



## Naturally toxic: natural substances used in personal care products

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Ursula Klaschka

## Abstract

**Background:** Nature offers an incredible diversity of chemical compounds that boast a wide array of physiological effects. Many natural substances are employed in personal care products. Which of these natural substances are hazardous ingredients? How do European legal instruments regulate natural substances with toxic effects?

**Results:** 1,358 natural substances appear in the 'International Nomenclature of Cosmetic Ingredients' (INCI list, 'inventory ..... of ingredients employed in cosmetic products') [Commission Decision 96/335/EC], most of them are herbal products, others are of animal, fungal, or bacterial origin. Out of these, 655 natural substances are enrolled in the EU database for classification and labeling, with 56% classified as hazardous chemicals, 38% classified due to their hazards to human health (35% due to their effects on skin and eyes), and 21% due to their hazards to the environment. 53 natural substances in the INCI list are classified as carcinogens, mutagens, and substances toxic to reproduction. Many classifications are not in line with expectations from experience, such as severe classifications of substances derived from some basic food plants or lacking classification of known medical plants or plants with sensitizing potential.

Classification and labeling is a trigger for the registration requirements according to REACH. It must be assumed that there are more substances that should undergo the REACH process among the 703 natural substances that do not turn up in the C&L inventory.

**Conclusions:** Many natural substances used in personal care products have toxic properties. The interdisciplinary compilation and analysis of regulatory instruments concerning natural substances revealed some inconsistencies which need further analysis and urgent correction to ensure prudent handling in consumer products.

**Keywords:** Classification and labeling; CLP regulation; Cosmetics; Cosmetics regulation; Hazardous substances; INCI; Natural substances; Personal care products; REACH

## Background

Substances obtained from plants, animals, or other organisms have always enjoyed great popularity as ingredients in conventional personal care products or in natural cosmetics. Which natural substances employed in personal care products are hazardous ingredients? How are they regulated?

Natural substances are substances which occur in nature. There are various definitions, for example according to REACH (Art. 3 (39)) [1] 'substances which occur in nature: means a naturally occurring substance as such, unprocessed or processed only by manual, mechanical or gravitational means, by dissolution in water, by flotation,

by extraction with water, by steam distillation, or by heating solely to remove water or which is extracted from air by any means'. In this study, a subset of natural substances originating from defined organisms which are applied in personal care products is considered. Most natural substances are complex mixtures of compounds belonging to various chemical substance classes, e.g. alkaloids, lipids, peptides, phenolics, sugars, terpenes [2-4]. The compositions of these mixtures derived from a certain species can vary. For example the composition of natural substances derived from a plant depends on the conditions of the plant growth like climate or soil parameters, on the harvest time, on production methods, or on storage conditions [5] and of course on the parts of the plants which were used. Even morphologically identical plants can

Correspondence: klaschka@hs-ulm.de  
University of Applied Sciences Ulm, Prittwitzstr 10, D-89075 Ulm, Germany

contain different chemical secondary metabolites, so called chemotypes [6].

Many natural compounds are known to be physiologically active in the organisms of origin executing special physiological roles, such as storage or defense. Many are secondary metabolites and present in only minor concentrations in the organism of origin [2]. Their physicochemical and their physiological effects are as manifold as their chemical structures. In most cases, the mechanism of action is not known, but effects, such as anticancer, antimicrobial, antifungal, molluscidal, insecticidal, effects on skeletal muscles, blood pressure action, and gastroprotective action, have been observed [2,3,6,7]. These potent effects can be used to the advantage of human health (e.g. some natural pharmaceuticals, (e. g. glycosides from *Digitalis* sp. like digitoxin help against heart trouble) or to the disadvantage of the consumer (e.g. elevated doses of digitoxin lead to intoxications) [2].

The focus of this study was on natural substances derived from plants, animals, mushrooms, or bacteria which are listed in the 'Inventory ..... of ingredients employed in cosmetic products' (INCI list [8]). The aim was to analyze the European regulatory requirements for these substances with a special emphasis on classification and labeling according to the CLP regulation [9].

According to the CLP regulation, manufacturers and importers have to notify the classification and labeling to the European Chemicals Agency (ECHA) regardless of the production volumes. The CLP regulation provides for two approaches: on one hand, the harmonized classification which applies predominantly on effects of high concern, like carcinogenicity, germ cell mutagenicity, toxicity for reproduction as well as on substances which are persistent, bioaccumulative, and toxic, and which leads to partial classifications. The harmonized classifications are the minimum mandatory classifications listed in Annex VI of the CLP regulation. On the other hand, self-classification for all other hazardous properties is effectuated by the manufacturer, importer, or downstream user. Notifiers need to make sure that their self-classifications are correct: They need to consider all accessible existing information, evaluate their reliability, relevance, and adequacy in an expert judgment with a weight of evidence approach and use the evaluated data for self-classification [9-11].

## Results and discussion

### Natural substances used in personal care products

The international INCI list contains more than 16,000 ingredients [12], and the published European list [8] that was used in this study consists of around 8,500 substances. 1,358 ingredients specified in the INCI list are natural substances derived from organisms (according to the selection criteria as described in the 'Methods' section) (Table 1).

Out of these, 655 appear in the C&L inventory [13], which is the official European database that contains classification and labeling information on notified and registered substances received from manufacturers and importers.

The INCI list [8] was scanned for natural substances derived from natural organisms according to the criteria described in the methods. 1,358 natural substances were found. Out of these, 655 natural substances appear in the C&L inventory with 369 being classified as hazardous substances.

CAS and EC numbers are a prerequisite for the unequivocal retrieval of the classification and labeling of a definite substance in the C&L inventory. It was found that some substances appear in the INCI list with identical EC and CAS numbers, even when they have different origins and names (e.g. *Betula alba* bark extract and *Betula alba* leaf extract, both with CAS number 84012-15-7 and EC number 281-660-9, or *Citrus aurantium amara* flower distillate and *Citrus aurantium amara* peel extract both with 72968-50-4 and 277-143-2). It is apparent that these 'substances' should be differing chemical mixtures. Similar inconsistencies were found a number of times but could not be investigated further in this study.

