SUITABILITY OF CELINDE SUNSCREEN FORMULATION (PANTALLA SOLAR Y AMBIENTAL FPS 60+ PA+++) FOR PREGNANT WOMEN

Date 19/01/2021

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Suitability assessment of a cosmetic product for its use by pregnant women

1 Object of the report

Celinde Cosmetics SL requires bspoke to review and assess the toxicological profile of the substances included in the cosmetic product PANTALLA SOLAR & AMBIENTAL SPF 60+ PA+++ consisting in a sunscreen cream. Particularly, the focus of this assess should be the safety of use of this formulation by pregnant women and also by those in the stage of breastfeeding.

2 Introduction

In day life humans are exposed to chemical substances from various sources such as medical drugs, foods, cosmetics, and other consumer products. Among all those chemical substances some could be toxic and other are suspected to be toxic for humans and/or animal. In particular, cosmetic products are widely used by women and men of all ages, including those women in the child-bearing age. Cosmetic products contain various chemical substances that can enter humans via different routes of exposure. Most cosmetics products are applied on the skin and their ingredients can reach the systemic circulation across the cutaneous barrier, but exposure can also occur via inhalation or ingestion.

Pregnant women are recognized as a vulnerable consumer group by the Scientific Committee on Consumer Safety (SCCS), who is responsible of assessing the safety of cosmetic products ingredients. Nevertheless, the SCCS does not state on their guides a specific approach to assess the safety of products intended to use during pregnancy. This is probably due to the European Union Regulation which states that, before making available on the market any cosmetic product, it should have a product information file (PIF) where an expert should assess the safety of the product (including its toxicology profile). During this assessment, for every substance a Margin of Safety (MoS) is calculated and if the result is above a stated value (normally 100) the ingredient is considered safe. This procedure was elaborated by the SCCS on their guides and the chosen default MoS value of 100 is an uncertainty/assessment factor that is based on a factor of 10 for the extrapolation from test animals to an average human being and another factor of 10 taking into account the variations withing the human population. Thus, the uncertainty factor of 10 used for the intra-species extrapolations also cover the pregnancy stage.

Therefore, any cosmetic product with a PIF and a positive safety assessment may be considered safe for use, even during pregnancy and breastfeeding.

But, although the stated over these lines, the SCCS also considers that “where necessary, exposure of vulnerable consumer groups could be assessed separately”

Some chemical substances -including those used in cosmetic products- can sometimes be considered safe for use by an expert committee even if they are toxic or suspected to be toxic for humans. There are different reasons for that, but mainly due to their high threshold for toxicity and the lack of a safe and readily available alternative. Another possibility is the scientific advance and the development of new studies that show properties of concern in substances already evaluated as safe and in use. When those kind of substances under concern are in use in a cosmetic formulation a specific assessment becomes relevant and necessary.

Pregnant women are particularly vulnerable to the potential risk of endocrine disruptors because pregnancy is a vulnerable time for the development of the embryo and fetus due to their immature metabolism, being thus the fetal stage (and also childhood) some of the most sensitive periods of human life because of the balance in the hormonal system required during these stages development.

3 Review procedure

As stated in point 2, during this review it is assumed that the cosmetic product has a correct PIF and that a safety assessment has been carried out by an expert. Therefore, in order to review the substances included in the product from the perspective of its use during pregnancy, focus will be put -mainly- on the studies about endocrine disruptor properties but also in developmental/teratogenic studies.

Where no data nor studies are available, the exposure to the substance will be assessed and the risk evaluated through its systemic bioavailability.

It should be noted that other studies like carcinogenicity and mutagenicity are considered covered by the standard safety assessment (PIF) as those affect the user in the first instance, regardless of whether they are pregnant or not.

The data used in this report will be gathered from European Union risk assessments, SCCS and European Food Safety Authority (EFSA) opinions, other official risk assessments and the most up to date literature on the substance available in the data portals.

For the purpose of reviewing the literature, databases like PubMed and Google Scholar were used and the search terms included (among others) androgen, estrogen, thyroid, reproductive, teratogenic, endocrine disruptor as well as the INCI name (or CAS number) of the targeted substance.

4 Discussion

As already mentioned, this assessment will consider that a previous safety assessment is done by an expert and the product is considered safe. This review will be focused on the reproductive/teratogenic toxicity and on the potential as endocrine disruptors of the substances contained in the cosmetic product.

The evaluated product is a sunscreen cream, so its foreseeable use is the dermal application. Moreover, according to the SCCS (SCCS/1602/18) for sunscreen products an aggregate exposure is considered and an amount of 18 g/day is used by default in MoS calculations (but is not meant as a recommended amount to be applied by the consumer though). This information is remarked because, although the main

via of penetration into the body is dermal it is expected that consumers use large amounts of product during its application.

The cosmetic product is composed by 42 (declarable) substances being water the ingredient base with a concentration of 53.8%. After carefully review the available data about reproductive toxicity and endocrine disrupting properties (ED properties) for the remaining 41 substances the main concern comes from the use of three UV filters: Ethylhexyl methoxycinnamate (CAS: 5466-77-3), Octocrylene (CAS: 6197-30-4) and, in a lesser extent, Butyl methoxydibenzoylmethane (CAS: 70356-09-1).

UV filters, especially those of chemical action, have in their structure aromatic rings (phenolic type) needed to absorb the UV light. But this also allows these compounds to interact with the binding pocket of animal molecules turning them into potential endocrine disruptors.

Ethylhexyl methoxycinnamate and Octocrylene are present in the cosmetic product at concentrations up to 4% and 2%, respectively. Ethylhexyl methoxycinnamate is being evaluated by different expert Panels as a suspected endocrine disruptor. Moreover, there are some in vivo evidence suggesting it reproductive toxicity. Octocrylene is also in the spotlight of the European Commission due to concerns related to its potential endocrine disruption properties and the SCCS has been requested for a scientific opinion on Octrocrylene which is expected to issue during 2021.

On the other hand, Butyl methoxydibenzoylmethane is present in the cosmetic product at a concentration of 4% but, unlike the previous substances, evidence of hormone-like activity was reported only on in vitro assays and that results were not corroborated in vivo.

At this point it should be noted that the dose needed for these substances to produce endocrine disruptive effects are (typically) very high, and much higher than the expected dose systemic available via dermal application of a cosmetic product. Nevertheless, the mechanism of how this endocrine activity is produced not are always know so, whether these endocrine actions can produce adverse effects on human at low concentration levels are not clear.

Therefore, despite these three UV filters being substances approved by the European Regulation on cosmetic products, in the context of a risk assessment specific for the vulnerable consumer group of pregnant women, and from a general perspective there exists an unacceptable risk associated to their presence in cosmetic products.

Focusing on this particular product, the three UV filters of concern are provided by the same raw material manufacturer which claims (through the appropriate documentation) that these three filters are contained together in a mixture that is encapsulated in a double-layered sphere (i.e., like a liposome). According to the manufacturer, these spheres have an average size of 200-500 nm and a negatively charged outer layer. The manufacturer claims that these aggregates cannot reach the bloodstream because non absorption into the skin takes places. Although there is not included any transdermal study by the manufacturer, based on the size of the spheres and in its negative charge, absorption through the stratum corneum is expected to be negligible. The stability of these spheres through the entire self-life

of the product should also be probed and guarantied in order to prevent the availability of the ingredients under concern.

Apart from the mentioned UV filters, only a couple of remarkable facts should be highlighted. First the presence of Titanium dioxide, a cosmetic ingredient for which many of its commercial types has been subject of safety assessments these days due to its recognized carcinogenic behavior. Nevertheless, this risk is exclusively associated to the potential exposure of respiratory tract, which is not expected during the use of this product. Second, for the ingredients Gossypium herbaceum callus culture, Polygonum aviculare extract, Alteromonas ferment extract and Acetyl hexapeptide-49 there is a considerably lack of toxicological data, but limited data also suggest no known risks. Moreover, their concentration on final product (≤0.15%) is low and toxicity associated to their bioavailability is not expected.

The rest of the substances evaluated des not present reproductive toxicity or teratogenicity and there is not data suggesting a potential endocrine disruptor behavior.

Impurities present in raw materials have been also evaluated (see section 9) and no risk is expected due to their presence at their concentration in final product.

5 Conclusion

After reviewing the ingredients contained in the cosmetic product **PANTALLA SOLAR & AMBIENTAL 60+ PA+++**, an unacceptable risk for pregnant women associated to the use of this sunscreen cream has not been identified.[1]

This opinion only is valid under the premise that the encapsulation system to isolate into a sphere the UV filters Ethylhexyl methoxycinnamate, Octocrylene and Butyl methoxydibenzoylmethane is efficient and stable.

6 Recommendations/suggestions

It is recommended to request evidence of the absence of transdermal absorption for the raw material SunCat MTA as well as evidence of its long-term stability in a typical formulation.

[1] This opinion is based on the scientific data available in the literature at the date it is issued. Therefore, any new study published after that date must be independently revised and assessed.

7 Quantitative formula

The substance composition of the cosmetic product, in decreasing order of concentration, is showed.

INCI	CAS	COMPOSITION (%)	INCI	CAS	COMPOSITION (%)
AQUA	7732-18-5	53,783	STEARETH-20	9005-00-9	0,225
CYCLOPENTASILOXANE	541-02-6	5	LECITHIN	8002-43-5	0,2
BUTYL METHOXYDIBENZOYLMETHANE	70356-09-1	4	CI 77492	51274-00-1	0,18
ETHYLHEXYL METHOXYCINNAMATE	5466-77-3	4	GOSSYPIUM HERBACEUM CALLUS CULTURE	-	0,15
DICAPRYLYL ETHER	629-82-3	3	SILICA	7631-86-9	0,12
PHENYLBENZIMIDAZOLE SULFONIC ACID	27503-81-7	3	ETHYLHEXYLGLYCERIN	70445-33-9	0,1
PROPANEDIOL	504-63-2	3	CI 77491	1309-37-1	0,06
SQUALANE	111-01-3	3	POLYGONUM AVICULARE EXTRACT	84604-04-6	0,04
ETHYL MACADAMIATE	214495-31-5	2,9955	CI 77499	12227-89-3	0,03
BUTYLENE GLYCOL	107-88-0	2,679975	ALTEROMONAS FERMENT EXTRACT	-	0,02
TITANIUM DIOXIDE	13463-67-7	2,61	CITRIC ACID	5949-29-1	0,0085
OCTOCRYLENE	6197-30-4	2	POTASSIUM SORBATE	24634-61-5	0,008
C8-22 ALKYL ACRYLATES/METHACRYLIC ACID CROSSPOLYMER	-	1,92	SODIUM BENZOATE	532-32-1	0,008
TRIETHANOLAMINE	102-71-6	1,9	TOCOPHEROL	10191-41-0	0,003
CETYL ALCOHOL	36653-82-4	1,05	MALIC ACID	97-67-6	0,0015
GLYCERYL STEARATE	31566-31-1	1,05	ACETYL HEXAPEPTIDE-49	-	0,000025
SODIUM POLYACRYLATE	07/04/9003	1	CITRONELLOL	106-22-9	<0,2
PHENOXYETHANOL	122-99-6	0,92	D-LIMONENE	5989-27-5	<0,2
GLYCERIN	56-81-5	0,7425	GERANIOL	106-24-1	<0,2
PEG-75 STEARATE	9004-99-3	0,45	HYDROXYCITRONELLAL	107-75-5	<0,2
CETETH-20	9004-95-9	0,225	LINALOOL	78-70-6	<0,2

Table 1. Quantitative composition of the cosmetic product.

Substances will be reviewed following the same order as in Table 1, except for water which is non-toxic.

8 Substance review

8.1 CYCLOPENTASILOXANE (CAS: 541-02-6)

Cyclopentasiloxane (D5) is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioning-emollient and/or solvent. It was twice evaluated by the SCCS on Opinions SCCS/1241/10 and SCCS/1549/15 and considered safe for use in

sunscreens lotions at concentrations up to 44%. Sunscreen products in the form of spray or aerosol at concentrations of 35 and 40%, respectively, are not considered safe due to the inhalation exposure. Nevertheless, that opinions are based in the estimate exposure using the PBPK modelling and which differs from the SCCS approach that overestimate the internal systemic dose.

At the concentration of use in the product object of this report (5% in final product) the substance will be considered safe even using the overestimated exposure scenario described by the SCCS for the aggregated exposure.

8.1.1 Reproductive toxicity

On the SCCS reports there are two studies about reproductive toxicity being both a two-generation reproduction toxicity (WIL, 1996; WIL, 1999; Siddiqui et al, 2007). Cyclopentasiloxane was administered via inhalation to Sprague Dawley rats at a maximum concentration of 132 and 160 ppm, respectively.

In the study carried out by WIL (1996), reproductive parameters (fertility, mating, days between pairing and coitus, gestation and parturition), mean body weights, body weight gains and food consumption, mean numbers of implantation sites and mean live litter size were not adversely affected by test material exposure at exposure levels. No exposure-related effects on pup viability throughout lactation and no exposure-related clinical signs were noted in the pups in either the 26 or 132-ppm groups. Pup sex ratios and mean pup weights were unaffected by exposure to the test material at any exposure level. No internal findings related to the test material were noted at either exposure level in females. A NOAEC of 132 was established.

In the study carried out by WIL (1999) and by Siddiqui et al (2007), no parental toxicity in the F0 and F1 generations was seen at exposure concentrations. F0 and F1 reproductive performance was not affected at any concentration. No test-article-related total litter losses occurred. No neonatal toxicity was evident in the F1 and F2 generations at the concentrations used. No F2 developmental neurotoxicity was evident at any concentration. Based on the results of this study, the NOAEL for parental toxicity, reproductive toxicity, neonatal toxicity, and developmental neurotoxicity is considered to be 160 ppm.

Although an increase in male pup anogenital distance was identified in this study, which may indicate an anti-estrogenic or androgenic effect, other studies failed to show such hormonal activity.

8.1.2 Endocrine disruptor properties

Carcinogenic effects of Cyclopentasiloxane in Fisher F344 rats (uterine endometrial adenocarcinomas) were observed after 12 months inhalation exposure plus 12 months recovery, and after 24 months exposure, (Jean et al, 2015; RCC Cytotest Cell Research, 2005) but were only significant at the dose of 160 ppm (Young et al, 2016).

To understand the possible mode of action of Cyclopentasiloxane regarding uterine tumor induction different modes of action were proposed, including an endocrine-disrupting potential. In this context a series of experiments have been conducted to

examine the ability of Cyclopentasiloxane to disrupt endocrine pathways and no significant activity was observed in any of these studies (WEEL, 2017).

Cyclopentasiloxane did not show estrogenic or androgenic activity in rats at whole-body inhalation exposures as high as 160 ppm (Quinn et al., 2007). This result is consistent with the absence of D5 binding to human estrogen receptors or progesterone receptors using a reporter gene assay and other in vitro methodologies (Jean, 2005). A uterotrophic assay conducted in Sprague-Dawley and F344 rats exposed by inhalation to D5 was negative for estrogenic end points (Klaunig et al., 2015).

The ability of Cyclopentasiloxane to act as a dopamine agonist has been also investigated in several studies. Although there is some evidence for and against this hypothesis, the most robust studies did not indicate significant activity (WEEL, 2017).

8.1.3 Other considerations

Cyclopentasiloxane, as supplied, may contains trace amounts of Cyclotetrasiloxane (D4). Since D4 is classified as in the EU as toxic to reproduction category 2 (Repr 2 H361 according to Annex VI of Regulation (EC) No 1272/2008 (CLP-Regulation)).

The SCCS evaluated the overall aggregate exposure to D4 and concurs with the negligible risk due to D4 as an impurity of D5 at the level of the batches used in the dossier (D5 purity > 95%) and therefore the SCCS recommends that the level of purity of D5 in the cosmetic products put on the market should be kept as high as possible.

