Food and Chemical Toxicology 131 (2019) 110549

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Aggregate exposure modelling of vitamin A from cosmetic products, diet and food supplements

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ARTICLE INFO

Keywords:
Aggregate exposure
Retinol equivalents
Retinoic acid
Cosmetics
Consumer products
Food
Vitamin A

ABSTRACT

Realism is important in estimating consumer exposure to a substance, especially when accounting for exposure from multiple sources. Humans are exposed to vitamin A from food, dietary supplements and cosmetics products. A probabilistic aggregate exposure model was developed for estimating exposure distributions to vitamin A (as retinol equivalents) in pre-/post-menopausal, and menopausal women in European and US populations. Data from large dietary surveys were used, together with realistic and extreme case scenarios of cosmetics product use (including occurrence data for vitamin A presence in 17 cosmetic products). Results of absorbed exposure estimates were expressed as μg/kg bw/day by incorporating dermal and oral bioavailability data. The mean and 95th percentile (P95) aggregate exposures were below the EU Tolerable Upper Intake Limit (3000 μg/day; 45 μg/kg/day internal exposure dose (IED)), providing positive assurances of safety. The major source of vitamin A exposure is the diet, with cosmetics providing only a small fraction of total exposure (2–5% at P95). In addition to providing a realistic assessment of total vitamin A exposure, this work provides a case study on how to approach future complex aggregate exposure questions.

1. Introduction

Quantitative toxicological risk assessment depends upon reliable and realistic estimates of chemical exposure. In situations where people are exposed to the same substance from multiple sources, it is useful to derive an estimate of aggregate exposure from all relevant sources, in so far as the estimate is representative of real-life exposure. For example, in this study, consumers can in principle be exposed to vitamin A as present in different types of cosmetic products as well as in foods and dietary supplements. Historically, aggregate exposure calculations either have not been performed, due to a lack of data or approach, or a deterministic additive worst-case calculation has been performed, which can lead to a gross overestimation of real life exposure. In the EU, the Scientific Committee for Consumer Safety (SCCS) recommend in their 10th revision of the 'Notes of Guidance for the Testing of Cosmetics and their Safety Evaluation' (SCCS, 2018) that aggregate exposure "needs to be calculated in the case where several product categories contribute". The suggested method of calculating aggregate exposure in the first instance (first tier) by SCCS (2018) incorporates a simple deterministic approach adding together the maximum level of substance from 17 individual cosmetic product types in which the chemical might be present. Such methods assume that everybody in the population uses all the products containing the substance every day, and as such this grossly overestimates what happens in real life. To achieve a more realistic estimate of aggregate exposure, a tiered approach has been recommended that starts with the simple deterministic approach and evolves to a more complex person-oriented probabilistic approach (Delmaar and van Engelen., 2006; Meek et al., 2011; ECETOC, 2016; SCCS, 2018). Such probabilistic approaches have begun to be developed and proposed for a number of substances: parabens (Cowan-Ellsberry and Robinson, 2009; Gosens et al., 2013), diethylphthalate (Delmaar et al., 2014), cyclic siloxane D5 (Dudzina et al., 2015) and zinc pyrithione (Tozer et al., 2015). Here, we build on this work and present estimates of exposure from a probabilistic aggregate exposure model for vitamin A that takes into account both dietary and cosmetic/personal care product sources.

Vitamin A is a generic term for a family of organic lipid-soluble substances related metabolically to all-*trans*-retinol (Vitamin A_1) e.g.

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https://doi.org/10.1016/j.fct.2019.05.057
Received 2 January 2019; Received in revised form 14 May 2019; Accepted 30 May 2019
Available online 31 May 2019

retinal, retinoic acid and several provitamin A carotenoids (see Fig. 1). In foods of animal origin, the major source of vitamin A is primarily as retinyl palmitate, which is a retinol ester converted to retinol in the small intestine. The provitamin A carotenoids (i.e. beta-carotene - the orange pigment in carrots; alpha carotene and gamma-carotene) are the source of vitamin A in herbivores and omnivores that possess the enzymes β-Carotene oxygenases 1 and 2 (BCO1 and BCO2), which metabolises carotenes into retinol in the intestine and the liver. Other retinol esters such as retinyl acetate, retinyl palmitate and retinyl propionate are commercially produced and used in personal care products, such as anti-aging products applied to the skin that can reduce the appearance of fine lines and wrinkles. Vitamin A is also available as a dietary supplement. Therefore, consumers can be exposed to vitamin A from multiple products and by multiple exposure routes.

The human body needs vitamin A as an essential micronutrient for multiple biological functions and humans do not have the capability for *de novo* synthesis of compounds with vitamin A activity. Vitamin A is important for normal growth and development, for the maintenance of the immune system (Stephensen et al., 2001; Al-Tanoury et al., 2013) and is needed in the form of retinal in the retina of the eye to maintain good vision (Wald, 1968; Palczewski, 2010). Retinoic acid is the irreversibly oxidized form of retinal, and this stable form acts as a hormone-like growth factor in cells. Vitamin A deficiencies are associated with a number of health concerns relevant to children: intrauterine and post-natal growth retardation and a large array of congenital malformations collectively referred to as the "fetal vitamin A deficiency syndrome", observed in animals (Clagett-Dame and Knutson, 2011). In adults, vitamin A deficiency can lead to adverse effects on the eyes, immune system and reproductive function (Ross, 2014). Conversely, excessive exposures to vitamin A are also associated with adverse health effects, such as teratogenicity (Hathcock et al., 1990; Rothman et al., 1995), and changes in bone mineral density in humans, although the latter remains controversial (EFSA, 2015).

As vitamin A is found in the human diet, in dietary supplements and in personal care products, it is important when assessing the safety of vitamin A products to estimate the aggregate exposure as realistically and accurately as possible. In addition to providing an estimate of total vitamin A exposure, this work can be used as a case study on how to approach complex aggregate exposure evaluation in general.

The objectives of this study were to develop a probabilistic aggregate exposure model and to estimate the aggregate internal systemic exposure to vitamin A in pre-menopausal, menopausal and post-menopausal women from foods, dietary supplements and personal care products. Data were sourced for populations in both Europe and the United States of America (USA) and the outcomes were analysed separately.

2. Materials and methods

2.1. Retinol equivalents

In order to aggregate the exposure to different active forms of vitamin A, the various retinoids are converted to 'retinol equivalents' (RE). Based on molecular weight, 1 RE is defined as 1 μg of all–*trans*-retinol. For conversion of preformed vitamin A activity, expressed in International Units (IU) to RE, 1 RE is equivalent to 3.33 IU (Table 1). 1 μg of retinol is estimated to be biologically equivalent to 12 μg of carotenoids. As provitamin A carotenoids have a much lower potency as compared to vitamin A (EFSA, 2015) they are not considered in this assessment.

2.2. Data sources

2.2.1. Cosmetics products use

2.2.1.1. Criteria for cosmetics products selection in the assessment. In order to determine which cosmetics products should be included in an aggregate exposure assessment to provide a realistic reflection of what consumers are regularly exposed to, the occurrence of vitamin A and vitamin A derivatives in consumer products was investigated using the Mintel Global New Products Database (GNPD). Mintel GNPD (http://portal.mintel.com/) is an online database that tracks consumer product launches across the globe.

The database is divided into categories such as Face/Neck Care, Body Care, Eye Care, and Lip Care. Using the site's search function we were able to obtain the total number of products in each cosmetic and personal care product category. Adding the search string "retin" identified the ingredient names (Retinyl Formyl Aspartamate; Retinyl Palmitate; Tretinoin; Hydrocyanasatil Retinoate; Retinyl Acetate (non-food); Retinyl Proprionate; Retinyl Linoleate; Retinol; Retinyl Palmitate/Carrot Polypeptide) present in beauty and personal care categories and gives the subset of those products containing retinol and retinyl esters. By determining the number of stock-keeping units (SKUs) within a product category that contain retinol and retinyl esters, relative to the total number of cosmetic SKUs, the occurrence can be derived, which in this model is assumed to be the likelihood that a product contains a retinol or retinyl ester-containing ingredient. As the method has some uncertainty because it assumes equal market share of different products on the market, whereas in reality certain brands may have greater volume on the market than others, the occurrence was rounded up to the nearest 5%.

This simple method was used to derive the occurrence for retinol and retinyl esters in the cosmetic categories. Product types considered to be regularly used by consumers (at least once per week) that had an occurrence for retinol and retinyl esters greater than 1% in Europe or North America were included in this assessment. Table 2 gives the occurrence in Europe (EU) and North America (NA) calculated using the method described. Fig. 2 shows the stability of occurrence data over a period of 10 years, providing evidence of the conservative nature of the values used for occurrence in the exposure modelling.

