Analysis of the current vitamin A terminology and dietary regulations from vitamin A_1 to vitamin A_5

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Abstract: Dietary recommendations on vitamin intake for human food fortification concerning vitamin A in various countries, larger economic zones and international organizations are mainly based on the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) "Codex Alimentarius standards". The general vitamin A terminology is based on regulations of the International Union of Pure and Applied Chemistry (IUPAC) that are used to describe the involved derivatives. These regulations and terminology were set up in the middle of the last century. Starting with the decade of the 80ies in the 20th century a large improvement of molecular biological methodologies, background physiological mechanisms as well as analytical techniques contributed to a large diversification of this simply claimed vitamin A terminology. Unfortunately, the following terminology and governmental regulations for food fortification are imprecise and non-harmonized. In this article we tried to unravel this terminology for updating terminology, nutritional suggestions and governmental regulations for vitamin A, which are currently based on various uncertainties. According to the current regulations, the newly found vitamin A_5/X can be included in the current vitamin A terminology as "vitamin A_5" or alternatively or even in parallel as a new vitamin A-independent terminology as "vitamin X". Based on the detailed knowledge of research from the early beginning of general vitamin A pathway identification towards detailed research of the last decades the commonly used and simplified term vitamin A with relevance for governmental recommendations on vitamin intake and food fortification advice was now more correctly sub-categorized to further vitamin A_1, and A_5 sub-categories with vitamin A_1-alcohol as retinol, vitamin A_2-alcohol as 3,4-didehydroretinol and vitamin A_5-alcohol as 9-*cis*-13,14-dihydroretinol as their mainly relevant vitamin forms present in the human organism. Here we suggest and advise how the vitamin A terminology and further governmental regulations should be organized depending on a successful unraveling of the organization of the current vitamin A terminology.

Keywords: dietary recommendations, retinol, retinoic acid, beta-carotene, provitamin A

Introduction

Recommendations for essential micronutrients are suggested by local and international governmental organizations. Based on suggestions from nutrition experts and public health science experts, clear and precise recommendations are not always possible and vary from country to country and depend on individual sub-populations. The research field for suggesting nutritional recommendations is complex and still ongoing with active research highlighting various aspects [1, 2, 3]. Currently, different national and international health organizations therefore have recommendations which slightly differ [1, 2, 3].

Here we focus on vitamin A, where a novel study points out, that a new vitamin A subcategory or an independent new vitamin was found, while not fitting perfectly to the current regulations and categorization. We summarize what vitamin A is, based on international organizations' point of view, as well as, based on a novel updated comprehensive science-based summary.

The term vitamin A is addressed – in addition to other vitamins – in the "Codex Alimentarius" [4, 5] and the mentioned dietary recommendations for each vitamin are only relevant for humans. The term "vitamin" describes essential micronutrients in the organism and is also co-used for non-standardized relevance in other species for speculated essential micronutrients and vitamin-like acting derivatives. Various national, international organizations take "Codex" standards, as an international basis for adapting safety and governmental based regulatory advices for food content, food fortification and dietary supplements with a focus on vitamins [4] including continuous updates [5].

For the addressed lay audience "old-fashioned" print journals focusing on the elderly population with a "general"-, "health"- and "women"-focus as well as for the younger population websites, like the most popular knowledge source encyclopedia website "wikipedia" and personalized web 2.0 blogs and channels further focus on the dissemination of these regulatory recommendations. This information is mainly based on dissemination of regulatory

advice by recommendation suggested by expert consortia for dietary references values and safety issues from competent national and international organizations like the European Food and Safety Authority (EFSA) in Europe [6, 7], the National Academies of Science, Engineering and Medicine [8], the Food and Drug Administration (FDA) in the USA [9] or on the international level the World Health Organization (WHO) [10].

This omnipresent information about vitamins, and here especially about vitamin A, are unfortunately based on lack of knowledge and uncertainties which are addressed and summarized in this article. To start improving and optimizing this information on vitamin A, firstly a focus on a commonly adapted and unique terminology should be discussed which should be the basis for a clear and transparent international regulatory situation for vitamin A safety and healthy nutritional recommendations.