8.1.4 Summary on substance Cyclopentasyloxane (D5)

Cyclopentasiloxane shown evidence of effects in the liver, lung and uterus following repeated-dose inhalation exposure. If it is used on spray/aerosol products, exposure to D5 may lead to air concentrations above the value where SCCS considered that D5 may be aerosolized and locally toxic (SCCS/1549/15).

The uterine endometrial adenocarcinomas seen in the 2-year bioassay on rats, at the highest dose (160 ppm), are not considered to be biologically relevant for human risk assessment purposes (Klaunig et al., 2015).

Based on the available data, Cyclopentasiloxane does not show reproductive toxicity nor endocrine disruptor properties.

The presence of Cyclotetrasiloxane (D4) as an impurity must be keep as low as possible (D5 raw material purity > 95%).

8.2 BUTYL METHOXYDIBENZOYLMETHANE (CAS: 70356-09-1)

Butyl methoxydibenzoylmethane (avobenzone) is a permitted UV filter (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products with a maximum allowed concentration of 5% in final product.

8.2.1 Reproductive toxicity

In a developmental toxicity study (equivalent to OECD TG 414), Füllinsdorf-Albino SPF rats (36 mated females/group) were given 0, 250, 500 or 1,000 mg/kg bw/day by gavage on day 6 to day 17 of gestation (12 days). No dose-related adverse effects were seen on any parameters and a NOAEL for maternal, developmental and embryotoxicity of 1,000 mg/kg bw/day was concluded (ECHA, 2020A)

8.2.2 Endocrine disruptor properties

Butyl methoxydibenzoylmethane (avobenzone) was evaluated by the SCCNFP (2001) and in its opinion it has no estrogenic effects that could potentially affect human health.

Avobenzone showed no progesterone receptor antagonism, but weak ERα agonism and AR antagonism (Schreurs et al., 2005). Ma et al. (2003) did not find androgen receptor binding, and the compound showed no activation of MCF7 cells and no effect in uterotrophic assay (Schlumpf et al., 2001). This data was evaluated by the Danish Centre on Endocrine Diruptors (Axelstad et al., 2013) concluding that there was not enough evidence to conclude whether the substance has endocrine disruptive properties or not.

In an in vitro androgen (AR) and glucocorticoid (GR) reporter gene assays using the MDA-kb2 cell line avobenzone showed activity as AR antagonist, GR agonist and also thyroid hormone receptors (TR) antagonist using the GH3.TRE-Luc reporter cell line (Klopčič et al., 2017). These results are in agreement with previous reports (Schreurs et al.2005; Ma et al., 2003; Schlumpf et al., 2001) and appear to depend considerably on the species and cell type used, and on the different concentration range and different criteria used for positive agonist/antagonist test results.

Avobenzone showed a slightly induction of estrogen receptor-alpha in vitro, but that result was not corroborated by in vivo zebra fish assay. Reporter gene assays showed only weak antagonism of androgen receptor and no influence on progesterone receptor. No endocrine activity was reported. (ECHA, 2020A)

Avobenzone is not listed on the European Commission priority list of potential endocrine disruptors or on the SIN list of endocrine disrupting chemicals (SIN list database, 2020).

8.2.3 Summary on substance Butyl methoxydibenzoylmethane (Avobenzone)

There are not many available studies about substance Avobenzone. Butyl methoxydibenzoylmethane does not show reproductive toxicity and, based on the available data avobenzone showed hormone-like activity on in vitro assays but that results were not corroborated on in vivo assays. No endocrine disruptor activity is reported at the present time for this substance.

8.3 ETHYLHEXYL METHOXYCINNAMATE (CAS: 5466-77-3)

Ethylhexyl methoxycinnamate (Octyl-methoxycinnamate, OMC) is a permitted UV filter (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products with a maximum allowed concentration of 10% in final product.

Although substance 2-ethylhexyl 4-methoxycinnamate with CAS 5466-77-3 is included in the ECHA portal as a pre-registered substance, there is available the registration dossier of substance 2-ethylhexyl trans-4-methoxycinnamate (with CAS 83834-59-7) which is an isomer of the former one and which toxicological data can be extrapolated.

8.3.1 Reproductive toxicity

In a two-generation toxicity study (OECD TG 416), Wistar rats (25 animals/sex/group) were given dietary levels of 0, 150, 450 or 1,000 mg/kg bw/day. A NOAEL for systemic parental toxicity, fertility and reproduction parameters and developmental toxicity of 450 mg/kg bw/day was concluded (systemic parental toxicity: based on body weight, gross pathology, organ weights and histopathology; fertility and reproduction parameters: based on secondary number of implantations sites and secondary delayed sexual maturation; developmental toxicity: based on pup weights). (ECHA, 2020B)

In a developmental toxicity study (performed equivalent or similar to OECD TG 414) Füllinsdorf albino rats (20-36 mated females/group) were given OMC at 250, 500 or 1,000 mg/kg bw/day by gavage from day 7 to day 16 of gestation. No adverse effects were observed and a NOAEL of 1,000 mg/kg bw/day for maternal toxicity and developmental toxicity was concluded (highest dose level). (ECHA, 2020B)

In a developmental toxicity study (performed equivalent or similar to OECD TG 414), Swiss rabbits (20 mated females/group) were given OMC at 80, 20 or 500 mg/kg bw/day by gavage on day 7 to day 20 of gestation. Body weight gain was slightly impaired in parental animals and significantly decreased in the foetuses in the highest dose group. A NOAEL of 500 mg/kg bw/day was established for both maternal and developmental toxicity. (ECHA, 2020B)

8.3.2 Endocrine disruptor properties

Ethylhexyl methoxycinnamate is listed on the European Commission priority list of potential endocrine disruptors and on the SIN list of endocrine disrupting chemicals (SIN list database, 2020). This substance is being evaluated by the European Chemical Agency (ECHA) under the CoRAP program and it is also under assessment by the ECHA endocrine disruptor (ED) Expert Group. (ECHA, 2020C)

As stated by Ruszkiewicz et al (2017) in a recent report about the toxicology of active ingredients in sunscreen products, several studies indicated that OMC acts as an endocrine disruptor due to the ability to interfere with endocrine system at different levels (Klammer et al., 2007; Schlumpf et al., 2004; Seidlová-Wuttke et al., 2006). In vitro and in vivo studies in rodents have shown that OMC have estrogen activity (Klammer et al., 2005, Schlumpf et al., 2001). In humans OMC exposure has minor, but statistically significant effects on the levels of testosterone and estradiol (Janjua

et al., 2004) and interferes with functions of human sperm cells in vitro (Schiffer et al., 2014). There are also studies showing evidence that OMC disrupts the normal neuroendocrine mechanism in a sex-dependent manner (Klammer et al., 2007, Carbone et al. 2010; Szwarcfarb et al., 2008).

Concern about the OMC effect in humans, especially their role in endocrine, reproductive, cardiovascular and neurodegenerative diseases are compiled in a recent review published by Lorigo et al. (2018) where the authors review the available data about the toxicity associated to OCM and the high and constant exposure of humans to this substance due to its widespread use as active component in sunscreens.

8.3.3 Summary on substance Ethylhexyl methoxycinnamate (OMC)

There are a significant number of studies suggesting the potential activity as endocrine disruptor of the substance OMC. At the present time, it is being evaluated as a suspected endocrine disruptor by different panels of expert in order to determine its endocrine disruptive activity.

Moreover, some in vivo studies suggest reproductive toxicity at the higher doses tested. A NOAEL value of 450 mg/kg bw/day was established based on critical effects that includes organ weights, non-neoplastic histopathology, parental toxicity, fertility and reproductive parameters, and developmental toxicity.

8.4 DICAPRYLYL ETHER (CAS: 629-82-3)

Dicaprylyl ether, also known as Dioctyl ether, is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioning-emollient and/or solvent.

8.4.1 Reproductive toxicity

In a prenatal developmental toxicity study (OECD 414), Dicaprylyl ether was administered to 25 Sprague-Dawley female rats at dose levels of 100, 300 and 1,000 mg/kg bw orally, by gavage from the 6th to 19th day of pregnancy. Under the present test conditions, the no-observed-effect level (NOEL) was above 1,000 mg/kg bw for the dams. The NOEL for the fetuses was also above 1,000 mg/kg bw. No test item-related malformations or variations were noted during external/internal examination of the fetuses or soft tissue examination; skeletal examination revealed no test item-related malformations, variations or retardations.

In conclusion, the test substance possessed no teratogenic or embryotoxic properties. No test item-related increase was noted in the incidence of malformations, variations and retardation tested until the dose of 1,000 mg/kg bw. (ECHA, 2021A)

8.4.2 Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.4.3 Summary on substance Dicaprylyl ether

Dicaprylyl ether does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.5 PHENYLBENZIMIDAZOLE SULFONIC ACID (CAS: 27503-81-7)

Phenylbenzimidazole sulfonic acid and its salts were evaluated by the SCCS on its Opinion SCCS/1056/06 and considered safe for use in sunscreens lotions at concentrations up to 8% (as acid) in the final product. Nowadays, Phenylbenzimidazole sulfonic acid is a permitted UV filter (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products with the maximum allowed concentration of 8% (as acid) stated by the SCCS committee.

8.5.1 Reproductive toxicity

In a prenatal developmental toxicity study (conducted as a limit test and conformed to OECD 414 and method B.31 of Annex V to Directive 67/548/EEC), the sodium salt of the Phenylbenzimidazole sulfonic acid was administered to 25 Wistar rats. Two dose groups (25 animals each) were used, one test- (1,000 mg/kg bw) and one control group (0 mg/kg bw). They were dosed from day 6-15 post coitum and kept off-dose from day 16-19. There were no signs of toxicity in dams. All females were sacrificed on day 20 post coitum and the fetuses were removed by Caesarean section and examined for macroscopic malformations. About 2/3 of them were examined for skeletal and 1/3 for organ malformations. Fetuses were weighed, inspected macroscopically for external malformations and prepared for inspection for visceral and skeletal malformations (by transverse section and double staining respectively). They did not show any such malformations. Skeletal variations were the same (nature and frequency) in test- and control group.

In conclusion, Phenylbenzimidazole sulfonic acid (Na-salt) did not reveal maternally toxic effects and was neither embryotoxic nor teratogenic at the limit dose of 1,000 mg/kg bw/day. (ECHA, 2021B)

8.5.2 Endocrine disruptor properties

Two in vitro screening assays (both GLP compliant), one for oestrogen- and one for androgen receptor binding properties are described in the SCCS Opinion SCCS/1056/06 for the sodium salt of Phenylbenzimidazole sulfonic acid. The test substance did not show affinity for the AR-receptor nor for the ER-receptor. IC_{50}-values could not be calculated.

One in vivo test (GLP compliant) for oestrogenic effects was undertaken by an in vivo uterotrophic assay in immature rats using as test substance the sodium salt of Phenylbenzimidazole sulfonic acid. At the highest concentration tested (200 mg/kg bw) there were no clinical signs of toxicity throughout the dosing period. Food consumption and body weight development was the same in test and control groups.

At necropsy no gross pathological findings except enlargement of uteri in positive controls became manifest (SCCS/1056/06).

In conclusion, these studies showed the absence of an oestrogenic potential for the Phenylbenzimidazole sulfonic acid (Na-salt).

8.5.3 Summary on substance Phenylbenzimidazole sulfonic acid

Based on the available data, Phenylbenzimidazole sulfonic acid does not show reproductive toxicity nor endocrine disruptor properties.

8.6 PROPANEDIOL (CAS: 504-63-2)

Propanediol is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as viscosity controller and/or solvent.

8.6.1 Reproductive toxicity

In a prenatal developmental toxicity study (OECD 414) 1,3-Propanediol was administered to Sprague-Dawley pregnant rats at concentrations of 0, 250, or 1,000 mg/kg by oral gavage on gestation days 6-15. Maternal toxicity was evaluated via clinical observations, body weight, and food consumption. The ovaries and uterus were removed and a macroscopic examination of the internal organs was conducted. The fetuses were removed from the uterus and were counted, sexed, assessed for viability, weighed and length measured, examined externally for malformations and dissected and examined for macroscopic malformations.

No substance related mortality or clinical signs were observed in the dams. No substance-related pathological changes were detected at autopsy. No distinct influence on the prenatal development was detected. All fetal parameters were within the normal range of the control group.

In conclusion, 1,3-Propanediol did not possess teratogenic properties and the maternal and fetal NOAELs were determined to be 1,000 mg/kg (ECHA, 2021C).

In a repeated dose 90-day oral toxicity study (OECD 408 and EPA TSCA 798.2650) Crl:CD (SD) BR rats (10/sex/group) were administered 1,3-propanediol by oral gavage daily for 91 or 92 days at concentrations of 100, 300 and 1,000 mg/kg/day. A concurrent control group (10/sex) was administered the vehicle, deionized water. Spermatogenic endpoints were evaluated for all males at termination. This included a motility/viability assessment, a morphology assessment and the enumeration and epididymal and testicular sperm numbers and sperm production rate.

There were no treatment-related effects on spermatogenic endpoints (mean testicular and epididymal sperm numbers, sperm production rate and sperm motility and morphology) at 1,000 mg/kg (highest dose tested) (ECHA, 2021C).

8.6.2 Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.6.3 Summary on substance Propanediol

Propanediol does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.7 SQUALANE (CAS: 111-01-3)

Squalene is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as hair and skin conditioning, emollient and refatting.

8.7.1 Reproductive toxicity

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) was evaluated the developmental toxicity and the two-generation reproductive toxicity of substance Squalane (Phytosqualan).

The test item was administered orally (by gavage) to three groups, each consisting of ten male and ten female RccHan®:WIST rats, daily for at least 4 weeks (including two weeks prior to mating, through mating, pregnancy and early lactation for females) at the following dose levels: 0, 100, 300 and 1,000 mg/kg/day.

Developmental toxicity endpoint: no differences from the control group were recorded in mean body weight. No morphological findings were recorded. Regarding motor development, no differences from the control group were recorded. No macroscopic findings were recorded at necropsy.

Two-generation reproductive toxicity endpoint: no mortality was recorded in any sex. No test-item-related differences from the control group were recorded in males. No test item-related alterations were recorded. For F0 generation the dose of 1,000 mg/kg can be considered the NOEL for both male and female fertility ant mating performance whereas 100 mg/kg can for female breeding. For F1 generation the dose of 1,000 mg/kg can be considered the NOEL.

Regarding these results, the Squalane is considered to be non-toxic to reproduction (ECHA, 2021D).

8.7.2 Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.7.3 Summary on substance Squalane

Squalane does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.8 ETHYL MACADAMIATE (CAS: 214495-31-5)

Ethyl macadamiate is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioning.

8.8.1 Reproductive toxicity

At the present time, there is no data available in the literature about the reproductive toxicity of the Ethyl macadamiate.

8.8.2 Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.8.3 Other considerations

Ethyl macadamiate is an emollient fatty acid derived from the ester of ethyl alcohol and macadamia nut oil. Its primary constituents are ethyl oleate and ethyl palmitoleate (Chemical Book, 2021).

Both substances, Ethyl oleate and Ethyl palmitoleate, are pre-registered substances in the ECHA portal and are included in an inventory (Annex III inventory) of substances likely to meet criteria of Annex III to the REACH Regulation, i.e., substances predicted as likely to meet criteria for category 1A or 1B carcinogenicity, mutagenicity, or reproductive toxicity. But it should be noted that the inventory is not a tool for classification, it only shows indications for concern. (ECHA, 2021E)

Fatty acid ethyl esters (FAEEs), like ethyl oleate and ethyl palmitoleate, are nonoxidative metabolites of ethanol, highly correlate with prenatal alcohol exposure, and their relevance was demonstrated in study where increased levels of five FAEE (only ethyl oleate was included in that study) were significantly associated with poor mental and psychomotor development in the first 2years of age (Peterson, 2008 in Kwak, 2010).