2.2.1.2. Frequency of application and cosmetic product consumption. Frequency of application data was used as available from Kantar Worldpanel (http://www.kantarworldpanel.com): subject and consumption data were collected for the European population from consumer product consumption surveys over a seven-day period in 2007 and 2008 for France, Germany, Spain and Great Britain; data were also collected from 2007 to 2008 for the USA. Data for eye shadow, mascara, face powder, blusher, eye brow pencil and make up remover were sourced from Biesterbos (2012). Data for eye cream were sourced from an internal Procter & Gamble study (2009, unpublished communication). Data were incorporated into the Creme Care & Cosmetics™ (Creme Global,201[1]) aggregate exposure model, which is also available as the Creme RIFM Model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017), and allows estimation of aggregate exposure to ingredients in cosmetic products in European and US consumers. For lipsticks, this includes oral intake estimates.

2.2.1.3. Amount per product use. Data in Creme Care and Cosmetics on amount (mg) per use of the following cosmetic products was taken from the following references: body lotion, lipstick, face cream, shampoo (Hall et al., 2007); eau de toilette, conditioner (Loretz et al., 2008); liquid make-up foundation, hair styling, hand cream, shower gel (Hall et al., 2011); liquid hand soap (Comiskey et al., 2015); mascara, face powder, blusher, eye brow pencil and make up remover, data (Biesterbos, 2012); eye cream (Proctor and Gamble (unpublished report 2009)), described in Comiskey et al. (2015).

2.2.1.4. Retention factors for each product. Retention of cosmetic

[1] Creme Care & Cosmetics: Aggregate Exposure from Real Consumer Data. Available from http://www.cremeglobal.com/products/cosmetics/.

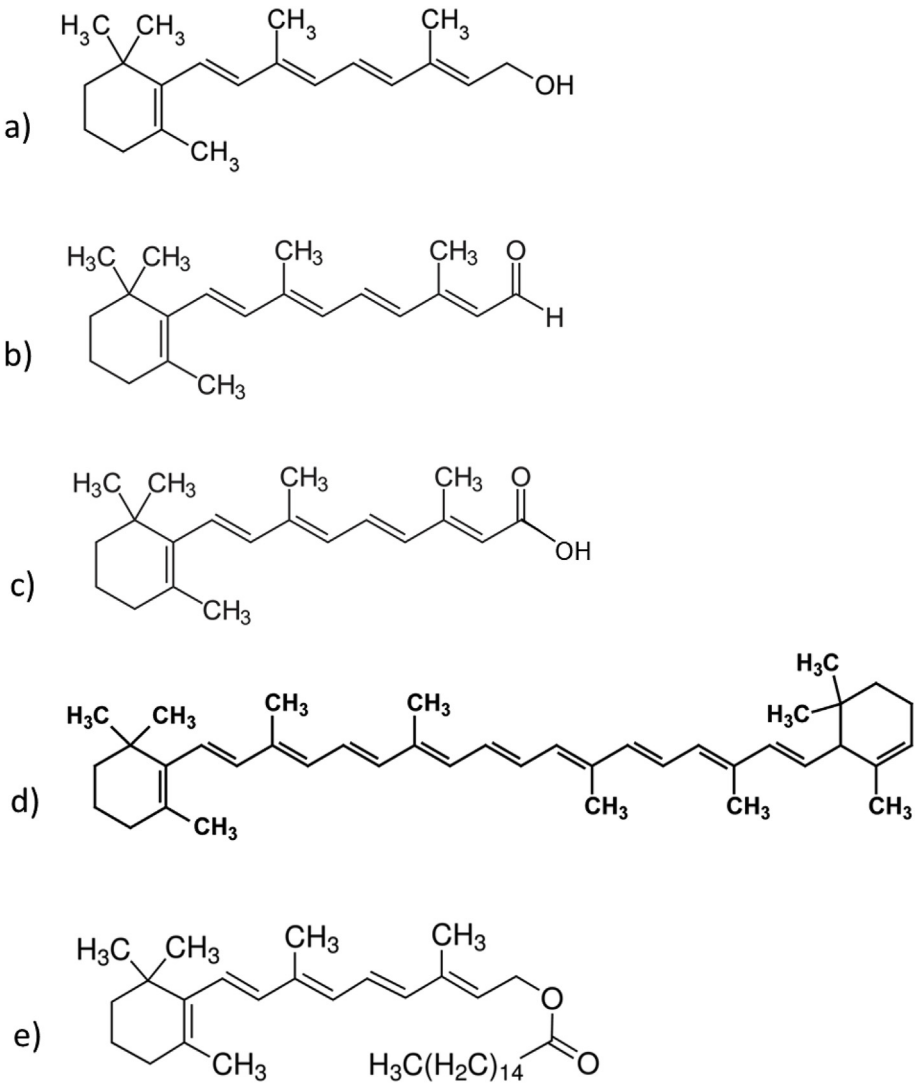


Fig. 1. Chemical structure of a) retinol, b) retinal, c) retinoic acid, d) beta-carotene (an example of a carotenoid) and e) retinyl palmitate (an example of a retinol ester).

Table 1
Calculation of retinol equivalents for retinol acetate and retinol palmitate.

	Vitamin A activity in International Units (IU)	Vitamin A activity in Retinol Equivalents (μg RE)
Retinol (1 mg)	3333	1000
Retinyl acetate (1 mg)	2907	872
Retinyl palmitate (1 mg)	1818	546

products on skin varies depending on the product type with leave-on products (e.g. leave-on creams and cosmetics) conservatively set to 100%, hair styling set to 10% and rinse-off products (shower gel, liquid hand soap) set to 1% by default (SCCS, 2018).

2.2.1.5. Concentration distribution for RE in each product. In order to determine the concentration of RE within the products a number of sources were surveyed including the FDA's Voluntary Cosmetic Registration Program (VCRP), published external opinions (BfR, 2014, CIR, 1987, 2008; Fiume and Heldreth, 2017, Ries and Hess, 1999; VKM, 2012) and internal databases in Procter & Gamble (P&G). The concentration values and distributions for RE that were input into the model for different cosmetic products are provided in Table 2. Following expert review of the concentration data by P&G, it was determined that the concentration range should be 0.01–0.3% within each category and was best described as a uniform distribution. Although there is mention in the Cosmetic Ingredient Review (CIR, 1987) of occasional use as high as 1% in the US, the range of 0.01–0.3% is consistent with the rationale used by the Norwegian Scientific Committee (VKM, 2012); according to Nohynek et al. (2006), retinol and retinyl esters are used in skincare products and cosmetic preparations at concentrations of up to 0.3% (retinol) or 0.55% (retinyl palmitate). Given higher concentrations are irritating to the skin, they are considered to be unsuitable for cosmetic use (Ries and Hess, 1999; Fluhr et al., 1999). As a result, this range was input into the model as the realistic scenario that best reflects the current market situation.

2.2.1.6. Scenarios for cosmetics products use. Different scenarios were considered for the concentration and occurrence data of RE in cosmetic

Table 2
Product types in assessment, concentration range of retinol equivalents in each product, amount of product used per day and occurrence used in the modelled scenario and occurrence data for vitamin A in cosmetic products in Europe and North America, based upon the Mintel GNPD (as accessed 3–5 June 2014). Scenarios S1a, S1b, S2a and S2b (as described in Section 2.2.1.6) used different input data as marked in the Table.*Note the concentration in Eye Make Up (Brow) for S2a, S2b was at a maximum concentration of 0.54%.[#]'Face cream' includes moisturisers, creams, lotions and variants that contain sun protection factors. $Refer to sources in section 2.2.1.3.

