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Regulatory status of *N*-alkylamide containing health products

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ABSTRACT

N-alkylamides (NAAs) are secondary metabolites occurring in more than 25 plant families. Plants containing NAAs are traditionally used in food for flavouring, tingling, pungent and saliva-enhancing properties but also to treat various diseases. NAA containing products are abundantly available on the market as food, cosmetics, medical devices and medicinal products. However, no unambiguous legal product classification is applied for these products. In this study, the different health product classes from a European viewpoint are discussed in relation to the pharmacokinetic and pharmacodynamic properties of the NAAs, their applied dosage and claimed usage.

1. *N*-alkylamides

N-alkylamides (NAAs) are an important group of secondary metabolites in plants, attracting attention because of their numerous reported bioactivities. NAAs, available in more than 25 plant families (*e.g.* Asteraceae, Piperaceae, Lauraceae, Solanaceae), possess *i.a.* antimicrobial, insecticidal, antifungal, anti-inflammatory, immune-modulating and analgesic effects. Well-known, traditionally and medically important plants containing NAAs are *Anacyclus pyrethrum*, *Spilanthes acmella*, *Achillea millefolium* and *Echinacea* species, all belonging to the Asteraceae family. Furthermore, *Capsicum annuum* (Solanaceae) and *Piper* species (Piperaceae) are also plants rich in NAAs.

NAAs consist of a fatty acid chain which is linked to an amide part through a peptide bond. Because of the structural diversity in these two parts, they can be classified based on the combination of the fatty acid chain (F, from 1 to 13) and amide part (M, from 1 to 13). More than 400 NAAs are already discovered and their chemical name, occurrence, physicochemical properties and reported functionalities are gathered in the online database Alkamid® (Boonen et al., 2012).

NAAs are mainly found in plants and their related plant extracts, purified to different extent, but are also microbial and mammalian products, and are even chemically synthesized, such as palmitoylethanolamide (PEA) (Paladini et al., 2016).

In most countries, NAA containing plants have not only been used in food, but also for therapeutic purposes. Ethnopharmacological studies investigate these plant medicines in particular ethnic populations (Paulraj et al., 2013; Sutovska et al., 2015). This is generally grouped in the term 'traditional medicine' which is defined by the World Health Organisation (WHO) as "the total of knowledge, skills, and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" (WHO/EDM/TRM/2000.1, 2000). Sometimes, traditional medicines are considered synonyms for complementary alternative medicines (CAM). Well-known traditional medicines include the Ayurveda and traditional Chinese medicine (TCM), both encompassing NAAs containing plants.

Products containing NAAs are widely available on the market as *i.a.* food supplements, medicinal products, cosmetics and medical devices. Using the European regulatory-legal frame, the legal status of these NAA containing health products will be discussed.

2. Classification of health products

The legal, regulatory classification, and hence the requirements for placing these NAA products on the market, is an important aspect for the patient/consumer, the manufacturer/distributor and for the competent authorities in an attempt to acquire correct information, create

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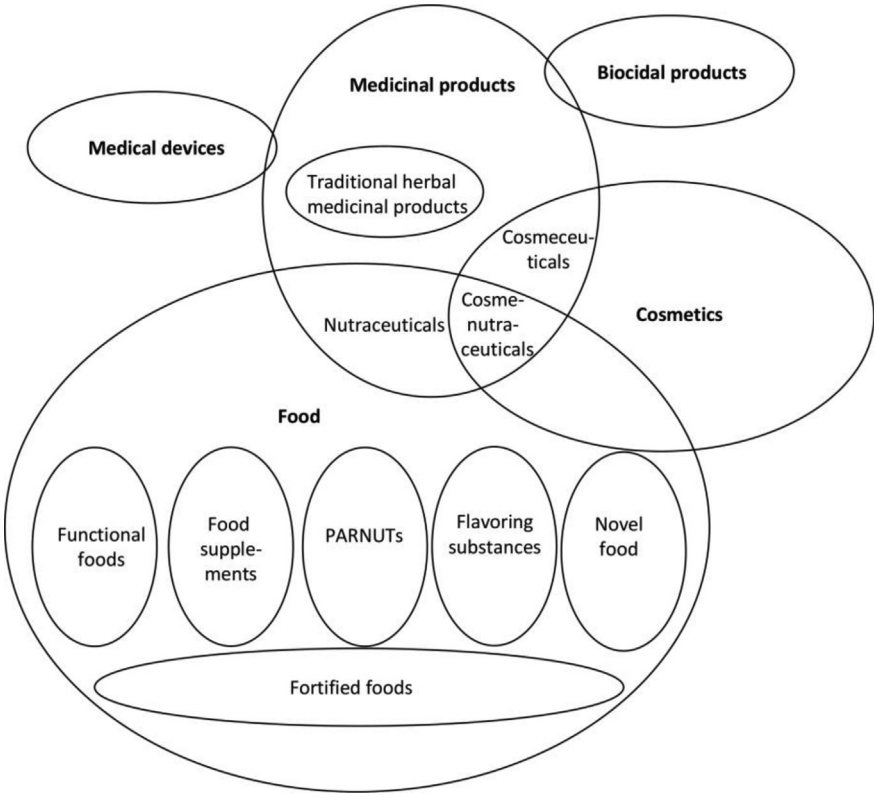

Fig. 1. Product classification.

added value and protect the different stakeholders of the society at large. This 'classification' system should be considered as a tempo-spatial characteristic, *i.e.* changing in time and dependent on the country/region. Currently, however, the guiding principles in product classification are globally relatively similar. For the sake of transparency and focus, we will use the European legal and regulatory frame to elaborate the different health product classifications possibly applicable to NAAs. A schematic overview is given in Fig. 1.

