SAFE COSMETICS
for young children

European Committee for Cosmetics and Consumer Health (CD-P-COS)

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2nd Edition

Safe cosmetics for young children

A guide for manufacturers and safety assessors

European Committee for Cosmetics and Consumer Health (CD-P-COS)

European Directorate for the Quality of Medicines & HealthCare

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Contents

Foreword

In recent decades, the range of cosmetic products has become considerably diversified and specialised, targeting all age groups in the population. The number of cleansing, perfuming and care products (including bubble baths, oils, talcum powder, creams, lotions and perfumes) available for children has consistently increased. As young children are often more sensitive to certain toxic effects, such products – particularly the 'leave-on' products – must be devoid of harmful chemicals. Product packaging, another potential source of chemical risk, must also be safe and the risk of injury or accidental ingestion of small parts such as screw caps must be minimised.

Council of Europe Resolution CM/ResAP (2012) 1 on safety criteria for cosmetic products intended for infants (presented in Part I of this publication) calls upon the governments of European countries to implement measures ensuring that any product placed on the market first undergoes an appropriate safety assessment. Published in 2012, the first edition of *Safe cosmetics for young children* also highlighted the importance of carefully evaluating the safety of cosmetic products for infants.[1]

To provide state-of-the-art guidance and support for manufacturers and safety assessors, the European Committee for Cosmetics and Consumer Health (CD-P-COS) critically reviewed the safety criteria published in the first edition for the purposes of this second edition (Part II of this publication). Several other changes have been made, for example, the existing chapter on ingredients used in cosmetic formulations has been expanded to include sections on

1 Please note: in Resolution CM/ResAP (2012) 1 and the guide for manufacturers and safety assessors that supplements it, the term 'infant' is used to mean all children under the age of three.

nanomaterials and endocrine disruptors and both the calculation of exposure and the product-specific 'margin of safety' have been aligned with the current version of the Scientific Committee on Consumer Safety (SCCS) *Notes of guidance for the testing of cosmetic ingredients and their safety evaluation* [1]. The recommendations for fluoride use in toothpaste for young children have also been updated to reflect more recent regulations and guidelines.

The European Network of Official Cosmetics Control Laboratories (OCCLs) has closely monitored cosmetics presented in containers made to look like toys, e.g. bottles in the shape of dolls or cartoon characters and several market surveillance studies were carried out to check the compliance of so-called 'kids' cosmetics' with the applicable rules. Banned ingredients (including colorants, preservatives and lead), as well as high concentrations of allergens and impurities (including nitrosamines) were found, raising concerns for the authorities and demonstrating that efforts for due enforcement must be pursued.

Consumers should be encouraged to pay attention to cosmetic ingredients and to carefully select care products based on their intended use.

This guide may be further revised under the aegis of the European Directorate for the Quality of Medicines & HealthCare (EDQM), a directorate of the Council of Europe, to take into account future scientific or analytical developments related to cosmetics.

Legal context

Council of Europe Resolution CM/ResAP (2012) 1 on safety criteria for cosmetic products intended for infants describes the measures that supplement EU Regulation 1223/2009 on cosmetic products.[2] This regulation sets forth that 'there shall be *inter alia* a specific assessment for cosmetic products intended for use on children under the age of three'. Basic principles for the evaluation process have been laid down by the SCCS *Notes of guidance* [1].

The information provided in this guide may be of use to Council of Europe member states, including those that are not members of the European Union. It is without prejudice to other current requirements, guidelines and good manufacturing practices that concern all cosmetic products.

2 See under *References*.

Acknowledgements

Special thanks go to the rapporteurs from Belgium, the Czech Republic, France, the Netherlands and Spain who initiated the work project, provided background information and drafted the recommendations.

Their dedication and expertise, combined with very efficient working methods, made it possible to compile a practical guide that provides a short overview of physiological development in early childhood and advice for those who are responsible for establishing product safety in the context of cosmetic care.

The Council of Europe Committee for Cosmetics and Consumer Health (CD-P-COS) launched the review of the initial text and approved the release of the 2nd edition.

Cosmetics experts from the competent authorities of Finland, Italy and Spain conducted a comprehensive critical review of the documentation and prepared the amendments presented in this new edition of the guide. Their expert contribution is gratefully recognised and appreciated. The competent authorities in Belgium, Lithuania, Slovenia and Switzerland also made valuable contributions in support of this work.

Great appreciation is also due to the EDQM Secretariat for co-ordinating the work, translating relevant contributions and final editing of the document.

Part I.
Council of Europe Resolution CM/ResAP (2012) 1 on safety criteria for cosmetic products intended for infants[3]

Adopted by the Committee of Ministers on 14 March 2012
at the 1137th meeting of the Ministers' Deputies

3 In the Resolution and the guidance document that supplements it, the term 'infant' is used to mean all children under the age of three.

The Committee of Ministers, in its composition restricted to the representatives of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia[4] ('the Convention');

Recalling the Declaration and Action Plan adopted by the Third Summit of Heads of State and Government of the Council of Europe (Warsaw 16-17 May 2005), Chapter III – *Building a more humane and inclusive Europe*, Article 1. *Ensuring social cohesion*, in particular laying down protection of health as a social human right and an essential condition for social cohesion and economic stability;

Recalling Resolution Res (59) 23 of 16 November 1959 extending the activities of the Council of Europe in the Social and Public Health field on the basis of a Partial Agreement, and Resolutions Res (96) 34 and Res (96) 35 of 2 October 1996 revising the rules of the Partial Agreement;

Having regard to the decisions of the Committee of Ministers of 2 July 2008 (CM/Del/Dec (2008) 1031) to dissolve the Partial Agreement in the Social and Public Health Field and to transfer activities related to cosmetics and food packaging to the European Directorate for the Quality of Medicines and HealthCare (EDQM) as of 1 January 2009; whereby the EDQM became responsible for developing harmonised approaches to ensure product quality and safety in the areas of cosmetic products and packaging materials for food and pharmaceutical products;

Considering the efforts made over several years (under the former Council of Europe Partial Agreement in the Social and Public Health Field) to improve the safe use of cosmetics;

Recalling Resolution ResAP (2005) 4 on sun protection products to optimise consumer protection;

Recalling Resolution ResAP (2006) 1 on a vigilance system for undesirable effects of cosmetic products ('cosmetovigilance');

4 States concerned [in 2012]: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, "the former Yugoslav Republic of Macedonia", Turkey and United Kingdom.

Recalling the Council of Europe Safety Survey on active ingredients used in cosmetics (published in March 2008);

Recalling the Council of Europe Publications on plants in cosmetics (Vol. I published in September 2002; Vol. II published in September 2001; Vol. III published in September 2006);

Considering that a high level of health protection should be ensured for children;

Considering the generally positive attitude towards baby products and their benefits, with the resulting risk of excessive use beyond hygienic purposes in terms of the number of products used as well as the quantity used of the individual products;

Considering that cosmetic products may be ingested orally by infants due to specific behaviours including sucking and licking of hands, arms and feet;

Considering also that various cosmetics of the 'leave-on' type are applied several times every day and that their ingredients may accumulate over time and contribute to long-term toxicities that are difficult to assess;

Recognising that infants are more sensitive to certain toxic effects of chemicals and, therefore, that special attention should be paid to the safety of cosmetic products that are intended to be used on them;

Acknowledging that several organs and vital physiological functions undergo significant development during childhood;

Being convinced that safety assessors and responsible persons for cosmetic products intended for infants will benefit from the specific recommendations laid down in a guidance document elaborated by the Committee of Experts on Cosmetic Products (P-SC-COS);

Taking into account the valuable contribution made by the Scientific Committee on Consumer Safety (SCCS) through their notes of guidance for the testing of cosmetic ingredients and their safety evaluation;[5]

Also taking into account Council Directive 76/768/EEC and Regulation (EC) No. 1223/2009 that lay down specific requirements for cosmetics for children

5 The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 7th revision, SCCS/1416/11, (2011).

under the age of three and that form the basis of the guidance document elaborated by the Committee of Experts on Cosmetic Products (P-SC-COS);

Recommends to the governments of States Parties to the Convention that they adopt legislative and other measures aimed at reducing the health risks for infants, arising from exposure to cosmetic products and their ingredients, according to the principles set out in the appendix to this Resolution. These recommendations shall not prevent governments from maintaining or adopting national measures that implement stricter rules and regulations.