Product	Concentration RE (min-max)	Amount product (mg/day) Mean, P90[$]	Occurrence (%)	Occurrence (%)	Mintel Occurrence (%)	
	S1a, S1b (uniform) S2a, S2b (max*)		S1a, S2a	S1b, S2b	Europe	North America
Shower Gel	0.01–0.3	11340, 18671	5	10	1.3	4.4
Liquid Hand Soap	0.01–0.3	2400, NR	10	10	0.9	9.1
Shampoo	0.01–0.3	6034, 10456	5	10	1.3	4.0
Conditioner	0.01–0.3	13770, 28200	10	10	2.0	6.1
Face Cream[#]	0.01–0.3	906, 1536	15	20	5.9	10.9
Eye Cream	0.01–0.3	200, NR	20	20	11.6	18.9
Body Lotion	0.01–0.3	4543, 7822	10	10	3.1	7.0
Hand Cream	0.01–0.3	1058, 2156	15	20	5.0	14.2
Lipstick	0.01–0.3	24.61, 56.53	5	10	4.3	3.4
Liquid Make Up	0.01–0.3	225, 513	5	10	1.4	1.7
Hair Styling	0.001–0.3	1914, 4000	5	10	0.5	2.9
Make-Up Removers	0.01–0.3	1500, NR	3	10	1.7	2.2
Eye Make-Up (Brow)	0.01–0.3*	0.3, NR	5	10	1.4	1.6
Mascara	0.01–0.3	8.6, NR	5	10	1.0	2.1
Eau de Toilette	0.01–0.3	530, 1450	5	10	0.0	1.3
Blushers	0.01–0.3	4.2, NR	5	10	1.2	2.9
Face Powder	0.01–0.3	4.2, NR	5	10	1.4	1.9

products, as follows:

Scenario 1a (S1a) (Europe & USA) – Realistic – a uniform distribution of RE concentration with minimum value *a* (typically 0.01%, except 0.001% for hairstyling products) and maximum value *b* (0.3%) with the RE occurrence data set approximately to the nearest upper 5% of the level determined in the Mintel GNPD (for both Europe and USA), as shown in Table 2. This rounding up of occurrence was applied to compensate for uncertainties present in the database (such as incomplete market coverage for a given product category). This is to ensure that refinements using occurrence in the model are sufficiently conservative. This scenario is believed to best represent realistic RE exposure in cosmetic products.

Scenario 1b (S1b) (Europe & USA) - Exaggerated occurrence - a uniform distribution of RE concentration with minimum value a (typically 0.01%, except 0.001% for hairstyling products) and maximum value b (0.3%) with the occurrence data set to the nearest upper 10% for all products compared to the occurrence determined for both European and North American women according to Mintel data (see Table 2). In this deliberately more conservative scenario, the occurrence of RE in products is increased in a number of product categories by > 10%. This models a situation where a larger number of products (than are currently on the market) contain RE than is currently expected, and therefore adds some conservatism to the assessment.

Scenario 2a (S2a) (Europe only) - Exaggerated fixed RE concentration - RE concentration set at the maximum value *b* (0.3%) of the uniform distribution for all products in Table 2. As per Scenario 1a, the RE occurrence data was set approximately to the nearest upper 5% of the level determined in the Mintel GNPD as shown in Table 2. This reflects an exaggerated and unrealistic exposure where all the RE-containing products contain the highest concentration of RE.

Scenario 2b (S2b) (Europe & USA) – Most conservative and highly unrealistic - RE concentration set at the maximum value *b* (0.3%) of the uniform distribution for all products in Table 2. As per Scenario 1b, the RE occurrence data was set higher, to the nearest upper 10% for most products, to introduce further conservatism compared to the level determined in the Mintel GNPD (considering both Europe and USA), as shown in Table 2.

2.2.2. Dietary survey data

Data from both Europe and the United States of America (USA) were used in separate analyses of these geographical populations.

2.2.2.1. Europe. Three national dietary surveys were used:

- The Netherlands: the Dutch National Food Consumption Survey (DNFCS), 2007–2010.
- Ireland: The North/South Ireland Food Consumption Survey (NSIFCS), 1999–2001.
- United Kingdom: The National Diet and Nutrition Survey (NDNS), 2008–2011.

The details of the populations studied in these surveys are shown in Table 3.

For the present analyses, the female populations recorded within each of these surveys were broken down further into the following age groups to represent pre-menopausal, menopausal and postmenopausal women respectively:

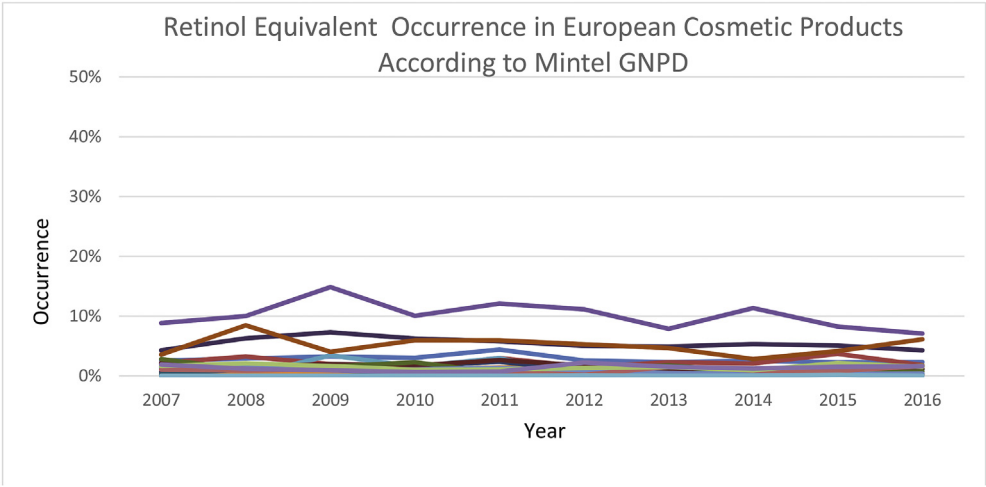
- 18–44 years (Netherlands: $n = 665$; Ireland: $n = 474$; UK: $n = 364$)
- 45–54 years (Netherlands: $n = 163$; Ireland: n = 148; UK: $n = 159$)
- 55 + years (Netherlands: $n = 288$; Ireland: $n = 95$; UK: $n = 318$)

As the menopausal age will vary amongst individuals, these age groupings aim to capture these cohorts of women.

These countries have been noted elsewhere to have higher intakes of RE compared to other European countries (Flynn et al., 2009) and therefore were chosen so as not to underestimate dietary intake of retinoids in the European population.

The occurrence of RE in foods was recorded in each of the three dietary consumption surveys. The RE value assigned per food was obtained from the McCance & Widdowson 5th edition dataset (Holland et al., 1995) for the Irish and UK dietary surveys and from the Nevo dataset (Dutch Food Composition Database). These datasets contain detailed nutrient and micronutrient information on a comprehensive list of foods. Each time a food containing RE in the consumption surveys was consumed, the RE value assigned to that particular food in the McCance & Widdowson or Nevo databases were incorporated into the

a)



b)

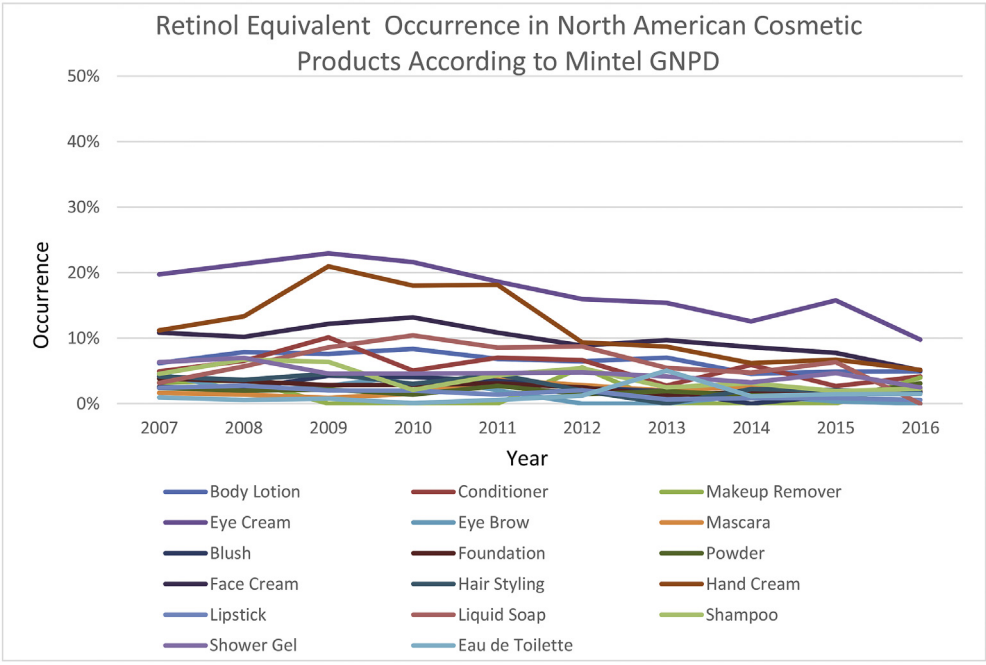


Fig. 2. Occurrence (% retinol equivalents) data in cosmetics products a) for European and b) North American products from the Mintel GNPD, over a period of 10 years (2007–2016).