2.1. Medicinal products

To clarify the terms used in the text below, some terms will first be defined. A medicinal product (MP) is defined as "(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis." Hence, there are two "classes" of medicinal products: (a) by presentation or (b) by function. Herbal medicinal products (HMP) are defined as "any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations". Furthermore, herbal substances are defined as "whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)", while herbal preparations are "preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates" (Directive 2001/83/EC). Next to the conventional medicines, also non-conventional medicines exist, *i.e.* complementary and alternative medicines (CAM), of which homeopathic medicines are part of it, but will not be further discussed in this work.

Herbal medicinal products are licensed and marketed in Europe according to Directive 2004/24/EC, which amends Directive 2001/83/EC related to medicinal products for human use (Directive 2004/24/EC). Individual herbal medicinal products are nationally licensed by Member States (MS). Due to Directive 2004/24/EC, the licence of herbal substances and preparations became more harmonised across the EU. Furthermore, in Directive 2004/24/EC, a subcategory of HMPs is introduced, namely the traditional herbal medicinal products (THMPs). Herbal medicinal products can reach the market in the European Union (EU) as (a) a traditional use HMP (simplified registration procedure by a Member State) and (b) a well-established use (WE) HMP (marketing authorisation by MS or European Medicines Agency (EMA)). In case of WE HMP, the active substances are in use in the EU for at least 10 years and enough safety and efficacy data must be available. No proof of clinical efficacy is needed for THMPs as this efficacy is plausible due to their traditional long-standing use. Registration as THMP is only possible if the product has been used for more than 30 years of which at least 15 years in at least one country of the EU (Chinou et al., 2014; Getman, 2011; European Medicines Agency (EMA)). Independent of the type of registration procedure, the quality of the HMP must always be guaranteed. The Committee on Herbal Medicinal Products (HMPC), one of the seven scientific committees of the EMA, prepares the EU herbal monographs, consisting of the scientific opinion of the HMPC on efficacy and safety data of a herbal substance or preparations for medicinal use. These monographs consist of two parts: a well-established use and a traditional use part. Monographs include important information about the composition, pharmaceutical form, therapeutic indications, posology and method of administration,

contraindications, special warnings and precautions for use, interactions with other medicinal products, information in case of pregnancy and lactation, ability to drive and use machines, undesirable effects, overdose information, pharmacokinetic (PK) and pharmacodynamic (PD) properties and preclinical safety data. The final monographs are published by the EMA and are used as a reference by a traditional use registration applicant (traditional use part) or by a marketing authorisation applicant (WE use part). The MS can consult these monographs for the examination of an application, however monographs have no legally binding character. But to favour the harmonisation, and avoid discrimination and unfair competition, if there is a deviation from the monographs, an appropriate justification is needed. Besides the monographs, there exist also list entries: "the EU list of herbal substances, preparations and combinations thereof for use in THMP", which is legally binding and is published by the European Commission (EC) (Chinou et al., 2014; European Medicines Agency (EMA)).

The expressed juice and dried expressed juice from fresh flowering aerial parts of *Echinacea purpurea* for example, are classified as medicinal products. It is a traditional herbal medicine for use in the treatment of small superficial wounds based upon long-standing use. Moreover, the HMPC concluded that purple coneflower herb medicines to be taken by mouth can be used short term for the prevention and treatment of common colds as well.

2.2. Food

The purpose of the implementation of the general food law, Regulation (EC) No. 178/2002, was to provide assurances of high level protection for consumers of all kinds of foods *e.g.* dietetic foods, food supplements, 'functional foods' and 'nutraceuticals' (Coppens et al., 2006). Food (or foodstuff) is defined as "any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. 'Food' includes drink, chewing gum and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment." Food does not include "feed; live animals unless they are prepared for placing on the market for human consumption; plants prior to harvesting; medicinal products within the meaning of Council Directives 65/65EEC and 92/73/EEC; cosmetics within the meaning of Council Directive 76/768/EEC" (Regulation (EC) No 178/2002). The European Food Safety Authority (EFSA) was implemented in Regulation (EC) No. 178/2002 and provides scientific advice for the Community's legislation. MS collaborate with EFSA to follow up the missions of the EFSA. Herbal products can be seen as food as they comply with the applicable food law Regulation (EC) No. 178/2002 and if they do not comply with the definition of medicinal products. EFSA discusses which type of botanical ingredients may be used and which health claims are allowed (Getman, 2011).

Several subtypes of food are legally defined, which are discussed hereafter.