8.8.4 Summary on substance Ethyl macadamiate

Although there are not available studies about the reproductivity toxicity and the potential behavior as an endocrine disruptor for the complex substance Ethyl macadamiate, there are some concern about its main two constituent's ethyl oleate and ethyl palmitoleate. However, none of the revised data can be considered an evidence of the existence of a risk associated to the presence of the substance Ethyl macadamiate in cosmetic products.

8.9 BUTYLENE GLYCOL (CAS: 107-88-0)

Butylene glycol, also known as 1,3-butanediol, is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioning, humectant, solvent, and viscosity controller.

8.9.1 Reproductive toxicity

In a multigeneration study 25 rats of both sexes were fed either control diet or diets containing 1,3-butanediol at dose levels of 5, 10 or 24 % of the diet (equivalent to 2,500, 5,000 or 12,000 mg/kg bw per day). No treatment-related effects were seen on reproduction and lactation parameters for four of the five generations. The pregnancy rate of F1A rats decreased during five successive mating cycles, and no pups were born at the high-dose level group of the fifth series of litters (F2E generation). Excluding this group, the viability of F2 generation pups revealed no significant differences between litters or between control and test groups (Hess et al., 1981 in EFSA, 2011).

Fertility was not affected in a three-generation study in rats which received 20 % 1,3-butanediol in the diet (10,000 mg/kg bw per day) (Dymaza and Adams, 1969 in EFSA, 2011). A developmental toxicity study conducted as part of this multigeneration study showed no substantive evidence of developmental toxicity of 1,3-butanediol, although some fetotoxicity (e.g., delayed ossification of sternebrae) was noted at dietary levels of 10 and 24 %, levels associated with metabolic disturbances due to the nutritional value of 1,3-butanediol (Hess et al., 1981 in EFSA, 2011).

In another developmental toxicity study, pregnant Long-Evans rats were treated by gavage with 1,3-butanediol at levels of 0, 7.060, 4.236, or 706 mg/kg bw per day on days 6-15 of gestation (Mankes et al., 1986 in EFSA, 2011). Transient maternal sedation was observed at 7.060 and 4.236 mg/kg bw per day, but feed consumptions and maternal body weights were unaffected. A significant, dose-dependent decrease in pup birth weights was observed. At the highest dose, birth weights were preferentially and significantly decreased in male pups not contiguous in utero to female siblings. Other offspring of the highest dose group were not affected and did not differ significantly from controls. Skeletal changes observed were considered by the authors to reflect the birth weight reductions, rather than being indicative of developmental toxicity (Mankes et al., 1986 in EFSA, 2011).

8.9.2 Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.9.3 Other considerations

The SCF evaluated 1,3-butanediol in 1996 and considered this substance as acceptable previous cargo (SCF, 1997 in EFSA, 2011). JECFA at its 23rd meeting in 1979 established an “Estimate of acceptable daily intake for man” of 0 to 4 mg/kg

b.w. for 1,3-butanediol and also published specifications (JECFA, 1980 in EFSA, 2011). 1,3-butanediol is listed in Commission Regulation 10/2011 as an acceptable substance in plastics, without restrictions on migration (acceptable food contact material). 1,3-butanediol is included in the EU register of flavouring substances used in or on foodstuffs and has been evaluated by EFSA for its use as a flavouring agent. EFSA concluded that the substance was of no safety concern as a flavouring at the estimated level of intake based on the MSDI approach (EFSA, 2009d in EFSA, 2011). 1,3-butanediol is permitted by the US FDA as a food additive in several direct and indirect applications.

8.9.4 Summary on substance Butylene glycol

Butylene glycol does not show reproductive/teratogenic toxicity, and, at the present time, no endocrine disruptor activity is reported. Moreover, its safety has been evaluated several times by expert panels in food stuff and its intake is considered safe.

8.10 TITANIUM DIOXIDE (CAS: 13463-67-7)

Titanium dioxide (TiO_2) (and its nano form) are permitted UV filters (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products with a maximum allowed concentration of 25% (individual or for the sum) in final product.

Its safety has been evaluated several times by the European Expert Committee SCCS: Opinion SCCNFP/0005/98 concerning Titanium dioxide; Opinions SCCS/1539/14, SCCS/1580/16 and SCCS/1583/17 concerning the nano form of titanium dioxide and its use in sprayable products; and recently, Opinion SCCS/1617/20 concerning the use of Titanium dioxide in cosmetic products that lead to exposure by inhalation.

As a summary, the SCCS conclude that the use of Titanium dioxide (and its nano form) in dermally applied products at a concentration up to 25% is safe. However, the use of Titanium dioxide (particularly in its nano form) in products that might lead to exposure of the consumer's lungs by inhalation is considered not safe.

The raw material object of this evaluation (EnhanceU-T-medium) is composed by a mixture of Titanium dioxide (79-87%), Silica (6-13%) and Iron oxides (2-6%) and with an average diameter (measured by DLS) of 397 nm. Therefore, the Titanium dioxide evaluated in this dossier is not a nano compound (so not fall under SCCS opinion SCCS/1583/17) and due to its concentration in the mixture is not a pigmentary material but a pearlescent (so not fall under SCCS opinion SCCS/1617/20).

The European Risk Assessment Committee (RAC) of ECHA issued in September 2017 an Opinion recommending a Carcinogen Category 2 classification (i.e. as a suspected human carcinogen) of TiO_2 (CAS 13463-67-7) by inhalation route only. Following this RAC recommendation, the European Commission on 4 October 2019 adopted for TiO_2 a classification as a 'Carcinogen Category 2 (inhalation)' for the purposes of adaptation to technical and scientific progress of the Regulation (EC) No 1272/2008

(CLP Regulation Annex VI entry); this classification applies to TiO_2 'in powder form containing 1% or more of particles with an aerodynamic diameter of ≤ 10 µm'.

8.10.1Reproductive toxicity

In an extended one-generation reproductive toxicity study (OECD 443) conducted with rats the effects of Titanium dioxide E171 (exact form not indicated but mainly nano-form) on the general and reproductive toxicity of the F0 Parents and of the F1 Pups from weaning until adulthood were evaluated at the used dose levels of 100, 300 and 1,000 mg/kg bw/day.

No test item-related influence was noted on the general toxicity and the reproductive performance of the parental animals of the F0 Generation as well as on the pre- and postnatal development of the F1 pups. No test item-related changes were noted during the histopathological examination and the examination of the intestines for aberrant crypt foci (ACF). There were no treatment-related effects on hormone levels (estradiol, estrone and testosterone, plus T3, T4 and TSH) in any of the treatment groups compared to controls. During their post-weaning development, the animals of the F1 Generation showed no signs of general toxicity. No test item-related influence was noted on the development of the reproductive system (levels of sexual hormones, time points of sexual maturations, number and length of estrous cycles, sperm parameter, detailed histopathological examination of testis and epididymides, number of primordial and growing follicles and number of corpora lutea in the ovaries). Also, no test item-related influence was noted on the reproductive performance of the F1 females (fertility index, gestation index, pre-coital time and gestation length) and on the pre- and postnatal development of the F2 pups until sacrifice on lactation day 4 (number of resorptions, stillborns, live born pups and the viability index after birth until lactation day 4). No test item-related influence was noted on the neurological function of the young adult male and female animals of cohort 2A. The neurohistopathological examination of the brains from the high dosed adult animals of cohort 2A and from the high dosed recently weaned animals of cohort 2B did not reveal any test item-related effects when compared to their control group. 2B did not reveal any test item-related effects when compared to their control group. The examination of the lymphpcyte subpopulations in the spleen and the anti KLH IgM serum levels revealed no signs of an adverse effect of the test item on the immune response after injection with KLH.

As a result, a NOAEL above 1,000 mg/kg bw/day of Titanium dioxide was established for general toxicity, reproductive toxicity, developmental toxicity, developmental neurotoxicity and developmental immunotoxicity (for F0 and F1 generations) (ECHA 2021F).

In a prenatal developmental toxicity study (OECD 414) the repeated dose oral administration of TiO_2 pg-2 (average diameter of 165 nm), at doses of 100, 300 and 1,000 mg/kg bw/day, to pregnant female Wistar rats from gestation day 5 through gestation day 19 produced no adverse toxicological effects in the females or foetuses or significant developmental effects at any administered dose. Based on the findings from this study, the NOAEL of TiO_2 pg-2 in the Wistar rat for both maternal toxicity and developmental toxicity is considered to be 1,000 mg/kg bw/day (ECHA, 2021F).

In another prenatal developmental toxicity study, the repeated dose oral administration of TiO_2 uf-2 (average diameter of 19 nm) to pregnant female Wistar rats at doses of 100, 300 and 1,000 mg/kg bw/ day from gestation day 5 through gestational day 19 produced no adverse toxicological effects in the females or foetuses or significant developmental effects at any administered dose. A NOAEL for TiO_2 uf-2 for both maternal and developmental toxicity in the Wistar rat is considered to be 1,000 mg/kg bw/day.

8.10.2Endocrine disruptor properties

Tassinari et al. (2014) investigated the possible reproductive and endocrine effects of short-term (5 days) oral exposure to anatase TiO_2 particles (0, 1, and 2 mg/kg bw/day) in Sprague–Dawley rats (n = 7/sex per group). Particles were characterised by SEM and TEM (average particle diameter 284±43 nm, with 10% particles <100 nm. Most of the particles were agglomerates up to 1.6 µm in diameter. TEM analysis showed two different shapes for primary nanoparticles: spherules of 20–60 nm and irregular shapes of 40–60 nm. Analyses included serum hormone levels (testosterone, 17b-oestradiol and triiodothyronine) and histopathology of thyroid, adrenals, ovary, uterus, testis and spleen. In addition, the spleen was examined by electron microscopy (SEM/energy-dispersive X-ray analysis) for the deposition of TiO_2 nanoparticles. In males from the 2 mg/kg bw per day group, feed intake was significantly decreased. Increased total titanium tissue levels were found in spleen and ovaries. Sex-related histological alterations were observed at both dose levels (i.e. 1 and 2 mg/kg bw per day) in thyroid, adrenal medulla, adrenal cortex (females) and ovarian granulosae, without general toxicity. Altered thyroid function was indicated by reduced triiodothyronine (T3) (males). Testosterone levels increased in high-dose males and decreased in females. Estradiol levels were not affected by treatment. In the spleen of treated animals, TiO_2 aggregates and increased white pulp (high-dose females) were detected, even though titanium levels in tissue remained low, reflecting the low doses and short exposure time. The authors suggested that their results should prompt a comprehensive assessment of endocrine and reproductive effects of nanomaterials.

In a study were male and female mice were administered TiO_2 in nano form at doses of 2.5, 5 and 10 mg/kg it was determined that exposure to TiO_2 NPs resulted in premature ovarian failure (POF), reductions in the levels of estradiol, progesterone and inhibin B and increases in luteinizing hormone, follicle-stimulating hormone, follicle-stimulating hormone/luteinizing hormone ratio, anti-Müllerian hormone, thyroid-stimulating hormone, free triiodothyronine, free tetraiodothyronine, anti-nuclear antibody and anti-thyroid peroxidase antibody levels in serum. The authors concluded the needed to improve public awareness of the hazards of oral exposure to TiO_2 NPs for female consumers (Hong, 2018).

In the extended one-generation reproductive toxicity study included in the previous Section 5.10.1 rats were treated with doses up to 1,000 mg/kg bw/day of TiO_2 and no treatment-related effects on hormone levels (estradiol, estrone and testosterone, plus T3, T4 and TSH) were detected (ECHA, 2021F).

8.10.3Other considerations

Dermal absorption is the most relevant entry route of chemicals related to sunscreen use. Several studies have analysed TiO_2 penetrance into intact or damaged skin using different models. Overall, studies demonstrated that TiO_2 NPs cannot permeate intact and damaged skin and can be found only in the stratum corneum and epidermis, without reaching the brain or peripheral organs (Ruszkiewicz et al, 2017).

Moreover, in the event of an accidentally ingestion it should be noted that Titanium dioxide (no nano) is a food additive (E171) that was re-evaluated by the EFSA panel in 2016 and they noted that the absorption of orally administered TiO_2 is extremely low, its bioavailability is low and it appeared to be independent of the particle size (EFSA. 2016).

8.10.4Summary on substance Titanium dioxide

Based on the reviewed data, titanium dioxide (micro and nano-form) is not expected to be toxic to reproduction. Moreover, according to the technical data sheet provided by the raw material manufacturer, the TiO_2 evaluated in this dossier is not in nano-form and therefore its systemic bioavailability through dermal application is expected to be negligible, so the concern about an endocrine disruption potential of TiO_2 nanoparticles is not applicable to the used substance.

Therefore, TiO_2 does not pose a risk to the consumer provided that its use does not might lead to exposure by oral ingestion.

8.11 OCTOCRYLENE (CAS: 6197-30-4)

Octocrylene is a permitted UV filter (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products with a maximum allowed concentration of 10% (as acid) in final product.

Octocrylene has been subject to a safety evaluation from SCCP in 1994, where the SCCP concluded that Octocrylene was not toxic, non-irritant and non-sensitizer.

8.11.1Reproductive toxicity

In an extended one-generation reproductive toxicity study (OECD 443) the possible effects of Octocrylene on reproductive performance of Wistar rats and the development of pups consequent to daily oral administration of various dietary concentrations (58, 163 and 550 mg/kg bw/day) were evaluated. At weaning, pups were distributed to different cohorts and were exposed to the same dose levels of the test substance as their parents during their growth into adulthood. Cohorts 1A and 1B of this study assessed reproductive performance and Cohorts 2A and 2B focused on neurodevelopmental endpoints. Animals of Cohort 1B were used for breeding a second generation.

Some general effects related to treatment were observed a the high-dose groups like a decreased terminal body weights and an increased relative liver and thyroid weight.

The decreased terminal body weights were considered to be adverse, whereas the increased liver and thyroid weights were considered to be adaptive changes in rats.

Regarding to fertility and reproductive parameters, no treatment-related effects were observed except for the lower mean number of implantation sites, and consequently, a lower number of pups delivered in female animals of the high-dose group of the F0-generation and of Cohort 1B of the F1- generation. This finding was considered adverse.

Regarding to general and sexual developmental parameters, in the high-dose group a lower body weight of F1 and F2 generation pups was considered to be related to treatment. Preputial separation, vaginal opening, and first estrus stage occurred later in Cohort 1A-generation offspring were also noted. However, these differences were not considered as delayed sexual development but as a consequence of delayed general development (lower pup weights). No other treatment-related effects were observed.

According to these findings, it was established a NOAEL of 163 mg/kg bw/day in females for parental effects (based on body weight); for fertility and reproductive performance (based on the lower number of implantation sites and the lower number of pups delivered); and for general and sexual development (based on the effects on pup body weights). There were no effects of the test item on neuro (developmental) parameters and a NOAEL for neuro (developmental) parameters was placed at 550 mg/kg bw/d in females (ECHA, 2021G).

8.11.2Endocrine disruptor properties

In a study where zebrafish (Danio rerio) were exposed to elevated concentrations of octocrylene for 28 days, the total body accumulation of octocrylene in zebrafish was found to reach 2321.01 ("L" level), 31,234.80 ("M" level), and 70,593.38 ng g(-1) ("H" level) when the average OCT exposure concentration was controlled at 28.61, 505.62, and 1248.70 μg/L, respectively. Although the extent of the effects on zebrafish differed at different accumulation levels, the induction of vtg1 and histological changes in the ovaries are indications of estrogenic activity and the inhibition of esr1 and androgen receptor (ar) showed antiestrogenic and antiandrogenic activity, respectively. Thus, as octocrylene could easily accumulate in aquatic life such as zebrafish, one of its most of concern hazards would be the disturbance of the histological development and its multiple hormonal activities (Zhang, 2016).

A recent study aimed to evaluate the aquatic toxicity of octocrylene (in particular to assess its reproductive toxicity and mechanism), showed that when Japanese medaka fish was exposed to octocrylene doses of 5, 50, and 500 mg/L for 28 days, Octocrylene inhibited spermatozoa synthesis and promoted mature oocytes maturation by histopathology, increased plasma sex steroid hormone (E2 and 11-KT) and VTG levels, and upregulated the expression of HPG-axis genes related to steroidogenesis and reproduction both in female and male medaka, which shows that it poses a great threat to the reproductive system of medaka and adversely affects their development (Yan, 2020).

