums and increased tooth sensitivity. Products with sodium chlorite as an active substance (product 3, 8 and 15 with a content in the interval of 0.09-1.0%) can, even in low concentrations, constitute a risk of mucosal irritation. In combination with the assessment of the effects of sodium chlorite, an assessment of the content of citric acid should also be included. This is due to the fact that citric acid is usually added to achieve acidic pH, which activates sodium chlorite by the release of chlorine dioxide as whitening agent. Added citric acid can be problematic as the substance is known to destroy the enamel of the teeth. However,

there is no upper limit in the Cosmetics Regulation regarding the content of sodium chlorite or citric acid.

Finally, it was found that the pH value of several teeth-whitening products was so low that it must be considered to constitute a risk of destroying the enamel of the teeth or causing corrosion damage to mucous membranes. There are no general limits of the pH values in cosmetic products.

1. Introduction

1.1 Background

Private consumers can purchase teeth-whitening products for personal use, and many of these products contain or release hydrogen peroxide as an active substance to achieve a whitening effect on teeth. According to Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (hereinafter referred to as cosmetics regulation), hydrogen peroxide and other compounds or mixtures hereof that release hydrogen peroxide have been prohibited since 2012 in teeth-whitening products for personal use with substance content or release exceeding 0.1%.

In 2019, the Danish Consumer Council (*Forbrugerrådet TÆNK*) examined a range of over-the-counter teeth-whitening products for content and release of peroxides, where it was found that in seven out of 11 products purchased on online marketplaces such as amazon.com, lightinthebox.com and aliexpress.com contained or released more than 0.1% of hydrogen peroxide, and that two out of the seven products contained/released more than 6% hydrogen peroxide, which exceeds the threshold value for products used by dentists.[3] Nordic Council of Ministers have examined products purchased via the internet from European distributors, where the Danish Chemical Inspection Service contributed with an investigation of five teeth-whitening products. The results obtained in this project showed that all five products violated the legislation, and one of the products violated the European legislation on hydrogen peroxide (Nordic Council of Ministers, 2020).

The regulation of peroxides in teeth-whitening products has resulted in marketing of teeth-whitening products for personal use without hydrogen peroxide and other hydrogen peroxide-releasing substances. Currently, there is limited knowledge on those substances used in the products as an alternative to hydrogen peroxide as well as mode-of-action and safety in using these products. In all cases, the products are regulated by the requirements in the cosmetics regulation on documentation of claims made for the cosmetic products, i.e., that products must have documentation for their whitening effect claimed marketing, and the requirement that it must be safe to use cosmetic products.

1.2 Aim

The main aim of the project was to generate knowledge on teeth-whitening products that can be purchased for personal use. The project includes a survey of the market for teeth-whitening products in Denmark and abroad, as well as a survey on active substances with (assumed) whitening properties used in these products. The survey involved an analysis of products for content or release of hydrogen peroxide and other selected active substances. For products, where the country of origin of the distributor is Denmark, the labelling, registration in the European Commission's cosmetic database, the Cosmetic Product Notification Portal (CPNP), and documentation for their assumed whitening effect was reviewed. Finally, it was assessed whether the usage of teeth-whitening products for personal use pose a threat to consumers.

The project focused on teeth-whitening products for personal use in the sense that teeth-whitening products included in this project may be purchased in physical shops or on the internet for use at home.

[3] https://taenk.dk/test-og-forbrugerliv/sundhed-og-personlig-pleje/tandblegning-saadan-faar-du-hvidere-taender, accessed on May 4, 2020.

2. Market for teeth-whitening products

This section describes the market for teeth-whitening products for personal use and the prioritization of products for purchase and subsequent analysis.

2.1 Strategy and method

2.1.1 Market screening

The market screening was conducted with an aim to acquire knowledge of teeth-whitening products that can be purchased by the consumer for personal use, and of product usage and content of (assumed) active substances for teeth whitening. The market screening for teeth-whitening products for personal use focused on private usage, that is, products for professional use by or from dentists were not included in the screening.

The screening was conducted by searching for teeth-whitening products on popular webshops/online marketplaces and by using google.com. From there, specific products and information on teeth-whitening products was acquired from, among others, manufacturers' websites, online articles from the Danish Dental Association (*Tandlægeforeningen*) and other professional sources as well as online product reviews or blogs etc. from non-professional sources. Furthermore, knowledge about products on the market was also acquired from the literature and experts.

Information on active substances and their whitening properties and, in some cases, on their mode-of-action was collected through literature sources and interviews. The search on products on google.com and webshops/online marketplaces complemented the acquired knowledge even further to create a more complete overview of the following information for typical teeth-whitening products for personal use on the market:

- product types and their use
- (assumed) active whitening substances
- occurrence
- distributors
- target group

Information such as ingredient list and user instructions on webshops varies considerably and was included to the extent that it was available during the screening. Most often, ebay.com, amazon.com and, in particular, Danish webshops have indicated such information, whereas the foreign webshops such as lightinthebox.com and wish.com rarely include this information. In those cases, where specific products included in this project were found to be exposed and promoted by influencers, a note has been added to each product individually (Appendix 1).

Based on the market screening for teeth-whitening products for personal use mentioned above, the products were assigned to their respective product types, and their occurrence was estimated on a relative scale from 1-5, where 5 is the most frequent occurrence.

2.1.2 Product search and selection of products for analyses

The fundamental criterion for the selection of products for purchase and subsequent analysis was to represent specific teeth-whitening products, which the Danish consumer is expected to purchase from distributors in Denmark, other countries in the EU[4] and from other countries outside the EU. For Danish distributors, only products from webshops were selected; although it also was a requirement that of some of these Danish webshops also should have a physical branch. From abroad, products from webshops and online marketplaces were the target.

Specific teeth-whitening products for personal use were identified by searching via google.com in both Danish and English, and by searching directly on from the following distributors and online marketplaces:

- Danish distributors, as different types of shops are represented (retail, department stores, supermarkets, webshops with a wide and small range of products, etc.):
  - with physical shops: bilka.dk, fotex.dk, magasin.dk, matas.dk
  - sales from webshops alone: apropro.dk, apotekeren.dk, coolshop.dk, coop.dk, helsebixen.dk, and webapoteket.dk
- international online marketplaces:
  - amazon.com, wish.com, ebay.com, cdon.com, lightinthebox.com

By searching on the less expensive international marketplaces (e.g., wish.com and ligthinthebox.com), it was found that the majority of products was from distributors outside the EU, while distributors of products on ebay.com were divided between China and UK. However, it was found that products sold by distributors in UK were often the same as from the distributors in China. In order to include distributors from several countries, the filter ”eBay Europa” and ”US Only” was applied. cdon.com was included based on having many Danish and, in particular, Swedish distributors, as well as based on being well-known and frequently used by Danish consumers.

Based on the estimated occurrence, four proposals were developed for the distribution of product types and distributor country of origin (Denmark, other countries in the EU, or outside the EU), each with an individual list of specific teeth-whitening products for selection/purchase according to screening results. In the list, concrete products, including a link to the product on the webshop, were described regarding distributor and distributor’s country of origin, product type, price, assumed active substance, usage, and target group. If the active substance was indicated, it was included on the list. Alternatively, an assessment of the product’s ingredient list was performed, if available, and then the assumed active substance was registered. Furthermore, a promotion, if any, via influencers was indicated. The target group for the usage of products was described based on either the indication on the product, accompanying description or the assessment of possible pictures on the product itself or on webshop. The distributor’s country of origin was not indicated for products on the online marketplaces lightinthebox.com and wish.com, but based on experience and the low price and free shipping it was assumed that the products are sold by distributors outside the EU. The products from amazon.com from distributors in the US were included in the screening, as they were often found as relevant (first hits on google search). However, these were not among the specific products for purchase, as amazon.com could not deliver the respective products outside the USA on the time of selection and purchase of products for this project.

Proposals with different relevant combinations of specific products were created based on the screening results. The Danish Environmental Protection Agency and Danish Technological Institute jointly selected the mix of products and, from this, the specific products for purchase and analyses in this project. Thereafter, the selected teeth-whitening products from Danish distributors were procured by the Danish Chemical Inspection Service. Sold out or products unavailable due to other reasons were replaced by purchase of corresponding products.

[4] UK is considered as part of the EU/the European market in this connection.

2.2 Description of market for teeth-whitening products for personal use

Many different teeth-whitening products are marketed for personal use. They can be divided into one group of products based on ingredients that are able to whiten teeth chemically, and another group of products based on the mechanical polishing of teeth.

Products that mechanically polish teeth so they are whitened primarily occur as powders, pastes and pens, and they contain a polishing agent in the form of, for example, hydrated silica, perlite or aluminium oxide **(Epple et al., 2019)**. In particular, many powder and paste products with activated carbon as polishing agent, which are used as a treatment product for brushing teeth for a limited period of time, were identified. Furthermore, a few examples of mechanical teeth-polishing pens that can be used to scrub teeth, have been identified. The chemical teeth-whitening products were found as teeth-whitening trays, pens, strips, whitening toothpaste and mouthwash. It is estimated that there in general are just as many mechanically polishing as chemically whitening teeth-whitening products on the market. Furthermore, the products can be divided into daily care or hygiene products or products used for treatment in a limited timeframe.

TABLE 4 shows the different types of teeth-whitening products and a corresponding description of their application and occurrence.

TABLE 4. Teeth-whitening products on the market divided into product types.

Product type	Whitening effect	Estimated occurrence*	Short description of a typical application method	Recommended use
Teeth-whitening tray	Chemical	5	A gel/liquid with chemically whitening agent is placed in a teeth tray, which is then inserted on teeth. Some products require subsequent light treatment.	Temporary treatment
Teeth-whitening pen	Chemical	3	A gel/liquid with chemically whitening agent is brushed on teeth with a pen or brush with a container (as a marker) with the chemically whitening gel/liquid inside.	Temporary treatment
Teeth-whitening strips	Chemical	2	One-time-use polymer strips with gel with added chemically whitening agent. Strips are removed from the one-time-use package and placed on teeth.	Temporary treatment
Whitening toothpaste	Chemical /mechanical	3	Used as supplement for or instead of a conventional toothpaste at tooth brushing.	Daily care/hygiene or temporary treatment
Mouthwash	Chemical	1	Liquid must be gurgled after teeth brushing.	Daily care/hygiene
Teeth-whitening powder/ -paste	Mechanical	3	Powder or paste with polishing agent is put on toothbrush, and teeth are brushed.	Daily care/hygiene or temporary treatment
Teeth-polishing pen	Mechanical	1	Pen is brushed against the surface of teeth.	Daily care/hygiene or temporary treatment

* Occurrence is estimated on a scale from 1-5, where 5 is the product type with the highest estimated occurrence and 1 is the lowest estimated occurrence on the market in general.

The duration of treatment for teeth-whitening trays, pens and strips varies between 10 and 60 minutes, and the treatment is performed once or several times during a limited period of time until the desired result has been achieved. It is often indicated that a certain period of time must pass before a new treatment can be started again. Furthermore, it varies from product to product whether brushing of teeth is required or not before treatment, and whether one should rinse one's mouth after treatment.

Whitening toothpastes are available as mechanically whitening, chemically whitening and as combined mechanical and chemical whitening products. Additionally, products for two different types of usage were found: products for daily care/hygiene and other products for treatment in limited period of time.

The occurrence of product types, as shown in TABLE 4, is estimated for the entire market irrespective of how products were found. In this screening, no significant differences in the occurrence of different product types have been detected upon comparison of distributors in Denmark, other countries in the EU and outside the EU. Exceptions are, however, teeth-whitening strips, which were found to a considerably lesser extent outside the EU compared to in the EU and Denmark. Whitening toothpaste was found to a great extent by searching in Danish, but there were almost no hits when searching in English, unless a specific search was made on "*whitening toothpaste"*, i.e. product-specific searches. This may be related to language-specific terms, since toothpaste products exist, but do not occur by the same word searches, which find all other teeth-whitening products. Thus, it is expected that ordinary searches on teeth-whitening products outside Denmark will results in considerably few toothpaste products, while toothpaste products in Danish searches, as mentioned in methodology chapter, are the most popular teeth-whitening products. In addition, only a few mouthwash products with whitening effect were identified, and they were only identified from Danish distributors, which is most likely related to the choice of language terms in searches similar to toothpaste.

2.2.1 Active substances and their whitening properties

According to Ulla Pallesen, Senior Dentist, at Department of Odontology, University of Copenhagen the scientific literature does not agree on the precise definition of teeth-whitening. However, she informs that the following definition of teeth-whitening is most frequently used in literature: "The use of an oxidizing chemical to remove spots or discoloration from a tooth." Therefore, this definition of tooth-whitening is used in this report.

Discoloration of teeth can be divided into intrinsic or extrinsic discoloration. Intrinsic discoloration is discoloration inside the enamel or in the dentine, and it occurs during or after the formation of teeth. However, extrinsic discoloration is discoloration on the surface of the tooth, and it can arise from food and beverages or smoking. Intrinsic as well as extrinsic discoloration can be removed with teeth-whitening products (Epple et al., 2019).

Ulla Pallesen informs that teeth-whitening, from a professional point of view, consists of a chemical removal of the pigment in the dental tissue, where large coloured molecules are degraded or removed, whereas physical removal of coloured elements on the outer layer of the tooth (such as tooth-cleaning or toothbrushing) are not characterised as teeth whitening.

Four primary factors are crucial for the whitening effect (Pallesen, 2020):

- concentration of active substance

- treatment time
- depth of discoloration
- type of discoloration

Light and heat, which are a part of some treatments, have no documented permanent effect, but can cause teeth dehydration and, thus, make them seem lighter. However, teeth will rehydrate very fast, and the effect will be lost (Pallesen, 2020).

During the market screening for teeth-whitening products, a number of different substances known, claimed or assumed to have a chemical whitening effect on teeth were identified in products:

- hydrogen peroxide and hydrogen peroxide-forming substances, including carbamide peroxide and phthalimidoperoxycaproic acid (PAP)
- chlorite and chlorite-forming compounds (e.g., hypochlorite, hypochlorous acid and chlorine dioxide)
- sodium borate[5]
- sodium bicarbonate
- organic acids such as citric acid and inorganic acids such as phosphorus acid

Discoloration of teeth consists of large, coloured molecules. Hydrogen peroxide and peroxide-forming substances generate free radicals that oxidize or degrade these large molecules into smaller molecules, which lightens the colour of the teeth (Pallesen, 2020).

The chemical substances used in professional teeth whitening are hydrogen peroxide in a concentration of up to 6% and carbamide peroxide in a concentration of up to 18% (corresponding to 6% hydrogen peroxide). The latter substance is used because it is alkaline and, thus, gentler towards gums and possibly lightens the teeth faster. Teeth-whitening products for personal use may contain/release up to 0.1% hydrogen peroxide according to the cosmetics regulation, and during the market screening, a number of products were found stating specific content of peroxide. Two products stated a particularly high content of 44% peroxide and 44% carbamide peroxide in the products, which can both be purchased from distributors outside the EU. The hydrogen peroxide-forming substance sodium perborate is also used in professional teeth whitening; however, only for whitening of teeth with root treatment by whitening the inner side of the tooth (Pallesen, 2020).

Ulla Pallesen has met several patients, who have experienced gum damage from using teeth-whitening products for personal use with more than 3% of hydrogen peroxide, which the patients have ordered abroad. However, she has not encountered patients who have been injured from using teeth-whitening products with the hydrogen peroxide content of 0.1%. According to Ulla Pallesen, the whitening effect is not achieved from hydrogen peroxide content below 3% (Pallesen, 1993).

The market screening showed that the oxidizing substance phthalimidoperoxycaproic acid (PAP) is used in teeth-whitening products. Studies have shown that PAP has a whitening effect on teeth. PAP can release hydrogen peroxide, but it is described in scientific literature that PAP in itself is whitening. That means that the whitening effect is not mainly due to the released hydrogen peroxide (Bizhang et al., 2017; Møller et al., 2018). As an alternative to peroxides (non-peroxide products), sodium chlorite can be used for teeth whitening by dissolving organic coloured pigmentation that has penetrated the tooth (Greenwall-Cohen et al., 2019).

[5] Sodium perborate is according to cosmetics regulation (1223/2009) an illegal ingredient in cosmetic products.

Acids can have a teeth-whitening effect because of the corrosive effect on the tooth surface, which becomes porous, making the tooth optically seem lighter. Acids such as, e.g., citric acid, can be used as a preservative in teeth-whitening products for personal use. However, no literature or other documentation has been found that proves the whitening effect of these organic acids. Hydrochloric acid is used professionally for local removal of white/brown discolorations from mineralization disturbances in the surface of tooth enamel, which corresponds to removing the extreme layer of the tooth by polishing (Pallesen, 2020). Some professional clinic treatments can include corrosion using phosphorous acid before whitening, as phosphorous in high concentrations corrode the enamel so that teeth seem lighter immediately after whitening. The whiter effect of the acid will disappear after a few days after tooth brushing, when the surface is polished. However, acid corrosion causes irreversible loss of substance and is, thus, not recommended (teaching material, 2019).

2.3 Selection of products for purchase

The project focused on the analysis of teeth-whitening products for personal use with a chemical whitening effect. A mix of these products was selected for purchase and analysis based on the screening results, i.e. the occurrence and knowledge of product types and specific products as well as the criteria for selecting products as described in section 2.1 on strategy and methodology.

Initially, 25 products were prioritized for purchase/procurement. Since fewer products were received than expected, possibly due to delivery delays caused by the COVID-19 situation, ten additional products[6] were subsequently purchased/procured, i.e., 35 products were, in total, purchased/procured for the project.

During the search for specific products, it was observed that the European products were primarily found from British distributors via ebay.com and Swedish distributors via cdon.com, which is reflected in the purchase list. Furthermore, a considerably large number of the relevant teeth-whitening products were found outside the EU via amazon.com from distributors in USA. However, these products were not possible to include since delivery outside USA was not possible during the relevant time frame of the project. Therefore, distributors from USA were underrepresented in product purchases. Finally, a range of products did not have an indicated country of origin of the distributor. The online marketplaces lightinthebox.com and wish.com do not indicate the country of origin of the distributor, but according to experience and the fact that the products were relatively cheap and with free shipping, it was assumed that the country of origin of the distributors may be China, and, hence, the country of origin was considered to be outside the EU when selecting these products.

2.3.1 Prioritization of product types and products for analyses

It was decided to focus on teeth-whitening products for personal use for a time-limited treatment. Based on the occurrence of these products found in the screening, the product types: teeth-whitening trays, teeth-whitening pens and teeth-whitening strips were included. Mouthwash was found in such low numbers that they were deemed not relevant for inclusion in the product mix. Whitening toothpaste was greatly represented but has a very different usage pattern (daily care/hygiene) compared to the other products and, thus, presumably a markedly different purchase pattern among consumers. Thus, the whitening toothpaste was deselected from the analysis in this project.

[6] All ten products from Danish or European distributors to increase the chances of delivery within an acceptable time frame given the time constraints of the project.

Beside selecting products divided between product types according to the estimated occurrence as described in chapter 2.2 and shown in TABLE 4, the purchases are based on the division between products purchased from distributors in Denmark, other countries in the EU and outside the EU, where distributors outside Denmark, but from other EU countries are included to a lesser degree. This is related to the fact that the screening led to a clear expectation that the Danish consumer would primarily purchase products either from Danish distributors or distributors with a country of origin outside the EU, as primarily teeth-whitening products from here are identified in the search.[7] The division between product types and distributor country of origin is shown in TABLE 5, and specific products for purchase are shown in Appendix 1.

TABLE 5. Division of the number of product types for purchase/procurement according to distributor country of origin.

Distributor country of origin	In total	Pen	Strips	Trays
Total	**35**	**14**	**5**	**16**
Denmark	**15**	6	2	7
Other EU countries	**7**	3	1	3
Outside the EU	**13**	5	2	6

In addition to reflecting the prioritization of product types and the distributor country of origin, the selected products for purchase represent those specific products that appeared in searches, as described in the chapter on strategy and methodology (section 2.1) with limitations as described in chapter 2.3. Furthermore, those teeth-whitening products are included, which occur early in the searches, and which the consumer will see first and most often.

As mentioned in the methodology chapter (section 2.1), not all webshops indicate ingredient lists or active substances on their websites. ebay.com, amazon.com and especially Danish websites often indicate ingredients and usage, whereas other foreign online marketplaces such as lightinthebox.com and wish.com rarely indicate this information. According to the available information found in the market screening, it was found that a broad range of active substances is used, which is also reflected in the products selected for purchase without specifically focusing on including products with information on active substances or assessment in relation to assumed active substances.

[7] More products were purchased/procured from both Denmark and other EU countries than initially decided, because the ten additional products were selected from these countries due to the project time frame.

3. Exposure scenarios

This chapter describes the selection and assessment of exposure scenarios regarding the types of teeth-whitening products for personal use purchased/procured for analysis.