2.2.1. Food supplements

Since Directive 2002/46/EC, food supplements have been harmonised in the EU. Food supplements are defined as: "foodstuffs with the purpose to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities". Food supplements thus contain substances with a nutritional or physiological effect such as nutrients (minerals and vitamins), essential fatty acids, amino acids and fibres. Specific rules are set up for vitamins and minerals and there is a positive list of vitamins and minerals that may be used in food supplements (Directive 2002/46/EC). For other substances than vitamins and minerals with a nutritional or physiological character, there is little harmonisation across the EU and national rules of the MS are applicable. Food supplements must meet Directive 2000/13/EC in which rules for food stuffs are described considering their labelling, presentation and advertising (Directive 2000/13/EC).

At the moment, no EU legislation for botanicals and derived preparations as food ingredients exists and therefore the general food law Regulation (EC) No. 178/2002 is applicable. These products must also comply with Regulation 1924/2006 on nutrition and health claims made on foods. Nothing is mentioned in the Regulation about the assessment of the safety of botanicals and botanical preparations in food. Therefore, the scientific committee of the EFSA issued a living document, "the Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements" (European Food Safety Authority, 2012). In the current list, *Anacyclus pyrethrum* is included, with *N*-alkylamides (for example pellitorine) indicated as chemicals of concern in the plant. On the other hand, a tincture of freshly harvested *Spilanthes oleracea* leaves is currently considered a botanical food supplement and is presented to alleviate thrush and nail infections.

2.2.2. Functional foods

There is currently no single legislative definition of 'functional foods'. First used in the 1980's in Japan, it means that this food can improve the health status of the body and decrease the risk of diseases. Products with a FOod for Specified Health Uses (FOSHU) symbol were seen in Japan as food where the function is superior to the taste. In contrast to Japan, in Europe, functional food is not considered as a separate food category, but it is more seen as a concept. The following definition of functional foods was given by the European Commission's Concerted Action on Functional Food Science in Europe (FuFoSE): "a food product can only be considered functional if together with the basic nutritional impact it has beneficial effects on one or more functions of the human organism, thus either improving the general and physical conditions or/and decreasing the risk of the evolution of diseases. The amount of intake and form of the functional food should be as it is normally expected for dietary purposes. Therefore, it could not be in the form of pill or capsule" (Siro et al., 2008). The USA-based Functional Food Center (Dallas, TX) suggested that a functional food definition should be harmonised and proposed a new definition: "natural or processed foods that contain known or unknown biologically-active compounds, which, in defined, effective non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management or treatment of chronic disease" (Martirosyan and Singh, 2015). Different types of functional foods have been defined: probiotics (live microorganisms if consumed in adequate numbers conferring a health benefit on the host), prebiotics (non-digestible food ingredients that beneficially affect the host by stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving host health), functional drinks, functional cereals, bakery products, spreads, functional meat and functional eggs (Siro et al., 2008). To regulate some aspects of functional foods, the general food law Regulation (EC) No. 178/2002 and Regulation (EC) No. 1924/2006 on nutrition and health claims made on foods are applicable (Regulation (EC) No 178/2002; Regulation (EC) No 1924/2006).

Products on the market must be safe and appropriately labeled and Regulation (EC) No. 1924/2006 came into force to harmonise rules between MS on the use of nutrition and health claims on foods. Prior to the authorisation of health claims on foods in the Community, EFSA carries out a scientific assessment. Different kind of claims can be used for functional foods: (1) nutrition claim, (2) health claim and (3) reduction of disease risk claim. A nutrient claim is defined as "any claim which states, suggests or implies that a food has particular beneficial nutritional properties due to (a) the energy (calorific value) it provides/provides at a reduced or increased rate/does not provide, and/or (b) the nutrients or other substance it contains/contains in reduced or

increased proportions/does not contain" (*e.g.* low energy, low sugar, fat-free), while a health claim means "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health" (*e.g.* helps maintaining acceptable cholesterol levels). A reduction of disease risk claim is defined as "any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease" (*e.g.* reduces cholesterol) (Regulation (EC) No 1924/2006). It is due to this Regulation that debatably, foods can have claims with the name of a disease in it. Only nutrition claims mentioned in Annex of the Regulation may be used and they must comply to the conditions of the Regulation. Foods with claims must also comply to Directive 90/496/EC considering general nutrition labelling for foodstuffs (Getman, 2011; Coppens, 2013; Council Directive of 24).

'Nutraceuticals' is another term frequently used which has no regulatory framework and is not considered as a specific food category (Coppens et al., 2006). The term nutraceutical is a combination of 'nutrition' and 'pharmaceutical'. It is often defined as a food or parts of food providing medical or health benefits, including the prevention and treatment of a disease (Corbo et al., 2014; Gulati and Ottaway, 2006). Nutraceuticals can be functional foods or food supplements (Bishop et al., 2015).

2.2.3. Novel foods

Foods and food ingredients belong to 'novel foods' if they have not been used to a significant degree for human consumption in the EU before 15 May 1997 (Regulation (EC) No. 258/97). Different categories of novel foods exist: "(1) foods and food ingredients with a new or intentionally modified primary molecular structure; (2) foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae; (3) foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use; (4) foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances" (Regulation (EC) No 258/97). The use of genetically modified organisms (GMOs) in food or feed is separately regulated by Regulation (EC) 1829/2003 (Regulation (EC) No 1829/2003).