The general current terminology of vitamin A/provitamin A

The "Codex Alimentarius" [4, 5] mentions just three substances: retinol as vitamin A, β-carotene as provitamin A and other alternative provitamin A carotenoids (Figure 1A). This current status unfortunately leaves many questions open, which are partially addressed in the IUPAC nomenclature of retinoids [11].

The vitamin A terminology

All starts with the *first uncertainty*: The term vitamin A is generally used, while the well-known subforms like vitamin A_1 and A_2 (Figure 1B) were not used, as such, in addition to the new form of vitamin A_5 [12]. Recently the subforms vitamin A_3 and A_4 were introduced [13], while these forms have no human relevance. The definition of a vitamin and its dietary recommendations are exclusively addressing humans and these two subforms have thereby no relevance for human intake recommendations. To avoid a further confusing overlap in terminology with these two subforms (Figure 1B) we named our new vitamin sub-category; vitamin A_5 [14].

It seems that vitamin A_2 [15, 16] and in consequence the term vitamin A_1 were skipped because likely the research focused exclusively on vitamin A_1. Two explanations for that imprecise, uncertain and confusing situation were possible: A) For simplification of regulatory purposes the term vitamin A was set equal with the used term vitamin A_1 or, B) because of less nutritional research on vitamin A_2, a non-obvious and a rather not completely examined nutritional relevance was seen and just the general term "vitamin A" was used compromising the further options for diversification into vitamin A_1 and A_2. Unfortunately, vitamin A_2 research is very limited, with a general share of 0.2% of vitamin A publications. 141 total publications and 21 publications were found in the PubMed database, when adding the additional term "nutrition" between 2000 and 2023 (status August 2023). For vitamin $A_{(1)}$ we found ∼61.000 publications and ∼11.400 with the additional term "nutrition" in the same time frame (results from a PubMed search performed at the same day).

The *second uncertainty*, is that in general the term "vitamin A" is mostly equally used with term "retinol" [17]. This is not precise and also not correct. Due to the general definition of a vitamin, the term "vitamin A" describes all compounds which can reverse a "vitamin A" deficiency [6, 17]. This would mean in consequence just retinol, retinyl esters, provitamin A carotenoids and retinal belong to the group of vitamin A (Figure 1C) [18, 19, 20, 21, 22].

The *third uncertainty*, what do the terms retinol, retinyl esters and retinal mean precisely (Figures 1C and 1D)? Here again a simplification was used. Since the last decades, when using better scientific methodologies and especially better analytical methodologies, difficulties in interpretation arise. Taken the example of retinol, it must be stated, that if A) this terminology includes the α- and/or β-configuration [11] and, if B) total retinol as a sum of a larger array of retinol isomers ranging from the major occurring all-*trans*-isomer to further 13-*cis*-, 11-*cis*-, 9-*cis*- and further single isomeric retinol isomers, as well as double-isomeric structures like 9,13-di*cis*-retinol (Figure 1D) are included [1]. For retinol, focusing on retinol isomers some publications already exist [23, 24, 25], while the large array of scientific studies did not address the structural modifications which fall also under the general "retinol" configuration.

Focusing on retinyl-esters the current information on different esters and isomers is relatively scare [26, 27]. Further research was mainly focusing on eye related topics with relevance for molecular biological focus on disease states in vision [28, 29, 30, 31]. For retinal which has in our view no or a very minor nutritional relevance we did not focus on vision-related research in retinal isomer identification [24, 28, 32, 33, 34]. As known the retinal isomerization is generally seen highly important for the visual process while the eye tissue from livestock animals in general have no nutritional relevance as the eye tissue of livestock is not used for further processing to human food products.