Appendix to Resolution CM/ResAP (2012) 1

Article 1. **Definitions**

Cosmetic product – a product that complies with the definition given in Regulation (EC) No. 1223/2009 of 30 November 2009 on cosmetic products.

Cosmetic ingredient – any natural or synthetic substance or mixture that has been selected and intentionally added to the product composition.

Infant – a child under the age of three years.

Article 2. **Scope**

The provisions of this Resolution relate to all cosmetic products placed on the market in one or more States Parties to the Convention that are intended or can reasonably be expected to be applied to infants for cosmetic purposes.

Article 3. **General requirements**

3.1 A cosmetic product intended for use on infants should be safe for his or her health when it is being used under normal and foreseeable conditions, taking into consideration the physiological characteristics, application area and infant-specific behaviour that may increase exposure to certain substances or to their toxic effects.

3.2 The product should comply with the basic requirements for cosmetic ingredients and finished cosmetic products, notably Regulation (EC)

No. 1223/2009, and should follow the general principles stated in the *Notes of guidance for the testing of cosmetic ingredients and their safety evaluation (SCCS).*

3.3 The presentation of a cosmetic product intended for use on infants, and in particular its form, odour, colour, appearance, packaging, labelling, volume or size, should not endanger their health and safety due to confusion with food.

3.4 The cosmetic product should contain no more than a strict minimum number of ingredients; the following substances (including impurities) should not be present:

- substances with carcinogenic or mutagenic properties or substances that are toxic for reproduction (CMR),
- substances with endocrine disrupting activity,
- substances that are candidates for inclusion in Annex XIV of Regulation (EC) No. 1907/2006 (REACH),
- substances that are potent allergens.

3.5 Substances used in replacement of the substances stated above should adhere to the same safety criteria described herein.

3.6 The unintended presence of impurities or traces thereof, originating from raw materials, packaging materials, manufacturing process or from chemical changes or interactions in the finished product should be assessed.

3.7 Preservatives should be used at the lowest efficient concentrations.

3.8 The maximum tolerable concentration indicated in the guidance document for certain ingredients such as terpenes should not be exceeded.

3.9 The container and packaging of the cosmetic product should provide appropriate protection to ensure physicochemical stability and avoid microbiological contamination during storage, distribution and use. The materials used should be inert and should not release any toxic substances into the product.

Article 4. **Risk assessment**

4.1 When assessing risk, the exposure scenario should account for long-term toxicity and, as far as possible, cumulative daily exposure to the same ingredients originating from different sources.

4.2 On the basis of the toxicological data or in the absence of sufficient data, additional uncertainty factors proportionate to the degree of potential risk should be applied if there is reasonable cause for assuming higher sensitivity of an infant to a given substance.

Article 5. **Documentation**

5.1 The specific safety assessment of cosmetic products for infants should be documented as required by Regulation (EC) No. 1223/2009 and made readily accessible to the competent authorities.

5.2 Sufficient data on the toxicity profile of each ingredient, notably data reported in scientific literature, should be documented.

Article 6. **Labelling**

The instructions for use and general precautionary measures on the label should be sufficiently clear to ensure the safe use of the product and, in particular, to avoid any misuse.

Article 7. **Guidance document**

To support the implementation of the provisions of this Resolution, a guidance document has been prepared by the Committee of Experts on Cosmetic Products (P-SC-COS),[6] approved by the Consumer Health Protection Committee (CD-P-SC)[7] and is available from the European Directorate for the Quality of Medicines and HealthCare (EDQM), a directorate of the Council of Europe. This guidance document will be regularly updated.

6 Dissolved on 31 December 2017.

7 Dissolved on 31 December 2017; tasks transferred to the European Committee for Cosmetics and Consumer Health (CD-P-COS) (steering committee).

Part II.
Guidance on safety criteria for cosmetic products intended for infants

Introduction

Cosmetic products, when used under normal or reasonably foreseeable conditions of use, must be safe. Safety assessment has to be performed for each finished cosmetic product, notably taking into consideration the toxicological profile of the ingredients, their chemical structure, possible interactions and exposure.

Recognising the fact that children under the age of three might be more sensitive to certain toxic effects of chemicals, and thus the need to pay special attention to the safety of cosmetic products that are intended to be used in this population, Regulation (EC) No. 1223/2009 [2] of the European Parliament and of the Council of 30 November 2009 on cosmetic products (EU Cosmetics Regulation) sets forth that: "there shall be *inter alia* a specific assessment for cosmetic products intended for use on children under the age of three".

Council of Europe Resolution CM/ResAP (2012) 1 and the present guidance document on safety criteria for cosmetic products for infants (heretofore, defined as all children under the age of three) supplement the aforementioned regulation. They describe key factors to be considered when elaborating the product and its safety report. These practical recommendations are without prejudice to other current requirements and guidelines that concern all cosmetic products. They are intended for manufacturers or those in charge of marketing, as well as safety assessors of cosmetic products. They may also be useful for producers, distributors and importers of ingredients. Some specific ingredients and products are discussed in the Annex to these guidelines.

Main principles

The use of cosmetics on infants requires special attention. Infants are more sensitive than children over 3 years and adults to certain toxic effects of substances. In addition, their levels of exposure may be higher due to different physiological characteristics and specific behaviours. Specificities relating to physiological and anatomical characteristics are discussed in the section on Physiological characteristics and associated risks and conditions of exposure in Exposure characteristics and associated risks.

Physiological characteristics and associated risks

Skin

The major characteristics of infant skin are summarised below [3, 4].

Characteristics of the skin tissue of infants born at full-term

It is generally accepted that skin maturity is attained at full-term birth, or within a few hours or days, or even 4 weeks thereafter, depending on the anatomical or functional characteristics concerned:

- full-term newborns and infants have a stratum corneum and a skin barrier function equivalent to adults [5–9];
- the thickness of the epidermis is identical to that of adults;
- the mechanical resistance of the dermal-epidermal junction is also identical in full-term babies and adults;
- the dermis is hyper-elastic;

- eccrine sweat glands are functional from birth and apocrine sweat glands are non-functional until puberty;
- skin vascularisation is transiently immature until approximately 4 weeks of age;
- the water-lipid film, or vernix caseosa, has a very variable quantitative and qualitative composition at birth. Its role in mechanical and possibly bacterial protection remains unclear; however, there is evidence supporting both prenatal and postnatal functions, including protection of the skin in the intrauterine environment and during transition from the intrauterine to an extrauterine environment [10];
- bacterial flora colonises the skin of newborns within a few days or even a few hours, and its composition depends on the mode of delivery [11];
- the pH is neutral and decreases very rapidly within the first days of life. It settles between pH 4.5 and pH 6, which is suitable for the resident saprophytic flora.