Table 3
Information on the populations and methods of dietary surveys.

	DNFCS (2007–2010)	NSIFCS (1999–2001)	NDNS (2008–2011)	NHANES (2009–2010)
Country	Netherlands	Ireland	United Kingdom	USA
No participants	3800	1379	1491	8406
Age Range	7–69 years old	18–64 years old	19–94 years old	1-88 + years old
Supplement database	Yes	Yes	Yes	Yes
Methods used	2 × 24-h recalls	7-day estimated food record	4-day food diary	2 × 24-h recalls

nutrient intake assessment in the Creme Nutrition® model (McNamara et al., 2003). The intakes of RE from food in European subjects was the same in all four aggregate exposure models.

2.2.2.2. USA. The dietary intake section of the U.S. National Health and Nutrition Examination Survey (NHANES) – the What We Eat in America (WWEIA) data, was used for this analysis. The survey is regionally representative, is conducted every year and aims to survey approximately 5000 people annually. The details of the populations studied in these surveys are shown in Table 3. A detailed explanation of the exact methodology adopted for the NHANES 2 study (2009–2010) is explained elsewhere (Ahuja et al., 2012).

For the present analyses, the female population was broken down further into the following age groups to represent pre-menopausal, menopausal and postmenopausal women respectively:

- 18–44 years (n = 1265)
- 45–54 years (n = 465)
- 55 + years (n = 1038)

As the menopausal age will vary amongst individuals, these age groupings aim to capture these cohorts of women.

The NHANES survey records detailed nutrient and micronutrient information on a comprehensive list of foods, including the occurrence and amount of vitamin A (in retinol equivalents) in foods consumed by the survey participants. Each time a food containing vitamin A in NHANES was consumed, the vitamin A value assigned to that particular food was incorporated into the nutrient intake assessment in the Creme Nutrition® model. Vitamin A values in this case include all forms of the vitamin (i.e. both pre-formed and pro vitamin A). The intakes of vitamin A from food in USA subjects was the same in all four aggregate exposure models.

2.2.3. Dietary supplements

Vitamin A is also used as a dietary supplement in both Europe and the USA.

2.2.3.1. Europe. The national dietary consumption surveys in Table 3 also recorded data on dietary supplement use and therefore data from these surveys were included in the present analyses.

In relation to supplements, the concentrations for RE used in this project were obtained directly from the Irish, Dutch, and UK dietary survey data. These surveys recorded all types of supplements (e.g. tablet, liquid), including the brand name, consumed during the survey period, with the actual concentration levels of the relevant vitamins/minerals. Therefore, all retinol and retinyl ester concentration levels in the supplements utilised in this investigation are the actual levels reported on the product label and recorded in the dietary surveys.

2.2.3.2. USA. For the USA analysis, a complementary dietary supplement database (the 24-Hour Dietary Supplement Use Database) was also utilised for the research in this project and was compiled in conjunction with the NHANES survey. This database recorded the supplement types (e.g. liquid, tablet) and amounts consumed by NHANES participants in the 24 h prior to the recall interview, with a total of 33 vitamins and minerals from supplements being recorded.

Although NHANES does record concentration levels for a variety of vitamins and minerals in dietary supplements, it did not record levels of Vitamin A or any of the variants of Vitamin A (e.g. retinol). Therefore, a complementary dietary supplement database (the 24-Hour Dietary Supplement Use Database) was used. This database was compiled in conjunction with the NHANES survey (CDC, 2016) It recorded the supplement types (e.g. liquid, tablet) and amounts consumed by NHANES participants in the 24 h prior to the recall interview, with a total of 33 vitamins and minerals from supplements being recorded.

For the present investigation, supplements which contained any form of vitamin A were included in the analyses (i.e. both pre-formed and post vitamin A, n = 2521). It was not always possible to distinguish what type of vitamin A was contained in a given supplement (e.g. being able to distinguish between retinol and beta-carotene). Furthermore, all concentration values for vitamin A in this database were presented as International Units (IU), which needed to be converted to micrograms (μg) of RE. A conservative approach was adopted of assuming all supplements that contained vitamin A contained it in the form of retinol. The following conversion was then used (based on standard conversion factors e.g. from National Institutes of Health Dietary Supplement Label Database Units of Conversion - see version 7.0.3, October 2018):IU (Vitamin A) to RE μg: IU/3.33 = RE μgExample: 5000 IU/3.33 = 1500 RE μg.

2.2.4. Dermal and oral bioavailability of vitamin A

Once the amount of vitamin A product exposure is estimated, dermal penetration is estimated for vitamin A systemic delivery from cosmetics and oral bioavailability following ingestion is estimated for food and supplement use.

2.2.4.1. Dermal penetration data. An in vitro dermal penetration study was conducted by Yourick on retinol and retinyl esters (Yourick et al., 2008). None of the available in vitro skin penetration studies exactly fulfilled the SCCS criteria for skin absorption studies but this study was regarded by the Norwegian Scientific Committee for Food Safety, VKM, as most closely fulfilling the criteria and was used by VKM to estimate the level of dermally absorbed retinol following cosmetic exposure at 5.7% (VKM, 2012). Data derived from the oil-in-water emulsion was chosen because it best mimics the vehicle used in cosmetic products as moisturisers. After 24 h, the skin absorption values were 3.0% ± 0.6 (SEM)(in viable skin) and 1.3% ± 0.1 (SEM)(as penetrated into receptor fluid). The value of dermally absorbed retinol was estimated by VKM to be 5.7% (conservatively assuming (3% + 2SEM) +(1.3% +2SEM)). This value corresponds well with the absorption value of 5.3% calculated from the human *in vivo* study by Franz and Lehman (1989) after topical application of retinoic acid. Therefore, a single dermal penetration factor of 5.7% was used for all products applied to the skin in our study.

2.2.4.2. Oral bioavailability. It has been reported that the oral bioavailability for retinol ranges between 75 and 100% (Sivakumar and Reddy, 1972; West and Sommer, 1987; Biesalski, 1997; Reboul, 2013). An oral bioavailability factor at the high end of the range, of 90% was assumed for this study.

2.3. Exposure model and statistical analysis

The exposure model was developed for simulated populations using a probabilistic approach for estimating systemic exposure, in a software system developed by Creme Global (www.cremeglobal.com). Exposure was calculated from a single product and as aggregate exposures to many products in individual subjects.

2.3.1. Calculating exposure from a single product

For an individual consumer, exposure to RE from product i is estimated as.

$$E_i = (F_i \times A_i \times X_i \times C_i)/BW$$

where each term on the right-hand side can be a fixed estimate or drawn from a distribution and each term is understood as follows:

E_i is the exposure to RE from group i products [μg/kg/day]
F_i is the frequency of applications/consumption events of group i products [day^{-1}]
A_i is the amount used per application/consumption event of group i products [μg]

X_i is the retention factor multiplied by the dermal penetration factor for group I products [proportion]
C_i is the concentration of RE in group i products [proportion]
BW is the consumer's bodyweight [kg].

2.3.2. Calculation of aggregate exposure

A group of products is one for which all included products are considered equivalent. For example, various brands and colours of lipstick, etc. are assessed together under the product group lipstick.

Aggregate vitamin A exposure for each individual subject is estimated by

$$E = \sum_{i=1}^{n} E_i$$

where E is the exposure to RE from all products [μg.day^{-1}]
E_i is the exposure to RE from group i products [μg.day^{-1}]
The distribution of E is then the distribution of systemic exposure to RE in the sample data. Applying the demographic weighting factors to these values gives the aggregate exposure to RE in the population.

2.3.3. Simulating human exposure

As it is not practical to directly measure the usage habits for the entire population, the method used was to create a simulated population based on a statistical representation of the population whose product usage habits reflect the real population (Hall et al., 2007, 2011). The exposure calculated using this simulated population, was then used as the estimate of the exposure for an individual consumer in the real population.

The simulation method employed uses a 'statistical bootstrapping' technique (Efron and Tibshirani, 1993) to assign measures of accuracy to the estimated statistics. Bootstrapping is a well-established and accepted method for measuring accuracy of sample estimates. This technique works by resampling (with replacement) from the original sample a large number of times, each time recalculating the relevant statistics. The variability in the resulting values provides a measure of the standard error in the estimate. The exposure estimates which are presented here include a "Standard Error" that is calculated using this bootstrapping technique.