The provitamin A terminology

An even more complicated topic is the provitamin A topic. Here again even more and further simplifications were

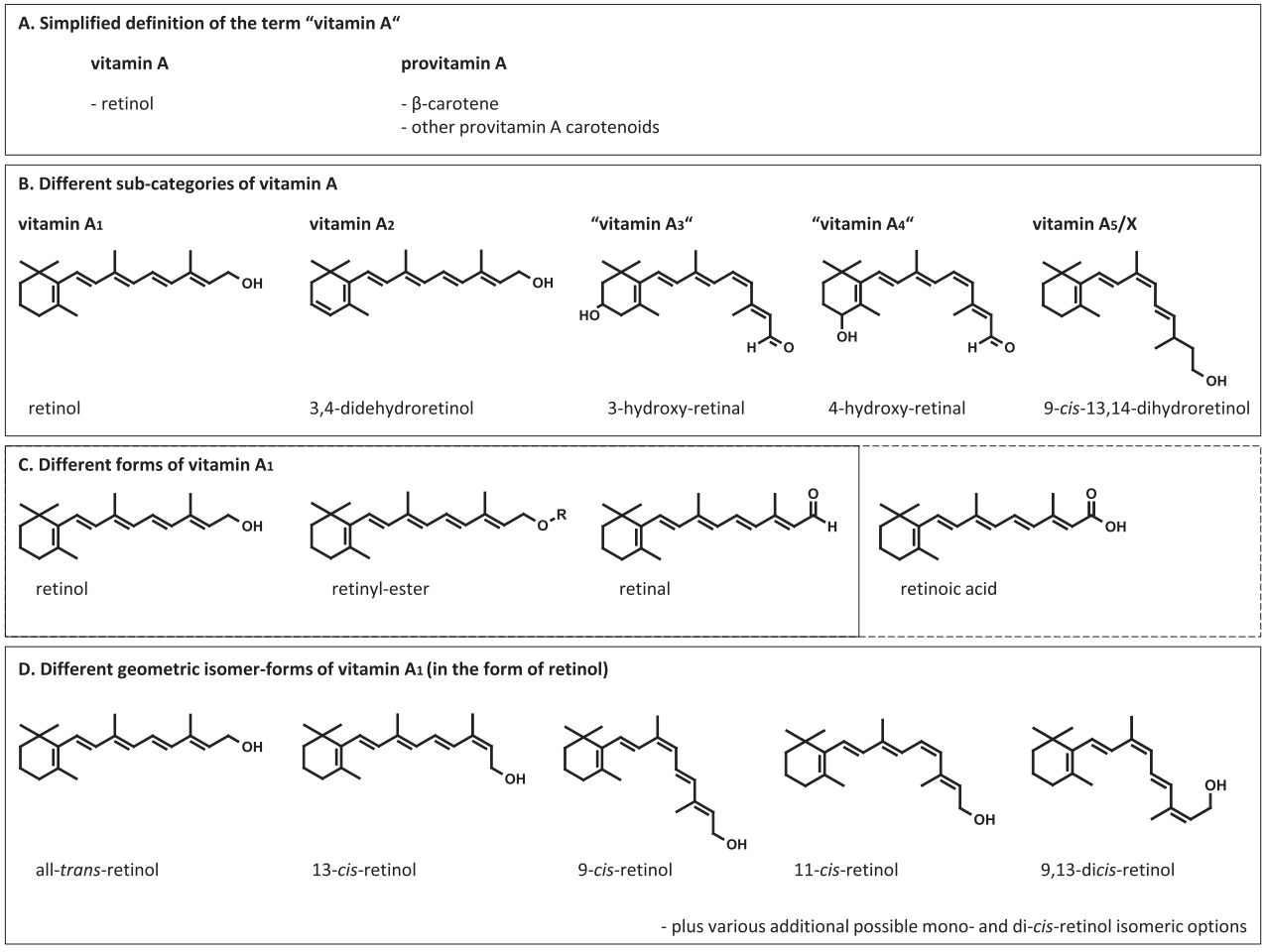

Figure 1. A) The simplified vitamin A terminology by currently used international organizations; B) Summary of structural formulas from different sub-categories of vitamin A ranging from vitamin A1, A2, "A3", "A4" to A_5; C) Summary of different forms of vitamin A1 separating retinoic acid which is associated but not part of the vitamin A_1 family; D) Summary of different geometric isomer-forms of vitamin A1-alcohol/retinol.

applied. The term provitamin A was mainly used equal with the term β-carotene.