However, a study based on technical innovations and non-invasive *in vivo* techniques, showed differences between infant and adult skin [12]. In particular, infant skin presented a thinner stratum corneum and epidermis than adult skin and, consequently, a less efficient barrier function. These differences, which have been confirmed at molecular level using biomarker expression analysis [13], should be taken into account when assessing the safety of cosmetic products for infants.

Characteristics of the skin tissue of premature babies

Prematurity is defined as birth before 37 weeks of amenorrhoea, i.e. up to 35 weeks of post-conception age. Approximately 15 million births annually are premature, translating to a preterm birth rate of 5 % to 18 % across 184 WHO member states [14].

The skin tissue of premature babies is structurally and functionally immature, so excellent body hygiene is essential. The skin barrier is normal from 32 weeks of reconstituted gestation and, in general, a rapid maturation of the skin of premature babies is observed, leading within 2 to 3 weeks to an epidermis similar to that of full-term babies [7, 15, 16]. This rapid maturation is triggered by the passage from an intrauterine liquid medium to an environ-

ment in contact with air, temperature changes, and friction with clothing and bedclothes, all of which promote normal colonisation by saprophytic flora.

Skin surface area to body mass ratio

The skin surface area to body mass ratio is higher in children than in adults [1]:

- 2.3 times higher in babies at birth,
- 1.8 times higher at 6 months,
- 1.6 times higher at 12 months,
- 1.5 times higher at 5 years.

Organs and systems in development

Some organs and systems are still undergoing significant development in infants. These developing systems are particularly sensitive to toxicological effects, and the level of sensitivity is age-dependent [17]. The developmental phase during which infants are exposed to a substance is as important as the level of exposure [18].

When assessing the safety of cosmetic products intended for infants, attention should be paid to possible toxicological effects on the nervous, immune, respiratory and endocrine systems.

Nervous system

Children have a relatively larger brain mass and higher cerebral blood flow than adults [18].

The blood-brain barrier is not fully developed until around 6 months. For lipophilic molecules with a low molecular weight, passage through the blood-brain barrier is probably similar, irrespective of the maturity of the brain, but passage of non-lipophilic molecules through the blood-brain barrier may be different [3, 4].

Rapid brain growth in humans begins in the third trimester of pregnancy and slows down 2 years after birth [18]. Growth and differentiation in the brain continue even after the age of 3 to 4 years.

Neurotoxic substances such as ethanol, vitamin A, organic mercury and inorganic lead have been demonstrated to affect neural development over the entire period from conception to young adulthood [18].

Immune system

Humoral immunity. Concentrations of immunoglobulin G (IgG) equivalent to those of adults are attained at 5 to 6 years of age. Adult equivalent IgA and IgM concentrations are reached at 10 to 12 years and at 1 to 2 years, respectively. Up to around 2 years of age, infants have limited humoral immunity and have reduced defences against some infectious agents [18].

Cellular immunity. At birth, cellular immunity is present in rudimentary form and only reaches adult proportions at the age of 4 years. Exposure to substances that affect the development of cellular immunity may lead to an increased susceptibility to certain forms of cancer and infections. Furthermore, the risk of contracting asthma, allergies and some auto-immune disorders may be increased by changes in cellular immunity [18].

Perinatal exposure to immunotoxins may cause immunotoxicity at doses that have no effect in adults. Lead is an example of a substance with a disruptive effect on the immune system of infants [18].

Respiratory system

The lungs develop continuously from embryogenesis to early adolescence. During the first years of life, there is a considerable increase in the number of alveoli and the alveolar surface area. The number of alveoli rises to the adult level by the age of 8 years. Alveolar maturation continues up to the age of 18 years [18].

Prenatal exposure to environmental toxicants, such as tobacco smoke [19], and certain metals [20] has been shown to have an adverse effect on the developing lungs.

The quantity of air that children inhale per unit of time and weight is almost 3 times that of adults. Exposure through inhalation may be greater at a very young age, due to the greater respiratory volume per unit lung surface area [18].

Endocrine system

Children may be especially vulnerable to endocrine disruption, as their homeostatic mechanisms are immature. Gonadal function and fertility in the long term may be affected by substances that interfere with the hypophyseal-gonadal system [18].

The growth of epiphysial cartilage is stimulated by growth hormone produced in the hypophysis and may be affected by substances such as lead and other heavy metals resulting in growth disorders [18].

An optimal thyroid function is essential for normal brain development in newborns and children. For example, iodine may interfere with thyroid hormone levels and disrupt normal brain development [18].

In the pancreas, the islets of Langerhans continue to develop up to the age of 4 years. Exposure to toxic substances in the early stages of life may lead to fewer beta-cells with reduced function, which can cause diabetes mellitus [18].

In the adrenal glands, the adrenal medulla is functionally mature after 18 months, whereas the adrenal cortex is mature after approximately 14 years [17, 18].

Data on reproductive toxicity should be available to evaluate potential toxicity in infants [18]. Specifically, it is important to have data from a one-generation (or more) reproductive toxicity study. When there are indications that a substance may interfere with the development of organs or systems, specific data on juvenile toxicity may be needed [17].

When evaluating the toxicological information on a substance, it is important to take into consideration the toxicological end-point on which the no observed adverse effect level (NOAEL) is based and if this end-point is critical for infants. The effects found at exposure doses higher than the NOAEL should also be evaluated [18].

Safety assessment of products for infants should take into account potential critical periods of development but, for most substances, only limited information is available and it should be kept in mind that the critical periods of development may differ between animals and humans [17].

On the basis of available toxicological data, or if there are no relevant data, the use of an additional uncertainty factor may be justified if there is reasonable cause for supposing that infants are more sensitive than adults to the substance in question [17]. The additional uncertainty factor should be proportionate to the degree of potential risk [4].

Toxicokinetics and toxicodynamics

The biochemical and physiological characteristics of infants and adults are different [3, 21]. Most organs are not fully mature until they reach their final size. However, children have a significant portion of their adult physiological capacity from birth, albeit immature.

Variations in absorption, distribution, metabolism and excretion exist between infants and adults, particularly in relation to hepatic and renal functions [16]. For example, within weeks after birth, a decrease in renal resistance associated with an increase in blood pressure contributes to increasing renal blood flow. Similarly, between 6 and 12 months of age, the high serum levels of biliary acids decrease gradually to attain levels equivalent to those of adults.

At birth, all parts of the enterohepatic cycle, including biliary synthesis, conjugation, transport, secretion and re-absorption, are immature. Metabolic capacities are almost identical to those of adults at approximately 6 months of age and are fully mature at about 12 months. Infants can be more sensitive to certain substances than adults (e.g. caffeine), although generally they are less sensitive. Thus, as long as the level of exposure of infants to toxins remains below the saturation dose of the relevant detoxification system, the risk for children is not higher than for adults.

The safety report on a cosmetic product describes the toxicological hazard of the ingredients in the final formulation and the exposure scenario and classifies the associated risks on which the risk assessment of the product is based.

Conclusions on risk factors related to the characteristics of infants

- Infants have a higher skin surface area to body mass ratio than adults, which leads to a higher plasma concentration after absorption potentially inducing a systemic toxicity that is higher than or different from that of adults.
- Metabolic systems are functionally immature up to the age of about 12 months, resulting in variations in distribution, metabolism and excretion between infants and adults, with inter-individual variations in infants; these systems constantly develop up to approximately 2 years of age.