2.3.4. Combining data from multiple sources

It is necessary to combine multiple sources of input data (i.e. multiple surveys) to build the best overall model of usage habits for the population of interest. When combining data across different sources, the following approximation is often made: people within the same demographic group (country, age) tend to be more similar to each other (in terms of frequency of using products, amount of product used, which products are used together, and bodyweight) than to people in different demographic groups. Thus, when combining data from various sources, data were combined separately for corresponding demographic groups as in Hall et al. (2011) and McNamara et al. (2003).

In this study, the following five age groups were used to match the women subjects between cosmetics and food diaries:

- 18–24 years
- 25–34 years
- 35–44 years
- 45–54 years
- 55 + years

In this way, the dietary consumption surveys and cosmetics usage surveys have been matched to build the best overall model of usage habits for the population of interest.

The flow chart in Fig. 3 describes the steps of the aggregation model.

In the aggregate exposure model the following steps were followed:

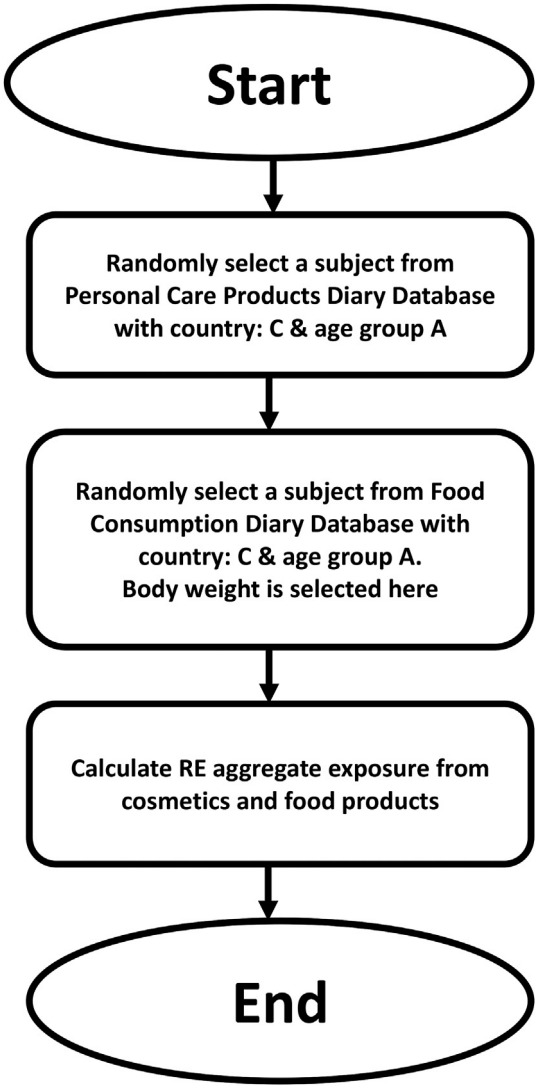


Fig. 3. Overview of the retinol equivalent aggregate exposure model.

Step 1: Randomly select a subject from a personal care products (PCP) use dataset: in this study this was the Kantar database for women in Europe (France, Germany, Spain or the UK) or USA;
Step 2: For a subject simulated in Step 1, assign a subject from one of the food diaries as follows:

1. If the subject selected in Step 1 is from a specific country, then randomly assign someone from the survey from the same country to this subject. The assigned subject must belong to the same age group (i.e. 18–24, 25–34, 35–44, 45–54 and 55 + years). The probability of selecting a given subject is calculated from this subject's statistical weighting.
2. Match dietary data. If the subject is from the USA or the UK, then a corresponding subject is chosen from either the NHANES or NDNS dietary surveys, respectively (i.e. matching US subjects with US and UK with UK). If the subject selected in Step 1 is from France, Germany or Spain, the following approach is used:
   a. Select a country (Ireland, or The Netherlands) based on female population size. Female population size in Ireland is approximately 2,315,553. Female population size in Netherlands is approximately 8,490,896. As a result, the probability of selecting Ireland is 21.4275%, whereas the probability of selecting Netherlands is 78.5725%.
   b. Suppose the selected country is Ireland. Next, randomly assign someone from the Irish Universities Nutrition Alliance (IUNA)

dietary survey to this subject. The assigned subject must belong to the same age group. The probability of selecting a given subject is calculated from this subject's statistical weighting. Record a bodyweight for this subject as this will be used to calculate Aggregate Exposure per unit bodyweight for this subject.

Step 3: Repeat Steps 1 and 2 for 100,000 times. As a result, we obtain a diary of 100,000 subjects with RE Intakes for both cosmetics and food diaries. For each subject, calculate aggregate vitamin A exposure as RE by adding the exposure from food and cosmetics sources. Both chronic and acute calculation are performed.

Step 4: Calculate summary statistics for the population generated in Step 3. (Both aggregate and aggregate per unit bodyweight exposure statistics: Mean, Standard deviation, P95, P99.)

Step 5: Use the bootstrapping technique to estimate the accuracy of the estimated statistics. The technique works by resampling (with replacement) from the original sample of 100,000 (simulated in Step 3) 1 000 000 times, each time recalculating the relevant statistics.

2.3.5. Model assumptions

There are a number of assumptions made in the model:

1. Frequency of use data from the Kantar diary for European countries (France, Germany, Spain and Great Britain) and the US for cosmetic products of interest (excluding eye shadow, mascara, face powder, blusher, eyebrow pencil, make up remover, eye cream) represent frequency of use data for these products amongst all EU and US citizens, respectively.
2. Frequency of use data from the Netherlands (Biesterbos, 2012) for eye shadow, mascara, face powder, blusher, eyebrow pencil, make-up remover represent frequency of use data for these products amongst EU and US citizens.
3. Frequency of use data from P&G for eye cream represent frequency of use data for these products amongst EU and US citizens.
4. Frequency of use data from the Dutch (DNFCS), Irish (IUNA), and UK (NDNS) dietary surveys represent frequency of use data for foods amongst EU citizens. Likewise, frequency of use data from NHANES dietary survey represent frequency of use data for foods amongst US citizens.
5. Amount per use data from the Colipa studies for cosmetics and additional data from the CTFA and Biesterbos studies for certain cosmetics represents amount per use data for these products amongst EU and US citizens.
6. Amount per use data from the Dutch (DNFCS) Irish (IUNA), and UK (NDNS) national dietary surveys represent amount per use data for food amongst EU citizens. Likewise, amount per use data from NHANES dietary survey represent frequency of use data for foods amongst US citizens.
7. The Mintel GNPD database contains a comprehensive list of cosmetic products sold across the European Union and North America.
8. Reported concentrations by BfR, 2014, CIR 1987, 2008; Fiume and Heldreth (2017), Ries and Hess (1999); VKM, 2012 and internal databases in P&G are representative of products available on the market.

3. Results

Estimates of the internal systemic exposure to RE from cosmetic products and dietary sources for both of the modelled EU and USA populations and the different scenarios for cosmetics use, are described below. The absorbed exposures are estimates after dermal and oral bioavailability have been taken into account.

Table 4
Europe – Cosmetics, dietary (food and supplements) and aggregate absorbed exposure to RE in μg/kg bw/day with standard error values for Scenario 1a.

Statistic	Age Group			
Cosmetics	18–44 years	45–54 years	55 + years	All
Mean	0.2 ± 0.004	0.2 ± 0.004	0.2 ± 0.004	0.2 ± 0.002
P5	0.0 ± 0	0.0 ± 0	0.0 ± 0	0.0 ± 0
P25	0.0 ± 0	0.0 ± 0	0.0 ± 0	0.0 ± 0
P50	0.0 ± 0	0.0 ± 0	0.0 ± 0	0.0 ± 0
P75	0.1 ± 0.002	0.1 ± 0.003	0.1 ± 0.002	0.1 ± 0.001
P90	0.4 ± 0.01	0.5 ± 0.01	0.3 ± 0.01	0.4 ± 0.004
P95	0.8 ± 0.02	0.9 ± 0.02	0.7 ± 0.02	0.8 ± 0.01
Dietary	**18–44 years**	**45–54 years**	**55 + years**	**All**
Mean	7.60 ± 0.10	8.40 ± 0.10	9.64 ± 0.10	8.40 ± 0.04
P5	1.30 ± 0.01	1.30 ± 0.02	1.61 ± 0.02	1.40 ± 0.01
P25	2.90 ± 0.02	3.30 ± 0.04	3.41 ± 0.01	3.18 ± 0.02
P50	4.70 ± 0.02	5.12 ± 0.04	5.64 ± 0.04	5.11 ± 0.01
P75	7.90 ± 0.04	9.90 ± 0.10	10.3 ± 0.10	9.20 ± 0.04
P90	14.9 ± 0.07	18.3 ± 0.20	19.9 ± 0.10	17.1 ± 0.10
P95	21.6 ± 0.20	26.8 ± 0.60	27.1 ± 0.30	24.8 ± 0.11
Aggregate	**18–44 years**	**45–54 years**	**55 + years**	**All**
Mean	7.80 ± 0.1	8.55 ± 0.1	9.81 ± 0.1	8.59 ± 0.04
P5	1.43 ± 0.01	1.48 ± 0.03	1.68 ± 0.03	1.52 ± 0.01
P25	3.10 ± 0.02	3.38 ± 0.01	3.48 ± 0.02	3.30 ± 0.01
P50	4.89 ± 0.02	5.43 ± 0.1	5.77 ± 0.03	5.30 ± 0.02
P75	8.30 ± 0.1	10.2 ± 0.1	10.7 ± 0.15	9.57 ± 0.1
P90	15.1 ± 0.1	18.4 ± 0.2	20.1 ± 0.2	17.4 ± 0.2
P95	21.8 ± 0.1	27.2 ± 0.5	27.3 ± 0.3	25.0 ± 0.2