The *first uncertainty*, provitamin A is a larger array of compounds starting with a sub-diversification into provitamin A_1 and provitamin A_2 (Figure 2). Provitamin A_2 is described as anhydrolutein/all-*trans*-3'-hydroxy-3,4-didehydro-β,β-carotene [35, 36], which is a precursor for 3,4-didehydroretinol, also called vitamin A_2-alcohol [15, 16], and further vitamin A_2 derivatives such as 3,4-didehydroretinal and 3,4-didehydroretinoic acid. The human relevance of provitamin A_2 is still questionable.

Provitamin A_1 comprises "β-carotene", which is again an imprecise term and is sub-diverted into β,β-carotene (simplified to β-carotene), α,β-carotene (simplified as α-carotene) and γ,β-carotene (simplified as γ-carotene) (Figure 2) [20, 37, 38, 39].

The *second uncertainty* "provitamin A" also includes β,β-carotene, α,β-carotene and γ,β-carotene geometric isomers like the known ones such as all-*trans*-, 13-*cis*-, 11-*cis*-, 9-*cis*- and various minor geometric isomers (Figure 2) [40]. It is to mention that from the "α,β-carotene" no geometric isomers are known while this is likely due to non-existing analytical standards and non-performed analytical determination in human organs and the human food matrices.

The *third uncertainty* regarding the provitamin A terminology is, that other carotenoids also belong to this group, which have a one sided vitamin A_1-acid precursor function like β-cryptoxanthin. This β-cryptoxanthin is the orange color of many fruits and with a large nutritional impact because it is present in oranges and orange juice (reviewed in [20]) which are preferably consumed daily in western diet and thereby contributing effectively in the achievement of recommended dietary allowance (RDA) of vitamin A.

In addition, there are apo-carotenoids of various chain lengths present in the human food matrix (reviewed in [20]). The nutritional relevance of apo-carotenoids is not well examined and restricted to moderate concentrations of apo-8′-carotenal in fruits (mainly oranges), vegetables