3.1 Method for exposure assessment

Exposure scenarios for teeth-whitening products are established with point of departure in the principles set out in the cosmetics regulation, and the guidelines indicated in applicable instructions and practice in the area.[8]

To conduct a risk analysis of the analysed teeth-whitening products, it is important to describe and assess the exposure of end-users to:

- which chemical substances the end-user is exposed to
- the concentration of the individual chemical substances
- the amount of the individual substances
- time per treatment
- number of treatments per day
- the duration of the treatment

From these data, which may be expected to vary significantly according to design, composition and use of the individual products, it is possible to calculate:

- the exposure to the individual substance available for systemic absorption in the body (using mg/kg bw/day).
- the exposure to the individual substance per surface unit in the exposed part of the oral cavity (in mg/cm^2) for the purpose of assessing the effect on the mucous membrane and the oral cavity. Another indication for the exposure of the mucous membrane surface is the concentration in the product indicated as either "%" or as "mg (substance) / g (product)" as this form of exposure unit is as frequently used as mg/cm^2 in the toxicological literature.

In 2017, the EU Scientific Committee on Consumer Products assessed hydrogen peroxide in teeth-whitening products and found that the exposure can vary from product to product and that the exposure assessment, therefore, should be based on data concerning the individual teeth-whitening product, its design and its use pattern including the actual content of active substances in the product (SCCP 2007).

In the section below, general considerations on estimation of the exposure for the different types of teeth-whitening products are described.

As the exposure assessment is based on the use of the products by private consumers (and not related to a dentist's use in a clinic), the exposure assessments are made from a worst-case perspective for the usage of the product. For instance, it is assumed that the gums and

[8] "The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation", last updated in 2018, and SSCP´s assessment of tooth whitening products "SCCP opinion on hydrogen peroxide, in its free form or when released, in oral hygiene products and tooth whitening products", 2007 (NB: SCCP is now called SCCS).

not only the teeth will be exposed during application. The assessment also takes into consideration intensive usage of the products with regard to the amount of product applied, duration and frequency of the applications.

3.2 Target group

In 2007, the EU Scientific Committee on Consumer Products "SCCP" made a detailed risk assessment of hydrogen peroxide in teeth-whitening products (SCCP 2007). The assessment only focused on the use of teeth-whitening products by adults, as no specific data for the assessment of risk by use of the products by adolescents and children was available.

On this basis, the exposure and risk assessment in this present report is primarily targeted at the adult consumer, but it is also considered to cover the possible of the products by adolescents. The target group, therefore, also includes any particularly sensitive groups such as pregnant women.

3.3 Tray with teeth-whitening agent

These products consist of a gel/fluid with chemical whitening agent that is either placed in a disposable tray in advance or delivered in syringes that the consumer uses to dose the gel in the tray. The recommended time per treatment for these products is stated to be 7-45 minutes per application and up to 14 consecutive days. It is assumed that by using trays, the consumer uses trays for both the upper and lower teeth. Since these trays are not adjusted to the dentition of the individual consumer, it is estimated that both teeth and gums are in direct contact with the teeth-whitening gel on the tray.

The exposure per day should be calculated according to body weight and the exposed surface.

Exposure according to body weight:

$$Exposure\ (g\ gel/kg\ bw/day) = \frac{amount\ of\ gel\ in\ a\ tray\ (g)}{body\ weight\ (kg)}\ x\ \textit{number of trays per day}$$

If the body weight of a consumer is set to 60 kg (used in the assessment in SCCP (2007) and recommended by SCCS (2018)), the following applies:

$$Exposure\ (g\ gel/kg\ bw/day) = \frac{amount\ of\ gel\ in\ a\ tray\ (g)}{60\ kg}\ \ x\ \ number\ of\ trays\ per\ day$$

Thereby, the exposure to the individual substances indicated in mg substance/kg bw/day can be calculated by multiplying the concentration of the substance in the gel (mg ingredient / g gel) in the equation:

$$Exposure(mg\ substance/kg\ bw/day) = g\ gel/kg\ bw/day)\ x\ conc.(mg\ substance/\ g\ gel)$$

This exposure is an indication of the total exposure, meaning both the amount of gel that stays in the oral cavity and the amount of gel that is dissolved in the saliva and swallowed during the application. SCCP (2007) indicates in this connection that between 10 and 25% of the gel is estimated to be swallowed during application.

Exposure per surface area:

$$Exposure\ (g\ gel/cm^2)\ = \frac{amount\ of\ gel\ \ (g)\ in\ the\ tray}{tray\ surface\ area\ (cm^2)}$$

Thereby, the exposure to the individual substances indicated in mg/cm^2 can be calculated by multiplying the concentration of the substance (mg substance / g gel):

$$Exposure\ (mg/cm^2) = Exposure\ (g\ gel/cm^2)\ \ x\ \ conc.\ (mg\ substance\ g\ gel)$$

As previously mentioned, the local exposure should be indicated as the ingredient concentration in the product either as % or mg/g gel.

Required data for the exposure assessment

Meaning that the calculation for the consumer exposure requires the following information:

- the amount of gel (g) in the tray (estimated from the included instructions)
- the concentration of active substance in the gel (findings of analysis in mg/g gel or w/w%)
- surface area (cm^2) of tray contact area (measurement of tray)

3.4 Strips with teeth-whitening agent

Teeth-whitening strips are single-use polymer strips with an added gel that contains chemical whitener. The product typically consists of two strips that are applied on the upper and lower teeth. The indicated treatment time is typically 30 minutes per treatment when used daily for 14 days. Even though the strip is designed to be applied to the teeth, it is also in direct contact with the gums between the teeth. Finally, it is also found likely that the layer of teeth whitening agent is dissolved and can flow into the oral cavity, where it can come into contact with the mucous membrane of the oral cavity or be swallowed. SCCP (2007) furthermore states that the entirety of the strip can in some cases be swallowed by the consumer.

Therefore, the exposure scenario bears considerable resemblance to the exposure scenario for the teeth tray products mentioned above, and the equation stated above will also be applicable for the calculation for the exposure of teeth-whitening products and their ingredients from strips.

Required data for the exposure assessment

- the amount of gel (g) on the strip (estimated from a weighing of the strip/gel)
- the concentration of active substance in the gel (findings of analysis in mg/g gel or w/w%)
- surface area (cm^2) of the strip (measurement of strip)

3.5 Pen with teeth-whitening agent

These products consist of a container with a gel/fluid containing chemical whitening agent that is applied to the teeth by means of a pen or brush attached on the container. For the products in mention, the typical number of applications is indicated as 1-2 times per day with a duration 10-30 minutes for up to 20 days. The teeth-whitening products are applied exclusively on the teeth, but it cannot be dismissed that the gum is accidentally touched with the pen during application. As the product is not dosed in advance according to a specific contact surface (which is the case for trays and strips), it can be difficult to ascertain the amount of teeth whitening gel/fluid used per application. The product can furthermore be applied more specifically to individual teeth, whereas trays are typically applied to several teeth simultaneously.

It is assumed from a worst-case perspective that several upper and lower teeth are treated during application, meaning that, as a basis, this exposure assessment relies on the same exposure surface as used for trays/strips. The worst-case scenario considers the total amount of the substances available for systemic absorption as it cannot be dismissed that the consumer may accidentally swallow the total amount of the applied gel immediately after application.

Required data for the exposure assessment

The following conditions/parameters are relevant for the assessment of the exposure from the pens:

- the amount of tooth-whitening gel or fluid in the pen (indicated on the container)
- information on the number of treatments included in the pen (data from the user instructions)
- frequency and duration of treatments per day (data from user instructions)
- the amount of tooth-whitening gel or fluid smeared per cm^2 (weighing in laboratory of amount of smear per cm^2)
- treatment area (as a worst case, the same area applicable for trays/strips is assessed)
- the concentration of active substance in the gel/fluid (analysis findings in mg/g gel, or w/w%)

4. Analysis of purchased teeth-whitening products

This chapter describes the process of analysing teeth-whitening products purchased for this project, including review of product declaration. Furthermore, chemical analyses have been performed with an aim to determine substances with whitening effect. Physico-chemical properties of products have also been analysed.

4.1 Analysed products

By purchase of teeth-whitening products, the delivery was found to be too long for a number of products, and some products were not delivered within the time frame the execution of the project. In this project it has been possible to include analyses of 25 teeth-whitening products. The delivery time has had an impact on the division of the analysed products in relation to product type and country of origin of distributors. The latter has been divided into three categories: Denmark, other EU countries and countries outside the EU. The division of in total 25 analysed products into three categories is illustrated in FIGURE 1 with an additional indication of the three product types: pens, strips, and trays.

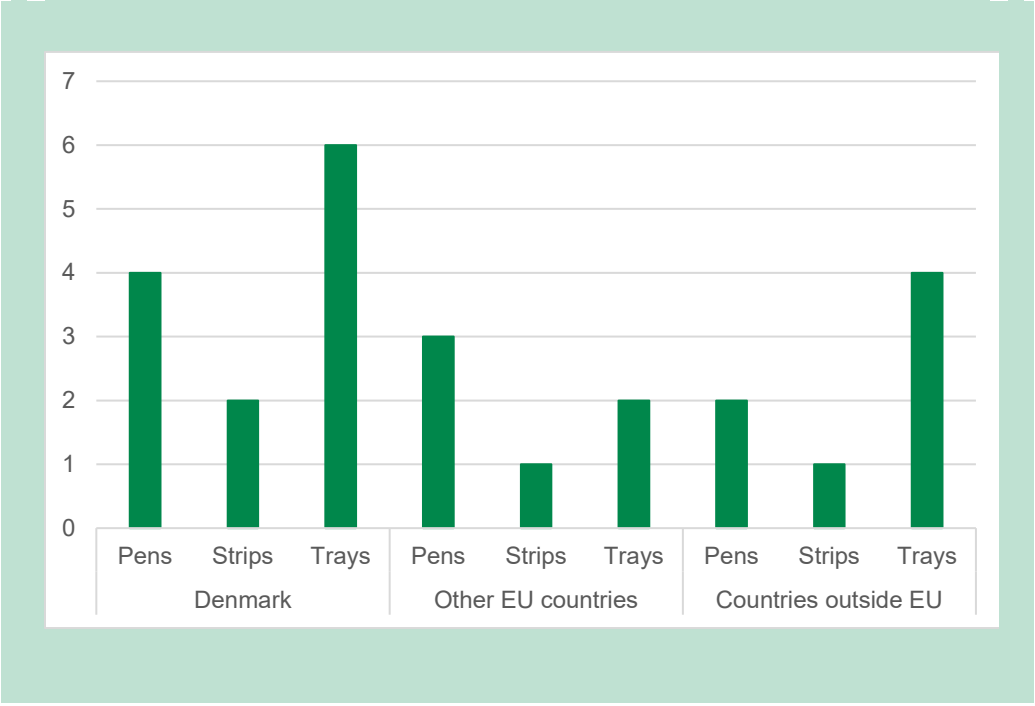

FIGURE 1. Division of analysed products in relation to distributors' country of origin and product type.

4.2 Product declarations

4.2.1 Legal conditions

Teeth-whitening products are legally defined as cosmetic products, and, thus, they must comply with the cosmetics legislation. The cosmetics regulation is the main legislation in cosmetics industry. It lists some substances that are forbidden to use in cosmetics (Annex II), as well as

some substances that are subject to limitations (Annex III). In Annex III, ref. no. 12 of the regulation hydrogen peroxide, and other compounds or mixtures that release hydrogen peroxide, (except ref. no. 1397, 1398 and 1399 of Annex II) appears. The concentration level of hydrogen peroxide (present or released) depends on the specific product type. In case of teeth-whitening products, the highest concentration allowed in the ready-to-use product is 0.1% in products for personal use, while it can be up to 6% in teeth-whitening products sold only to dentists.

In addition, the teeth-whitening products must comply with all other requirements stated in the cosmetics regulation as is valid for all other cosmetic products. It is also stated that a product must be safe in general according to chapter 3 in the cosmetics regulation, which is stated as follows:

"A cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use".

The following sections will focus on the review of selected teeth-whitening products based on the product ingredient list, as it is assessed from the ingredient list on product packaging whether the product complies with the requirements in the cosmetics regulation regarding usage or ban of substances in cosmetics.

4.2.2 Review of declaration of ingredients on selected products

In TABLE 6 below, the selected teeth-whitening products are described, and the ingredient lists have been included as they are given on the product packaging (i.e., incl. possible spelling and print errors). Then, the indicated substances have been checked according to the European Commission's cosmetic ingredient database (CosIng), where possible special requirements applying to each ingredient in the cosmetics regulation have been indicated. These requirements have been indicated in an additional column. To ensure the readability of this table, the exact same chemical name has been used as given in the ingredient list.

TABLE 6. Teeth-whitening product ingredient list and relevant application limitations for stated substances.

Distributor country of origin	Product type	Product No.	Declaration	Comments Limitations for use of substances, cosmetics regulation*
Denmark	Pen	1	Dimethicone, Petrolatum, PVP, Trimethylsiloxysilicate/ Dimethiconol Crosspolymer, Pentasodium Triphosphate, Silica, Aroma, Sodium Saccharin, Hydrogen Peroxide, Eugenol	*Hydrogen Peroxide* Annex III, ref. no.12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released
Denmark	Tray	2	GLYCERIN, PROPYLENE GLYCOL, CARBOMER, POTASSIUM ACESUFAME, MICA, TRIETHANOLAMINE, MENTHOL, SODIUM CARBONATE PEROXIDE, CI 77891	*TRIETHANOLAMINE* Annex III, ref. no. 62 Highest concentration in ready-to-use products, not rinse-off: 2.5% *SODIUM CARBONATE PEROXIDE* Annex III, ref. no.12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released
Denmark	Tray	3	Propylene Glycol, Glycerine, Aqua, Sodium Bicarbonate, Carbomer, Cellulose Gum, Triethanolamine, PVP, Menthol, Mica, Hydrogen Peroxide, CI 77891	*Triethanolamine* Annex III, ref. no. 62 Highest concentration in ready-to-use products, not rinse-off: 2.5% *Hydrogen Peroxide* Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released
Denmark	Tray	4	Sodium bicarbonate, Pomegranate Seed Extract, Chamomile Flower Extract, Aloe Leaf Juice, Carbomer, Deionized water, Propylene glycol, Glycerol, Carboxymethylcellulose sodium, Polyvinylpyrrolidone, Menthol	No limitations

Distributor country of origin	Product type	Product No.	Declaration	Comments Limitations for use of substances, cosmetics regulation*
Denmark	Strips	5	Glycerine, PVP, Ethyl cellulose, Phthalimidoperoxycaproic acid, Alcohol, Hydrated silica, Dicalcium phosphate, Disodium EDTA, Sodium hydroxide, Menthol	*Phthalimidoperoxycaproic acid* Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released. *Sodium hydroxide* Annex III, ref. no. 15a: pH <11 in the ready-to-use product
Denmark	Pen	6	Glycerine, non-peroxide, carbomer, pebermynte-olie, triethanolamine	*Triethanolamine* Annex III, ref. no. 62 Highest concentration in ready-to-use products: 2.5%
Denmark	Pen	7	AQUA, SODIUM CARBONATE, SODIUM BORATE, LIGUSTICUM CHUANXIONG EXTRACT, ASTRAGALUS COMPLANATUS EXTRACT, MENTHOL, THYMOL, DISODIUM EDTA, ALCOHOL, SODIUM HBENZO-ATENIACINAMIDEPENOXYETHANOL, CHLORPHENESIN, PARFUME	*SODIUM HBENZOATENIACINAMIDEPENOXY-ETHANOL* substance does not exist, most likely a faulty combination of the three substances: so-dium benzoate, niacinamide, phenoxyethanol. *SODIUM BORATE* Annex II, ref. no. 1396 **Forbidden to use in cosmetic products.** *SODIUM BENZOATE* Annex V, ref. no. 1 Highest concentration in ready-to-use products: 1.7% (acid)

Distributor country of origin	Product type	Product No.	Declaration	Comments Limitations for use of substances, cosmetics regulation*
				PHENOXYETHANOL Annex V, ref. no. 29 Highest concentration in ready-to-use products: 1.0% *CHLORPHENESIN* Annex V, ref. no. 50 Highest concentration in ready-to-use products: 0.3%
Denmark	Tray	14	WHITENING GEL INGREDIENTS: Glycerine, Propylene Glycol, Acrylated/C10-30 Alyl Acrylate Crosspolymer, Triethanolamine, Sodium Saccharin, Mica, Mentha Piperita (Peppermint) Oil, Sodium Carbonate Peroxide (Sodium Percarbonate), CI 77891 ---------- ACCELERATOR SPRAY INGREDIENTS: Aqua, Glycerine, Alcohol, Aroma, Poloxamer 188, Sucralose, Poloxamer 407, Sodium Lauryl Sulphate, Sodium Citrate, Caffeine, L-Menthol, Polysorbate 20, Sodium Benzoate, C10-16 Alcohols, CI 42090	*Triethanolamine* Highest concentration in ready-to-use products not rinse-off: 2.5% *Sodium Carbonate Peroxide* Annex III, ref. no. 12 max. release of 0.1% H_2O_2 ---------- *Sodium Benzoate* Annex V, ref. no. 1 Highest concentration in ready-to-use products: 1.7% (acid)
Denmark	Strips	27	PVP, Glycerine, Water, Polysorbate-80, Flavour, Citric Acid, Maltodextrin, Cellacefate	*Cellacefate = cellulose acetate phthalate* No limitations
Denmark	Tray	32	Glycerine, Sodium Bicarbonate, Mentha Piperita Oil, Sodium Coco-Sulphate, Xylitol, Chondrus Crispus Powder, Sorbitol, Aloe Barbadensis Leaf Juice, Punica Granatum Extract, Sodium Fluoride, Chamomilla Recutita Extract, Limonene, Linalool, Hydrogen Peroxide	*Sodium Fluoride* Annex III, ref. no. 31 Highest concentration in ready-to-use products: 0.15% (as fluor)

Distributor country of origin	Product type	Product No.	Declaration	Comments Limitations for use of substances, cosmetics regulation*
				Hydrogen Peroxide Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released
Denmark	Pen	33	Glycerine, Carbomer, 1,2-Propanediol, Sodium perborate (0.35%), Menthol, Saccharin Sodium	*Sodium perborate* Annex II, ref. no. 1397 **Forbidden to use in cosmetic products.**
Denmark	Tray	35	Aqua (Water), Glycerine, Poloxamer 188, Sodium Benzoate, Mentha Avensis (Peppermint) Leaf Oil, Potassium Sorbate, Sodium Saccharin, Phytic Acid, Limonene, BHT, CI 42090 (Blue No1)	*Sodium Benzoate* Annex V, ref. no. 1 Highest concentration in ready-to-use products: 1.7% (acid) *Potassium Sorbate* Annex V, ref. no. 4 Highest concentration in ready-to-use products: 0.6% (acid)
Other EU countries	Strips	8	Glycerine 68.10% Aqua 20.00% Cellulose Gum 10.00% Sodium Chlorite 1.00% EDTA 0.50% Citric Acid 0.20% D. L-Menthol 0.20%	No limitations
Other EU countries	Tray	15	Propylene glycol, Glycerol, Aqua, Carbomer, Carboxymethyl, Triethanolamine, Polyvinylpyrrolidone, Menthol, Sodium Percarbonate	*Triethanolamine* Annex III, ref. no. 62 Highest concentration in ready-to-use products not rinse-off: 2.5%

Distributor country of origin	Product type	Product No.	Declaration	Comments Limitations for use of substances, cosmetics regulation*
				Sodium Percarbonate Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released.
Other EU countries	Pen	16	Glycerine, Propylene Glycol, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Triethanolamine, Sodium Saccharin, Mica, Mentha Piperita (Peppermint) Oil, Sodium Carbonate Peroxide (Sodium Percarbonate), CI 77891	*CI77891 = titanium dioxide* *MICA= silicate minerals* *Triethanolamine* Annex III, ref. no. 62 Highest concentration in ready-to-use products not rinse-off: 2.5% *Sodium Carbonate Peroxide* Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released.
Other EU countries	Pen	28	Glycerine, Propylene Glycol, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Triethanolamine, Sodium Saccharin, Mica, Mentha Piperita (Peppermint) Oil, Sodium Carbonate Peroxide (Sodium Percarbonate) CI 77891	*CI77891 = titanium dioxide* MICA= *silicate minerals* *Triethanolamine* Annex III, ref. no. 62 Highest concentration in ready-to-use products not rinse-off: 2.5% *Sodium Carbonate Peroxide* Annex III, ref. no. 12

Distributor country of origin	Product type	Product No.	Declaration	Comments Limitations for use of substances, cosmetics regulation*
				Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released.
Other EU countries	Tray	29	No declaration	No declaration on the product.
Other EU countries	Pen	30	Water, Hydroxyethylcellulose, Glycerine, Sorbitol, Peg-40 Hydrogenated Castor Oil, Sodium Benzoeate, Menthol, Disodium Edta, Xylitol, Sucralose, Flavour, Citric Acid, Mentha Arvensis Leaf Extract	*Sodium benzoate* Annex V, ref. no. 1 Highest concentration in ready-to-use products: 1.7% (acid)
Outside the EU	Pen	10	WATER, ALCOHOL, MAGNOLIA, ASARUM, ANGELICA DAHURICA, GLEDITSIAE, SINENSIS FRUCTUS, THYME, BORAX, MENTHOL	*BORAX* Annex II, ref. no. 1396 **Forbidden to use in cosmetic products.**
Outside the EU	Tray	12	Propylene Glycol, Kosher Glycerine, Hydrogen Peroxide, Carbomer, Peppermint Essential Oil, Triethanolamine	*Triethanolamine* Annex III, ref. no. 62 Highest concentration in ready-to-use products not rinse-off: 2.5% *Hydrogen peroxide* Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released.
Outside the EU	Tray	20	Deionized Water, Peroxide, Glycerine, Potassium Sorbate, EDTA, Polysorbate 20, Triethanolamine, Carbomer, Flavour	*Peroxide* (it is assumed that there is hydrogen peroxide content or that it is released) Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released. *Potassium Sorbate*

Distributor country of origin	Product type	Product No.	Declaration	Comments Limitations for use of substances, cosmetics regulation*
				Annex V, ref. no. 4 Highest concentration in ready-to-use products: 0.6% (acid) *Triethanolamine* Annex III, ref. no. 62 Highest concentration in ready-to-use products not rinse-off: 2.5%
Outside the EU	Tray	21	Glycerine. Aqua. Povidone. Silica. Sodium Hydroxide. Natural Flavour. Sodium Saccharin. K12. Sorbitol. EDTA	*K12: used as abbreviation for* sodium lauryl sulfate (natriumlaurylsulfat) *Sodium hydroxide* Annex III, ref. no. 15a pH < 11 in the ready-to-use product
Outside the EU	Pen	22	Purified water, Hydrogen peroxide, Denatured alcohol, Polyvinyl pyrrolidone, Polyethylene glycol	*Hydrogen peroxide* Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released.
Outside the EU	Tray	24	Phthalimidoperoxycaproic Acid (PAP), Sorbitol, Glycerine, Water, Polyethylene Glycol-8, Propylene Glycol, Flavour, Hydroxuapatite, Sodium Hydroxide, Sodium Carboxymethyl Cellulose, Potassium Nitrate, Xanthan Gum, Hydroxyethyl Cellulose, Saccharin Sodium, Sodium Methylparaben, Aloe Barbadensis Leaf Extract (Aloe Vera), Chamomilla Recutita Flower Extract (Chamomile), Punica Granatum Seed Extract (Pomegranate)	*Phthalimidoperoxycaproic Acid* Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released. *Sodium Hydroxide* Annex III, ref. no. 15a pH < 11 in the ready-to-use product

Distributor country of origin	Product type	Product No.	Declaration	Comments Limitations for use of substances, cosmetics regulation*
				Sodium Methylparaben Annex V, ref. no. 12 Highest concentration in ready-to-use products: 0.4% (acid) for an ester, 0.8% (acids) for ester compounds.
Outside the EU	Strips	25	Aqua, Glycerine, Propylene Glycol, Cellulose Gum, Hydroxyethyl Cellulose, Silica, Phthalimidoperoxycaproic Acid, Dicalcium Phosphate, carbomer, Disodium EDTA, sodium hydroxide, Menthol	*Phthalimidoperoxycaproic Acid* Annex III, ref. no. 12 Highest concentration in ready-to-use products: 0.1% H_2O_2, present or released. *Sodium Hydroxide* Annex III, ref. no. 15a pH < 11 in the ready-to-use product.