- There is still a lack of knowledge on the age brackets corresponding to the different degrees of metabolic maturity.
- Organs or systems still undergoing significant development may be particularly sensitive to toxicological effects.
- Premature babies have more permeable skin and are metabolically immature.

Exposure characteristics and associated risks

The risk posed by a cosmetic product to infant health depends not only on its intrinsic toxic properties, but also on the degree and type of exposure.

There are 3 main characteristics that directly influence exposure to cosmetic products in infants:

- physiological characteristics mentioned in the previous section,
- specific application area,
- behaviours inherent to infants.

Many types of cosmetic hygiene products are used for children aged 0–3, such as skincare products and products for the nappy area. Most of them are used on a daily basis. In order to perform a specific safety evaluation, it is necessary to collect relevant exposure data for the finished cosmetic product [22].

Specific application area: buttocks

An infant's buttocks are a typical area for cosmetic application due to the use of nappies [23, 24].

The technology for the manufacture and design of disposable nappies has undergone considerable development in recent years, contributing to the reduction of nappy rash [4] and other skin conditions. In silico modelling of skin under the diaper has shown that good hygiene practices in diaper changing, in terms of both frequency and cleansing care, will ensure there is no significant impact on skin health and barrier properties [1, 25, 26]. However, the buttocks are a particularly sensitive area and are a focus for assessing exposure to cosmetic products, given the following conditions [3]:

- The buttocks are exposed to a moist environment due to the presence of urine.
- Ammonia released in the urine and the presence of faecal enzymes, together with other factors such as the use of alkaline soap, lead to an increase in the pH of the area.
- The presence of faeces, containing substances from the bilious cells, protease and lipase enzymes and micro-organisms from the digestive tract.
- The area is subjected to almost continuous occlusion and friction and often supports the child's body weight, with an increase in local temperature.

These conditions make the area prone to skin problems, such as infections, rashes or dermatitis, which render the skin more permeable to the ingredients in cosmetic products, and possibly facilitate their absorption.

Cosmetic products that are designed to remain on the skin (without rinsing or removal) are often applied several times a day in an attempt to prevent or alleviate the aforementioned conditions. As a result, infants are in contact with cosmetic products for extended periods of time under conditions of moisture, increased temperature, occlusion and friction that might enhance their absorption and thus increase exposure.

It is worth noting here that rigorous scientific data is lacking on the differences between the latest models of disposable diapers and their predecessors in terms of their effect on percutaneous absorption of, and therefore infant exposure to, cosmetic ingredients.

The Scientific Committee on Consumer Safety (SCCS) *Notes of guidance for the testing of cosmetic ingredients and their safety evaluation* [1] considers that for the development of baby cosmetics and the safety evaluation of products intended to be used in the nappy area, the potential impact of irritation on dermal absorption of the ingredients needs to be considered by the safety assessor. It is known that the physico-chemical properties of the substances under consideration also play a role. In addition, according to SCCS guidance, the susceptibility of this area to micro-organisms must also be taken into account. Therefore, baby cosmetics should be adequately preserved and formulated with an appropriate pH. Finally, it must be considered that cosmetic products are meant to be used on intact skin, and medical advice is necessary

in the case of real skin damage for which pharmaceutical products (and not cosmetics) should be used [1].

Behaviours inherent to infants: additional exposure

The pattern of exposure to cosmetic products can be very different in infants and adults due to the different behaviours they exhibit. In addition, there are enormous differences between the behavioural repertoires of infants of different ages [4].

A fundamental element of the intellectual development of infants is the exploration of their environment by means of manipulating objects, often by placing them in their mouth – a behaviour which increases significantly when the child is teething. There is no doubt that the products that are most accessible or familiar, as is the case with cosmetic products, are those that will most attract a child's attention. There is a risk of infants manipulating cosmetics containers with different shapes and closures while the adults carry out their hygiene. Cosmetic products that appear similar to toys, such as eau de cologne in a figurine-shaped container, are particularly noteworthy. The risk of confusion with foodstuffs should also be avoided, taking into consideration the presentation of the cosmetic product and, in particular, its form, odour, colour, appearance, packaging, labelling, volume and size.

Infants' behaviours create additional sources of exposure to the ingredients of cosmetic products. There are many possible scenarios, depending on the age and behaviour of the infant, including:

- accidental ingestion of the product when sucking the container or consuming its contents;
- ingestion of small amounts of the product, e.g. when swallowing some of the rinsing water after using a shampoo or bath gel or swallowing some toothpaste;
- ingestion of small parts of the container, e.g. screw caps or dosage pump heads;
- aspiration of liquids, especially dangerous in the case of products containing hydrocarbons;
- eye exposure to shampoos, bath foams, sprays or other types of cosmetic products, directly or indirectly.

A study of potential exposure scenarios for infants is therefore required in order to estimate typical levels of exposure in this age group. This includes exposure factors (amount/frequency) for products intended for children where amounts used cannot simply be scaled from adult use patterns (e.g. nappy cream, toothpaste). Expert judgement can be used to address specific exposure scenarios when using cosmetic products as they are intended to be used (e.g. including eye exposure and ingestion of small amounts of shampoo when swallowing some of the rinsing water) or scenarios for foreseeable misuse (e.g. accidental ingestion of small parts of the container or consuming its contents).

Because of mouthing, children can be exposed orally to products to which adults are only exposed dermally, and therefore a specific assessment for children could include more exposure scenarios [27].

Infant behaviour must be taken into account when assessing the safety of cosmetic products for infants, especially when calculating margins of safety (MoS); the need for additional uncertainty factors should be evaluated on a case-by-case basis.

Recommendations for the safety evaluation

The safety evaluation of a cosmetic product is the key factor for the formulation and release onto the market of safe products for infants.

Particular attention should be paid to the selection of an adequately qualified safety assessor who has the knowledge and expertise to ensure that the most appropriate criteria are applied during the safety assessment, taking into account each specific aspect related to both cosmetics and infants. The safety assessor should have the necessary technical and scientific knowledge to collect and evaluate relevant data to demonstrate that the products they are responsible for are safe.

The safety evaluation should take into account relevant developments in the field, including regulatory amendments, scientific opinions and input from market surveillance activities. In this context, the safety assessment should also include all available data on cosmetovigilance, i.e. the undesirable and serious undesirable effects caused by marketed cosmetic products.

Ingredients

The safety of a product formulation is initially based on the properties of its ingredients, which may already be known or the subject of specific studies.

Regulatory restrictions in the European Union concerning animal testing of cosmetic products and ingredients highlight the need to take into account all available data, using all the pertinent toxicology methods and including the most modern techniques, to enable in-depth analysis of the safety of cosmetic products.

Selection and quality of ingredients

Selection

Each manufacturer should implement a selection and exclusion process for the ingredients constituting a cosmetic formulation in order to ensure the safety of products intended for infants. For each ingredient, careful validation of the ingredient's supplier should be carried out. The specifications of ingredients should be properly documented together with the corresponding certificate of analysis. Criteria that should be taken into account include [1]:

- for chemically well-defined substances: availability of data on chemical composition, physico-chemical and microbiological specifications, particle-size distribution curve of substances, substance purity, impurities profile, availability of test methods;
- in-depth evaluation for specific substances according to their function;
- for complex ingredients (e.g. herbal extracts): availability of information on the nature and quantity of substances in the mixture, control of variability for mixtures of substances of natural or biotechnological origin, physico-chemical and microbiological specifications, purity criteria, impurity profile, availability of test methods;
- for fragrance or flavouring compounds: availability of data on the identification of ingredients including name and code number, qualitative and quantitative composition of substances in the compound and their relevant safety data;
- availability of state-of-the-art analytical methods for control tests on the substances and mixtures;
- reference to up-to-date scientific literature and opinions of expert committees (e.g. SCCS);
- availability of data on the toxicological profiles of the ingredients (chemical structure, tests performed by suppliers, in-house data, reviewed data from all reliable sources);
- information on specific ingredients made available after placing cosmetic products on the market, as well as data derived from cosmetovigilance activities;
- marketing history and literature on long-term exposure;
- regulatory status of the ingredient, for example, restricted use according to Annexes II-VI of the EU Cosmetics Regulation [2], as amended.