2.2.4. PARNUTS foods

Foodstuffs for particular nutritional uses (PARNUTS, encompassing dietetic foods) are defined as "foodstuffs which, owing to their special composition or manufacturing process, are clearly distinguishable from foodstuffs for normal consumption, which are suitable for their claimed nutritional purpose and which are marketed in such a way as to indicate such suitability" (Regulation (EU) No 609/2013). 'Particular nutritional use' means that particular nutritional requirements must be fulfilled for infants or young children in good health, people with disturbed digestive processes or disturbed metabolism or people having special physiological conditions. These products are intended to be consumed by a small part of the population. They encompass not only infant formulae and follow-on formulae, baby foods for infants and young children, food intended for use in energy-restricted diets for weight reduction (Regulation 609/2013), but also dietary foods for special medical purposes (FSMPs, as described in Regulation 2016/128) (Regulation (EU) No 609/2013; Commission Delegated Regulation (EU) No 2016/128). In Commission Regulation (EC) No. 953/2009 of 13 October 2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses, a list of substances (vitamins, minerals, amino acids, carnitine and taurine, nucleotides, choline and inositol) allowed to be added for specific nutritional purposes in foodstuffs for particular nutritional uses, is described (Commission Regulation (EC) No 953/2009). For other substances which are not listed like botanicals and fatty acids, there are no harmonised EU rules and their use as PARNUTS food is considered at a national level (Gulati and Ottaway, 2006).

2.2.5. Fortified foods

A list of vitamins and minerals which may be added to foods are described and specific rules are given (Regulation (EC) No 1925/2006). There is a harmonisation between MS considering the addition of vitamins and minerals and of certain other substances. The rules in Regulation (EC) No. 1925/2006 for vitamins and minerals are not applicable for food supplements covered by Directive 2002/46/EC. This Regulation is applicable for foods for particular nutritional use, novel foods and novel foods ingredients, food additives and flavourings, genetically modified food and authorised oenological practices and processes.

2.2.6. Flavouring substances in food

Flavourings and food ingredients with flavouring properties must fulfill the criteria laid down in Regulation (EC) No. 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in foods and amending Council Regulation (EEC) No. 1604, Regulations (EC) No. 2232/96 and (EC) No. 110/2008 and Directive 2000/13/EC. Flavouring products are "not intended to be consumed as such, which are added to food in order to impart or modify odour and/or taste; made or consisting of the following categories: flavouring substances, flavouring preparations, thermal process flavourings, smoke flavourings, flavour precursors or other flavourings or mixtures thereof." However, this Regulation does not apply to "non-compound foods and mixtures such as, but not exclusively, fresh, dried or frozen spices and/or herbs, mixtures of tea and mixtures for infusion as such as long as they have not been used as food ingredients" (Regulation (EC) No 1334/2008).

2.3. Cosmetics

A cosmetic product is defined as "any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours" (Regulation (EC) No 1223/2009). A toothpaste containing NAAs from *Echinacea purpurea* for example thus belongs to this class of health products, next to the anti-aging products containing the *Spilanthes acmella* flower extract. In annex II of Directive 76/768/EEC, a list is summarised of substances prohibited in cosmetic products, while annex III contains a list of substances which may not be included in cosmetic products, except if they are subject to the restrictions mentioned in annex III (Council Directive of 27 July 1976). Commission Regulation (EU) No. 655/2013 is about common criteria for the justification of claims used in relation to cosmetic products (Commission Regulation (EU) No 655/2013).

A term frequently used in the cosmetic industry for marketing purposes is 'cosmeceuticals' and is a combination of 'cosmetics' and 'pharmaceuticals'. It bears no legally defined definition. These are cosmetics having medicinal product-like properties, but are not considered as a separate product class. Ingredients of these products can affect the biological skin function (Sharma, 2011). A product in the borderline section between food (nutrient), cosmetics and medicinal products can be classified as 'cosmenutraceuticals', which is again not legally defined. These are products intended to be placed in contact with the external parts of the human body or with the teeth and the mucous membranes of the oral cavity, providing systemic health benefits, including the prevention and treatment of a disease.

Table 1
NAA containing products on the market.