In a statistically study of the concentration of 5 UV-filters -including octocrylene- in the urine of 40 women diagnosed with polycystic ovary syndrome (PCOS) -one of the most common endocrine disorder among females of reproductive age- the authors found that urinary Octocrylene concentrations and PCOS were positively associated in overweight and obese women, whereas no dose-dependent effect was observed (Gu, 2019).

The reproductive effects in animals and the endocrine disruption potential of octocrylene was discussed in a recent review where the authors, mainly based in the information included in the ECHA dossier (ECHA, 2021G) concluded that octocrylene based on the current available data, mainly short-term animal data, octocrylene does not show any endocrine disruption potential regarding reproductive and developmental parameters and does not induce developmental or teratogenic effects (Berardesca, 2019).

8.11.3Other considerations

The European Commission organized a public call for data on 16 May 2019 with a priority list of potential endocrine disruptors including the UV filter Octocrylene.[2]

The European Scientific Committee on Consumers Safety (SCCS) has been requested for a scientific opinion on Octocrylene based in the light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of octocrylene.[3] The SCCS approved this mandate by written procedure on February 2020 and with a deadline of 9 months, extended until January 2021.

8.11.4Summary on substance Octocrylene

Based on the available data, Octocrylene showed developmental/teratogenic effects at the high dose of 550 mg/kg bw/day (decrease in the number of implantation sites). No other effects on male and female fertility and reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters were observed.

Regarding is potential as endocrine disruptor, at present time and based on the current available data, there is some evidence of endocrine activity in animals (mainly aquatic animals) but there is a lack of specific and adequate studies (according to guidelines) in vitro and in vivo.

Despite Octocrylene not being listed on the European Commission priority list of potential endocrine disruptors or on the SIN list of endocrine disrupting chemicals (SIN list database, 2020), there is an obvious concern about the endocrine disruptor potential of Octocrylene that has led to the request for a scientific opinion of the SCCS.

[2] https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic-products_en

[3] https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs2016_q_040.pdf

8.12 C8-22 ALKYL ACRYLATES/METHACRYLIC ACID CROSSPOLYMER (CAS: NA)

C8-22 Alkyl acrylates/methacrylic acid crosspolymer is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as film former.

C8-22 Alkyl acrylates/methacrylic acid crosspolymer is a copolymer of C8-22 alkyl acrylate and methacrylic acid crosslinked with hexanediol diacrylate.

8.12.1Reproductive toxicity

Studies on the reproductive and developmental toxicity of C8-22 Alkyl acrylates/methacrylic acid crosspolymer were not found in the published literature. The risk profile of substance C8-22 Alkyl acrylates/methacrylic acid crosspolymer is evaluated trough the read-across concept between a family of Acrylates copolymer including crosslinked copolymers (i.e., crosspolymers) prepared from monomers that comprise, in part, acrylic acid and/or methacrylic acid.

Reproductive effects were not observed in a study in which rats were dosed orally with 4,500-or 90,000-Da molecular weight (MW) Sodium Polyacrylate. In this study, groups of 30 gravid rats were dosed with up to 3,000 mg/kg/day of the low MW test article in distilled water on days 6-15 of gestation, and the animals were killed on day 19 of gestation. Groups of 28-29 gravid rats were dosed with up to 1,125 mg/kg/day of the high MW test article in distilled water; 8 animals/group were dosed on days 6-13 of gestation and killed on day 13, and the remaining animals in each high MW-test article group were dosed on days 6-15 of gestation, and killed on day 10 of gestation (CIR, 2019).

Two studies were conducted in which an Acrylates Copolymer (as a fully polymerized copolymer of methyl methacrylate and ethyl acrylate) dispersion was sprayed onto powdered diet at a ratio of 1:10, and the coated diet was mixed with basal diet for testing. In the first study, groups of 20 mated female Wistar rats were fed 0, 500, or 2,000 mg dry copolymer/ kg bw/day on days 6 through 15 of gestation, and the gravid rats were killed on day 19 of gestation. In the second study, groups of 10 mated female New Zealand White rabbits were given the same dosages on days 6 to 18 of gestation, and killed on day 29 of gestation. There were no signs of maternal toxicity in rats or rabbits, and there were no reproductive or developmental effects observed for either species. The NOAELs for dams and fetuses were 2,000 mg/kg bw/day in both rats and rabbits (CIR, 2019).

8.12.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.12.3Other considerations

Polymethyl methacrylate-based cosmetic ingredients are large molecules and remain in particulate form (dispersed) in final preparations and thus will not likely cross the stratum corneum to induce systemic toxicity (CIR, 2019).

8.12.4Summary on substance C8-22 Alkyl acrylates/methacrylic acid crosspolymer

Based on the read-across evidence from other Acrylates copolymer, C8-22 Alkyl acrylates/methacrylic acid crosspolymer is unlikely to be a developmental/reproductive toxicant. Moreover, at the present time no endocrine disruptor activity is reported for C8-22 Alkyl acrylates/methacrylic acid crosspolymer.

8.13 TRIETHANOLAMINE (CAS: 102-71-6)

Triethanolamine, also known as TEA, is a restricted substance according to Regulation (EU) No 1223/2009 of cosmetic products, under the entry “Trialkylamines, trialkanolamines and their salts” with a maximum allowed concentration of 2.5% in leave on products. It is mainly used as buffering and surfactant.

8.13.1Reproductive toxicity

Under the ECHA registration dossier (2021H) of Triethanolamine, a Weight of Evidence (WoE) approach is conducted for the endpoint toxicity to reproduction using results from the registered substance TEA and studies performed with the structurally analogous substance MEA-HCl (CAS 2000-42-7).

Under the conditions of a two-generation reproduction toxicity study with MEA HCl, the NOAEL for systemic toxicity and fertility, reproductive performance in parental F0 and F1 Wistar rats is 300 mg/kg bw/day. The NOAEL for pre- and postnatal developmental toxicity in their offspring is 1,000 mg/kg bw/day.

In a screening reproduction/developmental toxicity study (OECD 421) where rats were exposed to TEA by gavage, the NOAEL for systemic toxicity as well as for reproductive performance and fertility in parental animals was established at 1,000 mg/kg bw/day, the highest dose tested. The NOAEL for postnatal toxicity in the offspring was 1,000 mg/kg bw/day, whereas the NOAEL for prenatal developmental toxicity was determined to be 300 mg/kg bw/day based on decreased numbers of implants and delivered pups, and an increased post implantation loss (ECHA, 2021H).

8.13.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.13.3Other considerations

Triethanolamine was evaluated under the European Community rolling action plan (CoRAP) as a suspected CMR, sensitizer and other hazard-based concerns, and according to the evaluation report (CoRAP, 2021) there are not concerns associated to its toxicity for reproduction or its potential as endocrine disruption.

8.13.4Summary on substance Triethanolamine

Despite Triethanolamine being self-classified under the hazard statement code H361 (Developmental toxicity) as that is probably due to the presence of a not-determined impurity/additive.[4]

According to the available literature, Triethanolamine does not show reproductive/teratogenic toxicity, and, at the present time, no endocrine disruptor activity is reported.

8.14 CETYL ALCOHOL (CAS: 36653-82-4)

Cetyl alcohol is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioning, opacifying, emulsion stabilizer, and viscosity controller.

8.14.1Reproductive toxicity

No reproductive toxicity studies were available on the ECHA registration dossier on hexadecan-1-ol but based on the weight of evidence (WoE) from other alcohols structurally similar there is no evidence of reproductive toxicity nor it is expected.

In a combined repeat dose reproductive/developmental toxicity screening study in rats (according to OECD 422) the reproductive toxicity of Dodecan-1-ol was evaluated. The materials were administered to male and female rats via the diet (oral feed) at concentrations up to 2,000 mg/kg bw/day during pre-mating, mating and gestation. Pregnancy rates, uterine parameters, time to pregnancy and gestation length indicated that fertility was not affected by exposure to Dodecan-1-ol. There were no microscopic changes observed in the reproductive organs (ECHA, 2021J).

In another reliable study according to OECD 422, development was assessed as part of a combined repeat dose and reproductive/developmental toxicity study. The NOAEL for maternal and foetotoxicity in rats was 2,000 mg/kg bw/day (highest dose level). There was no evidence of teratogenicity from the limited examination of the pups that was carried out. The result is read across from octadecan-1-ol (CAS 112-92-5) (ECHA, 2021J).

A read across feeding studies reported a lack of effects on the reproductive organs of rats receiving hexan-1-ol (NOAEL 1,127 mg/kg) (ECHA, 2021J). No adverse effects were noted at any of the dose levels administered during the study. No effects in reproductive organs have been observed in repeated dose studies with any category member.

In a reliable study performed to OECD guideline 407, a mixture of C12-C13 alcohols administered by gavage to male rats at up to 1,000 mg/kg bw/day for 28 days, had

[4] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/notification-details/33926/1492249

no effect on the absolute or relative weight of the testis and no abnormalities were evident on microscopic examination of the testis (ECHA, 2021J).

8.14.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.14.3Summary on substance Cetyl alcohol

Based on the weight of evidence from other alcohols across the category Cetyl alcohol is unlikely to be a developmental/reproductive toxicant. Moreover, at the present time no endocrine disruptor activity is reported for Cetyl alcohol.

8.15 GLYCERYL STEARATE (CAS: 31566-31-1)

Glyceryl stearate is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioning and surfactant.

8.15.1Reproductive toxicity

Studies on the reproductive and developmental toxicity of glyceryl stearate were not found in the published literature.

The risk profile of substance Glyceryl stearate is evaluated on the ECHA trough the read-across concept between a family of -well defined- substances contained in the Glycerides category that covers aliphatic (fatty) acid esters of glycerol.

The available data on the developmental toxicity/teratogenicity of Glycerides comprise reproductive/developmental toxicity screening studies as well as (pre-natal) developmental toxicity studies with category members. Only one study reported foetal effects in rabbits given 4,280 mg/kg bw/day of Medium Chain Triglycerides, attributable to maternal toxicity. The substance did not produce any effects in rats at the same dose level and in rabbits given 1,000 mg/kg bw/day.

Altogether, no effects on (pre-natal) development were observed in any of studies in rats, rabbits and mice. NOAEL values for (pre-natal) developmental toxicity were all at or well above the currently applied limit dose value of 1,000 mg/kg bw/day. Thus, no hazard was identified.

Based on the available data and following the category approach, all members of the Glycerides category are considered to have no toxic effects on intrauterine development. (ECHA, 2021K)

8.15.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.15.3Summary on substance Glyceryl stearate

Based on the read-across evidence from other aliphatic (fatty) acid esters of glycerol, Glyceryl stearate is unlikely to be a developmental/reproductive toxicant. Moreover, at the present time no endocrine disruptor activity is reported for Glyceryl stearate.

8.16 SODIUM POLYACRYLATE (CAS: 9003-04-7)

Sodium polyacrylate is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioning, absorbent, binding, emulsion stabilizer, film former and viscosity controller.

8.16.1Reproductive toxicity

Reproductive and teratogenic effects were not observed in a study in which rats were dosed orally with 4,500- or 90,000-Da molecular weight (MW) Sodium polyacrylate. In this study, groups of 30 gravid rats were dosed with up to 3,000 mg/kg/day of the low MW test article in distilled water on days 6-15 of gestation, and the animals were killed on day 19 of gestation. Groups of 28-29 gravid rats were dosed with up to 1,125 mg/kg/day of the high MW test article in distilled water; 8 animals/group were dosed on days 6-13 of gestation and killed on day 13, and the remaining animals in each high MW-test article group were dosed on days 6-15 of gestation and killed on day 10 of gestation. No treatment-related effects were observed (CIR, 2019).

8.16.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.16.3Other considerations

Sodium polyacrylate is the sodium salt of the polyacrylic acid. Due to its composition and molecular formula these substances are characterized by a series of parameters like a high molecular weight (>500Da); a high degree of ionization; a topological polar surface area > 120A; etc. that, according to the 10th revision of the SCCS notes of guidance, the cosmetic ingredients characterized by those physicochemical properties may be indicative of very low dermal absorption (SCCS, 2018).

8.16.4Summary on substance sodium polyacrylate

Sodium polyacrylate does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.17 PHENOXYETHANOL (CAS: 122-99-6)

Phenoxyethanol is a permitted preservative (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products with a maximum allowed concentration of 1% in final product.

Phenoxyethanol has been subject to a safety evaluation from SCCNFP in 1999 and more recently by the SCCS in 2016 where the committee concluded that Phenoxyethanol was safe at the maximum allowed concentration of 1%.

8.17.1Reproductive toxicity

A two-generation reproductive toxicity study in mice with 0, 0.25, 1.25 and 2.5% 2-phenoxyethanol in the diet was conducted according to an NTP protocol. Fertility was only minimally affected at the highest dose, but evidence of significant toxicity to the offspring was observed when 2-phenoxyethanol was administered at the mid- and high-dose level. Parental toxicity was reported at the mid- and high-dose level. For both males and females, the NOAEL for parental toxicity and reproductive toxicity was concluded to be the low dose, i.e. 0.25% in diet. For males, a NOAEL of 400 mg/kg bw/day was calculated. For females, the NOAEL was approximately 950 mg/kg bw/day. Two studies on developmental toxicity are available, one oral rat and one dermal rabbit study. In both studies, the NOAELs for developmental toxicity were higher than the NOAELs for maternal toxicity (300 mg/kg bw/day in both studies) (SCCS, 2016).

8.17.2Endocrine disruptor properties

There were no data included in the SCCS opinion on the endocrine activity of phenoxyethanol (SCCS, 2016). However, the June 2015 high-throughput Endocrine Disruptor Screening Program conducted by the US-EPA determined that phenoxyethanol has no oestrogenic activity (EPA, 2021).

Only three publications about the phenoxyethanol potential as endocrine disruptor were identified in the published data and all were part of the same cohort study. These three reports did not reveal that phenoxyethanol had any endocrine disrupting potential. The first study did not show any association between phenoxyacetic acid, the primary metabolite of phenoxyethanol, and cryptorchidism or hypospadias. The two other studies did not provide any evidence for a plausible association between phenoxyacetic acid and changes in SHBG, androgenic and oestrogenic activities in newborns. Concerning the thyroid effects, there are no indications from the animal studies of any effect involving the thyroid hormone pathway. Furthermore, the French National Agency for the Safety of Medicines and Health Products (ANSM) concluded that these data cannot be used to assess the endocrine disruption potential of phenoxyethanol (Dréno, 2019).

8.17.3Other considerations

Haematotoxicity is a predominant toxicological feature of 2-phenoxyethanol in vivo and in vitro. Dermal exposure of rats to 2-phenoxyethanol revealed much higher concentrations of 2-phenoxyacetic acid (phenoxyethanol main metabolite) in blood than after oral exposure. This may also be true for other species such as humans.

For these reasons and because dermal exposure is the relevant route of exposure of humans to 2-phenoxyethanol in cosmetic products, preference is given to dermal studies in rabbits. Given the much higher capacity of humans to metabolize 2-phenoxyethanol compared with rabbits, the toxicokinetic default factor of 4.0 can be reduced to 1.0 yielding a minimum Margin of Safety (MoS) of 25 instead of 100 for the safety assessment of 2-phenoxyethanol.

Children ≤3 years may be higher exposed to 2-phenoxyethanol in cosmetic products than adults.

A MoS of 25 is selected by the SCCS for the safety assessment also covers the safety of infants and babies to 2-phenoxyethanol exposure in cosmetic products (SCCS, 2016).

8.17.4Summary on substance Phenoxyethanol

The SCCS recently evaluated the safety of use of phenoxyethanol as preservative in cosmetic products and despite its opinion as it is safe for use, they established a lower MoS (25) for the safety assessment of this compound, mainly due to the risk associated to the exposure of babies <3 years.