These data and information should ensure that each ingredient, under normal or reasonably expected conditions of use, will be well tolerated.

Special attention must be given to the selection of perfuming constituents and preservatives, given their allergy-inducing potential. The real need for intentionally adding such substances should be carefully considered and, where this is the case, identification and qualitative and quantitative information about regulated substances in the fragrance (or flavour) compound and information relevant for a safety assessment should be included in the safety report.

The presence of any of the fragrance allergens listed in Annex III of the EU Cosmetics Regulation [2] must be indicated on the label if their concentration exceeds the defined limit. The concentration of such allergens in perfume compositions or natural oils should be minimised in finished products for infants and remain below the limit defined in Annex III of the regulation.

Preservatives should be used at the lowest concentrations necessary to ensure the preservation of the product, taking into account its formula, its packaging and the respect of good manufacturing practices in the manufacturing steps. Protective packaging limiting the risk of contamination during product use and/or specific manufacturing processes designed to reduce sources of degradation or contamination of the product should be preferred in order to reduce the need for preservatives.

Substances of very high concern that are candidates for inclusion in Annex XIV of Regulation (EC) No. 1907/2006 – Registration, Evaluation, Authorisation and Restriction of chemicals (REACH Regulation) [28] should be excluded from cosmetic formulations for infants, e.g. substances identified as potential endocrine disruptors, or substances which are persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) according to REACH Annex XIII, or substances classified as respiratory sensitisers [29].

Substances with a harmonised classification as carcinogens, mutagens or toxic to reproduction (CMRs) of category 1A, 1B or 2 under Part 3 of Annex VI to Regulation (EC) No. 1272/2008 (CLP Regulation) [30] are banned according to Article 15 of the EU Cosmetics Regulation and should not be present in the formulations of cosmetic products for infants. Substances with no harmonised classification as CMR under the CLP Regulation, but for which pertinent data have demonstrated potential genotoxicity, reproductive toxicity

or carcinogenicity (see, for example, IARC monographs [31]) should not be present in cosmetic products intended for infants. In the same way substances included in the registry of classification and labelling (CLH) intentions for a new or revised harmonised classification and labelling under the CLP Regulation, with a proposal to potential classification as a CMR substance should be excluded from cosmetic formulations for infants.

Nanomaterials

Developments in the field of nanotechnology have led to an increase in the use of nanomaterials in the formulation of cosmetic products.

Nanomaterials are characterised as having one or more dimensions in the nanoscale (1-100 nm). The small size and other characteristics such as shape, morphology and large surface to volume ratio, can confer distinctive characteristics compared to macro/bulk forms of the same substance. While these features might enable new innovations and product formulations, the use of nanomaterials in consumer products and the still incomplete database on their safety has raised concerns with regard to human health [32–34].

The EU Cosmetics Regulation covers the use of nanomaterials in cosmetic products, defining them as materials that are 'insoluble or biopersistent and intentionally manufactured' [2]. The EU Commission Recommendation on the definition of nanomaterial [35], which was revised in June 2022 [36], contains a different, more general definition. It is likely that these definitions will be revised and horizontal harmonisation across legislation will take place in the future.

Some categories of ingredients – colorants, preservatives and UV filters, as well as their 'nanoforms' – can be included in cosmetics under specific conditions of use; these are listed in Annexes IV, V and VI, respectively, of the EU Cosmetics Regulation. Per Article 31 of this regulation, substances can be added to the lists in the relevant annexes on the basis of SCCS opinions. For any other ingredient use, a specific safety dossier must be submitted for each nanomaterial prior to the final product being placed on the market, in order to allow the Commission to evaluate its safety. Where the Commission has concerns about the safety of nanomaterials that have been self-assessed by the dossier submitter, it may request a safety assessment from the SCCS.

The SCCS has identified several aspects of nanomaterials that are a basis for possible concern. These include physico-chemical aspects (size, solubility, chemical composition and toxicity, morphology, surface chemistry and coatings), exposure aspects (frequency and amount, potential for systemic exposure, accumulation) and other aspects (new properties, function, type of application) [37].

The SCCS provides recommendations for the safety assessment of nanomaterials intended for use in cosmetics, covering general safety considerations, material characterisation, exposure assessment, hazard identification and dose-response characterisation [38].

Since there are still knowledge gaps regarding possible adverse effects of nanomaterials on human health, the real need for intentionally including such substances in cosmetics for infants should be addressed when assessing product safety. In addition, as the methodology to assess nanomaterial safety is continuously evolving, attention should be paid to the use of appropriate methods.

According to the EU Cosmetics Regulation, cosmetic products containing nanomaterials must be labelled with the name of the ingredient followed by the word 'nano' in brackets so that it is possible to recognise products whose formulations contain nano-sized ingredients.

Endocrine disruptors

There is increasing concern over the use of endocrine-disrupting substances in different consumer products, including cosmetics. According to the World Health Organization International Programme on Chemical Safety (WHO/IPCS) definitions, 'An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations', and 'A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might lead to endocrine disruption in an intact organism or its progeny, or (sub)populations'.

The EU Cosmetics Regulation [2] does not contain specific provisions for endocrine disruptors, but regulates them in the same way as other cosmetic ingredients, based on the general requirements of the legislation. Restrictions on the use of ingredients are made based on the SCCS Opinion under Article 31 of the regulation and listed in the relevant annexes. However, substances

identified or considered as potential endocrine disruptors which have been classified as CMRs are prohibited under Article 15 of the regulation.

Endocrine-disrupting substances raise concerns for human safety. Furthermore, scientific knowledge and the relevant regulatory framework are likely to evolve rapidly and should be accurately applied. In order to avoid endocrine disruptors in consumer products, official sources of information, such as the Endocrine Disruptor Lists (EDlists.org), should be consulted.

The real need for intentionally adding substances to cosmetics for infants when these have been identified as potentially endocrine-disrupting should be assessed.

Quality of the ingredients

The quality of the ingredients determines the quality and safety of the finished product intended for infants. Impurities from all sources should therefore be minimised and evidence provided from analytical testing, including microbiological examinations.

Each ingredient should be fully characterised, and quality specifications provided that include references for suitable analytical methods.

For ingredients of natural origin, complete information should be provided on the origin of the raw material, the extraction method and any additional purification steps, the characteristic elements of the composition, the presence of preservatives and other additives, and the presence of contaminants [1].

For preparations used as raw materials, the components should be clearly identified and quantified.

Detailed specification sheets should be available for each raw material, with information on the analytical methods [39]. The degree of chemical purity should be determined.

Impurities in raw materials should be characterised and their presence restricted in order to avoid any detrimental effect on the safety of the finished product. The presence of impurities with CMR or endocrine-disrupting properties should be excluded. Since the presence of impurities in the formulation phase can have a detrimental impact on the safety of the final product, it is important to identify any unintended substance with a toxicologically relevant effect.