Table 2 illustrates that these natural substances are mainly produced from higher plants, but some are also animal products or originate from other organisms. This table also shows the number of notifiers who submitted the same classification and labeling information for a certain substance in the C&L inventory. In case a substance was classified differently by various notifier groups, only the clear majority was considered here. The number of notifiers ranges between one to more than 1,000 e.g. *Ricinus communis* oil (1,469 notifiers) and Xanthan gum (polysaccharide secreted from the bacterium *Xanthomonas campestris*) (1,357 notifiers). 208 herbal natural substances are notified by more than 500 notifiers. This indicates the dissemination of a substance but does not allow to estimate amounts produced per year (see also the section concerning REACH). It must be emphasized that substances itemized in the INCI list can be applied not only in personal care products but also in other products, e.g. food [2-4] or medicine [3,4,14]. Therefore, the number of notifiers does not need to correlate to the quantitative importance of a certain natural substance in the cosmetic market. However, the numbers show the abundance of companies involved in the classification and labeling of these natural substances.

Natural substances from animals are, for example, amniotic fluid, aorta extract, *Bombyx lipida*, brain extract, bubulum oil (oil from the feet of cattle), equus extract, heart extract, liver extract, marrow extract, maromota oil, or serum. Less than 500 and more than 100 companies

**Table 1 Overview of the number of substances analyzed in the study**

	Number of substances
INCI list	More than 8,500
Natural substances	1,358
Natural substances in the C&L inventory	655 (100%)
Natural substances classified	369 (56%)
Natural substances classified (effects on human health)	257 (39%)
Natural substances classified (effects on environment)	185 (28%)
Natural substances classified (effects on human health and environment)	177 (27%)
Natural substances classified (physical effects, effects on human health and environment)	94 (14%)

notified e.g. shellac, cera alba (beeswax), albumen (egg white), colostrum, lac powder, ovum, royal jelly.

The majority of animal or human material substances are not notified by any manufacturer or importer (e.g. embryo extract, neural extract, pellis lipida (animals' skin lipids), spleen extract, spinal cord extract, sus extract (extract from the skin of the pig), thymus extract (thymus glands extract), or umbilical extract.

Algae that are used for the production of natural substances are e.g. *Caulerpa taxifolia*, *Chlorella vulgaris*, *Chondrus crispus* (Irish moss or carrageen moss), *Corallina officinalis*, *Delesseria sanguinea*, *Fucus serratus*,

*Laminaria digitata*, *Laminaria japonica*, *Palmaria palmate* (dulse), and *Ulva lactuca* (sea lettuce). The extract of the brown algae *Fucus vesiculosus* (bladderwrack algae) has the greatest number of notifiers (123).

Most mushrooms entries are *Saccharomyces ferment*, and the yeast extract (faex extract) has the largest number of notifiers (115 notifiers).

Among the bacteria that are used for natural substances in personal care products are the following genera, e.g. *Aspergillus*, *Lactobacillus*, *Lactococcus*, and *Streptococcus*.

The lichen extracts are produced from *Evernia prunastri*, *Usnea barbata* (tree moss), and *Cetraria Islandica* (Iceland moss).

Table 3 shows examples of plant species from the INCI list which are used also in other applications but personal care or which are wild herbs. Some are widely used aromatic herbs, e.g. *Laurus nobilis* (laurel), *Myristica fragrans* (nutmeg), *Piper nigrum* (pepper), and *Zingiber officinale* (ginger). Others are food plants, e.g. *Allium cepa* (onion), *Arachis hypogaea* (peanut), *Citrus aurantium* (bitter orange), *Coffea arabica* (coffee), *Daucus carota* (carrot), *Glycine soja* (soybean), *Theobroma cacao* (cacao), *Triticum vulgare* (wheat), *Vitis vinifera* (grape), and *Zea mays* (corn). There are other plants known for their use as phytopharmaceuticals, e.g. *Arnica montana* (arnica), *Calendula officinalis* (calendula), *Chamomilla recutita* (matricaria, chamomile), *Valeriana officinalis* (valerian), and *Viscum album* (mistletoe). *Nicotiana tabacum* (tobacco) is also among the plant species used, as well as many wild or

**Table 2 Numbers of natural substances in the INCI list [8] originating from various organism genera**

Organism group	Number of substances in the INCI list	Number of substances which were notified in the C&L inventory by					Not in the C&L inventory
		>1,000 notifiers	500 to 1,000 notifiers	100 to 499 notifiers	10 to 99 notifiers	1 to 9 notifiers	
Higher plants	1,189	1 <sup>a</sup>	207	50	201	148	582
Animals and humans <sup>b</sup>	84	0	0	16 <sup>c</sup>	6	10	52 <sup>d</sup>
Mushrooms <sup>e</sup>	34	0	0	1 <sup>f</sup>	0	0	33
Algae <sup>g</sup>	31	0	0	1 <sup>h</sup>	3	6	21
Bacteria <sup>i</sup>	17	1 <sup>j</sup>	0	0	0	0	16
Lichens <sup>k</sup>	3	0	1	0	1	1	0
Total	1,358	2	208	68	212	165	703

Grouped according to the number of notifiers in the C&L inventory [13].

<sup>a</sup>*Ricinus communis* oil.

<sup>b</sup>In several cases the species was not named for mammalian substances.

<sup>c</sup>For example, shellac, cera alba (beeswax), albumen (eggwhite), colostrum, lac powder, ovum, royal jelly.

<sup>d</sup>No notifiers, e.g.: embryo extract neural extract, pellis lipida (animals' skin lipids), royal jelly extract, spleen extract, spinal cord extract, sus extract (extract from the skin of the pig), thymus extract (thymus glands extract), umbilical extract.

<sup>e</sup>Most entries are *Saccharomyces ferment*.

<sup>f</sup>Faex extract (yeast extract).

<sup>g</sup>For example: *Caulerpa taxifolia*, *Chlorella vulgaris*, *Chondrus crispus* (Irish moss or carrageen moss), *Corallina officinalis*, *Delesseria sanguinea*, *Fucus serratus*,

*Laminaria digitata*, *Laminaria japonica*, *Palmaria palmate* (dulse), *Ulva lactuca* (sea lettuce).

<sup>h</sup>*Fucus vesiculosus* extract (bladderwrack algae).