* **Bold text** indicates deviations from limitations stated in cosmetics regulation

The table shows that there is a range of substances that are bound to restrictions in the cosmetics regulation. TABLE 7 below shows a list of these substances with registration of the product types in which they are identified and where the products have been purchased.

Also, the table shows that product 27 (strips from Denmark) and product 4 (teeth tray from Denmark) do not have stated ingredients with substances which are bound to restrictions. Note that the declarations for product 16 and product 28 are identical.

TABLE 7. Overview of regulated substances, the specific restrictions and their occurrence in products.

Declared substances (most frequent listed first)	**Restrictions, cosmetics regulation**	**Products covered**
Oxidizing whitening agents		
Hydrogen peroxide	Annex III, ref. no. 12 Highest concentration in ready-to-use product: 0.1% H_2O_2, present or released	DK: 3T, 32T, 1P Other EU countries: - Outside the EU: 12T, 22P Five products in total
Sodium percarbonate	Annex III, ref. no. 12 Highest concentration in ready-to-use product: 0.1% H_2O_2, present or released	DK: 2T, 14T Other EU countries: 16P, 15T, 28P Outside the EU: Five products in total
Phthalimidoperoxycaproic acid (PAP)	Annex III, ref. no. 12 Highest concentration in ready-to-use product: 0.1% H_2O_2, present or released	DK: 5S Other EU countries: - Outside the EU: 21S Two products in total
Peroxide (i.e., substance is not clearly indicated)	Annex III, ref. no. 12 Highest concentration in ready-to-use product: 0.1% H_2O_2, present or released	DK: - Other EU countries: - Outside the EU: 20S One product in total
Sodium perborate	Annex II, ref. no. 1397 Forbidden to use in cosmetic products	DK: 33P Other EU countries:- Outside the EU: - One product in total
Other substances		
Triethanolamine	Annex III, ref. no. 62 Highest concentration in ready-to-use product, not rinse-off: 2.5%	DK: 3T, 6P, 2T, 14T Other EU countries: 16P, 15T Outside the EU: 12T, 20T Eight products in total
Sodium hydroxide	Annex III, ref. no. 15a pH < 11 in the ready-to-use products	DK: 5S Other EU countries: - Outside the EU: 21T, 25S, 24T Four products in total
Sodium benzoate	Annex V, ref. no. 1 Highest concentration in ready-to-use product: 1.7% (acid)	DK:35T, 7P, 14T Other EU countries: 30P Outside the EU: - Five products in total
Sodium borate (borax)	Annex II, ref. no. 1396: Forbidden to use in cosmetic products	DK: 7P Other EU countries: - Outside the EU: 10P Two products in total
Potassium sorbate	Annex V, ref. no. 4	DK: 35T Other EU countries: -

Declared substances (most frequent listed first)	Restrictions, cosmetics regulation	Products covered
	Highest concentration in ready-to-use product: 0.6% (acid)	Outside the EU: 20T Two products in total
Sodium methyl parahydroxybenzoate	Annex V, ref. no. 12 Highest concentration in ready-to-use product: 0.4% (as acid) for an ester, 0.8% (as acid) for ester compounds	DK: - Other EU countries: - Outside the EU: 24T One product in total
Sodium fluoride	Annex III, ref. no. 31 Highest concentration in ready-to-use product: 0.15% (calculated as fluor)	DK: 32T Other EU countries: - Outside the EU: - One product in total
Chlorphenesin*	Annex V, ref. no. 50 Highest concentration in ready-to-use product: 0.3%	DK: 7P Other EU countries: - Outside the EU: - One product in total

* occurs only in product 7P, which already contains sodium borate
T: Tray
S: Strips
P: Pen

According to the table above, 14 products contain hydrogen peroxide or substances that can release hydrogen peroxide, out of which one of the products contains sodium perborate, which is forbidden.

Among other oxidization agents, as shown in the table, sodium chlorite can also be mentioned here, which is a substance in product 8 (strips purchased in the EU), but no restrictions have been mentioned in the cosmetics regulation for this substance.

Furthermore, it can be seen that triethanolamine is the substance occurring most often in products (in total eight products). According to the CosIng database, this substance is used both as a surface-active cleaning substance and as a buffer, i.e., regulation of pH in the product.

4.2.3 Review according to regulatory requirements

The 12 products in this project with Denmark as the distributor's country of origin were reviewed to analyse whether these products comply with specific requirements in the legislation of cosmetic products. For these products, it was reviewed whether the product has been registered in the cosmetic database CPNP of the European Commission, whether the effect claimed for the product is documented and whether labelling on the packaging include the required information.[9]

In Article 13 of the Cosmetics Regulation, it is stated that all cosmetic products must be notified to the European Commission before the product is placed on the market. The notification must be submitted electronically by the responsible person to the European Commission's cosmetic database, CPNP. The information to be submitted to the Commission is described in

[9] Review has been carried out and described by the Danish Environmental Protection Agency, except the review of the declaration.

Article 13, paragraph 1. Furthermore, the same article, paragraph 2 describes additional actions required to be performed by the responsible person when the product is placed on the market. In paragraph 5 of the same article the information that the Commission must make accessible for the competent authorities is mentioned. In this project, it was found that 4 out of 12 reviewed products are not registered in the database.

Article 11 in the Cosmetics Regulation describes that for every cosmetic product, a product information file must be kept. Specific information and data are required to be included in the product information file. In Article 11, paragraph 2, point (d), it is stated that, where justified by the nature or the effect of the cosmetic product, the product information file must provide proof of the effect claimed for the cosmetic product. Upon the request of the Danish Environmental Protection Agency's control unit, the Chemical Inspection Service, the responsible person must be able to submit documentation that includes this proof. Afterwards, it is decided whether the documentation adequately can prove the effect claimed for the specific product.

For products included in this project with Denmark as the distributor's country of origin, the Chemical Inspection Service have requested the distributor to submit the above-mentioned documentation. Documentation was not submitted for 6 out of 12 products. Thus, the documentation can only be reviewed for the remaining six products. Documentation for 4 out of these 6 products was determined to be adequate in connection to proving the claimed effect of the product, while documentation for two of the products was not sufficient.

The container/packaging of a cosmetic product must bear specific information according to the requirements stated in Article 19 of the Cosmetics Regulation. In Article 19, paragraph 5 in the cosmetics regulation, it is stated that the language of the information mentioned in Article 19, paragraph 1, points (b), (c), (d), and (f) shall be determined by the law in the individual member states. In the Order on Cosmetic Products no. 803 of 21 June 2013 on cosmetic products (kosmetikbekendtgørelsen), which is in force in Denmark, it is stated that information in the mentioned points must be provided in Danish. Information that must be provided in Danish is as follows: Nominal content, date of minimum durability, particular precautions as well as the function of the cosmetic product.

For some of the information in Article 19, paragraph 1 certain exceptions exist, e.g., the nominal content must not be indicated on packaging with a content of less than 5 g or 5 ml. Also, the function of the cosmetic product must only be indicated explicitly if it is not clear from the presentation of the product. In practice, this means that should an average consumer be in doubt about the function of the product based on the product packaging, then the function must be written on the packaging in Danish.

The packaging of the 12 products have been reviewed for the required labelling information. The observations obtained in the review are shown in TABLE 8 and TABLE 9.

TABLE 8. Observations obtained in the review of labelling information in packaging for 12 products with Denmark as the country of origin for the distributors.

Required labelling information	Reference to legislation	Observations	Product No.
(Company) name and address of responsible person	CR[1] Article 19, paragraph 1, point (a)	No information provided	6, 27
Country of origin	CR[1] Article 19, paragraph 1, point (a)	No information provided	27

Required labelling information	Reference to legislation	Observations	Product No.
Date of minimum durability	CR[1] Article 19, paragraph 1, point (c) and KB[2]	No information provided	6
Particular precautions	CR[1] Article 19, paragraph 1, point (d) and KB[2]	Information is either missing or not provided in Danish	2, 7, 27, 33, 35
Batch number	CR[1] Article 19, paragraph 1, point (e)	No information provided	4, 6, 27, 35
Function	CR[1] Article 19, paragraph 1, point (f) and KB[2]	Information is either not provided in Danish or is not included in the product presentation	1, 7, 14, 27, 33, 35

[1] CR: Cosmetics regulation
[2] KB: The Order on Cosmetic Products (Kosmetikbekendtgørelsen)

The nominal content is the only labelling information with no observations, i.e., information has been indicated on the packaging for all 12 products. The requirement for this labelling information is stated in Article 19, paragraph 1, point (b) in the Cosmetics Regulation, and this is one of the labelling information that, according to the Order on Cosmetic Products, must be provided in Danish.

In Article 19, paragraph 1, point (g) in the Cosmetics Regulation, it is stated that the labelling on cosmetic products must contain a list of ingredients. A range of requirements exist for the list of ingredients, among others, that the list must be introduced with the word ”ingredients”.

In Article 19, paragraph 6, it is stated that information mentioned in paragraph 1, point g) must be expressed by using the common ingredient name set out in the glossary provided in Article 33. In the absence of a common ingredient name, a term as contained in a generally accepted nomenclature is to be used.

In Article 33, it is mentioned that the Commission must compile and update a glossary of common ingredient names. In this connection, the Commission shall take account of internationally recognized nomenclatures, including the International Nomenclature of Cosmetic Ingredients (INCI).

TABLE 9 shows the declarations for the 12 teeth-whitening products with Denmark as the country of origin of the distributors. Declarations have been added in the table as they are written on the products, i.e., with possible spelling errors, etc.

It has been reviewed whether the ingredient descriptions on each product have been indicated according to the glossary of common ingredient names, and whether the declaration starts with the word ”ingredients”.[10]

[10] Applied version of the glossary of common ingredient names: COMMISSION DECISION (EU) 2019/701 of April 5, 2019 establishing a glossary of common ingredient names for use in the labelling of cosmetic products.

In those cases, where deviations from the glossary of common ingredient names have been observed, the ingredient has been marked in italics, and the observation has been included in the column ”Observations”.

As it is shown in the table, nine out of 12 examined products have one or several deviations in relation to the regulatory requirements.

TABLE 9. Observations after examination of declarations for 12 products with Denmark as the country of origin of the distributors.

Product type	Product No.	Declaration	Observations
Pen	1	INGREDIENTS: Dimethicone, Petrolatum, PVP, Trimethylsiloxysilicate/ Dimethiconol Crosspolymer, Pentasodium Triphosphate, Silica, Aroma, Sodium Saccharin, Hydrogen Peroxide, Eugenol	No observations
Tray	2	INGREDIENTS: GLYCERIN, PROPYLENE GLYCOL, CARBOMER, *POTASSIUM ACESUFAME*, MICA, TRIETHANOLAMINE, MENTHOL, SODIUM CARBONATE PEROXIDE, CI 77891	One of the indicated ingredients does not comply with the glossary of common ingredient names (*POTASSIUM ACESUFAME*)
Tray	3	Ingredients: Propylene Glycol, Glycerine, Aqua, Sodium Bicarbonate, Carbomer, Cellulose Gum, Triethanolamine, PVP, Menthol, Mica, Hydrogen Peroxide, CI 77891	No observations
Tray	4	Ingredients: Sodium bicarbonate, *Pomegranate Seed Extract*, *Chamomile Flower Extract*, *Aloe Leaf Juice*, Carbomer, *Deionized water*, Propylene glycol, Glycerol, *Carboxymethylcellulose sodium*, *Polyvinylpyrrolidone*, Menthol	Six of the indicated ingredients do not comply with the glossary of common ingredient names (*Pomegranate Seed Extract*, *Chamomile Flower Extract*, *Aloe Leaf Juice*, *Deionizrd water*, *Carboxymethylcellulose sodium* and *Polyvinylpyrrolidone*)
Strips	5	Teeth whitening strips ingredients: Glycerine, PVP, Ethylcellulose, Phthalimidoperoxycaproic acid, Alcohol, Hydrated silica, Dicalcium phosphate, Disodium EDTA, Sodium hydroxide, Menthol	No observations
Pen	6	*Ingredienser*: Glycerin, *non-peroxid*, carbomer, *pebermynte-olie*, triethanolamin	The ingredient list is not introduced with the word ”ingredients” as required according to the cosmetics regulation. Two of the indicated ingredients do not comply with the glossary of common ingredient names (*non-peroxid* and *pebermynte-olie*)
Pen	7	INGREDIENTS: AQUA, SODIUM CARBONATE, SODIUM BORATE, LIGUSTICUM CHUANXIONG EXTRACT, *ASTRAGALUS COMPLANATUS EXTRACT*, MENTHOL, THYMOL, DISODIUM EDTA, ALCOHOL, *SODIUM HBENZOATENIACINAMIDEPENOXYETHANOL*, CHLORPHENESIN, PARFUM	Two of the indicated ingredients do not comply with the glossary of common ingredient names (*ASTRAGALUS COMPLANATUS EXTRACT* and *SODIUM HBENZOATENIACINAMIDEPENOXYETHANOL*)

Product type	Product No.	Declaration	Observations
Tray	14	WHITENING GEL INGREDIENTS: Glycerine, Propylene Glycol, *Acrylates/C10-30 Alyl Akrylate Crosspolymer*,Triethanolamine, Sodium Saccharin, Mica, *Mentha Piperita (Peppermint) Oil*, Sodium Carbonate Peroxide (Sodium Percarbonate), CI 77891 ---------- ACCELERATOR SPRAY INGREDIENTS: Aqua, Glycerine, Alcohol, Aroma, Poloxamer 188, Sucralose, Poloxamer 407, Sodium Lauryl Sulphate, Sodium Citrate, Caffeine, *L-Menthol*, Polysorbate 20, Sodium Benzoate, C10-16 Alcohols, CI 42090	Three of the indicated ingredients do not comply with the glossary of common ingredient names (*Acrylates/C10-30 Alyl Akrylate Crosspolymer*, *Mentha Piperita (Peppermint) Oil* and *L-menthol*)
Strips	27	PVP, Glycerine, *Water*, *Polysorbate-80*, Flavour, Citric Acid, Maltodextrin, *Cellacefate*	Three of the indicated ingredients do not comply with the glossary of common ingredient names (*Water*, *Polysorbate-80* and *Cellacefate*)
Tray	32	Ingredients: Glycerine, Sodium Bicarbonate, Mentha Piperita Oil, Sodium Coco-Sulphate, Xylitol, Chondrus Crispus Powder, Sorbitol, Aloe Barbadensis Leaf Juice, Punica Granatum Extract, *Sodium Fluoride*, Chamomilla Recutita Extract, Limonene, Linalool, Hydrogen Peroxide	One of the indicated ingredients does not comply with the glossary of common ingredient names (*Sodium Flouride*)
Pen	33	Ingredienser/ Ingredients Glycerin, Carbomer, *1,2-Propanediol*, *Sodium perborate (0.35%)*, Menthol, *Saccharin Sodium*	One of the indicated ingredients does not comply with the glossary of common ingredient names (*1,2-propanediol*, *Saccharin Sodium* and *Sodium perborate (0.35%)*)
Tray	35	Gel ingredients. *Aqua (Water)*, Glycerine, Poloxamer 188, Sodium Benzoate, *Mentha Avensis (Peppermint) Leaf Oil*, Potassium Sorbate, Sodium Saccharin, Phytic Acid, Limonene, BHT, *CI 42090 (Blue No1)*	Three of the indicated ingredients do not comply with the glossary of common ingredient names (*Aqua (Water)*, *CI 42090 (Blue No 1)*, *Mentha Avensis (Peppermint) Leaf Oil*)

4.3 Declared substances with whitening effect

After reviewing the declaration of substances for teeth-whitening products included in this project, a number of substances assumed to have a whitening effect have been identified. The substances are listed in TABLE 10.

TABLE 10. Substances with assumed whitening effect in examined teeth-whitening products.

Substance	CAS No.
Hydrogen peroxide	7722-84-1
Sodium percarbonate	15630-89-4
Sodium perborate	15120-21-5
Phthalimidoperoxycaproic acid (PAP)	128275-31-0
Sodium chlorite	7758-19-2
Sodium bicarbonate	144-55-8
Citric acid	77-92-9
Phytic acid	83-86-3

Four out of eight substances listed in the table above are peroxides. Sodium percarbonate and sodium perborate are hydrogen peroxide systems of carbonate and borate, respectively, from which hydrogen peroxide can be released. Phthalimidoperoxycaproic acid (PAP) is a type of peroxide described as peroxy carboxylic acid. This type of peroxide can also release hydrogen peroxide if it reacts with water. Peroxides are oxidation agents (see 4.3.1), which, among others, means that they may have whitening properties. Sodium chlorite is the only chlorine-containing substance in TABLE 10, which, similar to peroxides, is an oxidative whitening agent.

Three other substances stand out of the remaining substances in TABLE 10 as they do not have oxidative whitening properties. These three substances are citric acid and phytic acid, whose whitening properties are expected to be due to corrosion of tooth enamel or altered light refraction on enamel surface, as well as sodium bicarbonate, whose whitening properties are unknown.

The declarations for all 25 examined teeth-whitening products have been reviewed to identify substances, which are assumed to have whitening properties. The number of products with each of the listed active substances is shown in FIGURE 2. The declarations for two products have listed two potentially whitening substances: both an oxidizing substance and an acid or sodium bicarbonate (Products No. 3 and 8, see Appendix 1). These two products are included only once in the overview in FIGURE 2, as they have been registered as containing the oxidative whitening agent. In five products, the specific chemical whitening substance is either not indicated or missing entirely in the product declaration (Products No. 6, 10, 20, 21 and 29). These products are shown in FIGURE 2 as ”not identified”. For Product No. 6, ”non-peroxide” has been indicated in the declaration, and for Product No. 20 ”peroxide” has been included in the declaration. The last three products in the category “not identified” have no declaration of substances with a known whitening effect.