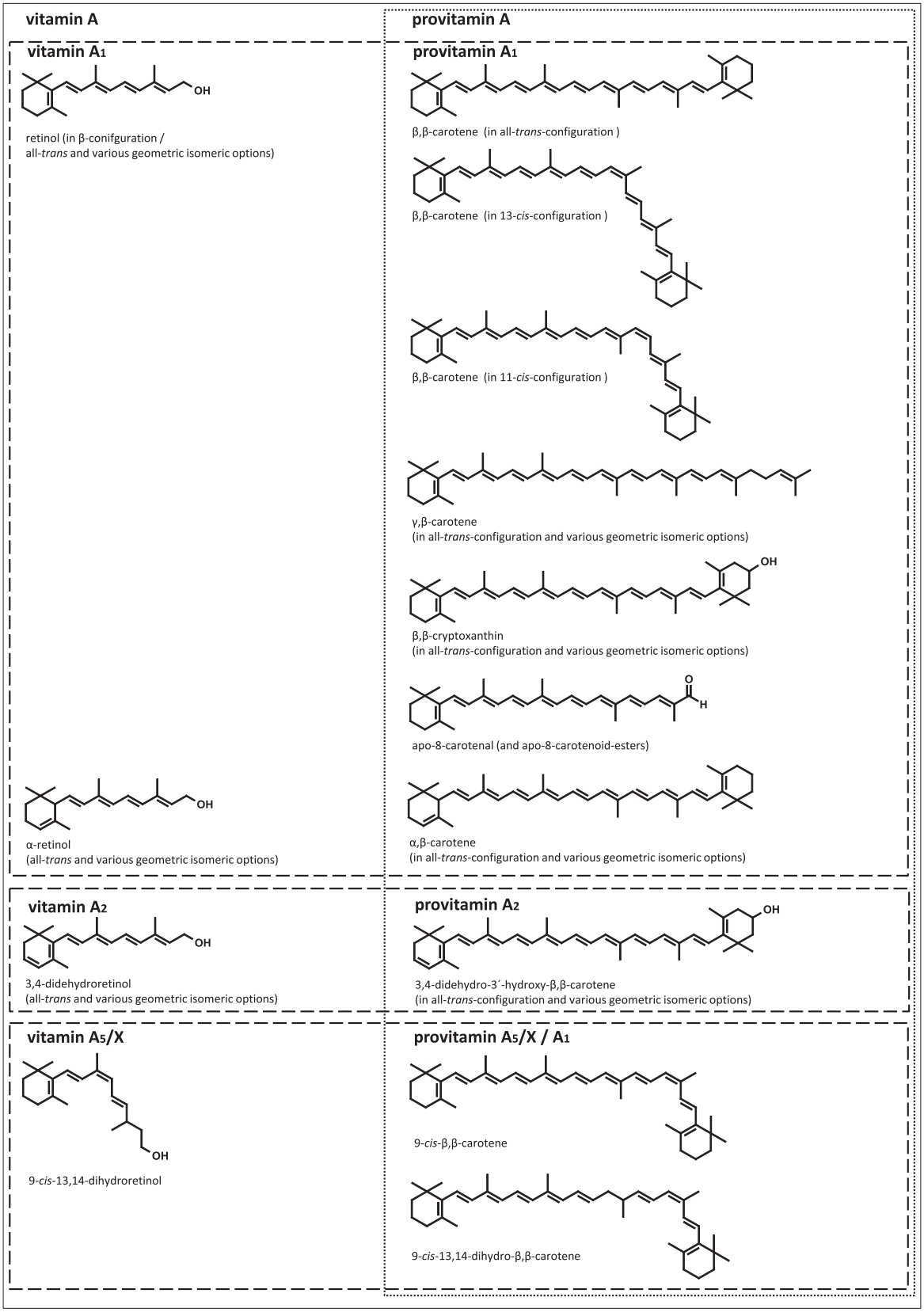

Figure 2. The complete vitamin A terminology based and subordinated currently described terminology including the novel identified vitamin A_5-sub-category. The vitamin A family is indicated by a surrounding by a slim box, Vitamin A_1, A_2 and A_5 sub-categories are indicated by a surrounding dashed line box and provitamin A is indicated by a surrounding dotted line box.

[41] and the human organism [42]. Of major human relevance are apo-8′-carotenal/E160e (likely mainly in the all-*trans* form) and apo-8′-carotenoic acid–ethyl ester (apo-8′-carotenoate)/E160f [43, 44]. These apo-carotenoids are mainly used as a food colorants for orange/yellowish coloration for livestock animals like poultry (mainly chicken) targeting a "consumer preferred" coloration of poultry meat (mainly chicken) as well as a deeper yellow orange color of egg yolk. This animal feed fortification is of strong indirect human relevance and these apo-carotenoids function represent additional provitamin A derivatives present in the human nutrition (Figure 2) [45, 46].

The vitamin A_5/X terminology

The newly introduced vitamin A_5 cluster is now in a partial overlap with the current provitamin A terminology. The direct precursor is the 9-*cis*-13,14-dihydro-β,β-carotene, which is just present in very minor amounts, identified in canned peach, while its standard derivatives used for analytical determination is just stable at temperatures of −20 °C [9]. The nutritional relevant precursor of the active vitamin A_5-acid, 9-*cis*-13,14-dihydroretinoic acid, was determined as 9-*cis*-β,β-carotene (9CBC), a derivative including an all-*trans*-side as well as a 9-*cis*-side, which can be cleaved by carotenoid oxygenases to active vitamin A_1- and to an active vitamin A_5-derivative [12, 14, 47]. This means that 9CBC can serve as a double precursor provitamin A carotenoid for both vitamin A (A_1 and A_5) pathways. This further means that 9CBC is the only provitamin A with a provitamin A_1 and provitamin A_5 precursor potential (Figures 2 and 3) [12, 14].

The problem of these current existing terminologies

The consequences of this imprecise and uncertain regulatory terminology is that likely a larger array of people with diverse functions and education worked on this topic and the simplification and uncertainty strategies were further manifested resulting now in a slightly confusing regulatory situation. A clarification and sub-categorization of this uncertain situation is now very difficult. A novel precise and updated terminology should be introduced and applied leaving out the summarized uncertain terms which were commonly misused. Updating the commonly used terminology will likely result in a highly confusing novel regulatory situation with an overlapping partly parallel usage of an imprecise "old" and a novel "precise" terminology. To remember, the current vitamin A definition was also used after chemical and mechanistic identification of "retinol" and "β-carotene", while "vitamin A" compounds were initially described as "fat soluble factor A", summarized in [11].