The microbiological quality of the raw materials should be checked.

Particular attention should be paid to the microbiological quality of water and ingredients of natural origin.

Safety data: availability, justification of usefulness of data

The safety assessment of ingredients in a cosmetic product must be performed by a qualified person using an appropriate 'weight-of-evidence' approach for reviewing data from all existing sources.

The intended use of the cosmetic product and exposure to its individual ingredients in the final formulation should be taken into account in the safety assessment.

The safety file should gather characterisation data and safety data for each ingredient.

Characterisation data

a. chemical identity,
b. physical form,
c. molecular weight,
d. characterisation and purity of the substance,
e. characterisation of the impurities or accompanying contaminants,
f. solubility,
g. partition coefficient (log $P_{o/w}$),
h. additional relevant physico-chemical specifications.

Safety data

i. acute toxicity,
j. irritation and corrosivity,
k. sensitisation,
l. percutaneous absorption,
m. repeated dose toxicity (90 days),
n. mutagenicity and genotoxicity,
o. carcinogenicity,
p. reproductive toxicity,
q. toxicokinetics,

r. photo-toxicity,
s. human data,
t. stability.

Safety data must be supplied for *a* to *i* and *l*.

However, it may be sufficient to supply safety data for *a* to *f* and *l* if it is demonstrated that:

- the substance is not bioavailable through the dermal route; and
- exposure by any other route than the skin is excluded, taking into consideration the foreseeable use and behaviours inherent to infants.

Photo-toxicity data is required for substances with photo-absorption properties. All other available relevant data should be added to the safety file of the cosmetic product, in particular epidemiological studies, environmental effects, relevant scientific publications, etc.

The absence of data in the safety file, where this occurs, should be justified by the safety assessor in order to guarantee the harmlessness of a given product, taking into account the formula, the conditions of exposure and normal or reasonably foreseeable use of the product [3].

Formulation

The number of ingredients used in formulations should be reduced to a strict minimum.

The qualitative and quantitative composition is chosen to ensure that the product is well tolerated by infants. The safety margin is determined by taking into account the skin surface area. With concentration ranges, toxicological considerations should be based on the highest concentration level.

Safety assessors should seek relevant information on the toxicity of cosmetic ingredients.

The evaluation of potential interactions between different ingredients may be based on experience (published data on related compounds/mixtures or theoretical considerations).

Exposure to the finished product

Exposure to the finished product and systemic exposure to the ingredients under normal or reasonably foreseeable conditions of use must be known in order to determine the concentration levels considered safe for ingredients and their MoS. This assessment should also be performed for regulated substances. For some categories of products for infants, exposure may be difficult to establish and the worst-case scenario should apply.

'Leave-on' products

'Leave-on' products are likely to be applied to infants up to several times a day. Additionally, the ingredients in such products may accumulate percutaneously over time.

These types of products contribute to long-term toxicities and potential multiple exposures, about which there is currently a lack of knowledge in view of the difficulties in assessing the extent of exposure.

It is recommended to undertake specific evaluations for 'leave-on' products for infants, both for ingredients and finished products, notably taking into account the long-term toxicities and, where possible, potential multiple exposures.

Toothpastes

Studies have shown that young children ingest much larger quantities of toothpaste than adults [40–42]. Infants aged 24 to 36 months ingest approximately 60 % of the toothpaste loaded onto a toothbrush [42]. In calculating the MoS, the assessor should consider that young children may ingest most of the toothpaste applied to the toothbrush.

Given that there is a strong positive correlation between the amount of toothpaste used and the amount ingested [42], a clear warning on the quantity to use and the need for supervision should be labelled on toothpastes for infants.

Recommendations on fluoride content in toothpastes are given in the Annex to this guidance document.

Calculation and analysis of margins of safety

Calculation of the MoS of a cosmetic ingredient depends on the systemic exposure to the ingredient and on its toxicological parameters.

The calculated MoS is compared with a reference MoS, which is comparable to the uncertainty/assessment factor used in risk and safety assessments to extrapolate from a group of test animals to an average human being, and subsequently from average humans to sensitive subpopulations such as children. According to the SCCS guidelines [1], a default value of 100 (10 × 10) accounting for inter- and intra-species differences is generally accepted and an MoS of at least 100 therefore indicates that a cosmetic ingredient is considered safe for use.

In the SCCS guidelines [1], MoS is calculated according to the following formula:

$$\mathbf{MoS = PoD_{sys}/SED}$$

where:

- PoD (point of departure) is a dose descriptor for the systemic exposure to a substance generally calculated from an NOAEL. Usually, the PoD_{sys} value is taken from historical NOAELs or BMD values from oral studies.
  - NOAEL – no observed adverse effect level (mg/kg/day). The NOAEL is defined as the lowest dose or exposure level where no (adverse) treatment-related findings are observed.
  - BMD – benchmark dose. The BMD is proposed as an alternative for the classical NOAEL and lowest observed (adverse) effect level (LO(A)EL) values.
- SED is the systemic exposure dose, estimated on the basis of the daily exposure and the level of dermal absorption.

If a BMD or an NOAEL cannot be identified from the available data, other dose descriptors such as the LOAEL may be used in the MoS calculation.

Regardless of the value used, for route-to-route extrapolation, e.g. from an oral NO(A)EL via a systemic NO(A)EL to a dermal NO(A)EL, both the dermal and the oral bioavailability should be taken into account.

When the oral bioavailability is considered as 100 % by default, the MoS for dermal exposure will in most cases be over-estimated. For products for infants, the determination of the MoS should be as accurate as possible and, when data are missing, the safest approach should be chosen.

For route-to-route extrapolation, the MoS should be determined according to the following calculation:

$$\mathbf{MoS} = \frac{\mathbf{NO(A)EL_{oral}} \times \mathbf{F_{oral}}}{\mathbf{D_{derm}} \times \mathbf{F_{derm}}}$$

where:

- F_{oral} is the bioavailability by the oral route,
- D_{derm} is the dermal dose expressed in mg/kg bw/day,
- F_{derm} is the bioavailability by the dermal route.

When data on oral bioavailability is not available, a default value should be applied. In its guidelines [1], the SCCS considers it appropriate to assume that no more than 50 % of an orally administered dose is systemically available. If there is evidence suggesting poor oral bioavailability (e.g. a poorly soluble particulate substance), it may be more appropriate to assume that only 10 % of the orally administered dose is systemically available.

In addition, for the determination of the MoS for infants, it is especially recommended:

- **For products likely to be applied on the buttocks**: to apply the precautionary principle of 100 % dermal absorption when calculating the systemic exposure dosage. This stringency is required because, as discussed in the section on Specific application area: buttocks, the buttocks are a particularly sensitive area for a number of reasons.
- **For all products other than those intended for the buttocks**: to also consider a theoretical dermal absorption of 100 % in cases where data on dermal absorption are not available or are only estimated from modelling (such as estimations based on the molecular weight and the octanol/water partition coefficient) [43].
- **For 'rinse-off' products**: to determine the cutaneous retention factor (R) of the product after rinsing in accordance with the instructions of use. This measured cutaneous retention factor is used for the calculation

of the MoS. In the absence of such data, a cutaneous retention factor of 10 % should be applied.

The concept of a cutaneous retention factor (R) was introduced by the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) in order to take into account rinsing and/or the dilution of finished products after applying to wet skin or hair (shower gel, shampoo, hair dyes, etc.). Cutaneous retention factors are now listed by category of products in the SCCS guidelines [1], e.g. 1 % for shower gels and shampoos.