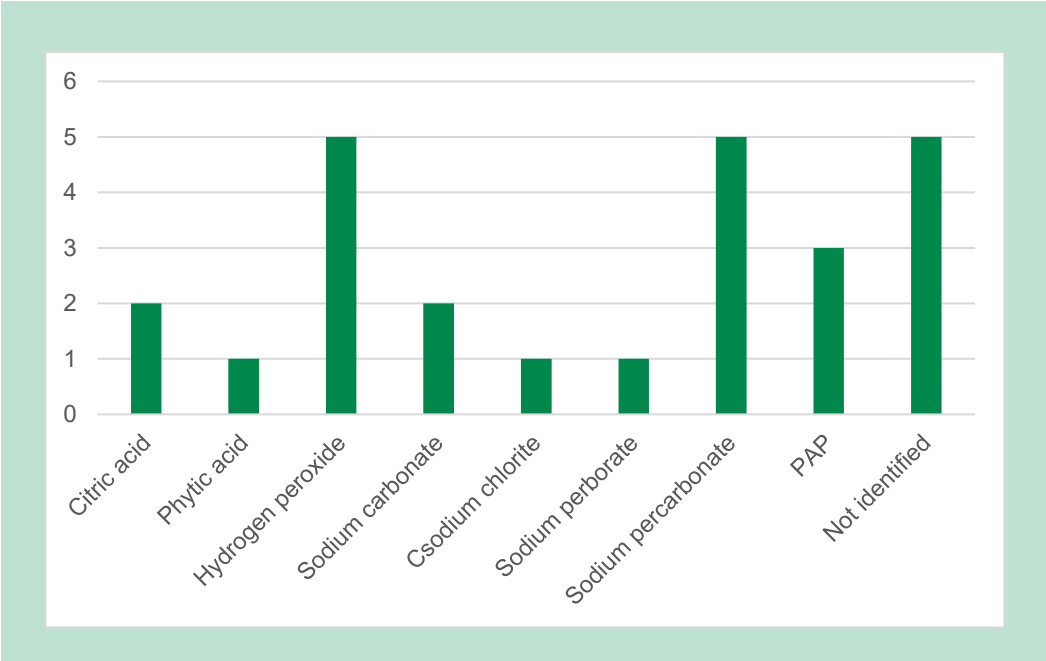

FIGURE 2. Distribution of declared substances with whitening properties in the examined teeth-whitening products.

A review of the teeth-whitening product declarations shoed that many products contain silica that might give the product a polishing effect. This way, the products can in addition to a chemical whitening effect also have a polishing effect (see chapter 2.2).

4.3.1 Measurements of oxidation potential

The oxidation potential for teeth-whitening products is measured with the aim to examine if the measured values can be used to assess the content of active substances in a product. The whitening effect of products for teeth whitening can be related to the ability of the oxidizing substances to undergo a chemical reaction with the coloured substances that are deposited in the teeth causing discoloration. The oxidizing substance extracts electrons from the coloured substances, which breaks bindings in the molecule causing loss of their colouring properties. In this way, the active substance possesses oxidizing properties. Peroxides and sodium chlorite, as listed in TABLE 10, are examples hereof.

As a part of the project, the oxidizing properties of teeth-whitening products were examined by measuring the oxidation potential (Appendix 2.1). The oxidation potential is a parameter describing the ease of electron transfer, and can, thus, be used as a measure for the potency of whitening substance(s) in the product. The oxidation potential for product number 28 has not been measured because of insufficient product matrix to carry out the measurements.

The measurement results are presented in

TABLE 11, where products are grouped according to the type of active substance declared for the product. For five products, the whitening substance was not identified (see explanation in section 4.3). Therefore, the active substance is indicated as ”Not identified” in TABLE 11.

The oxidation potential is measured for the product and for a dilution of the product in demineralized water. In some cases, it was impossible to perform the measurement on the undiluted product.

In many cases, a difference between the measurements of undiluted product and diluted product was observed. That can be related to the fact that the product composition can affect the measurements, or the mixture with water can activate the products. Dilutions with water will affect the pH and, thus, can have an impact on the oxidizing substance if the effect depends on the pH value. Other substances in the product besides the declared whitening substance can also affect the measured result of the oxidation potential, which can explain that there is no direct connection between the oxidation potential and the declared whitening substance. In a few cases, a great variation between two measurements of the same solution can be observed, which can be related to the inhomogeneity of the product or the mixture.

TABLE 11. Teeth-whitening product oxidation potential.

Declared whitening substance	Product No.	Oxidation potential for undiluted product [mV]	%RSD	Oxidation potential for diluted product [mV]	%RSD
Hydrogen peroxide	1	-	-	470	-
	3	300	1	300	3
	12	570	2	590	3
	22	710*	-	630	2
	32	260	1	270	1
Sodium percarbonate	2	650	1	790	3
	14	400	1	720	26
	15	410	1	340	15
	16	210*	-	200	5
Sodium perborate	33	220	1	370	2
PAP	5	-	-	650	2
	24	810	1	870	1
	25	-	-	660	0
Sodium chlorite	8	-	-	550	6
Sodium bicarbonate	4	320	2	510	28
	7	-	-	450	12
Citric acid	27	-	-	530	8
	30	190	6	200	1
Phytic acid	35	750	10	750	2
Not identified	6	-	-	760	3
	10	720	2	720	11
	20	550	3	590	1
	21	460	10	470	0.1
	29	330	1	340	2

- indicates that it was not practically possible to perform measurements

* indicates that only a single determination has been made

RSD: relative standard deviation for duplicate determination

For comparison, the oxidation potential was measured for reference solutions of four different substances (see TABLE 12). The four substances have been selected because they are used either in teeth-whitening products or have the same functional group as a substance used in teeth-whitening products. Peracetic acid represents PAP, as it was not possible to obtain a PAP reference solution before the analyses. It is assessed that peracetic acid can represent PAP because it is a peroxide with the same functional group (peroxy carboxylic acid) as PAP.

As appears in table 12, the measurements were performed for solutions with three different concentrations (0.1%, 0.5% and 1.0%). The results show no significant differences between measurements for different concentrations.

Carbamide peroxide is an example of a substance that can release hydrogen peroxide. Sodium hypochlorite is an example of a chlorine-containing, oxidative whitening substance.

TABLE 12. Oxidation potential for solutions of oxidative whitening substances.

Oxidation potential for a given concentration [mV]		0.1%	0.5%	1.0%
Substance	**CAS No.**			
Hydrogen peroxide	7722-84-1	540	560	560
Carbamide peroxide	124-43-6	520	530	540
Sodium hypochlorite	7681-52-9	680	710	740
Peracetic acid	79-21-0	680	700	710

Great variations are observed for oxidation potential measurements in different products with the same declared whitening substance. For products with a declared hydrogen peroxide, it was found that the content of hydrogen peroxide is very different (TABLE 13). Only two out of five products with a declared hydrogen peroxide have been proved to contain hydrogen peroxide (Products No. 12 and 22). For these products, the oxidation potential is considerably higher than for the other three products (Products No. 1, 3 and 32). Only in one case, the measured oxidation potential is at the same level as shown in measurements of the reference solution for hydrogen peroxide (Product No. 12). Therefore, it is not directly possible to confirm the content of the declared peroxide alone on the basis of measurements of the oxidation potential for the examined products.

The oxidation potential for solutions of sodium hypochlorite shows that the substance was more potent than other whitening peroxides (TABLE 12). The substance is present as hypochlorous acid/hypochlorite depending on the pH value. In this project, the market screening of teeth-whitening products identified hypochlorous acid/hypochlorite as used in products on the market but has not been declared in the products purchased. If a high oxidation potential was measured in a product, it can indicate that sodium hypochlorite is included in the product without being declared. Therefore, in total seven products with a high oxidation potential were analysed for the content of hypochlorous acid/hypochlorite (see chapter 4.54).

Measurements for oxidation potential can possibly be used as an indication that a product contains an oxidizing substance, and that it, thus, can have a whitening effect. Therefore, in the chapter ”Hazard assessment” a data search will be performed to describe a possible connection between the measured oxidation potential and whitening or harmful effects in connection with teeth-whitening.

4.3.2 pH value measurements

The acid-/base properties of teeth-whitening products have been examined by measuring the pH value of the products. A product with a low pH value has acid properties and can, thus, cause enamel corrosion and, thereby, remove discoloration (see chapter 2.2.1). These products can also cause other damage on, e.g., gums. Measurements have been performed for pH on 24 products (Appendix 2.2). pH for product number 28 has not been measured due to insufficient product matrix for measurements. Measurements have been performed for a solution of products in demineralized water. Thereafter, the pH value was estimated for products by converting the results. The estimated pH values for products are shown in TABLE 13.

By reviewing the declared substances, it is possible to identify a number of substances that will have an impact on the pH value of the product, which is why total composition of and ratio between substances is the decisive factor for the pH value of the product.

The following can be mentioned among the declared substances that are assessed to have an impact on the pH value of the products:

- sodium hydroxide
- sodium bicarbonate
- potassium sorbate
- citric acid
- sodium citrate
- triethanolamine
- sodium benzoate
- dicalcium phosphate
- phthalimidoperoxycaproic acid (PAP)
- sodium percarbonate
- sodium hypochlorite
- sodium borate
- sodium perborate
- phytic acid
- pomegranate extract

This complexity means that pH measurements are necessary to determine the product properties, and the results of pH measurements shown in TABLE 13 do show a great variation in pH values in the interval from 0 to 11.5. The pH value highly affects specifically the ability of substances to oxidize, which can be the reason for varying values in the oxidation potential (see chapter 4.3.1). Products with a pH value below 7 contain substances that react acidic by releasing one or several hydrogen ions to a base. Products with a pH value above 7 contain substances that have an alkaline reaction by receiving one or several protons from an acid.

Product No. 27 has an estimated pH value of 11.5, and, thus, cannot have a corrosive effect on teeth from citric acid as declared on the product.

TABLE 13 shows that four products (Products No. 5, 21, 25 and 24) declared sodium hydroxide. To be able to use this substance, the pH value in the final product must be below 11, which is the case for these products as their pH value is in the interval 2.9-7.0.

4.4 Analyses of whitening substances

All 25 teeth-whitening products have been analysed for content of whitening substances. Quantitative analyses have been performed for three different whitening substances: hydrogen peroxide, chlorite and hypochlorous acid/hypochlorite. The analysis results are presented in

TABLE 13 with information on the assumed whitening substance (chapter 4.3) and distributor's country of origin. Further, the results have been related to the results from measurements of oxidation potential and pH (chapter 4.3.1 and 4.3.2).

TABLE 13. Analyses results for examined teeth-whitening products.

Distributor's country of origin	Product type	Product No.	Declared whitening substance	Oxidation potential of diluted product [mV]	pH	Hydrogen peroxide [%]	Chlorite [%]	Hypochlorous acid /hypochlorite [mg/kg]
Denmark	Pen	1	Hydrogen peroxide	470	10.2	-	-	n.a.
	Tray	3*		300	10.6	-	0.07	n.a.
	Tray	32		270	3.5	-	-	n.a.
	Tray	2	Sodium percarbonate	790	3.5	0.09	-	-
	Tray	14		720	6.7	-	-	n.a.
	Pen	33	Natrium perborate	370	4.1	0.09	-	n.a.
	Strips	5	PAP	650	2.9	-	-	-
	Tray	4	Natrium bicarbonate	510	10.5	-	-	n.a.
	Pen	7		450	10.1	-	-	n.a.
	Strips	27	Citric acid	530	11.5	-	-	n.a.
	Tray	35	Phytic acid	750	6.9	-	-	-
	Pen	6	Not identified	760	2.4	n.a.	-	n.a.
Other EU countries	Tray	15	Sodium percarbonate	340	10.9	-	0.09	n.a.
	Pen	16		200	7.1	-	-	n.a.
	Pen	28		n.a.	n.a.	n.a.	-	n.a.
	Strips	8*	Sodium chlorite	550	8.2	-	-	n.a.
	Pen	30	Citric acid	200	4.3	-	-	n.a.
	Tray	29	Not identified	340	6.5	-	-	n.a.
Countries outside the EU	Tray	12	Hydrogen peroxide	590	3.8	10.8	-	n.a.
	Pen	22		630	4.0	1.9	-	-
	Tray	24*	PAP	870	5.9	0.04	-	**

Distributor's country of origin	Product type	Product No.	Declared whitening substance	Oxidation potential of diluted product [mV]	pH	Hydrogen peroxide [%]	Chlorite [%]	Hypochlorous acid /hypochlorite [mg/kg]
	Strips	25		660	7.0	-	-	-
	Pen	10	Not identified	720	0	-	-	-
	Tray	20		590	4.0	3.1	-	n.a.
	Tray	21		470	7.0	-	-	n.a.

n.a. – means "not analysed"
Analytical uncertainty: 9%U for pH, 20%RSD for hydrogen peroxide, 10%RSD for chlorite, 5%RSD for hypochlorous acid/hypochlorite
- below detection limit (0.01-0.05% for hydrogen peroxide (product-dependant), 0.001% for chlorite, 10 mg/kg for hypochlorous acid /hypochlorite
* The product is declared with another substance that may also have a whitening effect. The substances in question are: sodium bicarbonate for Product No. 3 and citric acid for Product No. 8.

** The analysis initially showed that this product apparently contained hypochlorous acid/hypochlorite. However, when the analysis method was investigated it was proven that the content of PAP in the product gives interference with the analysis method and therefore reason for a false positive result of hypochlorous acid/hypochlorite.

4.4.1 Hydrogen peroxide present in or released from teeth-whitening products

For all examined products, hydrogen peroxide content/release was determined by bioassay. The results hereof are presented in TABLE 13 except for results for two products (Product No. 6 and 28), which are not analysed due to insufficient product matrix for analyses. For six out of 23 teeth-whitening products, hydrogen peroxide was found either in the product or released from the product. However, it cannot be excluded that a hydrogen peroxide content/release can be determined in additional products in the project in a concentration below the detection limit of the applied analysis.

To determine hydrogen peroxide in teeth-whitening products, a catalase bioassay has been used (Appendix 2.3). In the assay, hydrogen peroxide in the product is converted enzymatically to water and oxygen according to a reaction: $2\ H_2O_2 \rightarrow O_2 + 2\ H_2O$. The measurement of formation of oxygen can, thus, be converted to a content of hydrogen peroxide in or released from the product.

In teeth-whitening products, the substances are regulated according to the EU cosmetics regulation, which means that the content of or the release of hydrogen peroxide may not exceed 0.1% (chapter 4.2.1). Using the above-mentioned assay, the hydrogen peroxide content/release is determined for the product. Analyses results of this assay can, thus, be compared to the threshold values of 0.1% to determine whether the teeth-whitening product is legal. The analysis results have shown that the concentration of hydrogen peroxide exceeds 0.1% in three out of 23 analysed products (Products No. 12, 20 and 22). Common for these products is the fact that the distributor's country of origin is outside the EU.

The analysis of Product No. 24 has shown that hydrogen peroxide is in the product or can be released from the product under the applied analysis conditions. Since the product is declared to contain PAP, it is assumed that hydrogen peroxide is released from PAP. That is because PAP is a peroxy carboxylic acid and releases hydrogen peroxide. Correspondingly, for product No. 2 and Product No. 33 hydrogen peroxide is presumably determined to be released from sodium percarbonate and sodium perborate, respectively, as declared on the products.

Peroxy carboxylic acids in teeth-whitening products can also release hydrogen peroxide, which can be determined by using the above-mentioned bioassay. To confirm that the assay can be used to determine hydrogen peroxide release from this type of peroxide, an analysis of peracetic acid has been performed. A sample of peracetic acid containing a known amount of hydrogen peroxide, which according to the certificate has been determined by titration (TABLE 14), has been analysed with the assay. The results are presented in TABLE 14 and show consistency within analytic uncertainty with hydrogen peroxide concentration declared in the sample certificate. The result also confirms that it is possible to determine hydrogen peroxide released from peracetic acid using the assay.

TABLE 14. Measurement of hydrogen peroxide content for peracetic acid.

Substance	CAS No.	Conc. H_2O_2 according to certificate (determined by titration)	Conc. H_2O_2 determined with bioassay
Peracetic acid	79-21-0	13.0%	14.0%

4.4.2 Chlorite content

All 25 products have been analysed for content of chlorite (Appendix 2.4). Only one teeth-whitening product out of 25 was declared as containing sodium chlorite (Product No. 8). After repeated analysis of this product, it was not possible detect the content of sodium chlorite. Chromatograms from the analysis show that the product most likely contains a degraded product from sodium chlorite, and that the product may have been added sodium chlorite.

In general, the analyses results show that two out of 25 analysed teeth-whitening products contain chlorite (TABLE 13). Common for these products (Products No. 3 and 15) is that they have not been declared with the content of chlorite. The products were purchased in Denmark and from other EU countries.

4.4.3 Hypochlorous acid/hypochlorite content

None of the examined products have been declared as containing hypochlorous acid/hypochlorite, but since it is known that hypochlorous acid/hypochlorite are used in teeth-whitening products, selected products were analysed for content of hypochlorous acid/hypochlorite. The analysed products were selected on the basis of measurements showing a high oxidation potential, which is comparable to the oxidation potential measured for sodium hypochlorite (see chapter 4.3.1). In total, seven products were analysed for hypochlorous acid/hypochlorite content (Appendix 2.5), but no confirmed content of hypochlorous acid/hypochlorite has been found in any of these. The results are presented in TABLE 13.

Product no. 24 was purchased outside of the EU and is the product in this project that contained the highest oxidation potential. That may indicate that the product contains a powerful oxidation agent. The analysis of the product initially showed that it contained hypochlorous acid/hypochlorite. However, an examination of the analysis method demonstrated that the content of PAP in the product gives rise to interference with the analysis method, meaning that the analysis for hypochlorous acid/hypochlorite was false positive. By analysing the product to which a known amount of PAP had been added, it was confirmed that a false positive result was in question.

Just as for product no. 24, product no. 5 was also declared to have a content of PAP, but no content of hypochlorous acid/hypochlorite was demonstrated. That means that this product does not have any false positive results. The reason might be that the product composition is decisive for whether PAP interferes with the analysis method for hypochlorous acid/ hypochlorite. Another reason could be that the amount of PAP in the products differs significantly.

4.5 Analyses of boron-based substances

Different hydrogen peroxide systems exist, where substances such as borates, pyrophosphates, carbonates, sulphates, silicates and amides can be a part of these. These systems are sources for active oxygen and are used as whitening agents. An example of such a system is sodium perborate, which is the oldest and most widely used whitening agent. According to the cosmetics regulation, it is forbidden to use the substance in teeth-whitening products (section 4.2.1). A number of other boron-based substances exist, and they are, likewise, forbidden to use in teeth-whitening products according to the cosmetics regulation.

One product out of all examined products (Product No. 33) has been declared with the content of sodium perborate and is, thus, not legal. The bioassay has determined a hydrogen peroxide concentration of 0.09%, which supports that the products contains sodium perborate. Two other products (Products No. 7 and 10) have also been declared with the content of boron-

based substances: sodium borate and borax, which are also illegal ingredients in cosmetic products.

Based on the fact that three of the purchased products contain illegal substances, it was decided to examine if other products also contain boron-based substances, though not being declared. Thus, the products declared with boron-based substances as well as nine additional selected products were analysed for the content of boron. The nine selected products have been selected randomly but have been divided equally between the distributor's country of origin and product type. The analysis results are presented in TABLE 15.

TABLE 15. Analysis results for boron in selected products.

Distributor's country of origin	Product type	Product No.	Declared boron-based substance	Boron [%]	Content converted to declared substance [%]
Denmark	Pen	33	Sodium perborate	0.04	0.37
	Pen	7	Sodium borate	0.13	0.60
	Pen	6	-	-	-
	Strips	27	-	-	-
	Tray	4	-	-	-
Other EU countries	Pen	16	-	-	-
	Strips	8	-	-	-
	Tray	29	-	-	-
Countries outside the EU	Pen	22	-	-	-
	Pen	10	Borax	-	-
	Strips	25	-	-	-
	Tray	20	-	-	-

- indicates that no content of boron has been detected above the detection limit (0.001%)
Analytical uncertainty: 15%RSD

The analysis results show that the content of boron is only found for products declared with boron-based substances. This is valid for Products No. 7 and 33. For Product No.10, it cannot be confirmed that the product contains borax above the detection limit.

4.6 Observations made regarding analysis results

The analysis of the examined products shows many discrepancies between the product declaration and the analysis result. In other cases, deviations from the cosmetics regulation requirements have been detected. Products, for which observations have been made, are listed in TABLE 16 with a more detailed description of the observation. However, it should be noted that the declaration of some products state a substance that was not detected during analysis. That might be because the concentration of the substance is below the detection limit of the analysis in question.

TABLE 16. Observations made for examined products.

Observation	Product No.	Distributor's country of origin
Concentration of hydrogen peroxide detected by analysis is above the legal threshold value of 0.1% (in the product or released)*	12, 20, 22	Outside the EU
Chlorite detected by analysis, but no chlorite-containing substance is listed in the product declaration	3	Denmark
	15	Other EU country
Boron detected by analysis, or a boron-based substance is indicated in the product declaration**	7, 33	Denmark
	10	Outside the EU
Hydrogen peroxide or a hydrogen peroxide-releasing substance is listed in the product declaration, but not detected by analysis	1, 3, 5, 14, 32	Denmark
	15, 16	Other EU countries
	25	Outside the EU
A chlorite-containing substance is listed in the product declaration, but not detected by analysis	8	Other EU country

* Annex III, ref. no.12 according to the cosmetics regulation
** Boron-containing substances are forbidden in cosmetic products according to Annex II in the cosmetics regulation (several reference numbers are included, among others ref. no. 1395)

4.6.1 Follow-up

The project, which will result in a risk assessment of the active substances in teeth-whitening products, has identified the following as active chemical whitening substances:

- hydrogen peroxide
- sodium percarbonate
- phthalimidoperoxycaproic acid (PAP)
- sodium chlorite
- sodium perborate

For these substances (except sodium perborate, which is a forbidden substance), a hazard assessment of substances will be performed, and exposure assessments for substances will be carried out according to the analysis results and user instructions for each product. Based on the knowledge on hazards and exposure, a risk assessment for products is prepared in Chapter 5.