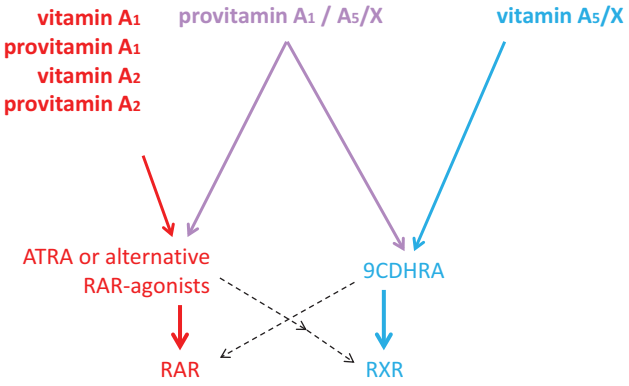

Figure 3. Mechanisms of action of vitamin A with the retinoic acid receptor (RAR)-pathways indicated in red color, the retinoid X receptor (RXR)-pathway indicated in blue color and the mixed RAR-/RXR-pathways indicated in purple color. Used abbreviations: All-*trans*-retinoic acid – ATRA, 9-*cis*-13,14-dihydroretinoic acid (9CDHRA).

Comparative terminology situation for other vitamins

For examples of vitamin B and vitamin D we summarize how a sub-categorization is organized depending on different criteria. This will also help to judge and apply such a sub-categorization for vitamin A with regard to the newly identified vitamin A_5 category. We have tried to compare these definitions with the current and future suggested situation for a comprehensive vitamin A terminology, further dietary suggestions and governmental regulations.

The vitamin D terminology

The term "vitamin D" is commonly used, while also here various sub-forms/analogues co-exist. In the popular knowledge many non-scientific backed-up information are summarized. The best example is the popular online encyclopedia website wikipedia (https://en.wikipedia.org/wiki/Vitamin_D/August 2023) where the questionable terms "vitamin D_1, D_2, D_3, D_4 and D_5" were listed, while it is not clear, if such terminology is backed by peer review based scientific references and review articles [48].

Preferably, an exclusive focus is put on the clearly described nutritional relevant derivatives of vitamin D_2 and vitamin D_3. While vitamin D_2 and vitamin D_3 describe similar substances present in different food matrices their main active metabolites were described as 1,25-dihydroxy-vitamin D_2 and 1,25-dihydroxy-vitamin D_3 [49], which both activate the nuclear hormone receptor the vitamin D receptor (VDR) transmitting the major know VDR-mediated effects [50].

Some studies focused on the nutrition – towards biological signalling effects and found parallel pathways for these

two slightly different substances. For regulatory purposes just the term "vitamin D" is used while vitamin D_2 and vitamin D_3 might be equally used and the added "2" and "3" could be used depending on what is added and addressed [48, 49].

The vitamin B terminology

"Vitamin B" is a cluster of very diverse substances which have one thing in common; they act as cofactors for enzymatic proteins to enable their activity. Here the different names like vitamin B_1 (thiamin), vitamin B_2 (riboflavin), vitamin B_3 (niacin, nicotinamide, nicotinamide riboside), vitamin B_5 (pantothenic acid), vitamin B_6 (pyridoxine, pyridoxal, pyridoxamine), vitamin B_7 (biotin), vitamin B_9 (folic acid, folate) and vitamin B_{12} (various cobalamins) describe substances with a very different distribution in the food matrix, a different function as a co-factor for specific proteins and a different nutri-kinetics in the human organism. It is clear, that likely also uncertainties are hidden in the vitamin B field, which are not addressed here and therefore mainly simplified terms were used in this review article.

Summary of used terminology and following regulatory pathways used for other vitamins with an example for vitamin B and D

For vitamin B different vitamin B sub-categories exist which address different derivatives with different functions and different nutritional origins while, for vitamin D different sub-categories exist which have a slightly different structure but are metabolized and transferring their biological mechanisms via exactly the same pathways.