From the perspective of pregnant women as a vulnerable group of users, the SCCS did not identify any risk associated to the reproductive toxicity of Phenoxyethanol. Moreover, there is no evidence at the present time in the published literature of a potential endocrine disruptor behavior of Phenoxyethanol.

8.18 GLYCERIN (CAS: 56-81-5)

Glycerin, also known as glycerol, is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioning, solvent, denaturant, humectant, and viscosity controller.

8.18.1Reproductive toxicity

In a two generation study, male and female rats (10/treatment) were dosed daily with glycerol (20% solution in water) during 8 weeks before mating. Females received glycerol throughout pregnancy or until weaning of the F1 generation (5 each). When the F1 generation was ~100 days of age, pups were killed except for 10/sex. These animals were used to produce the F2-generation. No effects were found on the reproductive efficiency of the parents, nor on the growth, fertility, reproductive performance of the untreated F1 generation, and no histological changes occurred in the tissues of both the F1 and F2 generation. Although the data are limited, a NOAEL of 2,000 mg/kg bw was identified from this study (OECD, 2002).

Rats, mice and rabbits were treated daily with glycerol at dose levels up to 1,310, 1,280 and 1,180 mg/kg bw (oral gavage), respectively, during part of the gestation period. The study protocol was in reasonable agreement with the requirements of the OECD 414 (1981). No maternal toxicity or teratogenic effects were seen at the highest dose levels tested (NTIS 1974). From these studies a NOAEL of 1,180 mg/kg bw can be derived (OECD, 2002).

A fertility study involving 64 males workers involved in glycerol manufacture reported no significant differences in sperm quality parameters (sperm counts and percent “normal” forms) (OECD, 2002).

8.18.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.18.3Other considerations

Metabolic disorders are linked to male reproductive dysfunction. There are evidence that obese men tend to accumulate metabolites (including glycerol) in tests which can causes temporary spermatogenesis arrest or, if it persists for some time, it may cause permanent oligospermia or even azoospermia (Crisóstomo, 2017).

8.18.4Summary on substance Glycerin

The evidence of effects on spermatogenesis (following intratesticular administration) are not considered relevant as an exposure route. These data do not cause concern in relation to reproductive effects from topical routes of exposure (OECD, 2002).

Based on the available data, it can be concluded that glycerol does not have any adverse effects on reproductive parameters. There was no evidence of teratogenicity. At the present time, no endocrine disruptor activity is reported in the published data for this substance.

8.19 PEG-75 STEARATE (CAS: 9004-99-3)

PEG-75-stearate is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as surfactant.

8.19.1Reproductive toxicity

Studies on the reproductive and developmental toxicity of PEG-75 stearate were not found in the published literature. The risk profile of substance PEG-75 stearate is evaluated trough the read-across concept between a family of -well defined- substances including PEG-8 stearate and PEG-40 stearate.

Feeding of 4% PEG-8 Stearate in the diet of young rats for three successive generations did not affect growth or fecundity. No micropathological changes were observed in the livers or kidneys of first-generation rats after 11 weeks on the diet, after 16 weeks in the second generation, and after 16 months in the third generation. The ratios of liver/body weight and kidneys/body weight were comparable for third generation and control animals (CIR, 1983).

Another three-generation study was carried out on rats fed diets containing 5%, 10%, or 20% PEG 8 Stearate. In both control and experimental groups, seven of ten matings were successful. The reproduction and lactation responses for the 5% group were not different from control responses. At the 10% and 20% levels, newborn litter

survival times were diminished probably as a result of maternal neglect. In the 20% group, there was some impairment of lactation efficiency as evidenced by lower weanling weights. In the 20% group, there was also a greater mortality rate of the nurslings. In the F2 and F3 generations, similar responses were reported. The overall level of reproductive performance was lower in the F3 generation for the animals fed the 20% PEG-8 Stearate diet (CIR, 1983).

Rats were fed diets containing 5%, 10%, or 20% PEG-40 Stearate in a three-generation study. For all groups including control, an average of seven out of 10 matings were successful. The lactation and reproduction responses for the 5% group were the same as for the control group. Survival of the newborn was slightly diminished for the 20% group. In the same group, there was an impairment of lactation. Similar lactation and survival responses were found for the two succeeding generations (CIR, 1983).

8.19.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.19.3Other considerations

The CIR panel evaluated the safety of PEG-75-Staearate in cosmetic products and concluded that, based in the present practices of use (concentration up to 6% in final product) it uses is considered safe (CIR, 2005).

8.19.4Summary on substance PEG-75 stearate

Based on the read-across evidence from other PEG-X stearates, PEG-75 stearate is unlikely to be a developmental/reproductive toxicant. Moreover, at the present time no endocrine disruptor activity is reported for PEG-75 stearate.

8.20 CETETH-20 (CAS: 9004-95-9)

Ceteth-20 is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as surfactant.

Ceteth-20 is the ethoxylated form (20 mol ethoxylated average molar ratio) of the (poly) hexadecane-1-ol compound and it is included in the family of alkyl PEG ethers.

8.20.1Reproductive toxicity

Studies on the reproductive and developmental toxicity of Ceteth-20 were not found in the published literature. The risk profile of substance Ceteth-20 is evaluated trough the read-across structural analogue source substance Alcohols, C9-11, ethoxylated (CAS 68439-46-3), which has an ethoxylation degree of 1-2.5 and Alcohols,C14-15AE7 (CAS 68951-67-7).

Weanling rats (male and female) were dermally exposed to Alcohols, C9-11, ethoxylated (CAS 68439-46-3) three times a week except during the mating periods.

Based on the results of the study which provided no indication for any reproduction and/or developmental toxicity, the NOAEL for reproductive and developmental toxicity was established at 250 mg/kg bw/day, the highest dose tested. Therefore, a NOAEL of 250 mg/kg bw/day is also considered for the target substance (ECHA, 2021L).

A reproductive toxicity study on a structurally similar material, C14-15AE7 (CAS 68951-67-7) was conducted at dietary levels of 25, 50 and 250 mg/kg bw/day. The 2-generation study did not show any potential for reproductive toxicity at the tested dose levels. The NOAEL for reproductive effects was greater than the highest tested dose of 250 mg/kg bw/day. Although the study was pre-GLP and not in full compliance with current OECD guidelines, the study provided sufficient information and was assessed to be scientifically reliable (ECHA, 2021L).

Further evidence for the lack of reproductive toxicity of alcohol ethoxylates has been provided by a range of subchronic oral feeding studies which investigated also any potential effects on the organs of the reproductive system. None of these studies revealed any adverse effects of exposure to ethoxylated alcohols on the reproductive system (ECHA, 2021L).

The comparable toxicokinetic and metabolic profiles, as well as their toxicological similarities for this and other toxicological endpoints, support the conclusion that insights from the reproductive toxicity study on higher ethoxylated alcohols are applicable to ethoxylated alcohols with an ethoxylation degree of 1-2.5 (ECHA, 2021L).

8.20.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.20.3Other considerations

The CIR panel evaluated the safety of Ceteth-20 in cosmetic products and concluded that, based in the present practices of use (concentration up to 4% in final product) it uses is considered safe (CIR, 2012). As an important note, the CIR panel noted that Ceteths should not contain 1,4-dioxane or ethylene oxide, which are possible oxidation products.

8.20.4Summary on substance Ceteth-20

Based on the read-across evidence from other alkyl PEG ethers, Ceteth-20 is unlikely to be a developmental/reproductive toxicant. Moreover, at the present time no endocrine disruptor activity is reported for Ceteth-20.

8.21 STEARETH-20 (CAS: 9005-00-9)

Steareth-20 is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as surfactant.

Steareth-20 is the ethoxylated form (20 mol ethoxylated average molar ratio) of the (poly) octadecane-1-ol compound and it is included in the family of alkyl PEG ethers.

Steareth-20 belongs to the same alkyl PEG ether family as previous substance Ceteth-20 (entry 8.20) with the only difference of two more carbons in the alkyl chain. Therefore, the same read-across procedure and data used to evaluate Ceteth-20 is used to review the safety of Steareth-20.

8.21.1Reproductive toxicity

See entry 8.20.1

8.21.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.21.3Other considerations

The CIR panel evaluated the safety of Steareth-20 in cosmetic products and concluded that, based in the present practices of use (concentration up to 20% in final product) it uses is considered safe (CIR, 2012).

8.21.4Summary on substance Steareth-20

Based on the read-across evidence from other alkyl PEG ethers, Steareth-20 is unlikely to be a developmental/reproductive toxicant. Moreover, at the present time no endocrine disruptor activity is reported for Steareth-20.

8.22 LECITHIN (CAS: 8002-43-5)

Lecithin is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as surfactant and skin conditioner.

Lecithin is a fatty substance widely occurring in animal and plant tissues and in egg yolk. It is composed mainly of phosphatidylcholine together with small amounts of other phospholipids (phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine), sphingomyelin, glycolipids and triglycerides. These substances are neutral or zwitterionic over a pH range from strongly acidic to strongly alkaline. These are not quaternary ammonium compounds similar to other salts of choline and its esters, and these are unlikely to be irritants (SCCS/1237/09).

8.22.1Reproductive toxicity

There are not available studies in the published literature about the reproductive toxicity of Lecithin.

In a chronical toxicity study, a group of 48 male and 48 female SPF Wistar rats was fed 4%(soya) Lecithin for 2 years, while a control group was fed commercial diet

only. The mean Lecithin intake was 1,470 and 2,280 mg/kg/day for males and females, respectively. No statistically significant differences were observed in mortality, feed consumption, or body weight between the treated and control groups (CIR, 2020).

8.22.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.22.3Other considerations

Lecithin is an essential constituent of all cells of the human body. The organism is able to synthesize phosphatides and the pathway of catabolism of lecithin in the organism is well-known.

Administration to human subjects of lecithin in daily doses varying from 22 to 83 g for two to four months to improve working capacity was not accompanied by any untoward reactions (Atzler & Lehmann, 1937 in FAO/WHO, 1974). Lecithin in large amounts (25-40 g per day) given for some months will frequently lower the serum cholesterol level. Intolerance to this amount limits its use (Merrill, 1959 in FAO/WHO, 1974). Some crude phosphatides (e.g., cardiac extracts) containing 93% lecithin showed pharmacological effects when given parenterally (Kunze, 1941 in FAO/WHO, 1974). It is not clear if the observed effects were due to unidentified by-products.

Since many observations have been made in man it is not considered necessary to calculate the safe intake level from animal experiments. It is considered that nutritional and clinical experience with lecithin is sufficiently extensive to compensate for the incompleteness of the experimental data (FAO/WHO, 1974).

8.22.4Summary on substance Lecithin

Based on the available data and in the fact that Lecithin is an essential constituent of all cells of the human body, Lecithin is not expected to have any adverse effect on reproductive parameters. There was no evidence of teratogenicity. At the present time, no endocrine disruptor activity is reported in the published data for this substance.

8.23 CI 77492 (CAS: 51274-00-1)

CI 77492 (hydrated iron (III) oxide) is a permitted colorant (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products without maximum concentration in final product.

8.23.1Reproductive toxicity

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) 12 males (49 days) and 12 females (14 days before mating to day 5 of lactation) Sprague-Dawley rat were feeded by gavage with doses up to 1,000 mg/kg bw/day of CI 77492.

In parent animals, no changes attributable to the test substance were noted in terms of the number of estrous cases, copulation index, number of days before copulation, fertility index, gestation length, gestation index, delivery conditions, nursing conditions, number of corpora lutea, number of implantation sites, or implantation rate. In the pups, no changes due to administration were observed in the total number of pups born, number of stillbirths, number of pups on lactation day 0, sex ratio on lactation day 0, delivery index, birth index, or live birth index. No changes due to administration were observed in the general condition of the pups. No changes due to administration were observed in the number of live pups on lactation day 4, or viability on lactation day 4. External observation revealed no changes due to administration. No changes due to administration were observed in the body weights. The necropsies of the pups revealed no changes due to administration.

A NOAEL of 1,000 mg/kg/day (equivalent to 201 mg Fe/kg bw/day) for reproductive toxicity and for reproduction/development offspring, F1 generation) was concluded for the male and female rats of the parent animals due to the absence of any relevant toxicological effects (ECHA, 2021M).

8.23.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.23.3Other considerations

Colorant CI 77492 belongs to a family or iron oxides (together with CI 77491 and CI 77499) used as food additives (E 172). In 2015 the Panel on Food Safety (EFSA) re-evaluated the safety of this compounds as additives (EFSA, 2015). The panel noted that, in the case of the CI 77492 (yellow iron oxide), there was a lack of toxicological data. Moreover, they also noted that commercial food grade CI 77492 is composed for more than 50% of primary particles with nano form.

Nevertheless, the Panel also considered that oral absorption of iron from iron oxides is low and the acute oral toxicity of iron oxides is greater than 10 g iron oxide/kg bw. Concerning reproductive and developmental toxicity, no signs of toxicity were observed in unpublished studies which were not available and could not be evaluated by the Panel.

The Panel concluded that an adequate assessment of the safety of E 172 could not be carried out because a sufficient biological and toxicological database was not available.

Refined exposure estimates show that exposure to E 172 ranged from 0.03 mg/kg bw/day for infants to 3.7 mg/kg bw/day for toddlers at the mean and from 0.1 mg/kg bw/day for infants to 9.5 mg/kg bw/day for toddlers at the 95th percentile for the non-brand-loyal scenario (EFSA, 2015).

8.23.4Summary on substance CI 77492

There is a noticeable lack of toxicological studies for CI 77492. Nevertheless, having in mind that it is used as food additive and that it has a very low absorption rate, is expected that systemic bioavailability via dermal exposition will be low to negligible.

So, based on the available data CI 77492 is not expected to have reproductive toxicity nor teratogenic properties. At the present time, no endocrine disruptor activity is reported in the published data for this substance.

8.24 GOSSYPIUM HERBACEUM CALLUS CULTURE (CAS: NA)

Gossypium herbaceum callus culture is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioner.

Gossypium herbaceum (Cotton) Callus culture is a suspension of the cultured callus cells of Gossypium herbaceum. Callus culture is the culture of dedifferentiated plant cells induced on media usually containing relatively high auxin concentrations or a combination of auxin and cytokinin under in vitro conditions.

8.24.1Reproductive toxicity

Studies on the reproductive and developmental toxicity of Gossypium herbaceum callus culture were not found in the published literature. The risk profile of substance Gossypium herbaceum callus culture is evaluated trough the weight of evidence concept using data from other cotton/seed oils (including Gossypium).

Sheehan et al. (1967 in CIR 2001) reported that feeding of Sprague-Dawley rats with 5%, 10% ,15%, 20%, or 30% Cottonseed (Gossypium) Oil (containing 1% cyclopropenoid fatty acids [CPFAs]) did not significantly affect the sexual maturity and reproductive performance of the F0 generation. Significant changes in sexual maturity and length of estrus cycle were noted in the F1 generation, but reproductive capacity was not altered. The 20% mortality in F1 newborns was contrasted with 100% mortality following dosing with 1% Sterculia foetida oil that could contain 50% CPFAs.

Singh, Lawrence, and Autian (1972 in CIR, 2001) investigated the teratogenicity of phthalate esters in rats. Test groups were injected with one of eight phthalate esters, one group received distilled water, and two groups (five rats each) received Cottonseed (Gossypium) Oil (5 or 10 ml/kg). All were injected on gestation days 5, 10, and 15. The number of corpora lutea, resorptions, dead fetuses, live fetuses, average weight of fetuses, and the number of gross and skeletal abnormalities in the Cotton-seed Oil group were not significantly different from the untreated control group.

8.24.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.24.3Other considerations

The cosmetic ingredients review Panel (CIR) has considered safe for use in cosmetic products substance Gossypium herbaceum (Cotton) seed oil at concentrations up to 32%. Nevertheless, the CIR Panel expressed concern regarding gossypol as an impurity for cotton-derived ingredients (present at a concentration of < 0.01% in refined cottonseed oil) due to its potential to cause irreversible infertility and to stop early pregnancies. (CIR, 2017).