3.1. Cosmetics exposure

3.1.1. Europe

The chronic absorbed exposures to RE for the realistic scenario (S1a) in European females for each age group combination and a range of percentiles in the distribution are summarised in Table 4. The mean absorbed exposure to RE from cosmetics is 0.2 ± 0.002 μg/kg bw/day across all age groups. There is a small variation amongst the three age groups in exposure at P95 ranging from 0.7 ± 0.02 to 0.9 ± 0.02 μg/kg bw/day, with the highest exposure occurring in menopausal women (0.9 ± 0.02 μg/kg bw/day).

3.1.2. US

The chronic absorbed exposures to RE for the realistic scenario (S1a) in US females for each age group combination are summarised in Table 5. The mean exposure to RE from cosmetics ranges from 0.3 ± 0.01 to 0.4 ± 0.01 μg/kg bw/day across all age groups. There is a small variation amongst the three age groups in exposure at P95 ranging from 1.35 ± 0.04 to 1.9 ± 0.1 μg/kg bw/day, with the highest exposure occurring in menopausal women (1.9 ± 0.1 μg/kg bw/day).

3.2. Dietary (food and dietary supplements) exposure

3.2.1. Europe

Estimated absorbed RE exposures resulting from dietary intake are presented overall in Table 4, and per country and per age group in Table 6. Each set of results include RE mean and P95 exposures (with corresponding error values) per country and per age group within that country.

The significant contributory food group to RE exposures from base foods in the Irish survey was that of 'Offal & Offal Dishes', with a mean daily average absorbed exposure to RE from this group of 1.7 ± 0.83 μg/kg bw/day. The other primary contributory food groups consisted of dairy food groups, including 'Wholemilk', 'Lowfat,

Table 5
USA – Cosmetics, dietary (food and supplements) and aggregate absorbed exposure to RE in μg/kg bw/day for Scenario 1a.

Cosmetics	18–44 years	45–54 years	55 + years	All
Mean	0.32 ± 0.01	0.4 ± 0.01	0.30 ± 0.01	0.34 ± 0.01
P5	0.00 ± 0.0	0.0 ± 0.0	0.00 ± 0.0	0.00 ± 0.0
P25	0.00 ± 0.0	0.0 ± 0.0	0.00 ± 0.0	0.00 ± 0.0
P50	0.00 ± 0.0	0.0 ± 0.0	0.00 ± 0.0	0.00 ± 0.0
P75	0.03 ± 0.001	0.1 ± 0.002	0.04 ± 0.002	0.04 ± 0.001
P90	0.40 ± 0.01	0.6 ± 0.03	0.50 ± 0.03	0.40 ± 0.01
P95	1.35 ± 0.04	1.9 ± 0.1	1.80 ± 0.1	1.53 ± 0.03
Dietary	**18–44 years**	**45–54 years**	**55 + years**	**All**
Mean	10.7 ± 0.04	12.0 ± 0.10	15.4 ± 0.10	11.9 ± 0.04
P5	1.77 ± 0.02	2.0 ± 0.03	2.4 ± 0.03	1.9 ± 0.01
P25	4.47 ± 0.03	4.8 ± 0.04	5.6 ± 0.07	4.7 ± 0.03
P50	7.51 ± 0.02	8.9 ± 0.08	11.3 ± 0.10	8.4 ± 0.02
P75	14.6 ± 0.10	17.2 ± 0.20	19.5 ± 0.10	16.2 ± 0.10
P90	22.3 ± 0.30	23.8 ± 0.10	28.7 ± 0.30	24.4 ± 0.10
P95	29.3 ± 0.30	30.5 ± 0.05	38.9 ± 0.50	30.9 ± 0.20
Aggregate	**18–44 years**	**45–54 years**	**55 + years**	**All**
Mean	11.0 ± 0.04	12.4 ± 0.1	15.8 ± 0.1	12.2 ± 0.04
P5	1.8 ± 0.02	2.1 ± 0.1	2.5 ± 0.02	2.0 ± 0.02
P25	4.6 ± 0.01	5.0 ± 0.02	5.9 ± 0.1	4.9 ± 0.01
P50	7.8 ± 0.02	9.1 ± 0.04	11.6 ± 0.1	8.7 ± 0.03
P75	15.0 ± 0.03	17.6 ± 0.2	19.9 ± 0.1	16.5 ± 0.03
P90	23.1 ± 0.1	24.7 ± 0.2	29.5 ± 0.4	24.8 ± 0.06
P95	29.6 ± 0.1	30.8 ± 0.2	39.4 ± 0.6	31.6 ± 0.1

skimmed and fortified milk', 'Butter', 'Egg & Egg Dishes' and 'Cheeses', with mean intakes ranging from 0.4 ± 0.3 μg/kg bw/day to 0.8 ± 0.6 μg/kg bw/day, respectively. The Irish survey indicated that 29.5%, 39.9% and 34.7% participants consumed supplements from the 18–44, 45–54 and 55 + age groups respectively.

A similar pattern was observed in the Netherlands as was observed in Ireland. The significant contributory food group to Vitamin A intakes from base foods was that of 'Meat and meat products', with a mean absorbed exposure of RE from this group of 3.7 ± 0.9 μg/kg bw/day. The other primary contributory food groups consisted of dairy food groups (or those containing dairy products), including 'Fat', 'Dairy Products', 'Cakes' and 'Egg & Egg Products', with mean RE absorbed exposure ranging from 0.38 ± 0.04 μg/kg bw/day to 1.8 ± 0.1 μg/kg bw/day, respectively. The Dutch survey indicated that 31.4%, 44.2% and 43.8% participants consumed supplements from the 18–44, 45–54 and 55 + age groups respectively.

Again, a similar pattern was observed in the UK, as was observed in Ireland & the Netherlands. The significant contributory food group to Vitamin A intakes from base foods was that of 'Liver & Dishes', with a mean absorbed exposure of vitamin A from this group of 2.9 ± 0.8 μg/kg bw/day. The other primary contributory food groups consisted of dairy food groups, including 'Butter', 'Cheese', 'Eggs and egg dishes', 'Reduced fat spreads' and 'Semi skimmed milk', with mean absorbed exposure ranging from 0.28 ± 0.02 μg/kg bw/day to 0.67 ± 0.07 μg/kg bw/day, respectively. Overall, offal (specifically liver and liver products) and dairy products were the primary contributory foods to vitamin A intakes among women aged 55 + years among UK, Irish and Dutch cohorts. The UK survey indicated that 19.8%, 35.9% and 42.1% participants, from the 18–44, 45–54 and 55 + age groups respectively, consumed supplements.

As the dietary inputs were identical for the four scenarios, the output (dietary exposure) is almost identical (there are very slight differences due to the random nature of the probabilistic sequences, but these are insignificant in terms of overall exposure). Therefore, the results of the dietary output for S1a are shown in Table 4 as a representation of the dietary output in any of the four scenarios.

Table 6
Mean and P95 dietary RE absorbed exposure, with corresponding standard error values in women from base foods, supplements and both sources combined in terms of micrograms daily (μg/kg/day), for Ireland, The Netherlands, United Kingdom and USA.