The assessment will be supported, to the extent possible, with knowledge of the measured oxidation potentials and also on the estimated pH values for products.

5. Risk assessment

5.1 Literature data, teeth-whitening products

5.1.1 Local effects in oral cavity and on teeth

For literature search on the effects of teeth-whitening products, it must be noted that the found literature focuses primarily on products used in dental clinics. Thus, the focus is on the professional rather than personal use. It is undoubtedly understandable that mainly the professional use has been the focus on tests, as the aim of these tests has most likely been to develop and assess whitening methods in the professional community and to ensure that the treatments are effective without causing unnecessary risk for patients. Whitening effects and impact on teeth and gums (mucous membranes and the underlying tissue) are, thus, described best in relation to strong teeth-whitening products used by dental clinics with a content of, e.g., carbamide peroxide of 10% or higher and hydrogen peroxide in concentrations of up to 30-35%. In general, professional dentists do not consider that products with a low content of hydrogen peroxide up to 0.1% can have a whitening effect (*Dahl & Pallesen 2003; Pallesen 2016; Carey 2014; Sommer et al. 2005, Eppe et al. 2019*).

In the above-mentioned articles it is stated that teeth whitening can cause side effects to a large or small degree in the form of symptoms from teeth, gums, and mucous membranes. In literature, the risk is indicated to increase proportionally with the concentration of the active substance in teeth-whitening product. The effects are described very consistently and include increased tooth sensitivity with a risk of toothache, impact on gum mucous membranes and underlying tissue (irritation, inflammation, and ulceration), as well as impact on tooth enamel (changes to surface structure, roughness, demineralization and decrease of enamel hardness). High concentrations of whitening agent that comes into contact with gums can cause corrosion and ulcers, which will require longer time to heal, or, in less serious cases, whitish corrosion on gums, which will disappear after a few days. Furthermore, it is described that the whitening agent can get absorbed in the dentin of the tooth and root cementum (tissue covering the surface of the root of the tooth), and that teeth with sensitive necks, where dentinal tubules (small canals in dentin) have a direct contact to the pulp (tooth nerve), can become highly sensitive after whitening (see FIGURE 3).

Histological examination of whitened teeth has shown reversible damaging effects on the odontoblast cells (cells on the inside of tooth bone that produces dentin), and impact on their production of dentin. Inflammation conditions in the nerve of the tooth are considered to cause the increased tooth sensitivity. Thus, less severe inflammation changes in the nerve of the tooth have been observed after teeth whitening with 10% carbamide peroxide. Irreversible tooth enamel erosion has been observed after whitening with 35% carbamide peroxide, while whitening with 10% carbamide peroxide has only a minor impact on enamel.

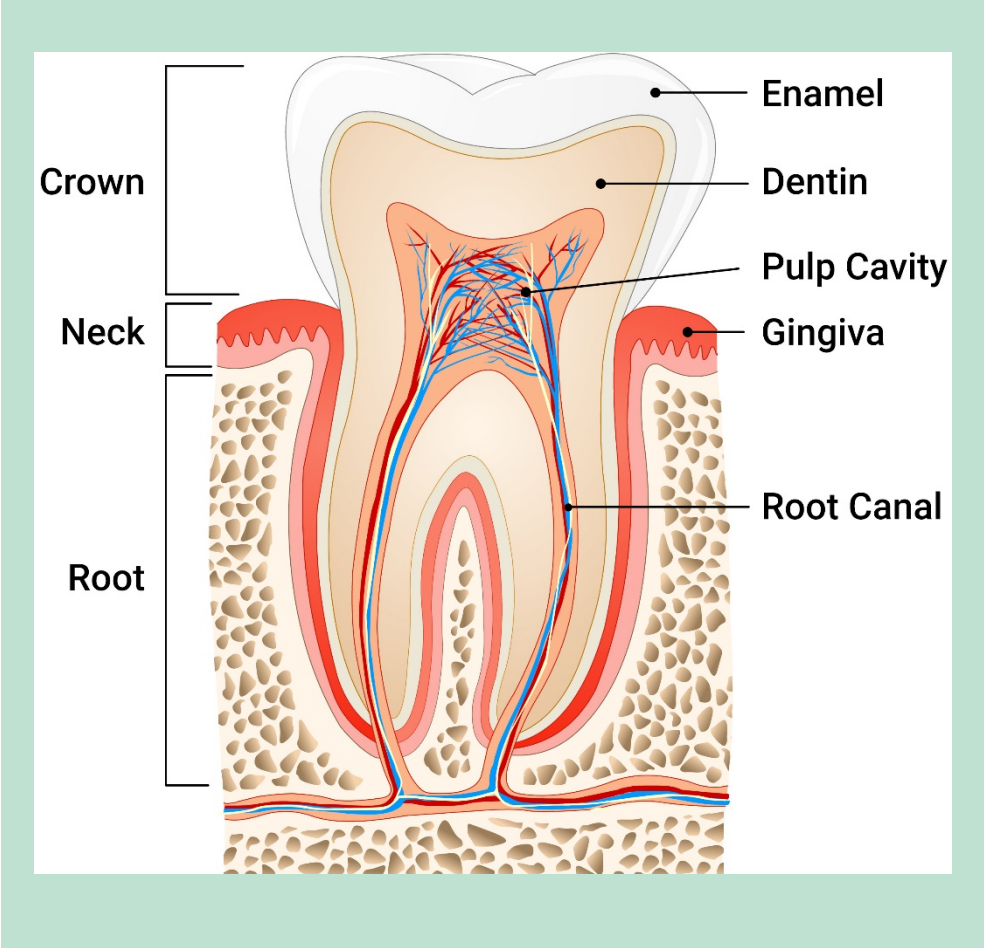

FIGURE 3. Illustration of a tooth, its anatomy and surrounding structures (© turhanerbas – stock.adobe.com).

Actual recent tests in relation to professional treatment

In a Scandinavian study, Bruzell et al. (2013) observed the side effects of teeth whitening carried out either at a dental clinic (28 patients) or by patients at home with a provided teeth-whitening product (143 patients). The dental clinic used a teeth-whitening gel with 25% or 35% hydrogen peroxide, which was applied on teeth directly in a single treatment of an approx. duration of 1 hour. The home treatment involved using teeth trays and a teeth-whitening gel with a content of 10-20% carbamide peroxide (indicated as corresponding to 3.6-7.1% hydrogen peroxide) during a period of up to 11 days, and a total treatment time of 12-154 hours, depending on the user instruction for the individual product. 14-21 days after the beginning of treatment, increased tooth sensitivity was reported for 50.3% of the patients using the home treatment and for 39.3% of the patients treated at the dental clinic. Irritation/ulceration in gums was reported for 14% of the patients following home treatment, and 35.7% of dental clinic patients. After additional 8.5-9.5 months, two of the patients using home treatment and three dental clinic patients still reported signs of side effects. The authors of the study concluded that an increased concentration in the teeth-whitening product and contact of teeth-whitening gel with gums caused increased negative effects. Furthermore, persons with previous increased tooth sensitivity, gum inflammation or tooth surface erosion showed an increased risk of side effects from the treatment. Finally, young persons in the age group of 17-24 years showed greater sensitivity regarding tooth sensitivity compared to older patients.

Ferraz et al. (2019) analysed the whitening effect and subjective symptoms regarding tooth sensitivity and effect on gums and mucous membranes in 54 patients, who received teeth-whitening treatment at a dental clinic. The treatment was performed using 6% and 15% hydro-

gen peroxide as a whitening agent and LED/laser light exposure to catalyse/activate the oxidation and whitening process. The treatment was three 10-minute treatments with one treatment at a time and one week break in between the treatments. The patients reported increased tooth sensitivity (29.6% of the group treated with 6% hydrogen peroxide and 44.4% of the group treated with 15% hydrogen peroxide). After two weeks, 57.7% and 53.8% patients, respectively, reported irritated gums. After assessment of the results of the 6-month treatment, the treatment with 15% hydrogen peroxide showed the best whitening results, but also lead to increased tooth sensitivity compared to the treatment with 6% hydrogen peroxide.

Studies on products for personal use

Literature review showed very few studies on teeth-whitening products for personal use, i.e., products purchased in retail stores, and which are, thus, expected to meet the requirements of the cosmetics regulation for sales directly to the consumers, i.e., with a maximum content or release of 0.1% hydrogen peroxide or other whitening active substances.

Wang et al. (2008) has made a comparison for the usage of teeth-whitening products with the content of 38% hydrogen peroxide, 20% carbamide peroxide, sodium borate (concentration not indicated) and a product for personal use (Rapid White) with a content of sodium chlorite and citric acid (concentrations not indicated) on removed teeth. In case of Rapid White, an acceleration liquid containing sodium chlorite must be applied on the teeth first, and after five seconds, a gel containing, among others, citric acid must be applied end left to have effect for ten minutes. This treatment must be repeated twice daily for ten days. Furthermore, the study involved a treatment with a citric acid solution, alone, with a pH value of 3.7 corresponding to the pH value of the teeth-whitening product. After treatments, which were all carried out according to distributor's user instructions, it was examined whether these treatments caused any changes to enamel chemistry and structure. The treatments with hydrogen peroxide, sodium borate or carbamide peroxide did not change the enamel, while the Rapid White product caused changes to both the chemistry and structure of the enamel. Based on separate treatments with sodium chlorite alone, and the citric acid gel alone, as well as a treatment carried out with a control solution of citric acid at pH 3.7, it was concluded that citric acid was the cause to changes in the enamel's surface and dissolution of the calcium in the enamel structure.

Greenwall-Cohen et al. (2019) analysed five teeth-whitening products for personal use purchased in retail stores on the British market to study the impact of these products on tooth enamel and their whitening effect. The study was performed by treating newly removed teeth. Three out of five products were declared with sodium chlorite, one product with sodium percarbonate and one product with PAP. The levels of concentration were not indicated.

The teeth were stored in green tea for five days to cause discoloration before they were treated with teeth-whitening products with a layer thickness of 2-3 mm according to user instructions. An initial treatment was performed twice for one hour to represent a scenario of excessive use of the products. During the following five days, the teeth were treated as indicated in user instructions for a treatment cycle. Two of the products with the content of sodium chlorite were formed as strips. Distilled water and a gel containing 10% carbamide peroxide was used as negative and positive control, respectively. In between treatments, the teeth were stored in saltwater solution.

For all teeth-whitening products, electron microscopy of the teeth revealed (even compared to the positive control) varying degrees of changes as a result of corrosion and erosion of teeth surface structure. This was most pronounced for one product with sodium chlorite and the product with PAP as whitening agents. These two products caused also a reduced hardness

of teeth surface measured by Vickers micro hardness method.[11] The whitening effect determined with Vita 3D Master[11] colour scale was poorer than distilled water for two of the products (including the product with PAP), while two products with sodium chlorite had a stronger whitening effect than the positive control. These two products were at the same time the only products formulated as strips.

In the study, it was mentioned that sodium chlorite was turned into chlorine dioxide (ClO_2) due to presence of an acid, and that this can cause reduced hardness of enamel. The product content of citric acid was assumed to accelerate the whitening process, but at the same time, citric acid is considered to cause tooth enamel erosion. The authors of this study also mention that an increased impact on the surface structure of the enamel will cause a rougher surface, which advances the deposit of colour pigments and may lead to calculus formation, which, thus, increases the risk of gum inflammation and marginal periodontitis. Overall, the authors concluded, subject to the limited sample material, that teeth-whitening products for personal use can whiten the teeth, but they can also damage the tooth enamel. Especially, sodium chlorite is considered to have an effect on teeth whitening.

Møller et al. (2018) carried out a study on peroxide-free teeth-whitening products sold directly to the consumer. Four products indicated as peroxide-free (one product contained PAP and another product contained sodium perborate, while the two last products contained sodium bicarbonate in combination with pomegranate extract) were tested against a peroxide-containing product with 10% carbamide peroxide. The pH values of all products were measured to be in the interval pH 3.2-6.1. In the whitening experiment, removed teeth were treated with the teeth-whitening gel according to product user instructions, and were stored in water in between the treatments. After the prescribed treatment cycle, all products showed a whitening effect except the product with sodium perborate. An assessment carried out eight months after the treatment showed a very low whitening effect of the two products with sodium bicarbonate and pomegranate extract, while the whitening effect was preserved in teeth treated with carbamide peroxide product. Teeth treated with PAP did not preserve the whitening effect, while teeth treated with sodium perborate had become darker. It was concluded that the four ”peroxide-free” products were considerably less effective compared to whitening with 10% carbamide peroxide.

Final assessment

Based on a general assessment of chapter 5.1.1, it is possible to highlight the following critical effects in the oral cavity, mucous membranes, and teeth after application of professional teeth-whitening product either in a dental clinic or using the products at home:

- increased tooth sensitivity/toothache
- roughness, demineralization, reduced hardness, and tooth enamel erosion
- gum irritation and corrosion, gum inflammation

These effects can typically be observed with teeth-whitening products with a high content of the active substance (carbamide peroxide ≥ 10% and hydrogen peroxide ≥ 25%). It is also stated that there is a shortage on studies on persons that use teeth-whitening products for personal use, where the content of active substances according to legislation may at a maximum correspond to a hydrogen peroxide content of ≤ 0.1%. This is most likely due to the fact that such products are not used by professional dentists because these products are not considered as effective enough to ensure teeth whitening (Sommer et al. 2005).

[11] Recognized methods for assessing teeth hardness and color.

The study on products for personal use in an experiment with removed teeth has indicated some whitening effect of products with sodium chlorite and citric acid, and in products with sodium bicarbonate and pomegranate extract (Greenwall-Cohen et al., 2019).

It is assessed that the data on teeth-whitening products with a high content of active whitening agents will provide a good understanding of the types of side effects to be aware of when using teeth-whitening products with a lower content of active substances.

5.2 Risk assessment of active whitening ingredients

The following active teeth whitening ingredients have been selected for risk assessment:

- hydrogen peroxide
- sodium percarbonate
- phthalimidoperoxycaproic acid (PAP)
- sodium chlorite

Below, in TABLE 17, the risk classification of the substances according to Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation) is given.

TABLE 17. Risk classification of selected whitening active substances.

Substance	CAS No.	Classification according to the CLP Regulation
Hydrogen peroxide*	7722-84-1	Ox. Liq. 1 H271*
(100%)		Acute tox. 4 H302*, H314*
		Skin Corr. 1A H314*
5-8%		Eye Irrit. 2; H318*
< 5%		No classification
Sodium percarbonate**	15630-89-4	Ox. Solid 3 H272
		Acute tox. 4 H302
		Eye Damage 1 H318
Phthalimidoperoxycaproic acid (PAP)**	128275-31-0	Org. Perox. D H242
		Eye Damage 1 H318
		STOT SE 3 H335
		Aquatic Acute 1 H400
Sodium chlorite**	7758-19-2	Ox. Liq. 1 H271
		Acute Tox. 3 H301
		Acute Tox. 2 H310
		Skin Corr. 1B
		STOT RE2 H373 (effect on the spleen)
		Aquatic Acute 1 H400
		Aquatic Chronic 3 H412

* Harmonised EU classification

** Classification used in the REACH registration dossier (no harmonised EU classification)

It is evident that all substances are classified with oxidizing properties. The substances also share a common property as they are classified as either corrosive or harmful to the eyes.

In the below description of the hazards of substances, the main focus will be on the data relevant for this project, i.e., data generated in relation to the usage of the substances in the teeth-whitening products. Moreover, recent expert assessments will be drawn upon to the widest extent possible. The NOAEL/LOAEL values of each substance will be identified for the most critical effects for the assessment of the hazard of the substance in terms of local and systemic effects. As stated in ”The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation” (SCCS 2018), the POD (Point of Departure) is chosen/calculated for use in the risk assessment. The POD value is the basis for the risk assessment. The POD value is estimated from an experimental NOAEL or LOAEL value as it can be necessary to downgrade this value by dividing with one or more uncertainty factors. Uncertainty factors can be used in cases where the experimental data are insufficient, for example, the duration of the study or if a NOAEL value is not available, in which case a LOAEL value must be used to estimate the POD value.

A literature search has been conducted for the substances above in terms of the name of the substances and their usage for teeth whitening (combinations of keywords: dental, tooth, bleaching and whitening). Furthermore, a search for more recent expert assessments of the substances has been made, and the REACH registration dossier of the substances has been searched. From the results of this search, the most relevant literature for the assessment of the substances has been chosen.

It should be noted that the NOAEL and LOAEL terms used in the rest of this project are used both in connection to the exposure measured as mg/kg bw/day (used for the assessment of systemic effects) and as % content or mg/cm^2 (used for the assessment of local effects).

5.2.1 Hydrogen peroxide

The EU Scientific Committee on Consumer Safety is the primary source for the risk assessment of hydrogen peroxide as they have assessed the safety of teeth-whitening products containing hydrogen peroxide or substances that release hydrogen peroxide (SCCP 2007).

Kinetics

Hydrogen peroxide is a naturally occurring metabolite in the organism and occurs in concentrations of <1 micromole. Hydrogen peroxide can penetrate the skin and mucous membranes but undergoes rapid spontaneous and enzyme-catalysed degradation in the underlying tissue. The local degradation in the contact site prevents absorption and distribution via the bloodstream. The red blood cells have, furthermore, a high capacity to degrade hydrogen peroxide (SCCP 2007).

Local effects

In a trial with rabbits, a 10% hydrogen peroxide solution caused a minor degree of skin irritation, while a similar concentration dosed in the eyes of the rabbits caused major eye irritation. In humans, the indicated limit for eye irritation is 0.1% hydrogen peroxide (SCCP, 2007).

Hydrogen peroxide is not assessed as being skin sensitizing (SCCP, 2007).

Systemic effects from repeated dosing

SCCP has determined a NOAEL value of 100 ppm in drinking water (corresponding to 0.01% or 26 mg/kg bw/day) from a 90-day trial on mice in which hyperplasia in the mucous membranes of the duodenum was observed during higher dosage. A 100-day trial on rats yielded a similar NOAEL value of 20 mg/kg bw/day in a trial with oral dosing via endoscopy on grounds

of reduced catalase activity in plasma at higher levels. Therefore, SCCP chose a NOAEL value of 20 mg/kg bw/day as the basis for the risk assessment (SCCP, 2007).

Carcinogenic effects

Hydrogen peroxide is assessed to have a mild carcinogenic effect, since an increased frequency of tumours was observed in the forestomach of rats dosed with 1% hydrogen peroxide in their drinking water. The mechanism behind this is unresolved, but potential mechanisms indicate chronic inflammation, decreased DNA repair or direct genotoxic effects (SCCP, 2007).

Effects on reproduction

The amount of available data is considered insufficient for the assessment of the reproductive toxicity of the substance, but the sparse data does not leave cause for concern (SCCP, 2007). The risk is evaluated to be low/hypothetical due to missing systemic absorption.

Cytotoxic effects

Furukawa et al. (2015) examined the cytotoxicity of hydrogen peroxide at various concentration levels and at different durations of exposure with human connective tissue cells from the gum. A hydrogen peroxide concentration of 0.0015% had no effect on the survival of the cells after 30 minutes, but a reduced survival rate was observed after 60 minutes. A concentration of 0.00015% did not affect cell survival after 60 minutes, while concentrations of ≥ 0.15% affected cell survival after just 90 seconds of exposure.

Data from teeth-whitening

SCCP (2007) examines a long list of clinical trials in its assessment of the use of teeth-whitening products containing hydrogen peroxide or substances that release hydrogen peroxide. The most relevant data for the assessment of hydrogen peroxide are listed below. It must be stressed that the data primarily comes from the use of products with 6-35% hydrogen peroxide, meaning a significantly higher concentration than the allowed maximum of 0.1% for sale to the consumer. Overall, SCCP (2007) concludes that the typical effects in connection to teeth whitening with hydrogen peroxide are increased tooth sensitivity, irritation of the mucous membranes of the oral cavity and gum, including irritation in the throat. The increased tooth sensitivity often occurs early in the treatment and is often temporary. Neither trays nor strips with hydrogen peroxide were found to have a worsening effect in connection to continuous usage over six months in comparison to short-term usage over 14-28 days.

In a study with adolescents in the age group 12-18, the effects of treatment using strips with 9.5% hydrogen peroxide (two times 30 minutes daily for two weeks) were compared to treatment using trays with 3.3% hydrogen peroxide gel (every night for eight hours over two weeks). In the group treated with 9.5% hydrogen peroxide, 13% experienced effects on the mucous membrane and gum and 18% experienced increased tooth sensitivity. Corresponding numbers for the 3.3% hydrogen peroxide group were 0% and 42%. All effects disappeared quickly after the treatment was discontinued (SCCP, 2007). Another study compared three months treatment (two times 30 minutes daily) of strips with either 6% or 9.5% hydrogen peroxide. In the group with 6% hydrogen peroxide, 6% experienced effects on the mucous membrane and gum, while 44% experienced increased tooth sensitivity. Corresponding numbers for the 9.5% group were 6% and 59%. All effects disappeared quickly after the treatment was discontinued (SCCP, 2007). Cases of strips with hydrogen peroxide being swallowed were reported in which minor symptoms occurred in the stomach and intestines (SCCP, 2007).