8.24.4Summary on substance Gossypium herbaceum callus culture

There is a considerably lack of toxicological data for Gossypium herbaceum callus culture and for other surrogates such as cottonseed oils.

However, based in the absence of reports about its toxicity and having in mind the commonly use of cotton-based extract and oils, Gossypium herbaceum callus culture is not expected to show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported for this substance.

8.25 SILICA (CAS: 7631-86-9)

Silica is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as abrasive, absorbent, opacifying, bulking, and viscosity controller.

Silica could be present in nano-and micro-sized form and it has been subject to a safety evaluation from SCCS twice. In 2015 was evaluated the safety of the nano-form and the SCCS opinion concluded that more information was needed. Later in 2019 a new opinion about its solubility was issued by the SCCS.

The CAS 7631-86-9 is typically associated to a class of colloidal silica composed by amorphous silica and with primary particle size of 15 to 40 nm (SCCS, 2015).

8.25.1Reproductive toxicity

Rats exposed to Py-SAS-NA-2, a hydrophobic pyrogenic synthetic amorphous silica (SAS), at dose levels of 0 or 100 mg/kg/day in a 2-year oral toxicity study were mated. The offspring was adjusted to 5 pups/sex/litter and allowed to mature. After 7 months, they were mated and their litters were also adjusted to 5 pups/sex/litter. No effects on reproductive performance, pre- and post-natal development were observed (SCCS, 2015).

The oral administration of Py-SAS-NA-2 at 500 mg/kg/day to rats during the mating, gestation and lactation periods produced no changes attributed to test item. Accordingly, under the conditions of the study, the No Observed Effect Level (NOEL) was above 500 mg/kg/day for male and female reproductive performance as well as pre-natal and post-natal development (SCCS, 2015).

The potential effects of SAS-G-1, a silica gel material, on embryo-foetal development were evaluated through daily oral gavage at 0, 13.4, 62.3, 289, and 1,340 mg/kg/day

to pregnant female mice during the sensitive period of organogenesis (gestation days 6 to 15). The administration of SAS-G-1 did not affect foetal survival and produced no changes in dams. The NOEL for maternal and developmental toxicity was therefore above 1,340 mg/kg/day (SCCS, 2015).

Likewise, the administration of SAS-G-1 to pregnant rats at the dose levels 0, 13.5, 62.7, 292, and 1,350 mg/kg/day by gavage during the sensitive period of organogenesis produced no changes in dams and did not affect fetal survival rate. The soft tissue and skeletal abnormalities observed in animals given SAS-G-1 were similar in nature and incidence to those observed in the control group. Therefore, the NOEL for both maternal and developmental toxicity was above 1,350 mg/kg/day (SCCS, 2015).

Finally, the absence of maternal and developmental toxicity potential of SAS-G-1 was confirmed in two studies conducted in rabbits and hamsters. SAS-G-1 was administered at the dose levels 0, 16, 74.3, 345, and 1,600 mg/kg/day by gavage to pregnant rabbits and hamsters during the sensitive period of organogenesis. The test material had no toxic potential in dams and conceptuses, and specifically no teratogenic potential (SCCS, 2015).

Studies on prenatal developmental toxicity were carried out on different forms of SAS between 1973 and 2015 and according to OECD TG 414, TG 416 and similar protocols. Neither maternal toxicity nor embryo-foetal toxicity was observed at the maximal dose tested in various species (mice, rats, hamsters and rabbits). Based on the available studies, the NOAEL of the substance is estimated as ≥1,000 mg/kg bw/day for each species (ECHA, 2021N).

8.25.2Endocrine disruptor properties

In a review published in 2013 the effects of nanomaterials as endocrine disruptors were revised, including Silica nanoparticles (Lavicoli, 2013), some treatment related effects in male testis and sperm were associated to Silica nanoparticles.

On a paper published in 2018 oral exposure of mesomorphous silica nanoparticle (250 mg/kg), to mice during pregnancy affects steroidogenesis taking place in the CL of pregnant mice (via progesterone biosynthesis) and the testis of male offspring (via testosterone bio-synthesis) exposed in utero through a shift in the steroidogenesis-related gene expression profile (StAR and P450scc). Foetal NPs exposure to MSN (250 mg/kg bw) disturbs the reproductive functions of the male by causing gross pathological changes in testis like prominent epithelial vacuolization, decrease in the seminiferous tubule diameter, seminiferous epithelium height and altered spermatogenesis (Bara, 2018).

8.25.3Summary on substance Silica

Based on the available data Silica is not expected to have reproductive toxicity nor teratogenic properties.

The family of Silica compounds is composed by a large group of substances with different size and shape. Nanoparticles are typically substances of concern due to it is well known high systemic bioavailability and its capacity to penetrate cellular

barriers. At the present time and based in the published literature, there is not expected that Silica with CAS number 7331-86-9 has activity as endocrine disruptor.

8.26 ETHYLHEXYLGLYCERIN (CAS: 70445-33-9)

Ethylhexylglycerin is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as deodorant and skin conditioner.

8.26.1Reproductive toxicity

The effects of Ethylhexylglycerin (Sensiva SC 50) on pregnancy and embryo-fetal development were evaluated in a prenatal developmental toxicity study involving groups of female rats of an unspecified strain (number of animals not stated). The test substance was administered by gavage at doses of 50, 200, and 800 mg/kg/day. None of the animals died. There were no treatment-related effects on terminal body weight, uterine weight, or absolute weight gain. Litter data and the results of macroscopic examinations of females were also unaffected by treatment, and the malformations observed in 3 fetuses at external examination were considered incidental. Based on these results the NOAEL was considered to be 800 mg/kg/d. CIR, 2013).

Based on the previous study result, the developmental toxicity of Ethylhexylglycerin (Sensiva SC 50) was evaluated in a 1-generation developmental toxicity study using groups of male and female rats of an unspecified strain. The test substance was administered orally at doses of 50, 200, and 800 mg/kg/d. Male rats were dosed daily for 10 weeks prior to pairing, after which dosing continued through the day before animals were killed. Female rats were dosed for 2 weeks prior to mating and during gestation and postpartum periods; dosing ended on postpartum day 20. Necropsy findings in animals found dead or killed did not reveal any treatment-related changes in tissues/organs. On day 21 postpartum, there were 17 to 23 females per group with live pups. Twelve females did not become pregnant. Estrous cycles were comparable between groups, but the fertility index for high-dose animals was lower when compared to controls. Data on prebirth loss and gestation length indicated no treatment- related effects on implantation. The no-observed-effect-level (NOEL) was 50 mg/kg/d for both sexes (CIR, 2013).

8.26.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.26.3Other considerations

There is an increasing concern about the potential activity of Ethylhexylglycerine as a contact allergen in cosmetic products. Following a search on the literature, 16 matches for word Ethlhexyglycerin (which represents all the entries) in the las 14 years are focused on the allergic contact dermatitis caused by Ethylhexylglycerin.

8.26.4Summary on substance Ethylhexylglycerin

Ethylhexylglycerin does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.27 CI 77491 (CAS: 1309-37-1)

CI 77491 (anhydrous iron (III) oxide) is a permitted colorant (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products without maximum concentration in final product.

8.27.1Reproductive toxicity

There are not -specific- studies available in the published literature about the reproductive toxicity of CI 77491.

8.27.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.27.3Other considerations

Colorant CI 77491 belongs to a family or iron oxides (together with CI 77492 and CI 77499) used as food additives (E 172). In 2015 the Panel on Food Safety (EFSA) re-evaluated the safety of this compounds as additives (EFSA, 2015) and noted that commercial food grade CI 77491 is composed for less than 50% of primary particles with nano form.

The subacute oral toxicity of nano red iron oxide (Fe_2O_3-30 nm) and microsized red iron oxide (Fe_2O_3- Bulk) were compared in rats given 0, 30, 300 or 1,000 mg/kg bw/day for 28 days (Kumari et al., 2012 in EFSA, 2015)). No loss in body weight, no change in feed intake, nor any adverse symptoms and mortality were observed in rats exposed to microsized red iron oxide or to 30 or 300 mg/kg bw/day of red iron oxide nanoparticles. However, rats treated with the high dose of nano red iron oxide (1,000 mg/kg bw/day) showed reduced body weight and feed intake, severe toxic symptoms and several disturbances in biochemical parameters, and adverse histopathological changes in the liver, kidney and spleen. The subchronic toxicity of red iron oxide (Fe_2O_3) nanoparticles (60–118 nm) was investigated by Yun et al. (2015, in EFSA, 2015) in a 13-week oral toxicity study according to the OECD TG 408. Rats received daily doses of 250, 500 or 1,000 mg/kg bw/day for 13 weeks by gavage. Fe_2O_3 nanoparticles had no significant effects on body weight, mean daily food and water consumption when compared to control groups. There were no treatment-related changes in haematological, serum biochemical parameters or histopathological lesions.

These studies indicated that the microsized particles of CI 77491 are less potent than the nanoparticles in causing toxicity in the exposed animals. Moreover, smaller nanoparticles could be more efficiently available to organs and tissues leading to more severe adverse effects (EFSA, 2015).

Red (Fe_2O_3) iron oxides, both in nano- and microform (7–30 nm and >100 nm, respectively), was positive in in vitro genotoxicity assays in mammalian cells, where induction of DNA strand breaks and micronuclei was observed. However, in vivo oral administration of both nano- and microsized red iron oxide did not elicit genotoxic effects.

The Panel also considered that oral absorption of iron from iron oxides is low and that the acute oral toxicity of iron oxides is greater than 10 g iron oxide/kg bw. Concerning reproductive and developmental toxicity, no signs of toxicity were observed in unpublished studies which were not available and could not be evaluated by the Panel (EFSA, 2015).

The Panel concluded that an adequate assessment of the safety of E 172 could not be carried out because a sufficient biological and toxicological database was not available.

Refined exposure estimates show that exposure to E 172 ranged from 0.03 mg/kg bw/day for infants to 3.7 mg/kg bw/day for toddlers at the mean and from 0.1 mg/kg bw/day for infants to 9.5 mg/kg bw/day for toddlers at the 95th percentile for the non-brand-loyal scenario (EFSA, 2015).

8.27.4Summary on substance CI 77491

There is a noticeable lack of toxicological studies for CI 77491. Nevertheless, having in mind that it is used as food additive and that is has a very low absorption rate, is expected that systemic bioavailability via dermal exposition will be low to negligible.

So, based on the available data CI 77491 is not expected to have reproductive toxicity nor teratogenic properties. At the present time, no endocrine disruptor activity is reported in the published data for this substance.

8.28 POLYGONUM AVICULARE EXTRACT (CAS: 84604-04-6)

Polygonum aviculare extract is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as deodorant and skin conditioner/emollient.

Polygonum Aviculare Extract is an extract of the herb of the Knotweed, Polygonum aviculare L., Polygonaceae.

8.28.1Reproductive toxicity

The data on toxicology of Polygonum aviculare extract and relevant preparations are limited. There is no information on reproductive and developmental toxicity.

8.28.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.28.3Other considerations

In 2016, the European Medicines Agency (EMA) reviewed the safety of Polygonum aviculare L., herba (EMA/HMPC/143659/2015) and in the corresponding assessment report some information about the use and safety of Polygonum aviculare relevant preparations can be consulted.

Female Wistar rats were gavaged with Polygonum aviculare, herba extract (1 mL) for 10 days. After 10 days rats were sacrificed and samples of brain - hypotalamus, adrenal glands, liver, kidney and small intestine (duodenum) were collected for further histological analysis. Using hematoxylin – eosine staining emphasizing the neuro – endocrine – pituitary – adrenal axis reaction as well as activity of enzymes (lactate dehydrogenase, succinate-dehydrogenase, Mg-dependent adenosine triphosphatase, cytochromoxidase) were investigated. The obtained results indicated that Polygonum aviculare, herba extract did not produce any pathological effects at the neuro-endocrine axis level and in the metabolism of the studied organs (Roman, 2008 in EMA, 2016).

There are no data available regarding single dose toxicity and non-clinical information on the safety of Polygoni avicularis herba. Other specific studies demonstrated protective effect on acetaminophen-induced cytotoxicity in human embryonic kidney cells and no cytotoxic effect on human neutrophils Tests on genotoxicity and carcinogenicity have not been performed. As there is no information on reproductive and developmental toxicity, the oral use during pregnancy and lactation cannot be recommended. Oral and oromucosal administration of Polygoni avicularis herba can be regarded as safe at traditionally used doses.

The long-term widespread use in the European Union and available data indicate no toxicological concern and potential risk associated with Polygoni avicularis herba use (EMA, 2016).

Following a search on the literature, a total of 22 entries match the word Polygonum aviculare extract. Main topics about this substance include its antioxidant and anti-inflammatory properties.

8.28.4Summary on substance Polygonum aviculare extract

There is a noticeable lack of toxicological studies for Polygonum aviculare extract. Nevertheless, having in mind that the exposition is via dermal application and he long-term widespread oral use in the European Union, no concern its expected derived from its use in cosmetic products.

So, based on the available data that Polygonum aviculare extract is not expected to have reproductive toxicity nor teratogenic properties. At the present time, no endocrine disruptor activity is reported in the published data for this substance.

8.29 CI 77499 (CI: 12227-89-3)

CI 77499 (iron (II, III) oxide) is a permitted colorant (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products without maximum concentration in final product.

8.29.1Reproductive toxicity

There are not -specific- studies available in the published literature about the reproductive toxicity of CI 77499.

8.29.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.29.3Other considerations

Colorant CI 77499 belongs to a family or iron oxides (together with CI 77491 and CI 77492) used as food additives (E 172). In 2015 the Panel on Food Safety (EFSA) re-evaluated the safety of this compounds as additives (EFSA, 2015) The panel noted that, in the case of the CI 77499 (black iron oxide), there was a lack of toxicological data. Moreover, they also noted that commercial food grade CI 77499 is composed for less than 10% of primary particles with nano form.

Black (Fe_2O_3) iron oxide, both in nano- and microform (7–30 nm and >100 nm, respectively), was positive in in vitro genotoxicity assays in mammalian cells, where induction of DNA strand breaks and micronuclei was observed. However, in vivo oral administration of both nano- and microsized black iron oxide did not elicit genotoxic effects.

The Panel also considered that oral absorption of iron from iron oxides is low and that the acute oral toxicity of iron oxides is greater than 10 g iron oxide/kg bw. Concerning reproductive and developmental toxicity, no signs of toxicity were observed in unpublished studies which were not available and could not be evaluated by the Panel (EFSA, 2015).

The Panel concluded that an adequate assessment of the safety of E 172 could not be carried out because a sufficient biological and toxicological database was not available.

Refined exposure estimates show that exposure to E 172 ranged from 0.03 mg/kg bw/day for infants to 3.7 mg/kg bw/day for toddlers at the mean and from 0.1 mg/kg bw/day for infants to 9.5 mg/kg bw/day for toddlers at the 95th percentile for the non-brand-loyal scenario (EFSA, 2015).

8.29.4Summary on substance CI 77499

There is a noticeable lack of toxicological studies for CI 77499. Nevertheless, having in mind that it is used as food additive and that is has a very low absorption rate, is expected that systemic bioavailability via dermal exposition will be low to negligible.

So, based on the available data CI 77499 is not expected to have reproductive toxicity nor teratogenic properties. At the present time, no endocrine disruptor activity is reported in the published data for this substance.

8.30 ALTEROMONAS FERMENT EXTRACT (CAS: NA)

Alteromonas ferment extract is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioner. Alteromonas ferment extract is an extract of the fermentation product of Alteromonas macleodii a marine bacterium.

8.30.1Reproductive toxicity

There are not -specific- studies available in the published literature about the reproductive toxicity of Alteromonas ferment extract.