Certain categories of products, in particular oily continuous-phase formulations such as bath creams, are not taken into account in current SCCS guidelines. Consequently, no retention factors have been standardised for these products. It would be inadequate to apply a retention value of 1 % on products other than shampoos and shower gels.

Due to the lack of available experimental data for the calculation of MoS for 'rinse-off' products intended for use on infants, a cutaneous retention factor of 10 % should be considered, except when the manufacturer has carried out specific testing.

A cutaneous retention factor of 10 %, which is more realistic than 1 %, avoids applying a worst-case scenario, i.e. a retention factor of 100 % which would be contradictory to the principle of rinsing.

Safety assessors are responsible for carrying out the proper safety assessment on the basis of the relevant information on the specific product, taking into account the state of the art of the most relevant technical documents such as the SCCS guidelines.

Finished cosmetic products

The finished cosmetic product is the product in its final container as it is placed on the market.

The primary container (in contact with the product) and the secondary packaging (the outer container) are labelled with all relevant information on the product, such as name, function, list of ingredients, instructions for use (where relevant), batch number, warnings and precautionary measures. The same labelling requirements should apply for products packaged at the point of sale.

Formulation of the product

For each finished product, a list of physico-chemical and microbiological specifications (parameters and limits) should be set and the relevant analytical methods to assess them should be indicated.

Proper storage of the finished product helps to maintain its stability and quality; therefore, information on specific storage conditions, where relevant, should be made available to distributors and consumers.

Microbiological quality

Microbiological quality is a key factor for product safety.

Microbiological specifications for cosmetic products intended to be used on sensitive body parts and on specific age groups should be carefully evaluated, especially for products intended to be used on mucous membranes, products which could be in contact with the eyes and products intended to be applied to irritated skin.

Microbiological contamination is a source of particular concern for products intended for infants. The total viable count for aerobic mesophilic micro-organisms should not exceed 10^2 CFU/g or 10^2 CFU/mL of the product. *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans* should not be detectable in 1 g or 1 mL of the product [1]. Standard ISO 21148 (General Instructions for Microbiological Examinations) [44] should be applied, i.e. to perform the microbiological tests in samples of at least 1 g or 1 mL of test product. Information on microbiological quality is important for assessing the effectiveness of the preservation system and the storage conditions.

Challenge testing should be performed on the finished product with micro-organisms from official collection strains [1]. The lowest effective concentration of preservatives should be determined on the basis of challenge test results.

Challenge testing for the preservative system should reproduce the method of application of the product under real conditions of use.

The long-term stability period and the period after opening (PAO), if relevant, should be determined by means of stability studies, and the efficacy of the preservative system should be assessed in the same container used for marketing the product.

Impurities

The presence of unintended substances could have an impact on the safety of the finished product.

Therefore, the level of impurities in the finished product should be determined and any impact on product safety should be assessed, taking into account any applicable legal requirements. Suitable state-of-the-art analytical methods should be used to detect and quantify the relevant impurities.

Traces are very small quantities of unintended substances in the finished product.

The presence in cosmetics of trace levels of prohibited substances, such as heavy metals, must be justified in an exhaustive way, and the level of technical unavoidability must be established. Some trace substances have a regulatory concentration limit.

Safety assessors should seek relevant information on the toxicity of impurities and take it into account in assessing the safety of the product.

Impregnated baby wipes

Cosmetic carrier materials, such as impregnated wipes or cotton, can release impurities that may affect the safety of the product. Impurities potentially released by such materials should be characterised and their presence should be restricted in order to avoid any detrimental effect on the safety of the finished product.

Product packaging

The characteristics of packaging materials in direct contact with the final product (suitability of primary container in terms of migration/adsorption factors, barrier properties, inert inner layer) may determine the safety of the cosmetic product, and container compatibility should be investigated.

The safety assessor must establish the safety of the packaging based on a study of its design, composition and compatibility with the formulation, combined with any possible effect due to contact with the external environment, purity

and stability of the material (in terms of leaching and migration phenomena or possible deterioration of the product in contact with the packaging).

Where there are safety or compatibility issues, the need to reformulate the product, replace the container or change the manufacturing process should be considered.

Appropriate packaging should be chosen for formulations sensitive to air or light in order to prevent any degradation of the product.

Stability tests should be conducted on the finished product in its final container to define the suitable storage conditions and to ensure that product specifications are maintained for the expected time of use of the product.

Packaging design

There are several risks associated with the design of cosmetic product packaging that are inherent to the behaviour of infants, e.g. accidental ingestion of the product, aspiration of liquids or ingestion of small parts of the container such as lids or fragments in the case of breakage. The safety assessor has to take into account the following aspects on a case-by-case basis:

- the need for a closure system that prevents infants from accessing the contents of cosmetic containers;
- containers should be designed so that contact will not result in physical injury, while also ensuring that the material used is suitable;
- whenever possible, the use of glass containers must be avoided, especially in products designed to be used with wet hands, such as bath gels, shampoos or oils [45];
- removable container parts, such as lids or dosage pump heads, must be sufficiently large that they cannot be swallowed. The quantity of product delivered should be just the amount suitable for the intended use;
- containers that look like foods, e.g. honey (transparent bottle with amber coloured product and surface resembling a hive), should be avoided in order to minimise the risk of ingestion. Toddlers are at risk of accidental poisoning because they are beginning to move around independently and are curious. A brightly coloured container may attract attention [46].

Containers made to look like toys, which can be used as such, e.g. bottles in the shape of dolls, must comply with applicable rules governing the safety of toys [47] as well as with applicable rules on cosmetic products.

Composition and stability

The stability of the cosmetic product affects the safety and quality of the final product.

In order to identify the best packaging for any cosmetic product, a study of the stability of the product in its final (commercial) immediate packaging must be carried out [1]. An in-use stability test should also be performed.

Stability data are important in order to determine the appropriate storage conditions for a product, its minimum durability and the PAO in the reasonably foreseeable conditions of use.

If relevant, the label should state the storage conditions to be followed in the distribution chain and by the end users.

Due to the physiological, metabolic and behavioural characteristics of infants, special attention must be paid both to the presence of toxic substances in the packaging that may be transferred to the product, such as phthalates, and to the presence of toxic substances that may be ingested by infants after playing with or sucking on the packaging, as for example, with certain printing inks.

Product use and labelling

Cosmetic products should comply fully with the definition, route of application and function of a cosmetic product and be distinguished from products whose functions are not in the scope of Council of Europe Resolution CM/ResAP (2012) 1 and the EU Cosmetics Regulation [2].

Many products for infants are multi-functional and their instructions for use should be sufficiently clear to avoid any misuse.

The general presentation of the product should prevent confusion between 'leave-on' and 'rinse-off' products.

For cleansing products, some of which are designed to be rinsed off with water and others to be applied and wiped away with cotton, the method of removal should be clearly described on the labelling.

Calculation of the exposure levels for safety assessments should reflect the labelled instructions for use and the reasonably foreseeable conditions of use.

Attention should be paid to claims used in the labelling which could be misleading when the presentation of the product is unclear or ambiguous.

A cosmetic product must not have in its labelling any claim (text, names, pictures or signs, trademarks or other elements) which could suggest, for example, a medical (preventing or treating symptoms or illnesses) or biocidal (e.g. insect repellent) effect.

Any product claiming a medical or biocidal effect must have received authorisation after undergoing a quality, safety and efficacy assessment according to the relevant applicable legislation.