Finally, a series of studies are referenced in which the effects on the tooth surface have been examined through treatment of extracted teeth. SCCP found that the results from these studies were disparate and assign this due to varying test design. Among other things, a tendency was observed in which studies that stored the teeth in artificial saliva between the treatments

found a significantly lower number of effects compared to those that stored the teeth in water. Some studies have, thus, observed corrosion and demineralisation by whitening with 35% hydrogen peroxide, while others by means of electron microscopy have found no effects. Correspondingly positive and negative observations have been reported at two weeks of whitening at 6-6.5% hydrogen peroxide (SCCS, 2007).

Studies of extracted teeth have shown that treatments with both 30-35% hydrogen peroxide and 6% hydrogen peroxide cause penetration and exposure of the tooth nerve to the substance, which can lead to minor inflammation and, thereby, likely be the cause of increased tooth sensitivity.

Overall, SCCP (2007) concluded that systemic effects from hydrogen peroxide-based teeth-whitening products can be assessed from a NOAEL value of 20 mg/kg bw/day and that local effects should be assessed based on irritation effects in the oral cavity and possibly the stomach/intestine in the case of the product being swallowed.

Final conclusion

The overall conclusion from SCCP (2007) states that products with 0.1% hydrogen peroxide or the release of up to 0.1% hydrogen peroxide are safe to use with regard to systemic effects and to local effects in the oral cavity and its mucous membrane. SCCP (2007) found that it was not possible to make a conclusion for products containing or releasing hydrogen peroxide from 0.1% and up to 6% as there is insufficient data on teeth-whitening products concerning this group.

From the data provided by SCCP (2007), it can be concluded that products with 6% hydrogen peroxide can lead to increased tooth sensitivity, irritation and inflammation in mucous membranes and gum, which is why the LOAEL value can be set to 6% for irritating effects, while a LOAEL of 3.3% is set for increased tooth sensitivity. SCCS (2018) recommends using a factor of 3 when extrapolating from LOAEL to NOAEL for minor degrees of effects. The risk assessment, therefore, uses a POD of 2% for irritation effects in mucous membranes and 1.1% for increased tooth sensitivity. A LOAEL and NOAEL of 0.0015% and 0.00015% hydrogen peroxide can be determined in an *in vitro* test for cytotoxicity in connection to one hour of exposure of human gum connective tissue cells. Considerably large differences in concentration in LOAEL *in vivo* are observed in comparison to *in vitro* (a factor 3%/0.0015% = 3000), and it is, therefore, considered to be quite difficult to include the *in vitro* data in the risk assessment.

5.2.2 Sodium percarbonate

The REACH registration describes sodium percarbonate as a mixture of sodium carbonate and hydrogen peroxide in the ratio 2:3. This means that 1 g of sodium carbonate:hydrogen peroxide (2:3) corresponds to 675 mg sodium carbonate and 325 mg hydrogen peroxide, i.e., that 1% sodium percarbonate corresponds to 0.33% hydrogen peroxide.

The REACH registration for sodium percarbonate contains few experimental data on the substance as reference is made to the creation and toxicity of hydrogen peroxide. Nonetheless, tests for acute oral toxicity, eye irritation and skin sensitization have been conducted. An oral LD_{50} value has been found in rats of 893 mg/kg bw for male rats. Sodium percarbonate was not found to irritate or sensitize skin, but it caused serious eye irritation (iris and conjunctiva) in rabbits. The toxicity of sodium percarbonate is to a high degree determined by the content of hydrogen peroxide, as the content of sodium carbonate can be regarded as with no toxicological relevance. EFSA (2010) has, thus, assessed that the usage of sodium carbonate as an additive in food does not constitute any health risk, which is why no upper limit for the usage of the substance has been made.

Final conclusion

Sodium percarbonate is assessed to possess the same hazard profile as hydrogen peroxide. The risk assessment of the substance should, therefore, be conducted in the light of the risk assessment for hydrogen peroxide.

5.2.3 Phthalimidoperoxycaproic acid (PAP)

The gross formula for PAP is $C_{14}H_{15}NO_5$. 1 g PAP is able to release 0.12 g hydrogen peroxide equivalent to 12%. A literature search has failed to yield any toxicological details on the substance. The search included, for example, a search in the ECHA database in which no toxicological data were registered in the registration dossier of the substance. No data on the substance were found in the PubMed database or in the Cosmetic Ingredient Review database.

PAP is marketed by Solvay, and the safety data sheets for PAP provide results from a number of unpublished internal test reports (Solvay 2018a, Solvay 2018b).

TABLE 18. Toxicological data for PAP (Solvay 2018a, Solvay 2018b).

Properties	Phthalimidoperoxycaproic acid, (PAP)
pH	4 (0.5% suspension)
Acute oral toxicity	LD_{50}: 2550 mg/kg (rats) OECD TG 401
Acute dermal toxicity	LD_{50}> 2000 mg/kg (rats) OECD TG 402
Skin irritation	Not skin irritating (rabbit) OECD TG 404
Eye irritation	Serious eye damage (rabbit) OECD TG 405
Skin sensitisation	Not sensitizing (guinea pig maximization test)
Mutagenicity	
In vitro	Negative
In vivo	OECD TG 471, 473 + Chromosome damage test, human lymphocyte Negative OECD TG 474 and TG 486
Repeated dose toxicity	NOAEL*: 100 mg/kg bw/day OECD TG 407 (28 days, orally)
Reproduction 2-generation test	NOAEL*: (fertility): 30 mg/kg bw/day NOAEL*: (teratogenic effects): 100 mg/kg bw/day OECD TG 416 (based on read-across from unindicated substance)

* It is not further specified in the studies where NOAEL has been determined, which types of effects have been observed.

Data from teeth-whitening

As mentioned previously in section 2.1.1, Greenwall-Cohen et al. (2019) have studied the effects of teeth whitening with a teeth-whitening product containing PAP. By conducting an electron microscopy of the teeth, it was possible to observe a corrosive and degrading effect on the enamel and a reduced tooth surface hardness.

Final conclusion

PAP is an acid with oxidizing properties. The substance is strongly irritating on the mucous membrane and can in connection with use in teeth-whitening products cause corrosion and reduced hardness of the enamel. On the basis of non-published company data, the NOAEL is determined to be 30 mg/kg bw/day for systemic effects based on fertility as critical effect. This

value is used as the POD value in the risk assessment. The data source is, however, uncertain as no further description of the toxicological studies is available.

5.2.4 Chlorite/sodium chlorite

The most relevant basis of assessment for chlorite is considered to be partly from the data on sodium chlorite, partly from REACH registration of sodium chlorite, and partly from a WHO assessment (2005).

Acute toxicity

In the REACH registration dossier for this substance, the oral LD_{50} value for rats is given as 284 mg/ kg bw, and the dermal LD_{50} value for rabbits is given as 134 mg/kg bw, which is the basis for the Acute Tox 3 classification for oral exposure and Acute Tox 2 classification for dermal exposure.

Local effects

In the REACH registration dossier for this substance, it is stated that in animal tests, sodium chlorite irritates the skin. In an *in vitro* test with human skin, an 8-hour exposure to 4.4% sodium chlorite solution resulted in the penetration of the skin corresponding to an absorption of 5%. A 31% solution resulted in a severe irreversible eye irritation, while a 9% solution resulted in moderate reversible impact on rabbit eyes, among others, reddening and oedema in conjunctival mucous membrane. The latter test was carried out in 2017 according to OECD TG 405. The substance is not considered to be able to cause skin allergy (skin sensitizing).

Systemic effects upon repeated dosage

Based on a 90-day test with rats that had drinking water added 0, 10, 25 or 80 mg sodium chlorite/L (corresponding to 0, 7.4, 18.6, or 59.7 mg/kg bw/day), WHO (2005) established a NOAEL value of 7.4 mg/kg bw/day as a result of inflammation conditions and gastric ulceration as well as increased weight of spleen and adrenal glands at high exposure levels.

Mutagenic effects

WHO (2005) indicates that sodium chlorite has caused mutagenic effects (damage to cell-genetic material) in bacteria. No effects were detected in *in vitro* tests with mammal cells regarding damage of genetic material. However, the *in vivo* test showed an increased occurrence of damage to genetic material in bone marrow cells in mice that received a single injection in the abdominal cavity. According to the REACH registration, the positive *in vivo* response only occurred in a test with a single dosage in the abdominal cavity, whereas tests with repeated dosage in the abdominal cavity or with repeated oral dosage did not result in effects, which makes it possible to conclude that the substance is not mutagenic.

Carcinogenic effects

Long-term studies with rats (85 weeks) and mice (80 weeks) showed no dosage-related increased occurrence of tumours at oral dosage of up to 41 mg/kg bw/day in rats and 68.6 mg/kg bw/day in mice (WHO, 2005).

Effects on reproduction

In a 2-generation study with rats, the animals received the dosage of sodium chlorite through drinking water in concentrations of 0, 35, 70, 300 mg/L. Based on this study, a NOAEL concentration of 35 mg/L could be determined (corresponding to 2.9 mg/kg bw/day), as the high exposure levels resulted in increased liver weight and neurological effects on both first- and second-generation offspring (WHO, 2005). In pregnant rabbits, a dosage of 26 mg/kg bw/day, from day 7 to day 19 in pregnancy caused decreased weight of new-born rabbits and delayed bone formation (WHO, 2005).

Data from teeth-whitening

Sodium chlorite ($NaClO_2$) is often used in teeth-whitening products together with citric acid to lower pH and, thus, facilitate the formation of chlorine dioxide, which has an oxidizing effect (Wang et al., 2008). As stated in the study by Wang et al. (2008) and Greenwell-Cohen (2019), teeth-whitening products based on sodium chlorite, as a result of their content of citric acid, can cause dissolution of calcium in tooth enamel and change its surface structure and hardness. Greenwell-Cohen (2019) indicates a relatively better whitening effect of sodium chlorite-citric acid products compared to other teeth-whitening products for personal use.

Final conclusion

Sodium chlorite is corrosive/highly irritating to mucous membranes in high concentrations. No data is available for the exposure of mucous membrane in oral cavity, but based on the data from an eye-irritation test, an LOAEL value of 9% can be set for reversible irritation effects on conjunctival mucous membrane (mucous membrane in the eye) after short-term exposure. Even though there is an uncertainty related to the transfer of quantitative data from the conjunctival mucous membrane to the oral cavity mucous membrane, these data are considered to be a better foundation than, for example, the usage of data from a skin irritation test. SCCS (2018) recommends that for extrapolation from LOAEL to NOAEL, a factor 3 is applicable for slightly lower degree of effects. In addition, there is uncertainty in case of extrapolation of effects after short-term exposure of the conjunctival mucous membrane, as tears will eliminate the test solution relatively fast. As the teeth-whitening product will expose the gum mucous membrane for up to 60 minutes (see chapter 6.3.4), an additional uncertainty factor of 3 is applied for this condition. Hereof, a POD value of 1% is achieved regarding mucosal irritation for the risk assessment.

As the basis for assessment of systemic effects, a NOAEL of 2.9 mg/kg bw/day is considered to be the best foundation for a POD value in case of increased liver weight and neurological effects, which complies with both the assessment by WHO (2005) and the assessment in the REACH registration dossier.

5.2.5 pH value and adverse effects

Table 19 below indicates data regarding pH and pK_s values for ingredients with acidic/base properties, which are either declared or determined by chemical analyses. The data is mainly obtained from the PubChem database and REACH registrations for substances.

TABLE 19. Substances and their acidic properties.

Substance	CAS No.	pH*	Source
Hydrogen peroxide	7722-84-1	50% solution: 2.02 1% solution: 5.4	REACH-reg.
Sodium percarbonate	15630-89-4	n.d.	-
Phthalimidoperoxycaproic acid (PAP)	128275-31-0	0.5% suspension: 4	Solvay 2018b

Sodium chlorite	7758-19-2	n.d.	-
Citric acid	77-92-9	5%: 1.8	REACH-reg
Triethanolamine	15879-01-3	0.1M: 10.5	PubChem
Sodium hydrogen carbonate	144-55-8	1%: 8.0-8.6 pKs 6.3	PubChem
Sodium carbonate	497-19-8	1%: 11.4	PubChem
Pentasodium triphosphate	7758-29-4	1%: 9.1-10.2	PubChem
Potassium sorbate	590-00-1	pKs: 4.76 (acid)	PubChem
Sodium benzoate	1011270-78-2	pKs: 4.2 (acid)	PubChem

n.d.: no data
* The shown values are indicated as they are stated in sources, i.e., the foundation and reliability of these data has not been subject to a closer assessment.

Dawes (2003) has analysed how the effects on tooth enamel depend on pH values and concludes that it is not possible to set a critical pH value alone. Other components in saliva can also have a great impact on the effects on tooth enamel. Calcium ions and phosphate ions, in particular, have a protective effect. Erosion can be observed in enamel of teeth stored in saliva at pH 6.5 with low content of calcium and phosphate, while this only occurs at pH 5.1-5.5 at higher levels of calcium and phosphate.

Degaldo et al. (2015) indicates a pH between 5.2 and 5.5 as critical for enamel erosion, while a critical pH for tooth bone is pH 6.7. For persons with a low saliva secretion, a range of products are found that can stimulate saliva secretion, e.g., products containing citric acid, which is assessed as critical due to the acidic properties of the substance. In their study, the teeth were stored in 5 ml of seven different saliva-stimulating products for two weeks, and this was compared to teeth stored in tap water and a 3% citric acid solution. The pH for seven products was in the interval 3.0-9.1, while pH in citric acid solution was 1.3. After storage in the liquid, the teeth were dried and weighed. The product with pH 3.0 had caused a loss of tooth weight of 9.6%, while the citric acid solution had caused a weight loss of 18.8%. All other products had caused no or a minor tooth weight loss.

Carvalho et al. (2015) points out that pH cannot be used alone to assess the risk of teeth damage, as the buffer capacity and other substances, among others, calcium content, are of great importance. Yoghurt, for instance, has a pH of 4, but is not considered to have a damaging effect on teeth, rather beneficial as a result of the high calcium content. Pallesen[12] mentions that a range of beverages and food products with their low pH can have a corrosive effect on teeth surface e.g. Coca-Cola with pH 2.5, apple juice with pH 3.6 and orange with pH of 3.4. However, the buffer capacity is assessed to have a lower impact on the corrosion than the degree of acidity. Acid corrosion can affect the light reflection making the tooth surface appear brighter, which faulty indicates a whitening effect on teeth.

Final conclusion

Mainly the acidic pH values have been studied in connection with degradation of tooth tissue, where enamel degradation is indicated to occur at pH 5.2-5.5 pH and below. Several authors mention the content of citric acid, in particular, as causing the risk of enamel degradation. When assessing enamel degradation, the exposure time is an important factor, which is why

[12] Personal communication with Ulla Pallesen, Senior Dentist, at Department of Odontology, University of Copenhagen

products with a long duration of the treatment per treatment constitute the greatest risk at comparable pH levels. No data have been found on the varying pH of solutions and their effect on mucous membranes in oral cavity and gums. Based on pH value alone, one should, in line with standards for classification and labelling of chemical products (CLP Regulation), consider products with pH of pH ≤ 2 and pH ≥11.5 as corrosive.

5.2.6 Oxidation potential and adverse effects

Via web-based searches it has not been possible to find literature sources describing any relation between the oxidation potential and adverse local effects.

5.2.7 Overall assessment of critical effect levels

Overall assessment of critical effect levels, TABLE 20 below, provides an overview of critical POD values according to the above-mentioned assessments.

TABLE 20. POD values for application in risk assessment for active whitening ingredients.

Substance CAS No.	POD Local effects	POD Systemic effects	POD Effects on teeth
Hydrogen peroxide 7722-84-1	2% (H) Irritation/inflammation of mucous membranes and gums	20 mg/kg bw/day (D) Impact of enzyme activity in plasma	1.1% (H) Increased tooth sensitivity
Sodium percarbonate 15630-89-4	As hydrogen peroxide	As hydrogen peroxide	As hydrogen peroxide
Phthalimidoperoxycaproic acid (PAP) 128275-31-0	As hydrogen peroxide (No data available for PAP)	30 mg/kg bw/day (D) Impacts fertility	Damaging effect on enamel No data available to establish POD
Sodium chlorite 7758-19-2	1% (D) Mucosal irritation	2.9 mg/kg bw/day (D) Impact on liver and nervous system	Damaging effect on enamel by presence of citric acid in product No data available to establish POD

(H): Based on human data
(D): Based on animal test data

When assessing teeth-whitening products with the substances indicated above, the product pH value must also be taken into account as early adverse effects on tooth enamel are considered to occur at pH values below 5.5, while more extensive corrosive effects on mucous membranes are considered to be possible at pH ≤ 2 or pH ≥ 11.5.

5.3 Exposure assessment of selected teeth-whitening products

Exposure estimates are created for the teeth-whitening products for which analysis results are available on the content of individual ingredients. Since the previously described hazard assessment on local effects only includes data for critical NOAEL/LOAEL values in the form of percentage content, the products will be risk assessed for local effects based on the content

percentage. Thus, the exposure will not be calculated in mg/cm^2 because it is not possible to perform a risk assessment in relation to the unit mg/cm^2.

For calculation of exposure, the following parameters described in chapter 3, must be taken into consideration:

- treatment time (per procedure)
- amount of product per treatment
- content concentration of the active ingredient
- number of treatments per day
- frequency of treatment (every day, every other day, once per week, etc.)

Local exposure

As mentioned above, the local effect for each individual component can alone be assessed based on the concentration of the individual substance.

Systemic exposure

For assessment of the systemic exposure, the starting point, according to guidelines in SCCS (2018), is a worst-case scenario, as it is evaluated that 100% of the applied amount of the active whitening ingredient is absorbed systemically.

For calculation of exposure, the user instruction for each individual product is used as a starting point, where data regarding the above-mentioned parameters has been collected. Furthermore, the volume of each individual packaging of the teeth-whitening gel is taken into consideration (see Appendix 3).

For calculation of the systemic dosage, the body weight of 60 kg is used as a starting point according to the recommendation by SCCS (2018), as products are evaluated to be suitable for adults and not children. With a body weight of 60 kg, possible usage by adolescents (late teens) is covered, as well.

5.3.1 Products with hydrogen peroxide

For Products No. 12 and 22, which are declared with hydrogen peroxide, the substance is also found in the analysis (see TABLE 13). Furthermore, hydrogen peroxide is found in product No. 20 despite the fact that hydrogen peroxide or any other hydrogen peroxide-releasing substance has not been indicated on the product.

Product No. 12, tray

The product includes nine gel treatments, and treatments are recommended to last 15 minutes every other day. For each treatment, 0.5 g of gel must be used. Measured H_2O_2-content: 10.8%.

The following exposure can be estimated on a day of treatment:

Exposure, local: 10.8% H_2O_2

Exposure, systemic = 0.5 g/d x 0.108 g H_2O_2/g / 60 kg x 1000 mg/g

Exposure, systemic = 0.9 mg H_2O_2/kg bw/day

Product No. 22, pen

The product must be used for 10 minutes two times per day. Treatment duration is not indicated. The product can be used very locally on each tooth, and it is, thus, evaluated that the product, in case of normal use, is applied to a more limited number of teeth at a time. The pen is designed with a turning mechanism, so that only a small amount of gel is delivered per turn, which means that extensive overdosage of the product is unlikely. In TABLE 31, Appendix 3, an area of 20 cm^2 has been applied with the pen, which corresponds to the usage of the pen both in the upper and lower part of the mouth. The total weight of the applied gel was 0.15 g. As a worst-case scenario, a consumer is considered who uses the product on *all* teeth twice a day corresponding to 2 x 0.15 g gel. Measured H_2O_2-content: 1.9%.

The following exposure can be estimated on a day of treatment:

Exposure, local: 1.9% H_2O_2

Exposure, systemic = 2 x 0.15 g/d x 0.019 g H_2O_2/g / 60 kg x 1000 mg/g

Exposure, systemic = 0.10 mg H_2O_2/kg bw/day

Product No. 20, tray

0.5 g of gel is applied to both upper and lower teeth tray per treatment. The treatment must last 20-45 minutes once per week. Measured H_2O_2-content: 3.1%.

The following exposure can be estimated on a day of treatment:

Exposure, local: 3.1% H_2O_2

Exposure, systemic = 2 x 0.5 g/d x 0.031 g H_2O_2/g / 60 kg x 1000 mg/g

Exposure, systemic = 0.52 mg H_2O_2/kg bw/day

5.3.2 Products with sodium percarbonate

Even though products No. 2, 14, 15 and 16 are all declared with the content of sodium percarbonate, the release of hydrogen peroxide was only detected for product No. 2.

Product No. 2, tray

1.5 g gel must be used per treatment. Two 15-minute treatments per day must be carried out. Measured H_2O_2-content: 0.09%.

The following exposure can be estimated on a day of treatment:

Exposure, local: 0.09% H_2O_2

Exposure, systemic = 2 x 1.5 g/d x 0.0009 g/g / 60 kg x 1000 mg/g

Exposure, systemic = 0.045 mg H_2O_2/kg bw/day

5.3.3 Products with PAP

Products No. 24 and 25 are declared with PAP, but release of hydrogen peroxide was only detected for Product No. 24. Measured H_2O_2-content: 0.04% corresponding to 0.33% PAP.[13]

Product No. 24, tray

1-5 ml gel must be used per treatment, and one treatment of 10-minute duration must be performed per day. Since the local effects, as stated in chapter 5.2.6, are risk assessed based on the toxicological data for hydrogen peroxide, the exposure of hydrogen peroxide is calculated:

Exposure, local: 0.04% H_2O_2

The systemic effects, as stated in 5.2.6, are risk assessed based on the toxicological data for PAP, the exposure is calculated for PAP:

Exposure, systemic = 1.5 g x 0.0033 g PAP/g / 60 kg x 1000 mg/g

Exposure, systemic = 0.083 mg PAP/kg bw/day

5.3.4 Products with chlorite

In the analysis, chlorite was detected in products No. 3 and 15 despite the fact that the products were not declared with this substance. Product No. 8 is declared with 1.0% sodium chlorite, yet chlorite was not detected in the analysis. Nevertheless, the exposure assessment has been performed for this product as it may be possible that the product has initially contained this concentration of sodium chlorite, where the chlorite ion has degraded into chloride during storage.