8.30.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.30.3Other considerations

In an open-label intra-individual study to assess the anti-aging efficacy of facial cream formulated with carnosine, Alteromonas ferment extract, crosspolymer hyaluronic acid, and a tripeptide the product was applied twice daily for 56 days in 33 women aged 45 to 65 years. The product was well tolerated with no adverse events reported during the study (Garre, 2017).

8.30.4Summary on substance Alteromonas ferment extract

There is a considerably lack of toxicological data for Alteromonas ferment extract, but limited data suggest no known risk.

Based in the absence of reports about its toxicity, Alteromonas ferment extract is not expected to show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported for this substance.

8.31 CITRIC ACID (CAS: 5949-29-1)

Citric acid, one of the constituents of the alpha-hydroxy acid family, is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as buffering and chelating. When Citric acid is present in a mixture with its silver salt (according to name Citric acid (and) silver citrate) the substance is a regulated preservative by Regulation (EC) No 1223/2009 with a maximum allowed concentration of 0,2% (corresponding to 0,0024% of silver) in final product.

8.31.1Reproductive toxicity

In four different studies, the oral administration of up to 425 mg/kg (body weight) of Citric acid to pregnant hamsters, rats and rabbits had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. No dose-related effect was detected (ECHA, 2021P).

8.31.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.31.3Other considerations

Citric acid is an intermediary substance in oxidative metabolism, being engaged in the tricarboxylic acid cycle. Citric acid and citrates occur in many foods and are normal metabolites in the body. Citric acid and its calcium, potassium, sodium, and ammonium salts are used as food additives.

Citric acid is a metabolic intermediate vital to the TCA respiration pathway found in all animal and plant cells. There is little evidence that citric acid and the citrate salts have deleterious effects, even in large doses. Indeed, there is some support for the fact that citric acid in the human diet is favorable by inhibiting the formation of calcium oxalate kidney and bladder stones. This statement is applicable to the citrate salts since once absorbed citrate salts will dissociate into citric acid and their counter-ion (ECHA, 2021P).

Main concerns about the use of Citric acid in cosmetic product are related to its potential as eye and skin irritant at low pH.

8.31.4Summary on substance Citric acid

Citric acid does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.32 POTASSIUM SORBATE (CAS: 24634-61-5)

Potassium sorbate is a permitted preservative (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products with a maximum allowed concentration of 0.6% (as acid) in final product.

8.32.1Reproductive toxicity

In a prenatal developmental toxicity study, Potassium sorbate was administered daily by gavage to 25 female Wistar rats at doses up to 340 mg/kg bw/day. The administration of Potassium sorbate had no clearly discernible effect on nidation or on maternal or foetal survival. The number of abnormalities seen in either soft or

skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls (ECHA, 2021Q).

The determinant of potential toxicity of Potassium sorbate is considered to be on the "sorbate" anion. Therefore, extrapolation from sorbic acid to potassium sorbate or vice versa is considered not to be restricted in any way.

In a developmental toxicity study, sorbic acid was administered to 25 female Himalayan rabbits during days 6-29 of gestation at doses of 300 and 1,000 mg/kg bw/day. No treatment-related maternal or developmental effects were observed at 300 mg/kg bw/day whereas some treatment-related effect was noted in the high dose group such as severe maternal toxicity, increased post-implantation loss, and severely reduced viability of foetuses. Based on these results, the NOAEL for maternal toxicity and teratogenic effects was stablished in 300 mg/kg bw/day (ECHA, 2021Q).

In a two generation reproductive toxicity (OECD 416), sorbic acid was daily administered to Crj: CD(SD) rats at doses of 300, 1,000 and 3,000 mg/kg bw/day. Some deaths on juveniles were noted at the highest dose tested but the authors associated them to intolerance to oral gavage treatment (at excessive dose levels) which often is a more important aspect rather than toxic effects induced by the test compound itself. The NOAEL for reproductive toxicity was established on 3,000 mg/kg bw/day for parents and 1,000 mg/kg bw/day for F-1 and F-2 generations (ECHA, 2021Q).

8.32.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor

8.32.3Other considerations

Sorbic acid is an its calcium and potassium salts are used as food additives. Under this particular use, the main concern associated to the ingestion of Potassium sorbate is associated to the high potassium intake (FAO, 1966).

8.32.4Summary on substance Potassium sorbate

Potassium sorbate does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.33 SODIUM BENZOATE (CAS: 532-32-1)

Sodium benzoate is a permitted preservative (positive list) in the Regulation (EU) No 1223/2009 of cosmetic products. with a maximum allowed concentration in final product of 2.5%; 1.7% or 0.5% (all as acid) depending on the product type.

Sodium benzoate was twice evaluated by the SCCS on Opinions SCCNFP/0532/01, final and SCCP/0891/05 and considered safe for use at the concentrations in final product of 2.5% (as acid, rinse-off); 1.7% (as acid, oral product) or 0.5% (as acid, leave-on).

8.33.1Reproductive toxicity

In four different studies, pregnant Wistar rats, pregnant CD-1 mice, pregnant Dutch-belted rabbits and pregnant Golden hamsters were feeded with Sodium benzoate by gavage on days 6-18 of gestation using doses up to 350 mg/kg bw. No effect on nidation or on maternal or fetal survival was detected; the number of abnormalities of soft and skeletal tissues did not differ from controls. The NOAEL was stablished on the higher dose tested (OECD, 2001).

A study using pregnant Wistar rats, dosed with 700, 1,400, 2,800, 5,600 mg/kg Sodium benzoate in the diet during the entire gestation showed no statistical difference in organ and bone abnormalities of fetuses between experimental groups and controls; growth of treated offsprings was similar to controls in rats dosed with 1,400 mg/kg/day; reduced food intake and decreased body weight of the pregnant rats especially in the 5,600 mg/kg group; 100% perinatal death rate; organ abnormalities of fetuses involved eye, brain and kidneys, in addition abnormalities of the skeletal system were found in rats dosed with >2,800 mg/kg/day. The authors concluded that the effects on the dams and fetuses at the 2,800 and 5,600 levels were due to reduced maternal feed intake in these groups, leading to malnutrition. The NOAEL for maternal toxicity and teratogenicity was stablished at: 1,400 mg/kg bw (OECD, 2001).

No data on reproductive effects and effects on fertility of Sodium benzoate are available. From the studies that are available on repeated dose and carcinogenicity no report on effects on the reproductive organs/tissues in both male and female laboratory animals are reported (ECHA, 2021R).

8.33.2Endocrine disruptor properties

A recent study conducted by Kehinde et al (2018) suggests that ascorbic acid and Sodium benzoate synergistically aggravates testicular dysfunction and that this is independent of oxidative stress status. Nevertheless, more studies on the effect of ascorbic acid on Sodium benzoate and the possible mechanism of action are needed.

At the present time, and based in the literature, there is not expected a potential activity of Sodium benzoate as an endocrine disruptor.

8.33.3Other considerations

Sodium benzoate is used as food additive. Its safety was evaluated in 2001 by the JECFA committee and founded safe and lack of carcinogenic, developmental, and reproductive potential ere demonstrated (FAO, 2001).

8.33.4Summary on substance Sodium benzoate

Sodium benzoate does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is not expected.

8.34 TOCOPHEROL (CAS: 10191-41-0)

Tocopherol, one of the constituents of Vitamin E, is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as antioxidant and as skin conditioner.

In 2001, the SCCS issued the Opinion SCCNFP/0494/01, final where stated that alpha-tocopherol acetate does not pose a threat to the health of the consumer.

8.34.1Reproductive toxicity

The risk profile of substance Tocopherol with CAS 10191-41-0 (i.e. dl-α-tocopherol) is evaluated trough the read-across of structurally related substances, namely tocopherol- and tocotrienol-derivatives that conform the Vitamin E family.

Sprague–Dawley rats (10 females) were fed a diet supplemented with 1,000 mg d-α-tocopherol/kg bw/day. The diets were administered for two weeks before mating and then throughout pregnancy and lactation. There were no adverse effects on survival, weight of pups, litter size, and no apparent teratogenic effects or effects on the timing of developmental milestones (EFSA, 2015B).

Pregnant Sprague–Dawley rats were supplemented orally with large amounts of vitamin E (up to 2,252 mg/kg bw/day of dl-α-tocopheryl acetate dissolved in corn oil) during gestation, or during gestation and lactation. The NOAEL for reproductive and developmental toxicity is ≥ 2,252 mg/kg bw/day, based on the observation that there are no significant, dose-dependent adverse effects on reproductive or developmental parameters investigated, at any dose (EFSA, 2015B).

Following a 90-day dietary study in which rats were fed a diet containing 0.5, 50 or 500 mg/kg bw/day vitamin E [d-α-tocopheryl poly(ethylene glycol) 1,000 succinate], respectively, half of the 1869 rats (15 animals/sex/dose) from each group were designated the parent generation (F0) and subsequently mated to produce two first generation litters (F1a and F1b). F0 rats had been ingesting their allocated diets for 112 days and 175 days when mated to produce the F1a and F1b generations, 1872 respectively. There were no adverse findings for any of the parameters or indices and NOAEL for reproductive toxicity in this study was ≥ 500 mg/kg bw/day vitamin E (EFSA, 2015B).

In a teratology study 75 pregnant rats were randomly assigned to five groups: one negative control group, one positive control group and three treatment groups. The positive control group received a diet containing technical grade opholate (concentration not stated). The treatment groups received a diet containing 0.5, 50 and 500 mg/kg bw/day vitamin E [d-α-tocopheryl poly(ethylene glycol) 1,000 succinate]. There were no treatment-related abnormalities in fetal development treated groups and the author conclude that d-α-tocopheryl poly(ethylene glycol) 1,000 succinate does not have adverse effects on organogenesis in rats up to doses of 500 mg/kg bw/day (EFSA, 2015B).

There are also studies in humans that investigate the potential effects of vitamin E and tocopherols on fertility and fetal development and as summary, no adverse

effects were seen. Indeed, some studies have shown that tocopherols have a positive effect on fetal growth and male fertility (EFSA, 2015B).

8.34.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor

8.34.3Other considerations

Tocopherols belong to the group of substances named vitamin E. Vitamin E is the collective term for a family of structurally related substances, namely tocopherol- and tocotrienol-derivatives, that exhibit, qualitatively, the biological activity of the naturally occurring d-α-tocopherol. Vitamin E is an essential vitamin and is naturally present in plant-derived foods, particularly fruit and vegetables.

Tocopherol-rich extract of natural origin (E 306), synthetic α-tocopherol (all-rac-α-tocopherol; dl-α-tocopherol; E 307), synthetic γ-tocopherol (dl-γ-tocopherol; E 308) and synthetic δ-tocopherol (E 309) are used as antioxidants in food, either individually or in combination, and are authorised under Annex II of Regulation (EC) No 1333/2008 on food additives (EFSA, 2015B).

8.34.4Summary on substance Tocopherol

Tocopherol does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.35 MALIC ACID (CAS: 97-67-6)

Malic acid, one of the constituents of the alpha-hydroxy acid family, is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as buffering.

8.35.1Reproductive toxicity

In three different studies the developmental toxicity of Malic acid was evaluated. Oral dosing of Malic acid in mice at doses up to 266 mg/kg and in rats at doses up to 350 mg/kg on days 6-15 of gestation, as well as in rabbits at doses up to 300 mg/kg on days 6-18 of gestation did not cause developmental toxicity. The test material had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in sham-treated controls (CIR, 2018).

In a multigenerational oral DART study, no significant adverse effects were observed in rats that received up to 10,000 ppm Malic Acid for 9 weeks prior to mating. No treatment-related effects at the highest dose teste were found (CIR, 2018).

8.35.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor

8.35.3Other considerations

Malate occurs in all living organisms as an intermediate in the citric acid cycle. It occurs in relatively high amounts in many fruits and vegetables. Malic acid has two stereoisomeric forms (L- and D-enantiomers), although only the L-isomer exists naturally.

Malic acid and sodium-, sodium hydrogen-, potassium-, calcium- and calcium hydrogen-malate (E 296, E 350–352) are authorised food additives in the European Union (EU) according to Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives. (EFSA, 2014).

8.35.4Summary on substance Malic acid

Malic acid does not show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported.

8.36 ACETYL HEXAPEPTIDE-49 (CAS: NA)

Acetyl hexapeptide-49 is a cosmetic ingredient not specifically regulated by the European Regulation (EU) No 1223/2009 of cosmetic products. It is mainly used as skin conditioner.

8.36.1Reproductive toxicity

There are not -specific- studies available in the published literature about the reproductive toxicity of Acetyl hexapeptide-49.

8.36.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.36.3Other considerations

The cosmetic ingredient review (CIR) Panel has recently valuated the safety of Acetyl Hexapeptide-8 Amide (also known as Acetyl Hexapeptide-8) in cosmetic products (CIR, 2020B). Despite the insufficient data available, the Panel concluded that Acetyl exapeptide-8 amide is safe in cosmetics at concentrations up to 0.005%.

8.36.4Summary on substance Acetyl hexapeptide-49

There is a considerably lack of toxicological data for Acetyl hexapeptide-49, but limited data suggest no known risk.

Based in the absence of reports about its toxicity, Acetyl hexapeptide-49 is not expected to show reproductive/teratogenic toxicity and, at the present time, no endocrine disruptor activity is reported for this substance.

8.37 CITRONELLOL (CAS: 106-22-9)

Citronellol is a cosmetic ingredient present in fragrances and that belongs to a family of substances which a well know potential as allergens. This family of -potential-allergens is regulated by the European Regulation (EU) No 1223/2009 of cosmetic products with labelling restrictions.

8.37.1Reproductive toxicity

In a prenatal developmental toxicity study (OECD 414) Citronellol was administered to Wistar rats by gavage at doses of 75, 250, 750 mg/kg bw/day on days 6-19 of gestation. No maternal toxic effect was detected, no test substance-related or spontaneous mortalities in any females of all test groups occurred and no treatment-related changes among hematological and clinical chemistry parameters were observed. Concerning embryotoxic/teratogenic effects, sex distribution and placental weights were comparable to control group, no soft tissue malformations nor external variations were recorded. Based on these results a NOAEL > 750 mg/kg bw/day was stated (ECHA, 2021T).

8.37.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor

8.37.3Other considerations

Citronellol (DL) is a flavouring agent used on food according to FAO/WHO report TRS 922-JECFA 61/75, monograph FAS 52-JECFA 61/289.

8.37.4Summary on substance Citronellol

There is a noticeable lack of toxicological studies for Citronellol. Nevertheless, this substance is vastly present as a fragrance component in cosmetic products and its safety as a potential allergen has been reviewed by the SCCS.

So, based on the available data, Citronellol has not reproductive toxicity nor teratogenic properties and at the present time, no endocrine disruptor activity is reported in the published data.

8.38 D-LIMONENE (CAS: 5989-27-5)

D-Limonene is a cosmetic ingredient present in fragrances and that belongs to a family of substances which a well know potential as allergens. This family of -

potential- allergens is regulated by the European Regulation (EU) No 1223/2009 of cosmetic products with labelling restrictions.

8.38.1Reproductive toxicity

Tsuji et al. (1975a in Kim, 2013) examined Wistar rats orally administered D-Limonene (0, 591, or 2,869 mg/kg/day) on day 9–15 of gestation and found decreases in body weight, increased number of deaths among dams, and delayed ossification, as well as reduction in total body and organ weight such as thymus, spleen, and ovaries in the offspring.

Kodama et al. (1977a in Kim, 2013) administered orally d-limonene (0, 591, or 2,363 mg/kg/day) to ICR mice on day 7–12 of gestation, which resulted in reduced growth in dams and a significantly increased incidence of skeletal anomalies and delayed ossification in the offspring. In another study by Kodama et al. (1977b in Kim, 2013), oral administration of d-limonene (250, 500, or 1,000 mg/kg/day) to Japanese white rabbits on day 6–18 of gestation showed no dose-related effects in the offspring. At the highest dose, there were some deaths accompanied by reduction in weight gain among dams, and at the intermediate dose growth retardation was noted.