Statistic	18–44 years (n = 474)			45–54 years (n = 148)			55 + years (n = 95)		
Ireland	Base Foods	Supplements (n = 140)	Both	Base Foods	Supplements (n = 59)	Both	Base Foods	Supplements (n = 33)	Both
Mean	5 ± 0.4	2 ± 0.3	7 ± 0.5	5 ± 1	3 ± 0.5	7 ± 0.8	6 ± 0.9	2 ± 0.6	8 ± 1.2
P95	14 ± 3.2	13 ± 1.1	23 ± 2.9	11 ± 6	14 ± 1.5	24 ± 4.8	27 ± 10.4	14 ± 2.9	33 ± 8.3
Statistic	18–44 years (n = 665)			45–54 years (n = 163)			55 + years (n = 288)		
Netherlands	Base Foods	Supplements (n = 209)	Both	Base Foods	Supplements (n = 72)	Both	Base Foods	Supplements (n = 126)	Both
Mean	7 ± 0.7	1 ± 0.2	8 ± 0.7	7 ± 1	2 ± 0.3	9 ± 0.7	9 ± 0.9	1 ± 0.2	10 ± 0.9
P95	20 ± 3	8 ± 0.9	22 ± 2	23 ± 4	10 ± 1	28 ± 2	23 ± 2.3	9 ± 1	24 ± 3
Statistic	18–44 years (n = 364)			45–54 years (n = 159)			55 + years (n = 318)		
UK	Base Foods	Supplements(n = 72)	Both	Base Foods	Supplements (n = 57)	Both	Base Foods	Supplements (n = 134)	Both
Mean	5 ± 0.6	1 ± 0.2	6 ± 0.7	5 ± 1	2 ± 0.4	7 ± 1	7 ± 0.8	2 ± 0.3	9 ± 1
P95	9 ± 4	11 ± 2	19 ± 4	12 ± 9	11 ± 1	18 ± 8	23 ± 11	13 ± 2	29 ± 8
Statistic	18–44 years (n = 1265)			45–54 years (n = 465)			55 + years (n = 1038)		
USAs	Base Foods	Supplements (n = 445)	Both	Base Foods	Supplements (n = 253)	Both	Base Foods	Supplements (n = 724)	Both
Mean	7.7 ± 0.3	2.8 ± 0.3	10.5 ± 0.4	8.0 ± 0.5	4.1 ± 0.5	12.1 ± 0.8	8.6 ± 0.3	6.8 ± 0.6	15.4 ± 0.7
P95	18.0 ± 0.9	14.8 ± 0.7	28.6 ± 2.0	22.6 ± 3.3	17.3 ± 1.5	30.5 ± 3.7	19.4 ± 1.8	22.8 ± 2.5	38.7 ± 2.5

Table 4 shows that the mean internal exposure to RE from food is 8.4 ± 0.04 μg/kg bw/day across all age groups. There is a variation amongst the three age groups in exposure at P95 ranging from 22 to 27 μg/kg bw/day across the age groups, with the highest exposure occurring in menopausal women (27.1 ± 0.3 μg/kg bw/day).

3.2.2. USA

RE dietary exposure results (mean and P95 values) for the USA per age group are presented in Table 6. The primary contributory food group to vitamin A intakes from base foods among U.S. females was 'Milk, fluid'; with intakes of 0.92 ± 0.06 μg/kg bw/day (18–44 years), 0.74 ± 0.06 μg/kg bw/day (45–54 years) and 0.98 ± 0.07 μg/kg bw/day (55 + years), with 'Mixtures, mainly grain, pasta or bread' also contributing significantly to intakes for all age groups (0.34 ± 0.04–0.68 ± 0.05 μg/kg bw/day). These values are based on mean intakes for total population.

Table 5 shows that the mean exposure to RE from diet is 11.9 ± 0.04 μg/kg bw/day across all age groups. There is a variation amongst the three age groups in exposure at P95 ranging from 30.5 ± 0.5 to 38.9 ± 0.5 μg/kg bw/day across the age groups, with the highest exposure occurring in women aged 55 years or over (38.9 ± 0.5 μg/kg bw/day).

3.3. Aggregate exposure

3.3.1. Europe

The chronic internal aggregate exposure distribution to RE from diet (including supplements) and cosmetics/personal care products for all scenarios are summarised in Table 7. The mean aggregate exposure to RE (all sources) for the realistic scenarios S1a is 8.6 ± 0.04 μg/kg bw/day across all age groups. There is a variation amongst the three age groups in exposure at P95 ranging from 21.8 ± 0.1 to 27.3 ± 0.3 μg/kg bw/day across the age groups, with the highest exposure occurring in post-menopausal women (27.3 ± 0.3 μg/kg bw/day).

Exposure to RE for each of the more conservative scenarios (i.e. S1b, S2a and S2b) as shown in Table 7 suggests exposure is not radically different and hence the data from the realistic scenario S1a are recommended for use in safety evaluation. Also, S1a provides the most realistic estimate of RE exposure.

3.3.2. USA

The chronic aggregate absorbed exposure distribution to RE from diet (including supplements) and cosmetics/personal care products are summarised for all scenarios in Table 8. The mean aggregate absorbed exposure to RE from all sources ranges from 11 ± 0.04 to 15.8 ± 0.1 μg/kg bw/day across all age groups. There is a variation amongst the three age groups in exposure at P95 ranging from 29.6 ± 0.1 to 39.4 ± 0.6 μg/kg bw/day across the age groups, with the highest exposure occurring in women aged 55 and over (39.4 ± 0.6 μg/kg bw/day).

Exposure to RE for each of the more conservative scenarios (i.e. S1b and S2b) as shown in Table 8 suggests exposure is not radically different and hence the data from the realistic scenario S1a are recommended for use in safety evaluation.

3.4. Source contributions

The results in Tables 7 and 8 (all scenarios) and in Figs. 4 and 5 (scenario S1a) show that diet is by far the main contributor to the mean absorbed exposure in each of the female sub-populations, as well as in

Table 7
Europe - Breakdown of Mean (P95 values in brackets) RE absorbed exposure in μg/kg bw/day with standard error values for scenarios S1a, S1b, S2a and S2b. for each age range and all combined.

Source	Age Group			
Scenario S1a (Realistic)	18–44	45–54	55 +	All
Cosmetics	0.2 ± 0.004 (0.83 ± 0.02)	0.2 ± 0.01 (0.90 ± 0.02)	0.20 ± 0.004 (0.73 ± 0.02)	0.2 ± 0.003 (0.80 ± 0.01)
Diet (including supplements)	7.6 ± 0.053 (21.6 ± 0.16)	8.4 ± 0.10 (26.8 ± 0.63)	9.64 ± 0.090 (27.1 ± 0.35)	8.4 ± 0.039 (24.8 ± 0.10)
Aggregate	7.8 ± 0.053 (21.8 ± 0.13)	8.6 ± 0.10 (27.2 ± 0.46)	9.81 ± 0.100 (27.3 ± 0.30)	8.6 ± 0.039 (25.0 ± 0.20)
Source	Age Group			
Scenario S1b (Exaggerated occurrence data)	**18–44**	**45–54**	**55 +**	**All**
Cosmetics	0.3 ± 0.004 (1.63 ± 0.04)	0.3 ± 0.01 (1.90 ± 0.1)	0.30 ± 0.01 (1.23 ± 0.03)	0.3 ± 0.003 (1.56 ± 0.03)
Diet (including supplements)	7.6 ± 0.1 (21.7 ± 0.1)	8.3 ± 0.1 (26.9 ± 0.6)	9.61 ± 0.1 (26.8 ± 0.6)	8.4 ± 0.04 (24.7 ± 0.1)
Aggregate	7.9 ± 0.1 (22.0 ± 0.1)	8.7 ± 0.1 (27.4 ± 0.3)	9.87 ± 0.1 (27.2 ± 0.4)	8.7 ± 0.04 (24.9 ± 0.2)
Source	Age Group			
Scenario S2a (Exaggerated fixed RE concentration)	**18–44**	**45–54**	**55 +**	**All**
Cosmetics	0.4 ± 0.01 (2.00 ± 0.04)	0.4 ± 0.01 (1.94 ± 0.1)	0.31 ± 0.01 (1.30 ± 0.03)	0.4 ± 0.004 (1.71 ± 0.03)
Diet (including supplements)	7.6 ± 0.1 (21.6 ± 0.1)	8.2 ± 0.1 (26.3 ± 0.4)	9.5 ± 0.1 (27.0 ± 0.4)	8.3 ± 0.04 (24.7 ± 0.1)
Aggregate	7.9 ± 0.1 (22.0 ± 0.1)	8.6 ± 0.1 (27.1 ± 0.4)	9.8 ± 0.1 (27.4 ± 0.2)	8.7 ± 0.04 (25.2 ± 0.2)
Source	Age Group			
Scenario S2b (Most conservative)	18–44	45–54	55 +	All
Cosmetics	0.6 ± 0.01 (3.40 ± 0.1)	0.70 ± 0.01 (3.84 ± 0.04)	0.40 ± 0.01 (2.20 ± 0.1)	0.6 ± 0.01 (3.22 ± 0.03)
Diet (including supplements)	7.6 ± 0.05 (21.5 ± 0.2)	8.29 ± 0.06 (26.5 ± 0.50)	9.50 ± 0.1 (25.7 ± 0.4)	8.3 ± 0.04 (24.3 ± 0.3)
Aggregate	8.1 ± 0.1 (22.2 ± 0.1)	9.02 ± 0.07 (27.6 ± 0.03)	9.88 ± 0.1 (26.8 ± 0.4)	8.9 ± 0.04 (25.3 ± 0.2)

Table 8
USA - Breakdown of Mean (P95 values in brackets) RE absorbed exposure in μg/kg bw/day with standard error values for scenarios S1a, S1b and S2b (no S2a) for each age range and all combined.