In summary, the major term vitamin D is used while two parallel pathways exist with vitamin D_2 originating from the plant derived food matrix and vitamin D_3 originating from animal derived food matrix (summarized in [17]). Both have the same target mechanism of action, the activation of the vitamin D receptor (VDR). Just the one term "vitamin D" is addressed in nutrient regulation while both terms "vitamin D_2" and "vitamin D_3" are used in nutrient claim labelling. In general food labelling only the term "vitamin D" is used for a general nutrient regulation and for the specific nutrient content claims.

Furthermore, each B-vitamin obtains a unique nutrient regulation including a specific nutrient claim labelling and nutrient content claim labelling for food products [17].

Summary, conclusions and consequences with a focus on optimized terminology for vitamin A

Comparable situations like for vitamins B and D with the used and proposed optimized vitamin A terminology are comparable to the newly identified vitamin A_5 category. The term "vitamin A_5" includes a cluster of substances which are physiologically- and nutritionally-relevant precursors of 9CDHRA which is seen as the only physiologically relevant ligand of the retinoid X receptors (RXRs), while vitamin A_1 and A_2 are seen as precursors for ATRA, all-*trans*-3,4-didehydroretinoic acid or alternative endogenous RAR-agonists of the retinoic acid receptors (RARs), summarized in Figure 3. Similar to the vitamin B group different derivatives are acting via a comparable mechanistic principle comparable to our vitamin A case, the activation of different nuclear hormone receptors the RARs and RXRs. In opposite, these "different" derivatives included under the vitamin A terminology are also comparable to the vitamin D cluster: Similar substances which cannot be inter-converted but are structurally related and are slightly differently distributed in the human food matrix but both transmit the same biological activity via activation of one mechanistic pathway, the activation of the nuclear hormone receptor, VDR.

More complex, even overlaps exist between the vitamin A_5 and vitamin A_1 pathways as A) 9CBC is seen as a double precursor provitamin and B) that the active vitamin A derivative ATRA and nutritional relevant RAR-ligand might be metabolized to 9-*cis*-retinoic acid (9CRA), which can activate the RXR [51, 52, 53, 54, 55]. The physiological and nutritional relevance of this isomer-activation pathway via 9CRA is seen critical and is discussed diverse [12, 14, 56, 57]. In addition, the active vitamin A_5 metabolite 9CDHRA serves as the physiological and nutritional relevant RXR ligand, while it can also activate the RAR and interacts here with the vitamin A_1-RAR-signalling pathway [14, 55].

Conclusions and suggestions

What does this mean in consequence for the novel claimed term "vitamin A_5" and the vitamin A_5 concept? Does it fall under the category "vitamin A" as a sub-category? It could be concluded, yes, but under the consideration, that such sub-categorization of vitamin A_5 will be followed by using the general and precise vitamin A terminology as outlined. The currently used terminology setting in the vitamin A field is still largely imprecise and should be made precise and unique especially focusing on skipping wrongly misused terminologies like setting vitamin A_1 equal with "vitamin A". It is recommended to national and international governmental authorities to commonly optimize and starting to unravel this uncertain and imprecise vitamin A terminology, setting up and aiming a clear and precise regulatory background for vitamin A labelling, health impact and for food fortification.

For the current nutrient claim with relevance for humans, it is suggested to put "vitamin A_5" under the umbrella of

general "vitamin A". For the nutrient content claims just provitamin A_5, representing also provitamin A_1, can be added partly to the general "vitamin A" nutrient content claim. Due to a different mechanism in creating a different ligand for a nuclear hormone receptor, like for B-vitamins, vitamin A_5 and provitamin A_5 both may need a separate nutrient content claim and likely also a separated nutrient claim. Unfortunately, it will be difficult to change the whole vitamin A regulatory and terminology quickly and it will very likely result, currently and later, in a mixed up situation with general vitamin A and it's non-precisely and uncertain regulated nutrient content and nutrient content claim.

As an alternative strategy – till the "vitamin A" definition is completely clarified –, a new category should be created, without "A". Here, because of the novel R"X"R activation potential of the equal "vitamin A_5" term, we co-established and suggested an alternative, preliminary new term "vitamin X" to be adopted and used, like summarized in Figure 3.

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Conflict of interest
Dr. Ralph Rühl is CEO and shareholder of CISCAREX.

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