There is no apparent evidence that Limonene produces teratogenic or embryotoxic effects in the absence of maternal toxicity (WHO, 1998).

Recently, based on an in vitro study with pregnant Sprague-Dawley rat, Hajagos-Tóth et al. (2015) suggested that l-limonene has an antioxidant effect and that both d-and l-limonene cause myometrial contraction through activation of the A_{2A} receptor and opening of the voltage-gated Ca^{2+} channel, and concluded that it is possible that limonene-containing products increase the pregnant uterus contractility, and their use should be avoided during pregnancy. Nevertheless, this study is the first evidence that limonene in low concentrations causes myometrial smooth muscle contraction and moreover studies on human myometrium were not carried out.

8.38.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.38.3Other considerations

D-Limonene is flavouring agent used on food according to FAO/WHO report TRS 928-JECFA 63/64, monograph FAS 54-JECFA 63/235.

8.38.4Summary on substance D-Limonene

This substance is vastly present as a fragrance component in cosmetic products and its safety as a potential allergen has been reviewed by the SCCS.

Based on the available data, D-Limonene is not expected to have reproductive toxicity nor teratogenicity and, at the present time, no endocrine disruptor activity is reported in the published data.

8.39 GERANIOL (CAS: 106-24-1)

Geraniol is a cosmetic ingredient present in fragrances and that belongs to a family of substances which a well know potential as allergens. This family of -potential-allergens is regulated by the European Regulation (EU) No 1223/2009 of cosmetic products with labelling restrictions.

8.39.1Reproductive toxicity

In a reproduction/developmental toxicity screening test (OECD 421) Geraniol was administered via dermal administration to groups of 10 male and 10 female Wistar rats (F0 animals) at dose levels of 0 (vehicle control; test group 0), 50 (test group 1), 150 (test group 2) and 450 mg/kg bw/d (test group 3) in order to observe the possible effects of the test substance on the integrity and performance of the reproductive system in both sexes. Due to severe dermal findings, the dose level for test group 3 was decreased to 300 mg/kg bw/d from study day 10 onwards.

Regarding clinical examinations, only signs of local dermal toxicity were observed for males and females at all dose levels. No changes in food consumption and body weight data were seen at any dose level.

Fertility indices for male and female animals were not impaired by test-substance administration. Regarding pathology, there were no treatment-related necropsy or histological findings in ovaries, testes or epididymides associated with dermal administration of the test substance. The local minimal inflammatory reactions in the skin of treated males (test groups 1-3) and females (test group 3 only) were regarded as related to treatment and adverse.

Based on these data a NOAEL for reproductive performance and fertility, systemic toxicity and developmental toxicity of 300 mg/kg bw/day was stated (ECAH, 2021U).

8.39.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.39.3Other considerations

Geraniol is flavouring agent used on food according to FAO/WHO report TRS 922-JECFA 61/75, monograph FAS 52-JECFA 61/289.

8.39.4Summary on substance Geraniol

There is a noticeable lack of toxicological studies for Geraniol. Nevertheless, this substance is vastly present as a fragrance component in cosmetic products and its safety as a potential allergen has been reviewed by the SCCS.

Based on the available data, Geraniol is not expected to have reproductive toxicity nor teratogenicity and, at the present time, no endocrine disruptor activity is reported in the published data.

8.40 HYDROXYCITRONELLAL (CAS: 107-75-5)

Hydroxycitronellal is a cosmetic ingredient present in fragrances and that belongs to a family of substances which a well know potential as allergens. This family of -potential- allergens is regulated by the European Regulation (EU) No 1223/2009 of cosmetic products with labelling restrictions and a maximum concentration of 1% in final product (except in oral products).

8.40.1Reproductive toxicity

There is a lack of specific data about the reproductive/developmental toxicity of Hydroxycitronellal. Therefore, the risk profile of substance Hydroxycitronellal is evaluated trough the read-across methodology from the structural analogue Citral (CAS: 5392-40-5) which also belongs to the family of terpenoids.

A reproduction toxicity screening test in rats was performed according to OECD Guideline 421 and GLP. Male and female Sprague Dawley rats were exposed to citral by gavage at dosages of 0, 40, 200, and 1,000 mg/kg bw/day. Male rats were treated for 14 days before mating, throughout the mating period, and up to day 46. Females were dosed from 14 days before mating, throughout the gestation period up to lactation day 3.

No test substance related effects were detected in terms of reproductive performance, parental organ weights or histopathology of the reproductive organs. Test substance related developmental toxicity was found at 1,000 mg/kg bw/d in terms of reduced pup body weights on postnatal days 0 to 4, whereas no other adverse effects were observed. The NOAELs for developmental toxicity and parental toxicity is set at 200 mg/kg bw/day. The NOAEL for reproductive toxicity in rats is set at 1,000 mg/kg bw/day (ECHA, 2021W).

Several repeated dose toxicity studies with citral provide supportive information concerning fertility. In subchronic and chronic studies of Fischer 344 rats or B6C3F1 mice, exposed to diets containing a microencapsulated preparation with citral for 14 weeks, histopathological assessment on adrenal gland, clitoral gland, mammary gland, ovary, parathyroid gland, pituitary gland, preputial gland, prostate gland, testis with epididymis and seminal vesicles, thyroid gland and uterus was performed. No adverse effects on these organs were noted that were attributable to a substance-specific effect (ECHA, 2021W).

In a developmental toxicity study, comparable to OECD Guideline 414, citral was orally administered via gavage to Wistar rats (0, 60, 125, 250, 500, 1,000 mg/kg bw/day) from day 6 to day 15 of pregnancy. Citral was found to be maternally toxic over the dose range tested, and severity of effects correlated with the dose applied. Citral induced gestational losses occurring earlier as the dose increased. Further developmental effects were observed from 125 mg/kg bw/day onwards, i.e. foetal growth retardation, increased incidences of minor skeletal abnormalities and increases in foetal spleen weights. The overlapping with overt maternal toxicity substantiates, that substance-induced developmental effects were secondary to maternal adverse effects. Based on these results, a LOAEL for maternal toxicity and developmental toxicity is set at 60 mg/kg bw/d and no NOAEL is established from this study (ECHA, 2021W).

In a developmental toxicity study comparable to OECD Guideline 414, Sprague-Dawley rats were exposed to citral by inhalation (0, 10, 34, 68 ppm or 63, 215, 430 mg/m^3) for 6 hours per day on gestation days 6 -15. Maternal toxicity was observed at 68 ppm. The number of corpora lutea, implantations, resorptions, foetal viability, litter size, and sex ratio were not adversely affected at any dose level. A NOAEC for maternal toxicity is set at 34 ppm (215 mg/m^3) and a NOAEC for developmental toxicity is set at 68 ppm (430 mg/m^3). (ECHA, 2021W).

In summary, signs of developmental toxicity have been observed after oral or inhalative exposure with citral in the presence of maternally toxic doses. No teratogenic effects, leading to specific malformations were found. Consequently, the observed effects on developmental toxicity are considered to be secondary to maternal toxicity (ECHA, 2021W).

8.40.2Endocrine disruptor properties

Abnormal development and lethal effects in chick embryos were studied by administering different doses of Hydroxycitronellal in olive oil by suprablastodermic injection on the third day of development. These studies showed a clear dose/response relationship. A dose of 2,150 µg/embryo gave 92.3% mortality. An equivalent level (90.3%) was obtained at 860 µg/embryo but this diminished to 50% at 86 µg/embryo, 18.7% at 43 µg/embryo while the solvent control gave 17.8% mortality. Observed abnormalities rose from 23% at 2,150µg/embryo to 32.2% at 860 µg/embryo and 37.5% at 86 µg/embryo but then diminished to 12.5% at 43 µg/embryo. Although these studies are of uncertain relevance to the assessment of risks to humans exposed to low doses, they show clear dose/response relationships with rates of teratogenic effects being lower than those of mortality (HERA, 2005).

Following the same read-across principle stated in the previous section, information about the structural analogue Citral is also included.

Administration of citral (210 mg /kg bw/day) to female rats for 2 years resulted in significantly decreased incidences of clitoral gland adenoma or carcinoma and of mammary gland fibroadenoma. Authors discussed these to be putatively related to an antiestrogenic effect of citral. Furthermore, data from literature indicate an induction benign and atypic prostrate hyperplasia (BPH and APH) in adolescent male rats after topical administration of citral. The postulated modes of action were putative interactions with testosterone levels or estrogen-like effects of citral (ECHA, 2021W).

A putative estrogenic activity of citral has been controversially discussed in literature on the basis of predominantly vitro data. However, Citral was found to be inactive in a rat uterotrophic assay (no increase of uterus weights as an indicator of estrogen-like activity) after oral exposure of 300 or 1,000 mg/kg bw/d for 3 days (ECHA, 2021W). This result is in line with the reproduction toxicity screening test in rats described above (OECD 421, GLP) that revealed no test substance related effects on reproductive ability, organ weights or histopathology of the reproductive organs, on delivery or on maternal behavior.

8.40.3Other considerations

Hydroxycitronellal is flavouring agent used on food according to FAO/WHO report TRS 896-JECFA 53/67, monograph FAS 44-JECFA 53/229.

8.40.4Summary on substance Geraniol

There is a noticeable lack of toxicological studies for Hydroxycitronellol. However, its structural analogue Citral (differing due to the presence of double bonds and lack of an additional hydroxyl residue but containing the same terpenoid structure) has been studied showing some evidence of reproductive and developmental toxicity mainly associated to parental toxicity.

Nevertheless, Hydroxycitronellal is vastly present as a fragrance component in cosmetic products and it is maxim allowed concentration is restricted. Moreover, its safety as a potential allergen has been reviewed by the SCCS.

So, having in mind that the available data belongs mainly to a surrogate, Hydroxycitronellal is not expected to have reproductive toxicity nor teratogenicity and, at the present time, no endocrine disruptor activity is reported in the published data.

8.41 LINALOOL (CAS: 78-70-6)

Linalool is a cosmetic ingredient present in fragrances and that belongs to a family of substances which a well know potential as allergens. This family of -potential-allergens is regulated by the European Regulation (EU) No 1223/2009 of cosmetic products with labelling restrictions.

8.41.1Reproductive toxicity

In a reproductive and developmental toxicity screening test (similar to OECD 421) female rats were orally (gavage) administered 0, 250, 500 and 1,000 mg/kg/day of coriander oil (containing 72.9% linalool). Males were excluded from the test system. Females were dosed throughout the 7-day premating period, mating, gestation and lactation (post-natal day 4).

The maternal NOEL for coriander oil was below 250 mg/kg/day, based on clinical signs, such as salivation and altered body weight gains and feed consumption. These changes were not considered to be evidence for strong toxicity, hence the NOAEL was set higher at 500 mg/kg/day. The highest-dosage (1,000 mg/kg/day) group had reduced delivered litter sizes, indicating in utero deaths, and significant incidences of pup mortality in the first four days postpartum. No adverse effects regarding mating, fertility or duration of gestation or parturition occurred in any treatment group. Clear adverse effects on reproductive performance and pup development occurred at 1,000 mg/kg/day, that also resulted in significant maternal clinical signs. In the absence of significant toxicity to the dams, test substance did not affect the reproductive performance or the developmental parameters of pups. The effects observed on reproduction and development are not, therefore, uniquely reprotoxic or developmentally toxic effects but general toxic effects. Therefore, the maternal and

developmental NOAELs were stablished to be 365 mg linalool/kg bw/day (ECHA, 2021X).

In a developmental toxicity study, one hundred pregnant Crl:CD(SD) rats were randomly assigned to four dosage groups (Groups I through IV), 25 rats per group. Linalool, or the vehicle, Corn Oil, was administered orally (via gavage) once daily on days 7 through 17 of gestation at dosages of 0 (Vehicle), 250, 500 and 1,000 mg/kg/day to rats in Groups I through IV, respectively.

The 1,000 mg/kg/day dosage of linalool caused non-significant reductions in body weight gain and also reduced absolute and relative feed consumption values during the dosage period. On the basis of these data, the maternal NOAEL of linalool is 500 mg/kg/day. Regarding the developmental toxicity, there were no adverse effects on embryo-fetal development and the developmental NOAEL is 1,000 mg/kg/day (ECHA, 2021X).

8.41.2Endocrine disruptor properties

At the present time, there is no evidence in the literature about a potential activity of this substance as an endocrine disruptor.

8.41.3Other considerations

Linalool is flavouring agent used on food according to FAO/WHO report TRS 891-JECFA 51/79, monograph FAS 42-JECFA 51/293.

8.41.4Summary on substance Geraniol

There is a noticeable lack of toxicological studies for Linalool. Nevertheless, this substance is vastly present as a fragrance component in cosmetic products and its safety as a potential allergen has been reviewed by the SCCS.

Based on the available data, Linalool is not expected to have reproductive toxicity nor teratogenicity and, at the present time, no endocrine disruptor activity is reported in the published data.

9 Traces of substances

Raw material documentation was revised and those impurities relevant for this assessment were noted and are summarized in the table (Table 2) below at the maxim possible concentration in final product according to the raw material providers declarations.

The criteria that those traces should fulfil to be included in the Table 2 is that they are harmonized by the ECHA as toxic for reproduction (CMR 1A, B or 2) and/or as endocrine disruptors (ED). On the basis of a conservative approach, those impurities self-classified as CMR or with a suspected potential as ED are also included.

Impurity	Concentration in the final product (%)	ECHA info (Repro. & ED)
Pb	0,00003	According to the classification provided by companies to ECHA in REACH registrations this substance may damage fertility or the unborn child (Repr. 1A); Officially recognized in the EU as Toxic to Reproduction (Harmonised C&L, Candidate list of SVHCs).
Cd	0,000006	According to the classification provided by companies to ECHA in REACH registrations this substance is suspected of damaging fertility or the unborn child (Repr. 2)
Hg	0,000006	According to the harmonised classification and labelling (ATP01) approved by the European Union, this substance may damage the unborn child (Repr. 1B)
Sb	0,000006	There is broad agreement in that a majority of data submitters agree this substance is Toxic to Reproduction (50% of REACH registrations). A majority of data submitters indicating this property of concern indicate that it may relate to an impurity / additive rather than the substance itself.
Ethylene oxide	0,00000402	According to the harmonised classification and labelling (ATP01) approved by the European Union, this substance may damage the unborn child (Repr. 1B); Under assessment as Endocrine Disrupting (ED list)
Toluene	0,0003	According to the harmonised classification and labelling (ATP01) approved by the European Union, this substance is suspected of damaging fertility or the unborn child (Repr. 2)
Octamethyl-cyclotetrasiloxane	0,005	According to the harmonised classification and labelling (ATP01) approved by the European Union, this substance is suspected of damaging fertility or the unborn child (Repr. 2)

Table 2. Compilation of impurities declared on raw materials.

Regarding the impurities it should be noted that concentrations stated in the table represents the worst-case scenario where the maximum declared concentration of each impurity was added up between raw materials.

The concentrations declared by the raw material manufacturers are below the acceptable limits and can be considered as technically inevitable (i.e. consequence of the manufacturing process).

Traces of forbidden substances like heavy metals are present at very low concentrations in the final product. Under the reasonably conditions of use of the cosmetic product (i.e., dermally applied) and due to the low transdermal absorption capability of this substances, systemic bioavailability is not expected.

Regarding substances Ethylene oxide and Toluene, they are declared as possible impurities but none are included in the composition list nor technical data sheet as a present impurity. Moreover, they concentration in final product in the worst-case scenario is low enough to expect a low systemic bioavailability trough dermal application.

Finally, Octamethylcyclotetrasiloxane (also known as Ciclotetrasiloxane, D4) is a well-known impurity from substance Cyclopentasiloxane (D5). The raw material provider declares that the maximum possible presence of Ciclotetrasiloxane is 0.1%, a value well under the limit stablished by the SCCS on its Opinion SCCS/1549/15 (D5 purity > 95%) to consider the presence of D4 as a risk.

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