Trade name (Company)	NAA containing plant or NAA ingredients	Intended use	Product classification
Spilanthes drops (A. Vogel)	*Spilanthes*	Strengthens sensitive skin of the feet (after swimming)	n/a
Spilanthes paracress drops (A. Vogel)	*Spilanthes oleracea* plant and leaves tincture	For fungal skin infections	n/a
Herbal extract made with Aloha (Hawaiipharm)	*Acmella oleracea* extract	n/a	n/a
Fungus fighter liquid (Herb Pharm)	*Spilanthes acmella* flowers	Cleanse and detoxify	Food supplement
Indolphar gel	Spilanthol	Forms a protective film that softens the pain of ulcers and small mouth disease	Medical device
Buccaldol mouth gel	*Spilanthes*	Analgesic, prevents inflammation of mouth mucus membrane	Cosmetic
Anti-wrinkle serum (Dermaviduals)	*Acmella oleracea* extract	Anti-wrinkle	n/a
Dentaforce mouthwash (A. Vogel)	*Spilanthes acmella*	Freshens breath, supports oral hygiene	n/a
Carrot & cranberry radiance face cream (EE's cosmetics)	*Spilanthes acmella* flower extract	helps to restructure, firm and smooth the face	n/a
Organic pomegranate anti-wrinkle care night cream (Dr. Scheller)	*Spilanthes acmella* flower extract	A conditioning, anti-wrinkle product to use at night to stimulate cell renewal for firmer facial contours	n/a
Intensive smoothing serum enriched with *Para cress* extract (Organic surge)	*Spilanthes acmella* flower extract	Rejuvenate, condition, protect	n/a
Relax-o-Firm Mask (QMS medicosmetics)	*Acmella oleracea* extract	Helps minimize facial expression lines and fine wrinkles. Herbal oils calm irritated and stressed skin, leaving it smooth and supple. Plant extracts target dryness and expression lines with visibly improved long-term results.	n/a
Natural herb tea (Best tea online)	*Spilanthes acmella*	Malignancy, bronchitis, tonsillitis, acute appendicitis, hepatitis, urinary tract infection.	Food
Echinacea Plus tea (Traditional Medicinals)	*Echinacea purpurea* herb, *Echinacea purpurea* root dry extract	Supports the immune system	Food
Echinaforce drops (A. Vogel)	*Echinacea purpurea*	Use in case of insufficient resistance to colds and flu	Traditional herbal medicinal product
Echinaforce tablets (A. Vogel)	*Echinacea purpurea*	Use in case of insufficient resistance, flu, colds	Traditional herbal medicinal product
Echinaforce hot drink forte + elderberry syrup (A. Vogel)	*Echinacea purpurea*	Resistance, accelerates recovery after illness	Food supplement
Echinaforce chewable tablets forte + vit C (A. Vogel)	*Echinacea purpurea*	Resistance	Food supplement
Echinaforce lip balm (A. Vogel)	*Echinacea* concentrate	Nourishes and protects	n/a
Echinaforce cream (A. Vogel)	n/a	Supports healing ability of the skin	n/a
Echinacea bonbons (A. Vogel)	*Echinacea*	Refreshing and soothing for the throat	n/a
Echinacin juice (Madaus)	*Echinacea purpurea*	Herbal medicine for colds, immune activated	Medicinal product
Virumed (Pk Peters Krizman AG)	*Echinacea purpurea* radix	For the prevention and treatment of cold sores	Medical device
EchinaCold effervescent tablets (Schwabe)	*Echinacea purpurea* dried juice	Relief of symptoms of common cold and influenza type infections	Homeopathic medicine
Echinacea throat spray (A. Vogel)	*Echinacea purpurea*	Natural relief for the discomfort of the throat	n/a
Parodontax gel fluor + Echinacea toothpaste (Parodontax)	*Echinacea purpurea*	For a complete oral care. *Echinacea* increases resistance	Cosmetic
Thyme + *Echinacea* syrup (Unipharma)	*Echinacea* tincture	Beneficial land soothing for the throat	n/a
Echinacea angustifolia 1x tablets (Schwabe)	*Echinacea angustifolia*	Immune stimulant	Homeopathic medicine
Echinacea & Goldenseal root capsules (Now)	*Echinacea purpurea* extract, *Echinacea angustifolia* extract	Immune system support	Food supplement
Echinacea pallida flower & herb powder (Terravitta)	*Echinacea pallida*	To support colds and chills, coughs, infections, inflammations, sore throat and much more	Food supplement
Herbal Akarkara capsules (Evaidyaiji)	*Anacyclus pyrethrum*	Improves physical strength of a fellow, aphrodisiac, corrects the metabolism and helps in expelling the unnecessary fluids out of the body, strengthens the immune system	n/a
Natural herbal Akarkara powder (Evaidyaiji)	*Anacyclus pyrethrum*	Improves physical strength of a fellow, aphrodisiac, corrects the metabolism and helps in expelling the unnecessary fluids out of the body, strengthens the immune system	n/a
Battle Fuel XT capsules (Muscle Pharm)	*Anacyclus pyrethrum*	Increase in strength, muscle growth & greater muscle hardness. To support estrogen regulation and anabolic processes	Food supplement
Pellitory extract (Making Cosmetics)	*Anacyclus pyrethrum*	Astringent	n/a
Pellitory cream (Bianca Rosa)	*Anacyclus pyrethrum*	n/a	n/a
Pellitory powder (Terra Vita)	*Anacyclus pyrethrum*	n/a	Food supplement
Anabeta capsules (PES)	*Anacyclus pyrethrum* root extract	Muscle transformation agent	Food supplement
Yarrow environmental solution herbal supplement spray (Flower Essence Services)	*Achillea millefolium* tincture and flowers, *Echinacea purpurea* tincture and flowers	n/a	n/a
Yarrow Flowers capsules (Nature's Way)	*Achillea millefolium* flowers	Ancient curative	Food supplement
Yarrow Oil (*Achillea millefolium*) (Health Aid)	*Achillea millefolium*	Sweet spicy aroma. Anti-inflammatory or for colds and influenza	n/a
Musculus Liniment ointment (The Herbs)	*Achillea millefolium* extract, *Capsicum annuum* extract, *Echinacea, angustifolia* extract	Cooling for the skin around muscles	n/a
Achillea millefolium 5 ch (Boiron)	*Achillea millefolium*	n/a	Homeopathic medicine
Maca *Lepidium Meyenii* capsules (Sanar Naturals)	*Lepidium meyenii*	Energy boost, stamina enhancer	Food supplement