Product No. 8, strips

For a treatment with a strip for upper and lower part of the mouth, 0.77 g gel is used. On the product, it is indicated that the strips must stay on for 30 minutes, and teeth must be rinsed after the treatment. There is no indication of the number of treatments per day or the duration of treatment. In the following, it is assumed that two treatments per day are performed. Indicated content of sodium chlorite: 1.0%.

The following exposure can be estimated on a day of treatment:

Exposure, local: 1.0% $NaClO_2$

Exposure, systemic = 2 x 0.77 g x 0.010 g $NaClO_2$/g / 60 kg x 1000 mg/g

Exposure, systemic = 0,26 mg $NaClO_2$/kg bw/day

Product No. 3, tray

1.0 ml gel is applied per treatment, and one treatment per day for 45-60 minutes must be performed. Measured chlorite content: 0.07% corresponding to 0.09% sodium chlorite ($NaClO_2$).

The following exposure can be estimated on a day of treatment:

[13] Since 1 g PAP can release 0.12 g H_2O_2, it corresponds to 0.04% x 1 g/0.12 g = 0.33% PAP.

Exposure, local: 0.09% $NaClO_2$

Exposure, systemic = 1.0 g x 0.0009 g $NaClO_2$/g / 60 kg x 1000 mg/g

Exposure, systemic = 0.015 mg $NaClO_2$/kg bw/day

Product No. 15, tray

1.0 ml gel is applied per treatment, and one treatment per day for 20-45 minutes must be performed. Measured chlorite content: 0.09% corresponding to 0.12% sodium chlorite ($NaClO_2$).

The following exposure can be estimated on a day of treatment:

Exposure, local: 0.12% $NaClO_2$

Exposure, systemic = 1.0 g x 0.0012 g $NaClO_2$/g / 60 kg x 1000 mg/g

Exposure, systemic = 0.020 mg $NaClO_2$/kg bw/day

5.4 Risk assessment of selected teeth-whitening products

For the risk assessment, the Margin of Safety value (MoS) is calculated according to SCCS (2019) as:

$$MoS = POD / SED$$

where:

POD: Point of Departure is established from the NOAEL or LOAEL value

SED: Systemic Exposure Dose, corresponding to the calculated systemic exposure of the substance.

The MoS value must be of a certain size in order to be able to consider the exposure as safe and without risk. For systemic effects, SCCS (2018) states that a MoS value of 100 and above is generally considered as acceptable, as this MoS value is high enough to ensure that uncertainties in relation to extrapolation of data from animal tests to humans (subfactor of 10) and individual differences in sensitivity in humans (subfactor of 10) are taken into account. If the MoS value is calculated from a POD value based on human data, a MoS value of 10 is considered to be adequate, as only a factor for individual differences between people should be used.

For local effects, SCCS (2018) does not correspondingly state an acceptable MoS value, but it is assumed that it could be smaller, as observed in, e.g., the case of irritation effects caused by a simple damage to cell membranes, where the sensitivity in humans is not considered to be higher than in animals. Thus, this approach is applied in the risk assessment in connection with the REACH regulation as described in the REACH guidance document R8 (ECHA 2012). However, a factor of 10 is maintained for individual differences between people.

5.4.1 Risk assessment of local effects

TABLE 21 below shows the calculation of MoS values for the oral exposure in oral cavity for effects on mucous membranes/gums and effects on teeth. POD and exposure values are indicated as a percentage content, which is why the above-mentioned equation is rewritten as follows:

$$MoS = POD\ (\%) / \text{exposure}\ (\%)$$

TABLE 21. Calculation of Margin of Safety (MoS) for local effects. Values stated in bold are considered to constitute a risk of effects.

Product No. **Product type** **Distributor's country of origin**	**Exposure**	**POD** **Local effects** **Mucous membrane/gums (S)**	**POD** **Local effects** **Teeth** **(T)**	**MoS** **(S)**	**MoS** **(T)**
	Hydrogen peroxide				
2 Tray Denmark	0.09% 2x15 min/day	2% (H) Irritation/inflammation of mucous membranes and gums	1.1% (H) Increased sensitivity	22	12
12 Tray Outside the EU	10.8% 15 min/2 day	2% (H) Irritation/inflammation of mucous membranes and gums	1.1% (H) Increased sensitivity	**0.19**	**0.10**
20 Tray Outside the EU	3.1% 20-45 min/week	2% (H) Irritation/inflammation of mucous membranes and gums	1.1% (H) Increased sensitivity	**0.65**	**0.35**
22 Pen Outside the EU	1.9% 2 x 10 min/day	2% (H) Irritation/inflammation of mucous membranes and gums	1.1% (H) Increased sensitivity	**1.1**	**0.58**
24 Tray Outside the EU	0.04% 10 min/day	2% (H) Irritation/inflammation of mucous membranes and gums	1.1% (H) Increased sensitivity	50	28
	PAP				
24 Tray Outside the EU	0.33% 10 min/day	Irritates mucous membrane No data available for establishment of	Damaging effect on enamel. No data available for establishment of	-	-
	Sodium chlorite				
3 Tray Denmark	0.09% 45-60 min/day	1% Irritates mucous membranes (D)	Damaging effect on enamel in presence of citric acid in the product	**11**	-
8 Strips Other EU countries	1.0% 2 x 30 min/day	1% Irritates mucous membrane (D)	Damaging effect on enamel in presence of citric acid in the product	**1**	-

Product No. Product type Distributor's country of origin	Exposure	POD Local effects Mucous membrane/gums (S)	POD Local effects Teeth (T)	MoS (S)	MoS (T)
15 Tray Other EU countries	0.12% 20-45 min/day	1% Irritates mucous membrane (D)	Damaging effect on enamel in presence of citric acid in the product	**8**	-

-: indicates that no data are available for assessment and MoS-calculation for effect
(D): POD based on animal test data
(H): POD based on human test data

Hydrogen peroxide

Products No. 12, 22 and 20 (all purchased from distributors outside the EU) contain or release hydrogen peroxide. For these products, the MoS values for irritation effects in mucous membranes and gums are calculated in the interval 0.19-1.1. The MoS values for increased sensitivity in teeth are in the interval 0.10-0.75. Since further consideration should be given to individual differences in sensitivity in the oral cavity and teeth, these MoS values are considered as too low. Therefore, according to data available for the usage of hydrogen peroxide in teeth-whitening products, the products are assessed to be able to constitute a risk of temporary irritation/inflammation in mucous membranes and gums as well as increased tooth sensitivity.

For Product No. 2 (purchased from distributor in Denmark) and Product No. 24 (purchased from distributor outside the EU), the MoS values are in the interval 12-50, which is why usage of these products is not assessed to constitute a risk of harmful effects on mucous membranes and teeth when using these products.

Sodium chlorite

For Product No. 8, a MoS value of 1 is reached, meaning that a sodium chlorite content of 1% may cause irritation in mucous membranes and gums. For Products No. 3 (purchased from distributor in Denmark), and 15 (purchased from distributor in EU), which both contain chlorite, MoS values have been calculated in the interval 8-11 for mucous membrane irritation effects. Furthermore, individual differences in the sensitivity of mucous membranes and teeth should be taken into consideration, and as POD is extrapolated from animal tests with a very short exposure time, these MoS values are not considered to be fully attributable. Temporary irritation effects from the usage of these products cannot be excluded.

5.4.2 Risk assessment of systemic effects

TABLE 22 below shows MoS values for systemic effects, which are calculated as follows:

MoS = POD (mg/kg bw/day) / calculated exposure (mg/kg bw/day)

TABLE 22. Calculation of Margin of Safety (MoS) for systemic effects.

Product No. Product type Distributor country of origin	Exposure	POD Systemic effects	MoS
	Hydrogen peroxide		
2 Tray Outside the EU	0.045 mg/kg bw/day from 3.0 g gel/day	20 mg/kg bw/day (D) Effect on enzyme activity in plasma	444
12 Tray Outside the EU	0.9 mg/kg bw/day from 0.5 g gel/ day	20 mg/kg bw/day (D) Effect on enzyme activity in plasma	22
20 Tray Outside the EU	0.52 mg/kg bw/day from 1.0 g gel/day	20 mg/kg bw/day (D) Effect on enzyme activity in plasma	38
22 Pen Outside the EU	0.10 mg/kg bw/day from 0.3 g gel/day	20 mg/kg bw/day (D) Effect on enzyme activity in plasma	200
	PAP		
24 Tray Outside the EU	0.083 mg/kg bw/day from 1.5 g gel/day	30 mg/kg bw/day (D) Effect on fertility	361
	Sodium chlorite		
3 Tray Denmark	0.015 mg/kg bw/day from 1.0 g gel/day	2.9 mg/kg bw/day (D) Effect on liver and nervous system	193
8 Strips Other EU countries	0.26 mg/kg bw/day from 1.5 g gel/day	2.9 mg/kg bw/day (D) Effect on liver and nervous system	11
15 Tray Other EU countries	0.020 mg/kg bw/day from 1.0 g gel/day	2.9 mg/kg bw/day (D) Effect on liver and nervous system	145

(D): POD based on animal test data
(H): POD based on human test data

However, it must be noted that exposure estimates are calculated assuming that 100% of the active substance content is absorbed systemically. Therefore, this procedure must be viewed as worst case and considerably overestimates a more realistic exposure. For instance, SCCP (2007) indicates that hydrogen peroxide reacts fast and that hydrogen peroxide concentration in a product will fall after placing it in the mouth. For strips, the SCCP has calculated an average concentration of hydrogen peroxide in the strip of 60-minute usage corresponding to 1/5 of the initial concentration.

For Products No. 2, 3, 15, 22 and 24, the MoS values are significantly above 100, which is why the usage of these products does not constitute a risk of systemic effects.

For Products No. 12 and 20 containing 10% and 3.1% hydrogen peroxide, respectively, the calculated MoS values are 22 and 38, respectively, based on these conservative exposure estimates. These products are principally not considered as safe according to animal test data. However, it is complicated to make a more precise conclusion on the basis of missing knowledge of the real systemic exposure. For Product No. 8, the calculated MoS value is 11 for exposure to sodium chlorite. In the same way as for products with hydrogen peroxide, it is also very complicated to assess, if this relatively low MoS value constitutes a risk as the exposure level is very conservative given that a large, but unknown, part of sodium chlorite content is expected to be reduced to chloride.

For Product No. 24, which contains PAP, a very high MoS value of 361 has been calculated for PAP (i.e., no risk).

According to the above, the usage of this product does not constitute a risk of effects in the intestinal tract.

5.4.3 Effects of pH

As indicated in section 5.2.5, degradation of tooth enamel may occur at low pH values up to 5.2-5.5. As mentioned, this assessment based on the pH value alone is uncertain, because the degradation of enamel will depend on the content of other ingredients in the product and saliva. No data have been found on pH and effect on mucous membranes and gums. However, based on the pH value alone, it is possible to consider products with pH ≤ 2 and pH ≥ 11.5 corrosive according to standards for classification and labelling of chemical products (CLP Regulation).

In TABLE 23 below, the products within the above-mentioned pH intervals are marked with a risk of corrosive effects on tooth enamel, ”T”, and mucosal irritation effects, ”S”.

TABLE 23. Assessment of measured pH values and risk of effects.

Distributor country of origin	Product type	Product No.	pH	Risk to tooth enamel (T) and mucous membranes (S)
Denmark	Pen	6	2.4	T
	Pen	33	4.1	T
	Pen	7	10.1	-
	Pen	1	10.2	-
	Tray	32	3.5	T
	Tray	2	3.5	T
	Tray	14	6.7	-
	Tray	35	6.9	-
	Tray	4	10.5	-
	Tray	3	10.6	-
	Strips	5	2.9	T
	Strips	27	11.5	S
Other EU countries	Pen	30	4.3	T
	Pen	16	7.1	-
	Pen	28	n.a.	-
	Tray	29	6.5	-
	Tray	15	10.9	-
	Strips	8	8.2	-
Outside the EU	Pen	10	0	T, S
	Pen	22	4.0	T
	Tray	12	3.8	T
	Tray	20	4.0	T
	Tray	24	5.9	-
	Tray	21	7.0	-
	Strips	25	7.0	-

It can be seen that ten out of 25 products have a lower pH value than pH 5.5, which means that they have the potential of damaging the enamel. Two products (Products No. 27 and 10) have pH values that indicate a risk of corrosion of mucous membranes.

Products with low and high pH values (pH ≤ 3 and pH ≥ 11.5), i.e., products that deviate most significantly from a neutral pH, are described below.

Product No. 5, strips, pH 2.9

The only substance with acidic properties stated in the product declaration is PAP. Other ingredients that have been added in smaller amounts are alkaline substances (dicalcium phosphate, disodium EDTA, sodium hydroxide). The low pH value is, thus, considered to be related to the use of PAP. The product is considered to constitute a risk of corrosive damage on teeth.

Product No. 27, strips, pH 11.5

Out of all the declared substances, citric acid (see TABLE 6) is the only substance with acid/base properties. Citric acid causes a low pH, which is why the declaration can be considered as insufficient as it does not include any alkaline ingredients. With the pH value of 11.5, the product is considered to constitute a risk of alkaline corrosive damage in mucous membranes.

Product No. 6, pen, pH 2.4

Out of all the declared substances, triethanolamine is the only substance with acid/base properties; and it is alkaline. Thus, it is not possible explain the product's low pH from the ingredient list. Based on the pH value of the product, it can be concluded that the product constitutes a risk of corrosive damage to the teeth.

Product No. 10, pen, pH 0

According to the declaration, the pen contains a range of plant-derived ingredients with unknown acid/base properties. Furthermore, the product contains disodium borate, i.e., a substance with alkaline properties. Thus, it is not possible to explain the low pH of the product from the declaration. Based on the product pH value, it can be concluded that the product constitutes a risk of corrosive damage to the teeth and mucous membranes/gums.

5.4.4 Oxidation potential and adverse effects

There is no data available to perform a risk assessment of the measured oxidation potentials of these products.

5.5 Identified risks and risk products

Local effects

Regarding the effects on mucous membranes/gums and teeth (increased tooth sensitivity), usage of products indicated in TABLE 24 constitutes a potential risk, as the identified MoS values are too low to render these products safe from effects on mucous membranes/gums and teeth.

TABLE 24. Teeth-whitening products with the risk of local effects.

Product No. Product type Distributor country of origin	Exposure	MoS Effects on mucous membranes/gums	MoS Increased tooth sensitivity
	Hydrogen peroxide		
12 Tray Outside the EU	10.8% 15 min/ 2 day	0.19	0.10
20 Tray Outside the EU	3.1% 20-45 min/week	0.65	0.29
22 Pen Outside the EU	1.9% 2 x 10 min/day	1.1	0.55
	Sodium chlorite		
3 Tray	0.09% 45-60 min/day	11	-

Denmark			
8 Strips Other EU countries	1% 30-60 min/day	1	-
15 Tray Other EU countries	0.12% 20-45 min/day	8	-

Products with the content of hydrogen peroxide concentrations of 1.9-10.8% are considered to constitute an increased risk of local effects on mucous membranes/gums and teeth in the form of increased tooth sensitivity. The remaining teeth-whitening products with a lower content of hydrogen peroxide (corresponding to 0.1% and below) are not considered to constitute a risk of local effects as they have significantly higher MoS values.

For products with sodium chlorite in the interval 0.09-1%, the calculated MoS values indicate an increased risk of local effects. This means that the usage of sodium chlorite as a whitening agent can be problematic, especially because there are no regulatory limitations on the usage of sodium chlorite in cosmetic products. Furthermore, citric acid is typically used in combination with sodium chlorite, and citric acid is known to corrode tooth enamel due to its acidic effect. Similarly, there is no limitations for the usage of citric acid in cosmetic products.

Systemic effects

In relation to with the chemical analysis performed for the risk assessment above, three products were identified with MoS values below 100. This usually indicates that these products constitute a risk of systemic effects as a result of systemic absorption of teeth-whitening agent.

TABLE 25. Teeth-whitening products with calculated risk of systemic effects.

Product No. **Product type** **Distributor country of origin**	**Exposure**	**MoS**
Hydrogen peroxide		
12 Tray Outside the EU	0.9 mg/kg bw/day from 0.5 g/ gel/ day with content of 10.8% H_2O_2	22
20 Tray Outside the EU	0.52 mg/kg bw/day from 1.0 g/ gel/dag with content of 3.1% H_2O_2	38
Sodium chlorite		
8 Strips Other EU countries	0.26 mg/kg bw/day from 1.5 g gel/day with 1.0% $NaClO_2$	11

However, the assessment is very uncertain as the exposure is calculated from a systemic absorption of 100% of hydrogen peroxide or sodium chlorite content in the product, and this can be seen as a conservative observation. Among others, a considerably large part of the active substances will react with the local oxidation of teeth and gums, which means that only a smaller part will be absorbed systemically.

Also, it must be noted that the rather low MoS values have been observed in case of usage of teeth-whitening products with 3.1-10.8% hydrogen peroxide content, and that the products, which meet the regulatory requirements for max. 0.1%, will have significantly higher MoS values, which indicates a safe usage.

pH-dependent effects

From the measurements of pH values in 25 teeth-whitening products, 11 products are considered to constitute a risk of effects based on measured pH values, see **TABLE 26**.

TABLE 26. Teeth-whitening products constituting a risk based on product pH value.

Distributor country of origin	Product type	Product No.	pH	Risk to tooth enamel (T) and mucous membranes (S)
Denmark	Pen	6	2.4	T
	Pen	33	4.1	T
	Tray	32	3.5	T
	Tray	2	3.5	T
	Strips	5	2.9	T
	Strips	27	11.5	S
Other EU countries	Pen	30	4.3	T
Outside the EU	Pen	22	4.0	T
	Pen	10	0	T, S
	Tray	12	3.8	T
	Tray	20	4.0	T

It is complicated to qualify the degree of risk for above-mentioned products, but especially products with the lowest and highest pH values (Products No. 5, 27, 6, 10) may be considered to constitute a risk. There are no general requirements for pH values of cosmetic products in the cosmetics regulation.

5.6 Conclusion on risks, uncertainties and limitations

5.6.1 Conclusion on risk assessment

In the risk assessment on teeth-whitening products, risks are assessed in relation to the following effects:

- local effects (irritation/inflammation) on mucous membranes and gums in oral cavity
- local effects regarding increased tooth sensitivity
- systemic effects related to absorption of the active teeth-whitening substance
- corrosive damage on mucous membranes or teeth caused by the pH value of the product

In total, 11 out of 25 studied teeth-whitening products were found to constitute a risk due to either a low pH value (pH ≤ 5,5) or a high pH value (pH 11.5). TABLE 27 lists the products where risks have been identified for the remaining effect parameters and provides an overview of the specific types of effects. It can be seen that only products with a high content/release of hydrogen peroxide (1.9-10.8%) can be identified with risks for several effect parameters at once.

TABLE 27. Overview products with detected risks for other parameters than pH.

Product No. Product type Distributor country of origin	Exposure	Risk of effects on mucous membranes/gums	Risk of increased tooth sensitivity	Risk of systemic effects	Risk due to pH
	Hydrogen peroxide				
22 Pen Outside the EU	1.9% 2 x 10 min/day	Yes	Yes	No	Yes
12 Tray Outside the EU	10.8% 15 min/2 day	Yes	Yes	(Yes)	Yes
20 Tray Outside the EU	3.1% 20-45 min/week	Yes	Yes	(Yes)	Yes
	Sodium chlorite				
8 Strips Other EU countries	1% 30-60 min/day	Yes	nd	(Yes)	No
3 Tray Denmark	0.09% 45-60 min/day	Yes	nd	No	No
15 Tray In the EU	0.12% 20-45 min/day	Yes	nd	No	No

nd: no data available for assessment
(Yes): indicates that the result is not conclusive due to highly uncertain exposure assessment

As an overall conclusion on the aim of the project, the identified risk products are listed according to the distributors' country of origin, see TABLE 28.

TABLE 28. Products with identified risks divided according to distributor's country of origin.

Distributor country of origin	Risk for tooth enamel and/or mucous membranes (incl. effects of pH) Product number	Number of analysed products
Denmark	2, 3, 5, 6, 27, 32, 33	12
Other EU countries	8, 15, 30	6
Outside the EU	10, 12, 20, 22	7
In total	14	25

It must be mentioned that products No. 12, 20 and 22 were the only products that exceeded the allowable limit of hydrogen peroxide content of 0.1% according to the cosmetics regulation.

In general, the risk assessment has indicated that teeth-whitening products with the content or release of the highest legally allowable concentration of 0.1% hydrogen peroxide can be con-

sidered as safe regarding both local and systemic effects from hydrogen peroxide, which complies with the assessment by SCCP (2007). Products with a content of hydrogen peroxide above 0.1% are considered to constitute a risk of temporary discomfort regarding irritation effects on gums and increased tooth sensitivity. Furthermore, the relatively low content (significantly below 1%) of sodium chlorite is assessed to constitute a risk of mucosal irritation of gums.