Annex. Recommendations for some specific ingredients

Fluoride in toothpastes

Dental caries can be largely prevented by maintaining a constant low level of fluoride in the oral cavity. Optimal fluoride can be obtained from different sources, such as fluorinated drinking water, salt, milk and toothpaste. Twice-daily tooth brushing with fluoride-containing toothpaste (1 000 to 1 500 ppm) should be encouraged [48]. Long-term exposure to an optimal level of fluoride results in substantially lower incidence and prevalence of tooth decay across all ages [49].

In children from 1 to 3 years of age, fluoride ingestion from all sources should not exceed the accepted adequate intake of 0.7 mg/day, which maximally reduces dental caries without causing undesirable effects such as fluorosis [49].

Recommended use of fluoride toothpastes in children in the European Academy of Paediatric Dentistry 2019 Fluoride Guideline [50]

Age	Fluoride (ppm)	Quantity of toothpaste (g)	Size
6 months–2 years	1 000: twice per day	0.125	Grain of rice
2–6 years	1 000*: twice per day	0.25	Pea
Over 6 years	1 450: twice per day	0.5–1.0	Up to full length of brush

* For children 2–6 years, 1 000+ fluoride concentrations may be considered based on the individual caries risk.

The Scientific Committee on Consumer Products (SCCP) concluded in its Opinion on the safety of fluorine compounds in oral hygiene products for children under the age of 6 years [51] that if the sole source of fluoride exposure is toothpaste containing between 1 000 to 1 500 ppm fluoride, there is minimal concern that children under the age of six will develop fluorosis, provided that such toothpaste is used as recommended.

When fluoride toothpaste is combined with other fluoride sources, such as fluorinated milk or water, the cumulative fluoride exposure must be taken into consideration for children less than 6 years of age. Therefore, care must be taken to ensure that a balance between maximising the preventive effect against dental caries and minimising the risk of dental fluorosis is maintained [50]. In addition, parents must be strongly advised to apply an age-related amount of toothpaste and assist/supervise tooth brushing until 6 years of age.

Both issues are addressed by Annex III of the EU Cosmetics Regulation [2] as amended by Regulation (EU) No. 344/2013 [52], which prescribes the following obligatory warning on toothpastes containing fluoride in concentrations of 1 000 to 1 500 ppm, unless it is already labelled as contra-indicated for children:

> 'Children of 6 years and younger: Use a pea sized amount for supervised brushing to minimize swallowing. In case of intake of fluoride from other sources consult a dentist or doctor.'

Toothpaste with a concentration of fluoride lower than 1 000 ppm can be considered for younger children regularly exposed to other sources of fluoride. However, the evidence for the prevention of dental caries with such products is limited [50].

Considering that infants ingest a greater percentage of the toothpaste used for brushing than older children [40–42], and that they could be attracted by the taste of some toothpastes, a clear warning on the quantity to use and the need for supervision should also be labelled on toothpastes for infants containing less than 1 000 ppm fluoride.

Terpenes

The presence of terpenes such as camphor, eucalyptol or menthol in cosmetic products can cause serious undesirable effects in infants. It is also the case

when those substances are constituents of essential oils. Adverse neurologic effects (e.g. convulsions) have been reported following topical use of preparations containing terpenes on infants [53–56].

In 2008, the Council of Europe and the French Health Products Safety Agency (AFSSAPS) recommended that the use of camphor, eucalyptol and menthol should be avoided in cosmetic products intended for infants [53, 54].

Nevertheless, the presence of low concentrations of camphor, eucalyptol or menthol in perfume compositions, for instance, was considered acceptable by AFSSAPS within the following limits:

- camphor: 0.015 % (150 ppm),
- eucalyptol: 0.1 % (1 000 ppm),
- menthol: 0.45 % (4 500 ppm).

This recommendation does not apply to oral hygiene products.

Some examples (not exhaustive) of essential oils containing camphor, eucalyptol and/or menthol include: *Artemisia* ssp, *Basilicum*, *Calamintha nepeta*, *Chrysanthemum balsamita*, *Chrysanthemum parthenium*, *Cinnamomum camphora*, *Elettaria cardamomum*, *Eucalyptus* ssp, *Lavandula* ssp, *Mentha* ssp, *Ocimum*, *Rosmarinus officinalis*, *Salvia* ssp, *Santolina chamaecyparissus*, *Tanacetum vulgare* and *Thymus mastichina* [53, 57].

A special warning against use in children should be included on the labelling of products containing camphor, eucalyptol or menthol destined for older consumers [53].

Sun protection products

Considering that sun protection products cannot provide full protection against health risks from UV radiation and that exposure to sun during childhood is an important contributor to the development of skin cancer at a later age, sun protection products intended for infants should not give the impression that they provide them with sufficient protection [58].

In the presentation of sun protection products for infants, it should be noted that infants under 1 year of age should be kept out of direct sunlight. Older infants should never be exposed directly to the sun without adequate protec-

tion, i.e. clothing, hat, sunglasses and (very) high protection sunscreens. Sun protection products should be applied generously and re-applied frequently, especially after swimming or towelling. Direct sun exposure should be avoided under extreme conditions and during midday hours (from 2 hours before peak UV radiation to 2 hours after) [59, 60].

For the safety assessment of sun protection products intended for infants, special attention should be paid to exposure and dermal bioavailability of the ingredients.

The use of sun protection products on infants potentially leads to higher exposure compared to adults, due to their higher skin surface area to body mass ratio (see Skin). In its 2002 Position statement on the calculation of the margin of safety of ingredients incorporated in cosmetics which may be applied to the skin of children [60], the SCCNFP concluded that, based on the fact that inter-individual variation is already taken into account by the uncertainty factor of 100, there was no general scientific justification for adding an extra uncertainty factor for the larger exposure surface area in children over the age of 1 year. However, considering that sun protection products are applied to large areas of body surface, the skin surface area to body mass ratio of infants should be taken into account, either at the level of conditions of exposure or at the level of MoS.

Concerning dermal bioavailability, industry selects sun screening agents with limited dermal penetrability so that the agent should ideally remain in the outer skin layer, where it creates a barrier against UV radiation [61]. Very low dermal absorption percentages of 1 % or less have been observed for individual sunscreen agents; however, exceptions exist for substances such as benzophenone-3 [62–64]. When data on dermal absorption are not available or are only estimated from modelling, a default value of 100 % dermal absorption should be used for the calculation of the MoS (see Calculation and analysis of margins of safety).

Within the European Union, UV filters used in sun protection products have to be authorised as such. Substances listed as authorised UV filters in Annex VI of the EU Cosmetics Regulation have generally been evaluated by the European Scientific Committee (the former SCCNFP, SCCP or the current SCCS). The safety assessor should carefully examine up-to-date opinions of this Sci-

entific Committee, with particular attention to specific exposure and vulnerability of infants.

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Shampoos, creams, lotions, oils, wet wipes for babies and young children: the number of cleansing, perfuming and care products available for children has increased considerably in recent decades, with new and attractive packaging and marketing to promote them. Yet the intended users – infants and young children – are sensitive to toxic effects of such products. Through this guide for manufacturers and safety assessors, the European Committee for Cosmetics and Consumer Health (CD-P-COS) seeks to identify, address and avoid such risks.

This 2nd edition reflects the state of the art in this field. It includes a new section on nanomaterials. Additional revisions concern information on endocrine disruptors, the margin of safety of cosmetic ingredients, safety evaluation criteria for finished products and recommendations for specific product use (e.g. fluoride, baby wipes).

This guide is intended to improve the safety of cosmetic products for infants and young children, in line with the mission of the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, of working towards better health for all.

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