<sup>i</sup>For example, the following genera: *Aspergillus*, *Lactobacillus*, *Lactococcus*, *Streptococcus*.

<sup>j</sup>Xanthan gum (polysaccharide secreted by the bacterium *Xanthomonas campestris*).

<sup>k</sup>Extracts from *Usnea barbata* (tree moss), *Cetraria Islandica* (Iceland moss), and *Evernia prunastri*.

**Table 3 Examples of herbal natural substances in the INCI list [8]**

Aromatic herbs	<i>Borago officinalis</i> (borage), <i>Laurus nobilis</i> (laurel), <i>Myristica fragrans</i> (nutmeg), <i>Piper nigrum</i> (pepper), <i>Prunus amygdalus amara</i> (bitter almond), <i>Rosmarinus officinalis</i> (rosemary), <i>Zingiber officinale</i> (ginger)
Food	<i>Ananas sativum</i> (pineapple), <i>Allium cepa</i> (onion), <i>Arachis hypogaea</i> (peanut), <i>Asparagus officinalis</i> (asparagus), <i>Beta vulgaris</i> (beetroot), <i>Citrus aurantium</i> (bitter orange), <i>Cocos nucifera</i> (coconut), <i>Coffea arabica</i> (coffee), <i>Daucus carota</i> (carrot), <i>Foeniculum vulgare</i> (fennel), <i>Fragaria vesca</i> (strawberry), <i>Glycine soja</i> (Soybean), <i>Juglans regia</i> (walnut), <i>Lactuca sativa</i> (lettuce), <i>Musa sapientium</i> (banana), <i>Oryza sativa</i> (rice), <i>Secale cereale</i> (rye), <i>Spinacia oleracea</i> (spinach), <i>Theobroma cacao</i> (cacao), <i>Triticum vulgare</i> (wheat), <i>Vitis vinifera</i> (grape), <i>Zea mays</i> (corn)
Official plants	<i>Achillea millefolium</i> (yarrow), <i>Aloe barbadensis</i> (aloe), <i>Arnica montana</i> (arnica), <i>Calendula officinalis</i> (calendula), <i>Chamomilla recutita</i> (matricaria, chamomile), <i>Eucalyptus globulus</i> (eucalyptus), <i>Echinacea spec.</i> (coneflower), <i>Mentha piperita</i> (peppermint), <i>Salvia officinalis</i> (sage), <i>Valeriana officinalis</i> (valerian), <i>Viscum album</i> (mistletoe)
Other agricultural crop plants	<i>Nicotiana tabacum</i> (tobacco)
Wild or garden plants	<i>Acer pseudoplatanus</i> (hazewood, great maple), <i>Bellis perennis</i> (daisy), <i>Berberis vulgaris</i> (barberry), <i>Betula alba</i> (birch), <i>Buxus sempervirens</i> (boxwood), <i>Castanea sativa</i> (chestnut), <i>Crocus sativus</i> (saffron crocus), <i>Equisetum arvense</i> (horsetail), <i>Ginkgo biloba</i> (maidenhair tree), <i>Hedera helix</i> (ivy), <i>Helianthus annuus</i> (sunflower), <i>Lupinus albus</i> (lupin), <i>Nasturtium officinale</i> (watercress), <i>Nerium oleander</i> (oleander), <i>Papaver rhoeas</i> (corn poppy), <i>Petasites hybridus</i> (butterbur), <i>Ranunculus ficaria</i> (pilewort), <i>Sambucus nigra</i> (elder), <i>Syringa vulgaris</i> (lilac), <i>Taraxacum officinale</i> (dandelion), <i>Trifolium pratense</i> (clover), <i>Tussilago farfara</i> (coltsfoot), <i>Urtica dioica</i> (stinging nettle)

Many natural substances in the INCI list derived from plants are known from other usages than cosmetic applications. Some popular plants are specified here with their respective common English names in brackets as examples.

garden plants, e.g. *Buxus sempervirens* (boxwood), *Castanea sativa* (chestnut), *Crocus sativus* (saffron crocus), *Equisetum arvense* (horsetail), *Hedera helix* (ivy), *Lupinus albus* (lupin), *Nerium oleander* (oleander), *Papaver rhoeas* (corn poppy), *Syringa vulgaris* (lilac), *Taraxacum officinale* (dandelion), *Tussilago farfara* (coltsfoot), and *Urtica dioica* (stinging nettle).

The INCI list indicates the possible functions in cosmetic products. Some natural substances are 'antiseborrheic', 'emollient', 'keratolytic', 'refreshing', 'skin conditioning', 'skin protecting', 'smoothing', 'soothing', 'solvent', or 'tonic'. Only one 'colorant' (*Beta vulgaris/Beta vulgaris* extract) and one 'hair dye' (*Lawsonia inermis* extract, which is the extract of the henna plant) is among them. Some are 'antimicrobials', but no one has the function 'preservative' (Note: There are many non-natural compounds listed in the INCI with the function 'preservative', e.g. benzylalcohol or benzylparaben.). For *Usnea barbata* extract, the function 'deodorant' and for ten other natural substances, e.g. *Citrus aurantium bergamia* oil, *Mentha viridis* oil, *Prunus amygdalus amara* oil, *Ruta graveolens* oil, and *Sambucus nigra* oil, 'masking' was the only function indicated. Some natural substances are 'deodorant' or 'masking' in addition to other functions, e.g. 'tonic'. Other cosmetic ingredients used due to their odor are listed in the INCI list part II 'Perfume and aromatic raw materials' [15] and not in the INCI list analyzed here. It was found that some substances with different INCI names, different origins, obviously different chemical compositions, and also different functions in a product were itemized with identical EC and CAS numbers in the INCI list, e.g. *Avena sativa* bran extract (abrasive), *Avena sativa* extract (emollient), and *Avena sativa* meal extract (soothing), all three with the CAS 84012-26-0 and the EC 281-672-4, or *Citrus aurantium dulcis* flower oil (astringent and tonic), *Citrus aurantium dulcis* flower water (skin conditioning), *Citrus*

*aurantium dulcis* peel cera (emollient and skin conditioning), *Citrus aurantium dulcis* peel extract (emollient, skin conditioning), and *Citrus aurantium dulcis* seed extract (skin conditioning), all five with the CAS 8028-48-6 and the EC 232-433-8.