5.6.2 Exposure assessment, limitations, and uncertainties

All teeth-whitening products have an included user instruction specifying the usage of these products. Since packaging sizes are adapted to the user instructions, the exposure assessments regarding the applied amount of the teeth-whitening product are considered to be very realistic. At the same time, it cannot be ruled out that some consumers overuse the products, e.g. by applying large amounts of the product, performing several treatments per day or too frequent treatments over a period of time. For the risk assessment of local effects, this is, however, not considered to have an impact on the size of the MoS value, as the risk is evaluated on the basis of %-content of whitening agents in products. The acute effects of the whitening agents are the ones that are considered to be critical, and are established in relation to acute effect parameters, where critical exposure has been indicated as %-content. In relation to risk assessment of systemic effects, the overuse will have an impact and will result in lower MoS values. However, this will unlikely change in risk assessments for hydrogen peroxide-containing products, as MoS values (200 and 444) for products with low content of hydrogen peroxide (0.09% and 0.04%) are significantly above 100, and are, thus, sufficiently robust to be able to include a possible overuse. For products with sodium chlorite, the MoS values significantly exceed 100 (143 and 193) as well, and as there are limits to how large an overuse can occur when dosing products in trays, the calculated MoS values are considered to be able to take this into account. Furthermore, the MoS value must also been seen in relation to the fact that 100% of sodium chlorite content is assumed to be absorbed systemically. This is considered to be a conservative approach, because sodium chlorite will be consumed locally in connection with its transformation into the reactive chlorine dioxide.

5.6.3 Effect assessment, limitations, and uncertainties

Hydrogen peroxide

Compared to other whitening agents, the best data foundation with the lowest uncertainty is available for hydrogen peroxide. Here, a wide range of human test data are available on side effects locally in the oral cavity and teeth when using hydrogen peroxide-based teeth-whitening products. Also, the data on effect levels for hydrogen peroxide are quite precise. The systemic effects of hydrogen peroxide are also considered to be very well studied, which is why the application of a NOAEL of 20 mg/kg bw/day in the risk assessment is a valid starting point.

Sodium percarbonate

Since sodium percarbonate is converted to sodium carbonate and hydrogen peroxide, the assessment of sodium percarbonate based on the data on hydrogen peroxide is considered to be reliable as the concentration ratio sodium percarbonate:hydrogen peroxide of 3:1 is taken into consideration.

PAP

PAP is connected to a high uncertainty because no details are available from the toxicological tests on the substance, only data from safety data sheets. Since PAP can be applied in a concentration of approx. 0.8% to achieve the release of 0.1% hydrogen peroxide, it is considered specifically important to acquire a more precise knowledge on the mucosal irritation effects and effects on tooth enamel of this substance. This is especially due to the fact that the substance possesses acidic properties alongside the oxidizing properties.

Sodium chlorite

A more precise knowledge on the NOAEL value and the mucosal irritation effects in the oral cavity is lacking for sodium chlorite. The substance is usually used in teeth-whitening products in combination with citric acid, which is why it is important to include the knowledge on citric acid and its effects on tooth enamel in the risk assessment of sodium chlorite-containing teeth-whitening products.

pH

There is some uncertainty in the assessment of teeth-whitening products' irritative/corrosive effects on teeth and oral cavity surfaces based on the measured pH values alone. The lowest uncertainty is, however, for products that deviate mostly from the neutral pH level, i.e. relatively strong acids and bases.

Besides the pH value, buffer capacity of the product can also be of importance in relation to the scope of adverse effects. However, the buffer capacity is not established nor studied in this project and is, thus, not included in the assessment.

5.6.4 Legal aspects

As mentioned above, the content of sodium chlorite, citric acid as well as the pH value of the product are critical parameters, where each of these can constitute a risk for a teeth-whitening product. Here, it can be mentioned that the cosmetics regulation, except for the content of hydrogen peroxide, does not establish restrictions of use regarding the content of sodium chlorite and citric acid in cosmetic products, just as there are no limits for the pH value of a cosmetic product. However, there are requirements that cosmetic products must be safe for human health. In order to prove this, all cosmetic products must be subjected to a safety assessment, and a safety report must be produced for each product before it is placed on the market.

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Appendix 1. Selected products

A range of teeth-whitening products were prioritized for purchase/procurement in the project. The products that were received within the given time frame were a part of the analysis program and are presented in Appendix 1.1. The remaining of the prioritized products, which were not received within the relevant time frame, are listed in Appendix 1.2.

Appendix 1.1 Products in the analysis program

TABLE 29. Overview of the prioritized products that are part of the analysis program.

No.	Product type	Distributor country of origin*	Price** in DKK	Assumed active substance Specified at the distributor *Indicated on packaging/declaration*	Description of usage Specified at the distributor	Target group***
1	Teeth whitening pen	Denmark	56	Peroxide *Hydrogen peroxide*	Not specified	Men *Symbol for men on the website* ♂
2	Teeth whitening tray	Denmark	338	Not specified *Sodium carbonate peroxide*	Usage not described. Sufficient for 20 applications.	Not specified
3	Teeth whitening tray	Denmark	595	Sodium bicarbonate, hydrogen peroxide *Sodium bicarbonate, hydrogen peroxide*	The gel is applied to the tray (0.5 ml on each tray). Time per application 45 min. Increase the time per application by 15-20 min. for each new application. Repeat daily until the desired result is achieved.	Women *Picture of a woman*
4	Teeth whitening tray	Denmark	400	Sodium bicarbonate *Sodium bicarbonate*	The gel is applied to the tray (0.75 ml on each tray). Time per application 10 min. Repeated six consecutive days. Max. 12 applications in a month. Maintain every 14 days with an application.	Not specified / adolescent[d]
5	Teeth whitening strips	Denmark	318	PAP[a] *PAP[a]*	The strips are extracted from the disposable packaging and applied to the teeth. Time per application 30 min. Repeated every day for two weeks. Following applications every other month or as required.	Not specified
6	Teeth whitening pen	Denmark	129	Carbamide, peroxide *Non-peroxide*	The gel is applied to the teeth. Time per application 30 min. Repeated twice a day up to 20 days. The gel must not come into contact with the gums.	Not specified
7	Teeth whitening pen	Denmark	139	Sodium bicarbonate, sodium borate *Sodium bicarbonate, sodium borate*	The gel is applied to the teeth. Time per application 30 min.	Not specified
8	Teeth whitening strips	Other countries in the EU, incl. UK (UK)	206	Sodium chlorite, citric acid *Sodium chlorite 1.0%, citric acid 0.1%*	The strips are extracted from the disposable packaging and applied to the teeth. Time per application up to 30 min.	Men *Mr. is part of the name*

No.	Product type	Distributor country of origin*	Price** in DKK	Assumed active substance Specified at the distributor *Indicated on packaging/declaration*	Description of usage Specified at the distributor	Target group***
10	Teeth whitening pen	Outside of the EU (China)	23	Not specified *Borax[b]*	The teeth are scrubbed with the gel for a minute. If the stains cannot be removed, the application can be repeated after a week.	Women *Picture of women*
12	Teeth whitening tray	Outside the EU (USA)	401	Peroxide, hydrogen peroxide, carbamide peroxide *Hydrogen peroxide*	The gel is applied to the tray (a drop). Time per application not specified.	Girls, women *Picture of a girl*
14	Teeth whitening tray	Denmark	359	Not specified *Sodium percarbonate*	The gel is applied to the tray. Time per application 10 min.	Adults *Picture of adult men and women*
15	Teeth whitening tray	Other in the EU, incl. UK (Sweden)	378	Not specified *Sodium percarbonate*	Not specified	Not specified
16	Teeth whitening pen	Other in the EU, incl. UK (Sweden)	148	Not specified *Sodium percarbonate*	The gel is applied to the teeth. Time per application not specified. Repeated 1-2 times daily. The desired effect is normally achieved after 1-3 applications.	Broad *Picture of adult man and woman*
20	Teeth whitening tray	Not specified	82	Peroxide *Peroxide*	The gel is applied to the tray (0.25 ml on each tray). Time per application 2-15 min.	Women *Picture of women*
21	Teeth whitening tray	Not specified	58	Not specified *Not specified*	The gel is applied to the tray. Time per application 7-15 min.	Girls, women *Picture of a girl*
22	Teeth whitening pen	Not specified	82	Peroxide *Hydrogen peroxide*	The gel is applied to the teeth. Time per application 10 min. Must not come into contact with the gums.	Women *Picture of women*
24	Teeth whitening tray	Not specified	487	PAP[a], sodium bicarbonate *PAP[a]*	The gel is applied to the tray. Time per application 10 min. Repeated six times.	Not specified
25	Teeth whitening strips	Outside of EU (China)	55	Not specified *PAP[a]*	The strips are extracted from the disposable packaging and applied to the teeth. Time per application not specified.	Women *Picture of women*

No.	Product type	Distributor country of origin*	Price** in DKK	Assumed active substance Specified at the distributor *Indicated on packaging/declaration*	Description of usage Specified at the distributor	Target group***
27	Teeth whitening strips	Denmark	189	Citric acid *Citric acid*	The strips are placed on the teeth. Time per application according to instructions on packaging typically approx. 30 min. Repeated approx. every other week.	Women *Picture of women*
28	Teeth whitening pen	Other countries in the EU, incl. UK (Sweden)	198	Not specified *Sodium percarbonate*	The gel is applied to the teeth. Time per application 15 min.	Broad
29	Teeth whitening tray	Other countries in the EU, incl. UK (Sweden)	304	Not specified *No declaration*	The gel is applied to the tray. Time per application at least 10 min. twice a day. After two weeks, the application can be reduced to 2-3 times per week.	Women *Picture of women*
30	Teeth whitening pen	Other countries in the EU, incl. UK (UK)	151	Citric acid *Citric acid*	Not specified	Women *Picture of female mouth*
32	Teeth whitening tray	Denmark	629	Sodium bicarbonate *Hydrogen peroxide*	The gel is applied to the tray. Time per application 30 min.	Women *Picture of women*
33	Teeth whitening pen	Denmark	349	Sodium perborate *Sodium perborate*	The gel is applied to the teeth. Time per application 30 min., after which mouth is rinsed with water. Application is repeated for 14 days.	Broad
35	Teeth whitening tray	Denmark	218	Not specified *Phytic acid*	The gel is applied to the tray. Time per application 15 min. Repeat procedure three times and rinse with water.	Women *Picture of women*

* Distributor country of origin: Danish, provided the distributor has a Danish CVR number. Others are determined based on the address provided on the website.
** Price incl. shipment and fees. The prices are observed between May and June 2020 and represent the total price the consumer was able to purchase and get the product shipped for.
*** The target audience of the product is described based on specification on the product, associated description or based on a estimation of any pictures on the product or the website.
a PAP: phthalimidoperoxycaproic acid.
b It is uncertain whether the substance has a whitening effect, but it is included in the list as a relevant ingredient because the substance is illegal in the products.
c Distributor country of origin not specified but presumed outside of the EU, based on experience, for example, due to being a relatively cheap product and free shipment.
d Has been promoted previously by the influencer Irina the Diva.

Appendix 1.2 Prioritised products that were purchased but not received

TABLE 30. Overview of prioritized products not received within the time frame for analysis.

No.	Product type	Distributor country of origin*	Price** in DKK	Assumed active substance Specified at the distributor	Description of usage Specified at the distributor	Target group**
9	Teeth whitening tray	Inside the EU, incl. UK (UK)	280	Sodium bicarbonate	Not specified	Not specified
11	Teeth whitening tray	Outside of the EU (China)	92	Carbamide peroxide	The gel is applied to the tray (0.5 ml). Time per application not specified. Must not come into contact with the gums.	Not specified
13	Teeth whitening pen	Outside of the EU (USA)	126	Carbamide peroxide, citric acid	The gel is applied to the teeth. Time per application 25-30 min.	Women *Picture of women*
17	Teeth whitening tray	Outside of the EU (Turkey)	294	Sodium bicarbonate, sodium chlorite	The gel is applied to the tray. Time per application not specified. Repeated 6 to 12 consecutive days.	Women *Picture of women*
18	Teeth whitening pen	Outside of the EU (USA)	289	Carbamide peroxide	The gel is applied to the teeth. Time per application 15-30 min. Repeated 10 to 15 days.	Not specified
19	Teeth whitening pen	Not specified	23	Carbamide peroxide, citric acid	The gel is applied to the teeth with a 1 mm thickness. Time per application 10-20 min. Repeated daily for a week.	Unisex
23	Teeth whitening strips	Not specified	46	Not specified	The strips are extracted from the disposable packaging and applied to the teeth. Time per application 30 min.	Broad *Picture of a woman, specified as unisex*
26	Teeth whitening pen	DK	440	Not specified	Not specified	Broad
31	Teeth whitening tray	DK	399	Not specified	Not specified	Broad
34	Teeth whitening pen	DK	345	Sodium bicarbonate	Not specified	Women *Picture of women*

* Distributor country of origin: Danish, provided the vendor has a Danish CVR number. Others are determined based on the address provided on the website.
** Price incl. shipment and fees. The prices are observed between May and June and represent the total price the consumer was able to purchase and get the product shipped for.
*** The target group of the product is determined based on specification on the product, associated description or on an evaluation of any pictures on the product or in the online store.
c Distributor country of origin is not stated but presumed to be China due to relatively cheap product and free shipment

Appendix 2. Methods

Appendix 2.1 Method 1: UA-274, Determination of oxidation potential

The oxidation potential is a unit of measurement for electric activity in aqueous solutions and is measured (ORP, oxidation reduction potential) by means of an electrode attached to a reference electrode. The ORP value is calculated from the difference in potential between the electrode and the reference electrode.

The calibration is performed by means of one-point calibration which is used to calculate the offset between Standard Hydrogen Electrode (SHE) measurement, standard value for a specific solvent and the actual measured value with the electrode (PotCAL). Offset is part of the calculation of the oxidation potential in samples. Both calibrated and non-calibrated signals are in mV.

Appendix 2.2 Method 2: UA-310, Determination of pH

pH is determined by potentiometric measurement with pH meter with combined glass electrode. The method is based on the published CIPAC MT 75.3 method. The calibration is performed with adequate buffers depending on the area of measurement (IUPAC buffers). The measurements are performed on diluted samples. Three determinations are made. pH in the sample is subsequently estimated by the degree of dilution.

Area of measurement: 1-12.
Expanded measurement uncertainty (%U): 9% (diluted samples

Appendix 2.3 Method 3: UA-275, Quantification of peroxides through bioassay

The method is also a published method of analysis for the determination of hydrogen peroxide, either present or released in teeth-whitening products[14]. The method quantifies hydrogen peroxides that can be degraded enzymatically by peroxidase (catalase). This applies at minimum to the following peroxides whose quantification has been validated in the reference method: Hydrogen peroxide (CAS no. 7722-84-1), urea peroxide (CAS No. 124-43-6), calcium peroxide (CAS No. 1305-79-9), sodium percarbonate (CAS No. 15630-89-4) and sodium perborate monohydrate (CAS No. 10332-33-9).

An increment is applied to an airtight chamber with de-oxygenated phosphate buffer containing catalase under stirring. The catalase will convert peroxides to oxygen and water. The amount of oxygen is measured continuously by means of a calibrated oxygen sensor (Clark-type microsensor (OX-NP, Unisense)). The change in oxygen level in the buffer is used to calculate the amount of peroxide in hydrogen peroxide equivalents as 1 mole of oxygen is created for every 2 moles of peroxide: $2H_2O_2 \rightarrow 2H_2O + O_2$.

Duplicate determination is performed for products that show a level of peroxide after application of method. Moreover, a dilution of the product is done to ensure the enzyme solution is not oxygen saturated.

Detection limit: 0.01-0.05% (depending on product).
Uncertainty is 20%RSD.

[14] Margit M. Fernqvist et al., Danmarks Miljøundersøgelser, Aarhus Universitet, Afdeling for Miljøkemi og Mikrobiologi, Miljøprojekt Nr. 1270 2009.

Appendix 2.4 Method 4: UA-247/UA-221, Determination of chlorite by ion chromatography

Chlorite is determined by ion chromatography with a conductivity detector. Identification and quantification are performed by means of external standards set before use and generation of the calibration curve. Control is made of the analysis results by use of external control fluid. Duplicate determination has been made.

Detection limit: 10 mg/kg.
Uncertainty: 10%RSD.

Appendix 2.5 Method 5: UA-247 Determination of free chlorine (hypochlorite/hypochlorous acid) by spectrophotometry

Free chloride is determined by spectrophotometric method by means of *N*,N-diethyl-p-phenylenediamine as defined in ISO 7393-2. The determination has been performed on ROHASYS equipment under use of Hach Lange kit 310 and quantified against known concentrations of free chloride. The kit has been validated in the Danish Environmental Protection Agency project no. 20224/15. Free chloride can be converted to hypochlorite/hypochlorous acid after pH measurements and calculation from pK_s. Duplicate determination has been made.

Detection limit: 10 mg/kg.
Uncertainty: 5%RSD.

Appendix 2.6 Method 6: UA-271 Determination of boron by ICP-OES

The analysis is made by ICP-OES in accordance with the Danish Technological Institute's method UA-271 with point of departure in reference method DS/EN ISO 11885:2009.

A weighed content sample (0.5 g sample, accurately weighed) was heated until clear on a heating plate with concentrated saltpetre acid. The resulting solution was diluted to 50 ml with Milli-Q water subsequently diluted 1-5 times with 2.8 M HNO_3. Duplicate determination has been made. Blank determinations were made accordingly.

Detection limit: 10 mg/kg.

Uncertainty: 15%RSD.

Appendix 3. Data for selected teeth-whitening products

TABLE 31. Use of selected teeth-whitening products based on information on packaging, product user instructions and measured data.

Product No.	Product type	Gel per application [mL]	Max. tray area [cm^2]	Time per application [min]	Frequency of applications	Number of applications per unit	Total contents of per unit	Weight of content from a single syringe that can be pressed out [g] (volume stated for syringe)	Weighed amount per application [g]	Comment for usage
2	Tray	1.5	20	15	Twice a day	20	30 ml	-	-	Spray thin layer, the gel is applied directly on the tray or directly on the teeth. Gel is seemingly easy to overdose. Calculated amount of spray per application: 0.225 g.
3	Tray	-	20	45-60	Once a day	-	3 x 3 ml	3.8293 (3 ml)	-	The tray is first shaped after the teeth. The area of the tray is adjusted so that the gum is not touched. The instructions do not specify the amount of gel that needs to be applied. It is however easy to use 0.5 mL gel on the upper tray and 0.5 mL on the lower tray (2 x 0.5 mL per application) for an unshaped tray which is 1/3 of the contents of a syringe. This amounts to nine applications per unit.
12	Tray	-	20	15	Every other day	-	5 ml	5.2901 (5 ml)	-	Dosing per application is "small drop". This easily amounts to 0.5 mL gel on the upper tray and 0.5 mL on the lower tray (2 x 0.5 mL per application). This amounts to five applications per unit. There are many large air bubbles in 5 mL gel.
15	Tray	-	20	20-45	Once a day	-	10 ml	12.9393 (10 ml)	-	The tray is first shaped after the teeth. Dosing per application is "small drop". This easily amounts to 0.5 mL gel on the upper tray and 0.5 mL on the lower tray (2 x 0.5 mL per application). This amounts to 10 applications per unit.
20	Tray	-	20	20-45	Once a day	-	10 x 3 ml	3,0146 (3 ml)	-	The tray is first shaped after the teeth. Dosing per application is "small drop". This easily amounts to 0.5 mL gel on the upper tray and 0.5 mL on the lower tray (2 x 0.5 mL per application). This amounts to 30 applications per unit..
24	Tray	1.5	20	10	Once a day for six days	6	3 x 3 ml	3.2195 (3 ml)	-	No comments

22	Pen	-	-	10	Twice a day	-	2 g	0.1478 g	The amount of gel required for an application is determined by weighing gel from the pen applied to an area of approx. 20 cm^2

- means that there are no specifications available on the product

Survey and risk assessment of teeth-whitening products for personal use

Since a legal restriction on hydrogen peroxide in teeth-whitening products for personal use was implemented in 2012, usage of several other active substances in this product type has been observed. Therefore, the Danish Environmental Protection Agency has wanted to aquire more knowledge on the market for teeth-whitening products for personal use, and to have clarified whether the products compose a risk to the consumers.

In the project, a survey on the market for teeth-whitening products for personal use and the active substances used in these products was conducted. Based on the survey, 25 products from webshops in Denmark and abroad was analysed for content or release of selected active substances, pH value and oxidation potential. For some of the products, it was reviewed whether a number of requirements from the cosmetic legislation were met and finally, a risk assessment was performed.

By chemical analysis, chlorite was found in two products and likewise, boron was detected in two products. Hydrogen peroxide was found in six products, whereas the concentration for three of these were higher than the legal threshold.

For 14 out of 25 products (56 %), it was assessed that as a result of the active substance or the pH value there was a risk for local effects in the mouth, including tooth enamel erosion, increased tooth sensitivity and irritation or corrosion of the gums and the oral mucous membrane. For three products, the assessment was that a risk of systemic effects was possible, but that it could’t be concluded.

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