(*continued on next page*)

Table 1 (*continued*)

Trade name (Company)	NAA containing plant or NAA ingredients	Intended use	Product classification
Maca powder (*Lepidium Meyenii*) (Wilderness Poets)	*Lepidium meyenii*	Naturally sweet and malty. It is a potent, healing food. It is known to increase stamina, stimulate libido, regulate hormones, and increase mental focus.	n/a
Whole Root Maca (Herb Pharm)	*Lepidium meyenii* dried roots	System restoration, promotes libido, function and fertility	Food supplement
Pure Castor Oil (Dève herbes)	*Ricinus communis*	Skin care, hair care, purgative, anti-inflammatory, lactation, birth control, treats menstrual disorders, rheumatism, constipation, indigestion, cough, cold, used on burns, wounds	n/a
Trikatu capsules, three spices (Ayurvedic)	*Piper longum, Piper nigrum*	Stimulating to digestion, burns away toxins and fats, clears digestive and respiratory channels, warms the body	Food supplement
Cayenne, *Capsicum annuum* capsules (Nature's Answer)	*Capsicum annuum* fruits	n/a	Food supplement
PeaPure capsules (RScience)	Palmitoylethanolamide	n/a	Food supplement
Pea cream (RScience)	Palmitoylethanolamide	For sensitive skin	n/a

n/a: not available.

2.4. Medical devices

A medical device is “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means” (Council Directive 93/42/EEC). Some medical devices look like medicinal products or cosmetics. Examples of medical devices in this area are Kamillosan ocean nose spray (moistens and cleans the nasal cavity), Sensodyne Rapid toothpaste (rapid pain relief in case of sensitive teeth), Flamigel (to treat minor wounds), Bepanthen cream (against itching) and Angifyt Naturactive throat spray (softens and cleanses the throat). An example of an NAA containing medical device is Indolphar gel, which can be used to reduce the pain of ulcers and small mouth diseases.

2.5. Biocidal products

Currently, biocides are regulated by the biocidal product Regulation (EC) No. 528/2012. Seen the ethnopharmacological use and insecticidal pharmacological properties of NAAs, a classification as biocide would not be unexpected. A biocidal product is defined as “any substance or mixture, in the form in which it is supplied to the user, consisting of, containing or generating one or more active substances, with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action; any substance or mixture, generated from substances or mixtures which do not themselves fall under the first indent, to be used with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action”. Germs and pests are examples of such harmful organisms. Biocidal products include preservatives, disinfectants and pest control products. Product-type 18 and 19, insecticides and repellents, respectively, are both product types belonging to the pest control products (Regulation (EU) No 528/2012).

3. *N*-alkylamide containing products on the market

Currently, NAA containing products are abundantly available on the market. However, the composition and quality of these products are often not well defined or uncontrolled. NAA containing products are presented under different forms by different companies with different health-related claims: (anti-inflammatory) skin gel (*e.g.* Buccaldol by A.B.S, contains *i.a. Spilanthes*, analgesic and prevents inflammation of the mouth mucus membrane), cream (*e.g.* Pea by RScience, contains palmitoylethanolamide, for sensitive skin and based on nutrient and protecting ingredients), ointment (*e.g.* Musculus Liniment by The Herbs, contains *i.a. Achillea millefolium* extract, *Capsicum annuum* extract *and Echinacea angustifolia* extract, cooling for the skin around the muscles), invigorating capsules (*e.g.* Cayenne, *Capsicum annuum* by Nature's answer, contains *i.a.* fruits of *Capsicum annuum*), immune-supporting chewable tablets (*e.g.* Echinaforce chewable tablets forte + vit C by A. Vogel, contains *i.a. Echinacea purpurea*, supports immune system), powder (*e.g.* Natural herb powder by Evaidyaiji, contains *Anacyclus pyrethrum*, aphrodisiac and improves physical strength and supports the immune system), liquid (*e.g.* Dentaforce by A. Vogel, containing *i.a. Spilanthes oleracea* extract, supports oral hygiene and freshens breath), anti-infectious tincture (*e.g. Spilanthes paracress* drops by A. Vogel, contains *Spilanthes oleracea*), syrup (*e.g.* Thyme and *Echinacea* syrop by Unipharma, containing *i.a. Echinacea* tincture, beneficial and soothing for the throat), throat analgesic pastilles (*e.g. Echinacea* bonbons by A. Vogel, contains *i.a. Echinacea*, refreshing and soothing for the throat), effervescent tablets (*e.g.* EchinaCold by Schwabe, contains dried juice of *Echinacea purpurea* herb, relieves symptoms of a common cold and influenza), tea (*e.g.* Echinacea Plus® tea by Traditional Medicinals, contains *Echinacea purpurea* and *Echinacea angustifolia*, supports the immune system), toothpaste (*e.g.* Parodontax gel fluor + Echinacea by Paradontax, contains *i.a. Echinacea purpurea*, for a complete oral hygiene, *Echinacea* supports the immune system), soothing throat spray (*e.g. Echinacea* throat spray by A. Vogel, contains *i.a. Echinacea purpurea*, relieves discomfort of the throat) and lip balm (*e.g.* Echinaforce lip balm by A. Vogel, contains *i.a. Echinacea* concentrate, caring and protective). A non-exhaustive list of typical products is exemplified in Table 1.