### Legal restrictions

#### Classifications according to the CLP regulation

Out of the 1,358 natural substances (Table 1), 703 natural compounds could not be found in the C&L inventory [13]. There are several reasons why a substance does not show up there: the classification was not notified yet, the substance might not have been scrutinized for its hazardous properties yet, or the substance is no longer produced, imported, or used by any company. In general, natural substances are self-classified by producers or importers. None of the natural substances appear in Annex VI of the CLP regulation, which is the list of harmonized classification and labeling of hazardous substances, whereas several single components of natural substances turn up there, such as e.g. nicotine, strychnine, atropine, digitoxin, papaverine, or aconitine.

Some notifier numbers appear repeatedly which might indicate the size of consortia that submitted the classifications to the ECHA: e.g. 14 substances were classified by 226 manufacturers or importers, 30 by 500, 45 by 747, and 26 by 748 manufacturers. Many natural substances are classified differently by various notifier groups. If the classifications differ between notifiers, they should make an effort to find a joint solution [9, Art. 41] which has apparently not been done for many natural substances. The differences could be the consequences of slightly different compositions or contaminations of the natural substances, of different data bases used, of the application of calculation methods instead of measured test

data, or of different classification approaches due to precaution or strategic reasons. It is also possible that some classifications are not correct. If the self-classifications of various companies differ, the classification which the clear majority of companies agreed upon is used in this study. It was not the purpose here to validate whether the majority is right or not. In most cases, the majority is clear. However, there were also cases, where one consortium of notifiers did not classify or label at all, whereas the other consortium of a similar size did. For example, *Brassica nigra* extract was not classified by 29 notifiers, whereas 28 notifiers classified it with H226, H301, H311, H315, H319, H330, H335, H400, and H410. Several substances were classified by only one company and not classified by many others.

Table 1 shows that 369 natural substances that appear in the C&L inventory are classified as hazardous substances. 257 substances are classified due to their hazardous effects on human health, and 185 substances are classified due to their hazardous effects on the environment. Eight substances are classified only because of their effects on the environment (e.g. tall oil H412 (352 notifiers)); 177 substances are classified due to their hazardous effects on human health and the environment, e.g. *Picea excelsa* extract H304, H315, H317, H319, H400, and H410 (500 notifiers) or *Lavandula hybrida* extract H304, H315, H317, H373, and H411 (748 notifiers).

136 substances were classified due to physical effects only (H225, H226) and 94 substances due to their physical, health, and environmental hazards, e.g. *Rosa damascena* extract H226, H315, H317, H318, H341, H351, and H412 (352 notifiers); *Melaleuca alternifolia* oil H226, H302, H304, H315, H317, H319, and H411 (981 notifiers).

Table 4 is a compilation of H phrases found for natural substances in the C&L inventory. The H-phrases due to physical properties (H226 and H225) may be mainly due to the solvents used for extraction or other preparation methods of the natural products. No natural substance is 'fatal if swallowed', but 45 are 'toxic' or 'harmful if swallowed'.

226 (35%) of the substances are assigned H phrases concerning effects on skin and eyes. Several natural products are called 'skin conditioning', 'skin protecting', or 'tonic' in the INCI list, even if they are classified due to their hazardous properties for skin or eyes (H310, H311, H312, H314, H315, H317, H318), e.g., *Nicotiana tabacum* extract (H312), *Pelargonium graveolens* oil (H304, H315, H317, H318, H412), *Ribes nigrum* extract (H304, H317, H411), *Rosa centifolia* water (H315, H317, H319, H341, H351), *Rosa damascena* distillate (H226, H315, H317, H318, H341, H351, H412), *Ruta graveolens* extract (H317, H411), *Thuya occidentalis* extract (H226, H301, H304, H317, H411), *Vanilla planifolia* extract (H317), *Verbena*

*officinalis* extract (H304, H315, H317, H411), and *Vetiveria zizanioides* extract (H315, H317, H319).

Many natural substances produced from food plants are classified due to hazardous properties, e.g. *Carum carvi* extract (H226, H302, H304, H315, H317, H400, H410), *Carum petroselinum* extract (H226, H304, H317, H400, H410), *Daucus carota* extract (H226, H304, H317, H319, H411), *Daucus carota* juice (H226, H304, H317, H319, H411), *Rosmarinus officinale* extract (H226, H304, H317, H373, H411), *Triticum vulgare* extract (H317), and *Foeniculum vulgare* oil (H226, H304, H315, H317, H319, H341, H351, H371, H400, H410).

Many plants are generally known for their ingredients of high sensitization potential [2], such as *Achillea millefolium*, *Arachis hypogaea*, *Arnica montana*, *Ginkgo biloba*, *Glycine max*, *Helianthus annuus*, *Inula helenium*, and *Ricinus communis*. 21 entries of natural substances in the INCI list originate from these plants, but only *Achillea millefolium* oil is classified due to its sensitization potential (H317).

Seven natural substances are classified as 'fatal', 'toxic', or 'harmful if inhaled'. Three notifiers classify a natural substance as 'May cause allergy or asthma symptoms or breathing difficulties if inhaled'. Eight substances are classified as 'May cause respiratory irritation', e.g. *Quillaia saponaria* extract (783 notifiers).

130 substances are classified with H304 'May be fatal if swallowed and enters airways', e.g. *Picea excelsa* extract and *Pinus sylvestris* leaf extract.

Carcinogens, mutagens, and substances toxic to reproduction (CMR substances) should be prohibited in cosmetic products according to Preamble (32) of the Cosmetics Regulation 1223/2009 [16], but there are exceptions for these substances where their 'use has been found safe by the SCCS' (Scientific Committee for Consumer Safety) [17]. Natural substances are classified 53 times with H341, H350, H351, H360, and H361 (H phrases indicating CMR substances), several of them with more than 500 notifiers.

Six natural substances are classified with H371, among them is *Lawsonia inermis* extract (the extract of the henna plant), classified also with H317. The active ingredient of the hair dye in the henna plant is 2-hydroxy-1,4-naphthoquinone, also called lawsone, CAS 83-72-7 EC 201-496-3 which is classified by the majority of notifiers (23) with H315, H319, and H335.

Many medicinal plants contain relevant physiological active ingredients. Some natural substances used for personal care products are produced from medicinal plants and are classified, e.g. *Chamomilla recutita* extract (H304, H315, H317, H412), *Chenopodium ambrosioides* extract (H301, H304, H311, H315, H317, H411), and *Valeriana officinalis* extract (H304, H317, H319, H400, H410), whereas others are not classified, e.g. *Arnica*

**Table 4 Classifications of natural substances from the INCI list [8] according to the C&L inventory [13]**

	(1)	(2)	(3)
H225	Highly flammable liquid and vapor	39	<i>Acacia catechu</i> (747), <i>Pyrus malus</i> extract (747)
H226	Flammable liquid and vapor	223	<i>Allium sativum</i> extract (747), <i>Pinus pinaster</i> extract (501)
H300	Fatal if swallowed	0	-
H301	Toxic if swallowed	9	<i>Allium sativum</i> extract (747), <i>Artemisia absinthium</i> extract (500), <i>Tanacetum vulgare</i> extract (128)
H302	Harmful if swallowed	36	<i>Prunus amygdalus amara</i> extract (847), <i>Prunus amygdalus amara</i> oil (22), <i>Sassafras officinale</i> extract (27), <i>Viola odorata</i> extract (746)
H304	May be fatal if swallowed and enters airways	130	<i>Pelargonium graveolens</i> oil (814), <i>Picea excelsa</i> extract (500), <i>Pinus sylvestris</i> leaf extract (502)
H310	Fatal in contact with skin	1	<i>Nicotiana tabacum</i> extract (27)
H311	Toxic in contact with skin	3	<i>Brassica nigra</i> extract (28), <i>Chenopodium ambrosioides</i> extract (69), <i>Piper methysticum</i> extract (7)
H312	Harmful in contact with skin	7	<i>Cinnamomum cassia</i> extract (834), <i>Cinnamomum zeylandicum</i> extract (247), <i>Prunus amygdalus amara</i> oil (23)
H314	Causes severe skin burns and eye damage (skin corrosive)	4	<i>Origanum majorana</i> extract (747), <i>Satureia hortensis</i> extract (748), <i>Thymus serpyllum</i> extract (129), <i>Thymus vulgaris</i> extract (750)
H315	Causes skin irritation	137	<i>Chamomilla recutita</i> extract (772), <i>Citrus aurantium dulcis</i> oil (109)
H317	May cause an allergic skin reaction	198	<i>Citrus medica limonum</i> oil (127), <i>Valeriana officinalis</i> extract (502)
H318	Causes serious eye damage	17	<i>Melissa officinalis</i> extract (128), <i>Rosa centifolia</i> oil (89)
H319	Causes serious eye irritation	58	<i>Rosa centifolia</i> water (69), <i>Valeriana officinalis</i> extract (502)
H330	Fatal if inhaled	2	<i>Brassica nigra</i> extract (28), <i>Tropaeolum majus</i> extract (13)
H331	Toxic if inhaled	1	<i>Piper methysticum</i> extract (7)
H332	Harmful if inhaled	4	<i>Artemisia vulgaris</i> extract (128), <i>Piper methysticum</i> extract (7), <i>Polianthes tuberosa</i> extract (748), <i>Prunus amygdalus amara</i> oil (23)
H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled	3	pollen extract (1), <i>Tabebuia impetiginosa</i> bark extract (1), <i>Tabebuia impetiginosa</i> leaf extract (1)
H335	May cause respiratory irritation	8	<i>Carum petroselinum</i> seed oil (23), <i>Quillaia saponaria</i> extract (783)
H336	May cause drowsiness and dizziness	0	-
H340	May cause genetic defects	0	-
H341	Suspected of causing genetic defects	24	<i>Artemisia dracunculus</i> extract (748), <i>Illicium verum</i> oil (748)
H350	May cause cancer	4	<i>Cinnamomum ceylandicum</i> extract (500), <i>Myristica fragrans</i> extract (500), <i>Myristica fragrans</i> oil (61), <i>Sassafras officinale</i> extract (27)

**Table 4 Classifications of natural substances from the INCI list [8] according to the C&L inventory [13] (Continued)**

H351	Suspected of causing cancer	23	<i>Artemisia dracunculus</i> extract (748), <i>Crocus sativus</i> extract (58), <i>Cymbopogon nardus</i> oil (747), <i>Foeniculum vulgare</i> extract (500), <i>Illicium verum</i> oil (747), <i>Laurus nobilis</i> extract (747), <i>Levisticum officinale</i> extract (749), <i>Ocimum basilicum</i> extract (500), <i>Pimpinella anisum</i> extract (747), <i>Rosa damascena</i> distillate (748)
H360	May damage fertility or the unborn child	1	<i>Urtica urens</i> extract (747)
H361	Suspected of damaging fertility or the unborn child	1	<i>Melia azadirachta</i> seed oil (1)
H362	May cause harm to breast-fed children	0	-
H370	Causes damage to organs	0	-
H371	May cause damage to organs	6	<i>Artemisia vulgaris</i> extract (128), <i>Foeniculum vulgare</i> oil (65), <i>Laurus nobilis</i> oil (64), <i>Lawsonia inermis</i> extract (1), <i>Ocimum basilicum</i> oil (84), <i>Rosmarinus officinalis</i> oil (89)
H373	May cause damage to organs through prolonged or repeated exposure	5	<i>Artemisia absinthium</i> extract (500), <i>Lavandula hybrida</i> extract (748), <i>Rosmarinus officinalis</i> extract (748), <i>Salvia officinalis</i> extract (500), <i>Salvia officinalis</i> water (500)
H400	Very toxic to aquatic life	74	<i>Apium graveolens</i> extract (501), <i>Valeriana officinalis</i> extract (502)
H410	Very toxic to aquatic life with long lasting effects	77	<i>Carum carvi</i> extract (504), <i>Citrus grandis</i> peel extract (575)
H411	Toxic to aquatic life with long lasting effects	63	<i>Coriandrum sativum</i> extract (766), <i>Daucus carota</i> extract (747)
H412	Harmful to aquatic life with long lasting effects	41	<i>Humulus lupulus</i> extract (747), <i>Illicium verum</i> oil (747)
H413	May cause long lasting harmful effects to aquatic life	5	<i>Origanum vulgare</i> extract (67), <i>Thymus vulgaris</i> oil (66), <i>Tropaeolum majus</i> extract (13)

Column (1) are the substance names in the INCI list.