The health-related claims of these products are very diverse, while no unambiguous and consistent product classification is applied. While some products explicitly claim the NAA (containing plant) as active ingredient, others present it as inactive excipient. They are sold as medicinal products (*e.g.* Echinacin liquid by Madaus, contains *i.a. Echinacea purpurea*, antiseptic properties in case of upper respiratory infections), food supplements (*e.g.* Anabeta by PES, containing *i.a. Anacyclus pyrethrum* DC root extract, muscle transformation agent), medical devices (*e.g.* Indolphar gel by I.D.Phar, contains *i.a.* spilanthol as aroma, reduces pain in case of mouth ulcers) or cosmetics (*e.g.*

Parodontax gel fluor + *Echinacea* by Paradontax).

4. Discussion of the classification OF *N*-alkylamide containing products

Each health-related product class has its benefits and disadvantages for the manufacturers on the one hand and the consumers/patients on the other hand, with the competent authorities as the go-between arbitrator protecting the society. Manufactures often want to avoid a medicinal product classification, as this requires the most stringent, time-consuming and expensive development and authorisation process. On the other hand, public health concerns ask for sufficient safety and information measures being installed before certain products are launched.

The classification decision falls within the competence of individual countries, and hence differences may exist for example among different Member States in Europe. In case of doubt, the Court of Justice of the European Union (CJEU) clarifies the interpretation of the different product classifications. In article 2 of Directive 2004/27/EC, amending Directive 2001/83/EC, it is also explicitly mentioned that in cases of a borderline product, which can be considered as a medicinal product but also as another product type, the medicinal product classification shall be applicable (Directive 2004/27/EC). Decisions must be taken for the whole product, taking into account all its characteristics and not for only one ingredient of it. The same ingredient can be used in *e.g.* food supplements as well as in medicinal products, depending on its use (Coppens, 2013).

Most *N*-alkylamide containing plants are marketed as a food supplement or cosmetic, and only very seldomly as a medicinal product. For the plants used in the medicinal products, community herbal monographs exist *i.e.* for *Echinacea purpurea* (L.) Moench, *Echinacea pallida* (Nutt.) Nutt., radix, *Echinacea angustifolia* DC., radix and *Achillea millefolium* L., herba (EMA/HMPC/577784/2008; EMA/HMPC/688216/2008; EMA/HMPC/290284/2009; EMEA/HMPC/332350/2008). Echinacin liquid is an example of such herbal medicinal product on the market. For the marketing authorisation of this product, it was possible for the applicant to rely on the community herbal monograph of *Echinacea purpurea* (L.) Moench, radix (EMA/HMPC/577784/2008). The therapeutic indication mentioned in the community herbal monographs of *Echinacea pallida* (Nutt.) Nutt. and *Echinacea angustifolia*, is the supportive treatment of a common cold, while *Achillea millefolium* is used for temporary loss of appetite, the symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating, and flatulence, the symptomatic treatment of minor spasm associated with menstrual periods and for the treatment of small superficial wounds (EMA/HMPC/688216/2008; EMA/HMPC/290284/2009; EMEA/HMPC/332350/2008).

4.1. Pharmacokinetic and pharmacodynamics interactions

Interactions with other drugs are increasingly becoming important due to *i.a.* polypharmacy in aging population (De Spiegeleer et al., 2016). Therefore, it is vital to consider the theoretically possible interactions from the mechanism of action and pursue further studies. Some studies have investigated the pharmacokinetic interactions of *Echinacea* preparations and other drugs (Ardjomand-Woelkart and Bauer, 2016). However, for other NAA containing products, no information is available. As an example, the well-known tingling effect of *N*-alkylamides is caused by blocking the two-pore potassium channels occurring in cells widespread over the body. The function of the two-pore potassium channels is to control the excitability of the cells by leaking potassium and these potassium channels are activated by some anesthetic drugs (Mathie and Veale, 2007). When two or more drugs are taken at the same time *e.g.* a product containing NAAs causing tingling effects and an anesthetic drug acting on the two-pore potassium channels, an interaction is theoretically not excluded, and its clinical relevance depends on dosing and pharmacokinetic considerations. Another example is related to the demonstrated interaction of NAAs with the endocannabinoid system. NAAs have shown to inhibit fatty acid amide hydrolase (FAAH), thereby enhancing levels of the endogenous cannabinoid (CB) receptor agonist anandamide. It has been demonstrated that FAAH inhibitors may impair the working memory in rats (Panlilio et al., 2016). Hence, as FAAH inhibitors influence some regions in the brain, it is not without any risk to take such substances. However, more human derived data are needed to evaluate the clinical relevance of the information obtained from *in vitro* and animal studies.