Column (2) are the CAS and EC numbers in the INCI list or in the REACH registrations and the production tonnage bands as given in the REACH registrations.

Column (3) are the H-phrases given by the clear majority in the C&L inventory with the number of notifiers in brackets and the H-phrases as given in the REACH registration dossier. The number of notifiers in the C&L inventory which classify a substances in the same way as in the REACH dossier is also listed.

*montana* extract, *Calendula officinalis*, or *Ricinus communis* oil.

H phrases due to hazardous properties for the environment are attributed 185 times to natural substances, with 184 for long lasting effects (H410, H411, H412, and H413), i.e. that these substances are not readily degradable.

### REACH

The following paragraphs in the REACH regulation [1] concern natural substances used in personal care products:

In the introduction, it says (35) ‘The Member States, the Agency and all interested parties should take full account of the results of the RIPs, (REACH Implementation Projects (added by the author)) in particular with regard to the registration of substances which occur in nature (Table 5).

There are exemptions from the obligation to register in accordance with Art. 2(7b) e.g. ‘Substances occurring in nature other than those listed under paragraph 7 (which are inorganic substances or petrochemicals (added by the author)), if they are not chemically modified, unless they meet the criteria for classification as dangerous according to Directive 67/548/EEC.’ The natural substances in the INCI list that are classified as hazardous substances should therefore be registered according to REACH. 19 natural substances in the INCI list are registered according to REACH with annual production tonnage bands up to 100,000 to 1,000,000 t/a (Table 5). As substances used as medicinal products, food and feeding stuff do not need to be registered, evaluated, and authorized according to REACH Art. 2(5), production volumes indicated in Table 5 cover the uses in other applications, e.g. in personal care products. The



**Table 5 Natural substances in the INCI list that are registered according to REACH in descending order of the production volumes**

(1)	(2)	(3)
Tall oil	8002-26-4/232-304-6 100,000 to 1,000,000 t/a	H412 (352) (not classified in the REACH dossier and also not classified by 200 notifiers)
<i>Citrus aurantium dulcis</i> extract, <i>Citrus aurantium dulcis</i> flower extract, <i>Citrus aurantium dulcis</i> flower oil, <i>Citrus aurantium dulcis</i> flower water, <i>Citrus aurantium dulcis</i> peel cera	8028-48-6/232-433-8 > 10,000 t/a	H225, H304, H315, H317, H400, H410 (500) H226, H304, H315, H317, H411 (REACH dossier and 62 notifiers)
<i>Eucalyptus globulus</i> extract	84625-32-1/283-406-2 1.000 to 10.000 t/a	H226, H304, H317, H411 (905) H226, H304, H315, H317, H411 (REACH dossier and 97 notifiers)
<i>Citrus medica limonum</i> extract, <i>Citrus medica limonum</i> juice, <i>Citrus medica limonum</i> juice extract, <i>Citrus medica limonum</i> juice powder, <i>Citrus medica limonum</i> peel extract	84929-31-7/284-515-8 100 to 1,000 t/a	H226, H304, H315, H317, H400, H410 (507) H226, H304, H315, H317, H410 (REACH dossier and 96 notifiers)
<i>Mentha arvensis</i> extract	90063-97-1/290-058-5 100 to 1,000 t/a	H315, H317, H411 (891) H302, H315, H317, H319 H401, H411 (REACH dossier and 6 notifiers)
<i>Mentha piperita</i> extract, <i>Mentha piperita</i> water	84082-70-2/282-015-4 100 to 1,000 t/a	H315, H412 (785) H315, H317, H319, H402, H412 (REACH dossier and 4 notifiers)
<i>Pogostemon cablin</i> extract (Patchouli ext.)	84238-39-1/282-493-4 (INCI) 939-227-3 (REACH registration) 100 to 1,000 t/a	H304 (792) H304, H411 (REACH dossier and 1 notifier)
<i>Myristica fragrans</i> extract	84082-68-8/282-013-3 10 to 100 t/a	H226, H304, H315, H317, H341, H350 (500) H226, H304, H317, H341, H350, H410 (REACH dossier and 31 notifiers)
<i>Myristica fragrans</i> oil	8008-45-5 10 to 100 t/a	H226, H304, H317, H350, H400, H410 (61) H226, H304, H317, H341, H350, H400, H410 (only in the REACH dossier and by no notifier)
<i>Eugenia caryophyllus</i> extract	84961-50-2/284-638-7 (INCI) 904-912-8 (REACH registration) intermediate only	H304, H315, H317, H319 (749) (not classified in the REACH dossier, whereas all notifiers classify the substance)

Column (1) shows the substance names in the INCI list.

Column (2) shows the CAS and EC numbers in the INCI list or in the REACH registrations and the production tonnage bands as given in the REACH registrations.

Column (3) shows the H phrases given by the clear majority in the C&L inventory with the number of notifiers in brackets and the H phrases as given in the REACH registration dossier. The number of notifiers in the C&L inventory which classify substances in the same way as in the REACH dossier is also listed.

other 350 natural substances which are classified and labeled according to the C&L inventory have not been registered so far. Some of them might be registered in 2018, the registration deadline for production volumes of 1 to 100 t/a. Furthermore, it must be assumed that some of the 703 natural substances that do not turn up in the C&L inventory so far also will have to be registered according to REACH in future. Classifications in the REACH registration are not in line with the classifications by the majority of notifiers in the C&L inventory as shown in Table 5.

If substances registered according to REACH are classified differently by various notifiers, registrants should be participants in a substance information exchange forum (SIEF) with the aim to agree classification and labeling ([1] Art. 29(2)). As some natural substances are CMR substances, as shown above, they might be candidates for REACH Annex XIV (list of substances subject to authorization) ([1] Art. 57). As data on cosmetic ingredients need not be transmitted in the supply chain

([1] Art. 2(6b)), it is not foreseen that the final formulator receives the information about classification and labeling.

None of the natural substances considered in this study is in the list of substances of very high concern (SVHC).

According to the REACH regulation, the chemical safety report does not need to consider the risks to human health from the use of cosmetic products ([1] Chapter 1 Art. 14(5b)). This is valid for synthetic ingredients as well as for natural substances.

#### Cosmetic regulation

There are several restrictions for natural substances used in personal care products.

Annex II of the Cosmetic Regulation [16] is the 'List of substances prohibited in cosmetic products'. It lists 35 natural substances, most of which are prohibited because they are highly toxic, such as *Atropa belladonna* L. (deadly nightshade) and its preparations, *Cantharides*, *Cantharis vesicatoria* (Spanish fly (beetle)), *Chenopodium*

*ambrosioides* L. (wormseed) (essential oil), *Claviceps purpurea* Tul. (ergot fungus), and its alkaloids and galenical preparations, *Conium maculatum* L. (poison hemlock) (fruit, powder, galenical preparations), *Prunus laurocerasus* L. (cherry laurel water), *Strychnos* species (e.g. *Strychnos nux-vomica*), and their galenical preparations, *Veratrum* spp. (false hellebore) and their preparations, and *Pyrethrum album* L. and its galenical preparations.

These natural substances are not listed in the INCI list but related substances produced by the same plants: For example, *Chenopodium ambrosioides* L. (essential oil) is prohibited, whereas *Chenopodium ambrosioides* L. (extract) is classified by 69 notifiers, and the INCI list indicates the function of 'skin conditioning'.

The oil from the seed of *Laurus nobilis* L. is prohibited in Annex II. However, *Laurus nobilis* extract of the leaves has the same CAS and EINECS numbers and was classified by 747 notifiers in the C&L inventory. (The oil from the fruits in the INCI list has a different CAS number and was classified by 64 notifiers in the C&L inventory).

Fig leaf absolute (*Ficus carica* L.) is prohibited when used as a fragrance ingredient, *Ficus carica* extract is classified by 74 notifiers in the C&L inventory, and the INCI list indicates the function 'skin conditioning'.

Verbena oil (*Lippia citriodora* Kunth.) is prohibited when used as a fragrance ingredient, *Lippia citriodora* Kunth. extract is classified by 128 notifiers in the C&L inventory, and the INCI list indicates the function 'tonic'.

Further restrictions exist for the origin of bovine products (e.g. adeps bovi, brain extract, marrow extract, or neural extract).

Annex III of the Cosmetic Regulation contains the 'List of substances which cosmetic products must not contain except subject to the restrictions laid down'. Oakmoss extract (*Evernia prunastri* extract) as a strong contact allergen is part of this list and must be named in the list of ingredients referred to in Art. 19(1)(g) when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products. Despite this restriction, there were 747 notifiers for oakmoss extract in the C&L inventory. According to the INCI list, oakmoss extract is used with the function of skin conditioning. Oakmoss is also listed in the INCI list part II (perfume and aromatic raw materials), together with treemoss extract (*Evernia furfuracea* lichen extract).

It is not evident to the author why the reference in the restriction of the cosmetic colorant *Beta vulgaris* (which has a strong red color) in the INCI list (IV 1) leads to a substance of green color.

#### **Red list of endangered species**

A dozen natural substances from the INCI list originate from plants that are on the red list of endangered

species in Germany (class 2 or 3) [18], e.g. *Drosera rotundifolia* (sundew), *Orchis morio* (green-veined orchid), *Gentiana lutea* (great yellow gentian), *Arctostaphylos uva-ursi* (bearberry), or *Arnica montana* (mountain arnica). There were no notifiers of *Drosera rotundifolia* (sundew) and *Orchis morio*. Also, no notifier is entered for *Arnica montana*, although this plant is used frequently for pharmaceutical products. Some plants which are endangered in Germany and used for the production of natural substances may be cultivated (e.g. *Gentiana lutea*, *Arctostaphylos uva-ursi*, and since recently also *Arnica montana*) or they may be collected in other countries (e.g. *Arnica montana*). *Gentiana lutea*, and *Arctostaphylos uva-ursi* are notified by 747, respectively 25 notifiers. There are additional rare and protected plants, which are used for the production of personal care products, but which are itemized in the INCI list and not in the German red list. For example, alpine valerian (*Valeriana celtica*, German name: Speick) is used by the German Speick company for the production of soap. This company was granted an exception permit for the collection of *Valeriana celtica* in the Austrian Alps.

#### **Conclusions**

The interdisciplinary analysis and compilation of the various regulatory instruments for natural substances used in personal care products reveals the heterogeneity of their origins, the relevance of their hazardous properties, and the importance to clarify relevant regulatory inconsistencies.

The following conclusions could be drawn, with each conclusion leading to further questions.

#### **Classifications**

The classifications in the C&L inventory must be assumed to be correct. However, some classifications are difficult to comprehend as they are not in line with expectations from experience, and some basic properties of the classification process make the interpretation difficult.

- In many cases, some notifiers classified the substance, whereas others did not. Could the differences be due to differences of the biological material used? Or could they be due to pesticidal or other contaminations, impurities, solvent residues, or added stabilizers or preservatives? Or could they be due to oxidation or other reaction processes of the ingredients?
- At several occasions, natural substances originating from plants with known toxic or physiologically active ingredients are not classified (e.g. *Achillea millefolium*, *Arachis hypogaea*, *Arnica montana*, *Ginkgo biloba*, *Glycine max*, *Helianthus annuus*, *Inula helenium*, *Ricinus communis*). Did the

preparation procedures destroy, separate or dilute the active ingredients sufficiently?