4.2. Regulation of N-alkylamides as food supplements or medicinal products

Besides the possibility to regulate NAA or acylethanolamide (*e.g.* PEA) containing products as medicinal products, they can also be registered as food supplements, governed by the food law. Currently, the list of the EU Register on nutrition and health claims includes no *N*-alkylamides or NAA-containing products. Food supplements have physiological and nutritional effects with the function to maintain health, while medicinal products exert pharmacological, immunological or metabolic properties with the purpose to treat or prevent a disease (Directive 2001/83/EC; Directive 2002/46/EC). The borderline between a medicinal product and a food supplement is sometimes subject to interpretation, confounded by the fact that the form of a food supplement closely resembles that of medicinal products, for example capsules, tablets or powder sachets. To comply with the definition of a food supplement, the nutrients or 'other substances' must have only a nutritional or physiological effect. While NAAs and PEA refer to 'other substances' in the food supplement definition, it has been demonstrated that these NAAs and PEA possess several pharmacological effects with different molecular targets already described. Even when a product is not presented as a medicinal product (presentation criterion), their mechanism of action applies to the second part of the definition of a medicinal product (functionality criterion), which is confirmed by the community herbal monographs of *Echinacea* species and *Achillea millefolium*, plants consisting of mixtures of NAAs. Often, a product is considered as a medicine if they potentially have an effect on the human body and affect the metabolism. However, this part of the definition alone cannot be the only reason to classify a product as a medicinal product. It is also important to consider the dose of the active substance(s). If the dose is below the dose able to restore, correct or modify a physiological function as established by the current state of scientific knowledge, then it is not a medicinal product. This has been elaborated/explicated by CJEU judgments: the argument that there is a human health risk at a lower (but sub-therapeutic) dose is on itself not sufficient to consider a product as a medicine; hence remaining its status as a food supplement (Case C-27/08, 2009). Furthermore, the claims and presentation of the products are also important to take into account for classification issues. Products resembling medicinal products as well as food supplements are often named nutraceuticals, although this is not a legally defined term. Besides food supplements, it should also be possible to consider NAA containing plants as functional foods, since these plants contain bioactive NAAs and have already shown beneficial effects on human body; they are able to reduce the risk of the evolution of a disease as well (Boonen et al., 2012). To present substances as functional food, it is important that the appearance of the product looks like 'normal food' and not in the form of capsules or pills (Siro et al., 2008). Although no NAA plant is currently included in the EU register on nutrition and health claims, this may change in the future (European Commission).

4.3. Regulation of N-alkylamides as a medical device

The classification of products containing NAAs as a medical device should also be questioned. In some countries, medical devices which have the appearance of a medicinal product, are sold in selected

distribution channels like the pharmacy (Art. 10bis (Attachment XIII)). Although medical devices may closely resemble medicinal products ('borderline products'), there is a difference between the two product classes (Manual on borderline and classification in the Community Regulatory framework for medical devices). The principal intended action of a medical device is obtained by physical means. For example, Virumed is a medical device as its main action is to block the UV rays, hence eliminating one of the factors eliciting cold sore caused by active Herpes simplex virus. The other components like *Echinacea purpurea* extract only assists in the functionality of the product by supporting the resistance (Virumed and medical device, 2016). Medical devices may thus contain medicinal substances having an ancillary action. The pharmacological action of these ancillary medicinal substances are subordinate to the physical action of the medical device (European Commission and DG Enterprise, 2001). Some of these medical devices are clearly very close to medicinal products.

4.4. Regulation of N-alkylamides as cosmetics

There are also NAA containing products on the market as cosmetics. Often, cosmetic products are closely related to medicinal products and borderline issues are judged by the European Court. An example of such 'cosmeceutical' issue was the discussion about the meaning of 'pharmacological action' in the definition of a medicinal product of Directive 2001/83/EC (Directive 2001/83/EC). The European Court decided that the definition explained in the Guidance Document on the demarcation between cosmetic products and medicinal products (Guidance document on the demarcation between the cosmetic products Directive 76/768 and the medicinal products Directive 2001/83) can be used, which states that for a medicinal product, there must be "an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response or blocks the response of another agent". Furthermore, the Court ruled that the 'cellular constituent' in the definition does not mean cellular constituents of the user's body, but it can also be cellular constituents of *e.g.* bacteria present in human body (Case C-308/11, 2012). From the pharmacological effects of NAAs described previously, the interaction between NAAs and cellular constituents is beyond any doubt. The classification of NAA containing products as cosmetics can be similarly treated. Studies have shown that the *N*-alkylamides spilanthol and pellitorine, after topical administration were able to penetrate the different cell layers (stratum corneum and viable cell layers) and reach the systemic blood circulation. These compounds then exert a pharmacological effect, *i.e.* they interact with cells. As previously listed in Table 1, there are products on the market containing *Spilanthes acmella* (contains spilanthol) and *Anacyclus pyrethrum* (contains pellitorine) in the form of a cream or gel. This raises the question if such products, marketed as cosmetics, still can be considered as such, because when topically applied, the viable cells in the skin and the blood circulation below these cells are clearly reached, resulting in a systemic exposure with rapid tissue distribution. Depending on the amount that reaches the blood and the corresponding pharmacological effect, classification of such borderline products, informally called cosme(nutra)ceuticals, should be reconsidered.

In conclusion, from their pharmacokinetic properties, *i.e.* absorbed in the systemic circulation and distributed, combined with their pharmacological activities, *i.e.* different molecular targets have been identified, the NAAs and their originating plant materials plausibly show beneficial health effects, supported by the ethnopharmacodynamic use, but also possess inherent risks (side effects, overdose, interactions, contraindications). Therefore, their use, and its related dose-rate, influencing the biological positive as well as negative functionalities, is a critical determinant for their legal-regulatory classification.

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Appendix A. Supplementary data

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