- The pharmaceutical properties, the composition, and the toxicity of natural substances have been studied for centuries and vast knowledge on natural compounds is gathered [2-4]. Have these indicators been always respected in the classification and labelling process as they should be [9-11]?
- Many natural substances do not (yet) appear in the C&L inventory. How many of them would need to be classified as hazardous chemicals?
- Many natural substances are classified due to their long lasting effects on the environment. Which components are responsible for these effects?
- Some natural substances derived from basic food plants are classified. Which chemical components are responsible for the respective classifications? For example, what makes *Allium sativum* extract (garlic extract) H301 'toxic if swallowed'? Which components are responsible that *Daucus carota* juice is classified with H226, H304, H317, H319, and H411?
- The classifications of the natural substances are self-classifications. How can a high quality standard be ensured?
- The C&L inventory is updated regularly, but the updated notifications are not flagged. This means working with an ever changing data set, which is especially annoying for a data compilation like in the present study that was effectuated over several months.
- Some identifications of natural substances produced by natural organisms are apparently inconsequential. Could the intense discussion about substance identity in the REACH process lead to improvement for the definition of natural substances in the INCI list?

## REACH

Classification and labeling is not only an interesting information for manufacturers and consumers, but it is also a trigger for the registration requirements according to REACH.

- Are there more than the 19 natural substances (Table 5) in the INCI list that should be classified as hazardous substances and registered according to REACH?
- According to the REACH regulation, the chemical safety report does not need to consider the risks to human health from the use of cosmetic products. What would be the result if it did consider these risks?
- In some cases, effects on the environment are described in detail e.g. effects of the hair dye henna on the development of zebra fish [19]. Were such

studies considered in the classification procedure? What are the results of risk assessments of natural substances which are used in large amounts?

The cosmetic regulation does not ask for a different safety evaluation of natural compared to synthetic ingredients. Is it still justified that natural products receive a special treatment in the frame of REACH?

## INCI list

The INCI list is a very valuable list, but several aspects need to be corrected in an update to come.

- Many natural substances, especially animal products, have no notifier. I assume that consumers consider several of the animal products as rather 'nauseating', e.g. testicular extract or sus extract, and would not want them on their body surface. Are they still relevant? If so, do they correspond to today's hygiene requirements?
- For several plants, the old taxonomic names are listed in the INCI list. Are there no notifiers for some of them because of the new taxonomic names?

## Consumer protection

Toxic effects of natural substances used in personal care products have been known for a long time and have led to many regulations to protect consumers and the environment. However, there are some relevant inconsistencies which make it rather difficult to believe that products containing natural substances are always safe.

- Many natural substances used in personal care products are classified as hazardous substances. The vast majority of health risk phrases concerned the hazardous effects on the skin. Why are many natural substances catalogued in the INCI list with the function of 'skin conditioning' if they are classified as substances with hazardous effects for the skin?
- Many natural substances in the INCI list are classified with H-phrases indicating CMR substances. Where and in what amounts are these substances used?
- Personal or environmental risks posed by a substance in personal care products depend on exposure to a certain substance. Are the exposures of concern? What are the risks for the environment and for consumers?
- Many natural substances used in personal care products are classified as hazardous substances. How many consumers know the classifications of natural substances, especially as long as the products need not be classified [20]? How could consumers

be informed about the hazardous properties and the relevant exposure of natural substances in personal care products [21]?

- Many natural organisms are endangered or live in declining habitats. How could sustainable production of natural substances be guaranteed?

Nature offers an incredible diversity of chemical compounds with a wide array of physiological effects. Natural substances are not only used in personal care products, but some are used in food, as spices, or in medicine (Table 3) [2-4,14]. The borderline between these uses is not sharp. Many herbal substances used as phytopharmaceuticals have hazardous properties [4], and many ingredients in natural flavorings have toxic properties (like beta-asarone, coumarin, hydrogen cyanide, methyl eugenol, capsaicin, eucalyptol, hypericin, thujone, aloin/aloe-emodin, berberine, and pyrrolizidine alkaloids [2]). Therefore, it is not surprising that many natural substances used in personal care products are naturally toxic, too, and demand a prudent handling and sensible regulations.

## Methods

As transparency is considered to be very important in the European chemical policy, the ambition of this study was to use publically available information only.

Substances were selected from the 'Inventory and a common nomenclature of ingredients employed in cosmetic products' [8,22] which originate clearly from a specific organism indicated by its scientific name. In most of these cases, the two partite scientific Latin name of the organism, the preparation (e.g. *Ricinus communis* oil), and a short description of the substance is given in the INCI list (e.g. *Ricinus communis* oil is the fixed oil obtained from the seeds of *Ricinus communis*, Euphorbiaceae. It consists primarily of the glycerides of the fatty acid ricinoleic) as well as the CAS and the EC number of the substance and the function in cosmetic products (for *Ricinus communis* oil: emollient/skin conditioning/moisturizing/smoothing/solvent). The natural substance can be 'total organism', 'tissue', 'extract', 'oil', 'water', 'juice', 'ferment', 'cera', 'powder', 'gum', 'root', 'butter', 'fruit', 'bran', or 'flour'. Fermented substances were considered, in case the respective fermenting microorganism was named. Entries were considered in case the species of origin was clear by the familiar name (e.g. cera alba is wax of the honey bee *Apis mellifera*).

The following entries were not considered further in the present study:

- Other natural substances that are applied in personal care products, but do not appear in the INCI list.

- Substances which underwent subsequent chemical reactions (e.g. hydrolyzation or lysis) (such as 'cocoyl hydrolyzed collagen, acid chlorides, coco, reaction products with protein hydrolyzates')
- Specific chemicals with a definite chemical structure (e.g. coco betaine)
- Substances with a common chemical structural property (such as cocoglycerides)
- Inorganic substances and substances on the basis of mineral oil
- Fragrances which are listed in the INCI list Section II 'Perfume and aromatic raw materials' [15]. This list contains approximately 2,750 substances; more than a quarter of them are natural substances according to the criteria of this study.

Classification and labeling of hazardous substances according to the European Regulation on Classification, Labelling and Packaging [9] can be found in the publically accessible C&L inventory database according to REACH Title XI [13]. Classification and labeling is an ongoing process, leading to a continuous update of the data. Data used here were collected between August 2013 and June 2014. CAS numbers or EC numbers were used preferentially in the C&L inventory to find the respective hazard classifications. Ingredients with neither a CAS nor an EC number in the INCI list were searched with their INCI names in the C&L inventory. For reasons of clarity and comprehensibility, only the H phrases are presented here, without the GHS symbols.

## Competing interests

The author declares that she has no competing interests.

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