Source	Age Group			
Scenario 1a (Realistic)	**18–44**	**45–54**	**55+**	**All**
Cosmetics	0.32 ± 0.01 (1.34 ± 0.04)	0.40 ± 0.01 (1.85 ± 0.10)	0.33 ± 0.01 (1.76 ± 0.1)	0.34 ± 0.01 (1.52 ± 0.03)
Diet (including supplements)	10.7 ± 0.04 (29.3 ± 0.28)	12.0 ± 0.10 (30.5 ± 0.05)	15.4 ± 0.13 (38.9 ± 0.5)	11.9 ± 0.04 (30.9 ± 0.15)
Aggregate	11.0 ± 0.04 (29.6 ± 0.08)	12.4 ± 0.10 (30.8 ± 0.16)	15.8 ± 0.13 (39.4 ± 0.6)	12.2 ± 0.04 (31.6 ± 0.14)
Source	Age Group			
Scenario 1b (Exaggerated occurrence data)	**18–44**	**45–54**	**55+**	**All**
Cosmetics	0.4 ± 0.01 (1.8 ± 0.05)	0.5 ± 0.01 (2.7 ± 0.1)	0.4 ± 0.01 (2.5 ± 0.1)	0.4 ± 0.01 (2.2 ± 0.04)
Diet (including supplements)	10.6 ± 0.04 (28.8 ± 0.2)	11.9 ± 0.1 (30.5 ± 0.02)	15.4 ± 0.1 (38.7 ± 0.4)	11.8 ± 0.04 (30.7 ± 0.1)
Aggregate	11.0 ± 0.05 (29.6 ± 0.1)	12.4 ± 0.1 (30.8 ± 0.2)	15.8 ± 0.1 (39.2 ± 0.6)	12.2 ± 0.04 (31.6 ± 0.1)
Source	Age Group			
Scenario 2b (Most conservative)	**18–44**	**45–54**	**55+**	**All**
Cosmetics	0.7 ± 0.01 (3.4 ± 0.1)	1.0 ± 0.03 (5.1 ± 0.2)	0.63 ± 0.02 (3.20 ± 0.1)	0.8 ± 0.01 (3.8 ± 0.1)
Diet (including supplements)	10.6 ± 0.04 (29.0 ± 0.2)	12.0 ± 0.07 (30.5 ± 0.08)	15.7 ± 0.1 (39.5 ± 0.8)	11.8 ± 0.04 (31.0 ± 0.2)
Aggregate	11.3 ± 0.04 (30.6 ± 0.3)	13.1 ± 0.1 (31.4 ± 0.2)	16.3 ± 0.1 (41.9 ± 1.3)	12.6 ± 0.04 (33.0 ± 0.1)

the total female population, with cosmetics providing only a very small contribution (2–5%) in all cases.

For the more conservative scenarios, the resulting contribution to the aggregate absorbed exposure at P95 is approximately 7% for S2a and S1b, and approximately 13% for the most conservative exposure in S2b.

4. Discussion & conclusions

Aggregate exposure assessments should be performed using a tiered approach (Delmaar and van Engelen, 2006; Meek et al., 2011), where the lowest tier (0) consists of a rough sum of exposure to each product, the middle tier (1) tends to be a semi-quantitative estimate, such as a deterministic estimate with conservative assumptions, and the highest tier (2) is a more realistic estimation of population exposure that is modelled using probabilistic methods and a person-oriented approach. The low tier estimates can be calculated quickly yielding conservative exposure values, and if this approach is lower than the “safe” toxicological exposure dose, then it may not be necessary to move to a higher tier. While exposure assessments at tier 2, using person-oriented probabilistic approaches to estimate exposure in populations, can be data-intensive and time consuming, they produce more refined and accurate estimates of population exposure, enabling the risk assessor to feel confident that the risk assessment is applicable to the population of interest. Another tier 2 refinement that more accurately reflects aggregate exposure estimations in populations is the incorporation of occurrence data, which describe the likelihood the ingredient is present in a product, since only the consumers using products containing the ingredient will be exposed. Incorporation of occurrence data into exposure assessments is being done already in the area of food safety (Mistura et al., 2013) and cosmetics safety (Tozer et al., 2015).

In this study, a tier 2 reliable and realistic model of vitamin A exposure in women has been developed using probabilistic techniques, occurrence data and a person-oriented approach. The data from this model provides a comprehensive assessment of the aggregate exposure of vitamin A, expressed as RE, coming from food, supplements, and cosmetic sources in both European and North American adult women populations.

From toxicological and clinical data, vitamin A has been deemed safe for use when total exposure does not exceed the Tolerable Upper Intake Limit (UL) 3000 μg Retinol Equivalents (RE) per day (SCF, 2002; VKM, 2012; EFSA, 2015), which equals 50 μg/kg bw/day intake for a 60 kg adult. The critical effect used for risk assessment purposes is teratogenicity (i.e., birth defects) based on human data with high intakes of vitamin A (Rothman et al., 1995). The No Observed Effect Level (NOEL) from retinol exposure in the diet and dietary supplementation is 4500 μg RE per day (equivalent to 75 μg/kg bw/day). The NOEL is divided by an Uncertainty Factor of 1.5 to account for inter-individual variability of susceptibility to adverse effects. The UL of 3000 μg/day equates to an internal exposure of 45 μg/kg bw/day in a 60 kg female, assuming 90% oral bioavailability. The results of this exposure study show that European and USA women (all age groups) are well below the UL.

In its 2002 opinion, the European Commission Scientific Committee on Food (SCF, 2002) advised to restrict RE intake to 1500 μg/day (equivalent to 25 μg/kg/day for a 60 kg adult) for postmenopausal women, who are at greater risk of osteoporosis and fracture. This recommendation is based on the reported associations between vitamin A and bone mineral density and the risk of bone fracture (Melhus et al., 1998) (Feskanich et al., 2002), but remains controversial as the available data did not provide sufficient evidence of causality, due to the possibility of residual confounding factors, and the data are not appropriate for establishing a UL. The European Food Safety Authority (EFSA, 2015) also could not establish quantitative correlations between retinol intake and bone health risk justifying the establishment of a lower UL for a specific population subgroup (elderly people). However, EFSA recommended a precautionary maximum intake of 1500 μg RE per day to serve as a guidance level (GL) for persons at a greater risk of osteoporosis and bone fracture (particularly postmenopausal women) until new data indicates the necessity of re-evaluation. This GL equates to an internal exposure of 22.5 μg/kg bw/day in a 60 kg female, assuming 90% oral bioavailability.

Previously, the Norwegian Scientific Committee for Food Safety conducted an aggregate exposure estimate for dietary and cosmetic sources in various human populations including adult women (VKM, 2012). The dietary study, based on two 24-h recalls, was analysed and a P95 intake of 1983 μg RE/day (29.75 μg RE//kg bw/day absorbed dose if assuming 90% oral absorption and 60 kg bodyweight) was estimated in adult women from supplements and diet. This estimate is similar to the dietary exposure estimates reported in this study, which were also based on assessments of dietary survey results from individual subjects. Other studies are supportive of the conclusion that dietary intakes are well below the tolerable UL. According to Flynn et al. (2009), in adults, the P95 intake of retinol from base diet ranged from about 400 μg/d (Spain) to about 2400 μg/d (Germany) in men and from about 280 μg/d (Spain) to about 1770 μg/d (Finland) in women. This corresponds to 13–80% and 10–58% of the UL in men and women, respectively. Jenab et al. found that for men, the mean intake of retinol from dietary

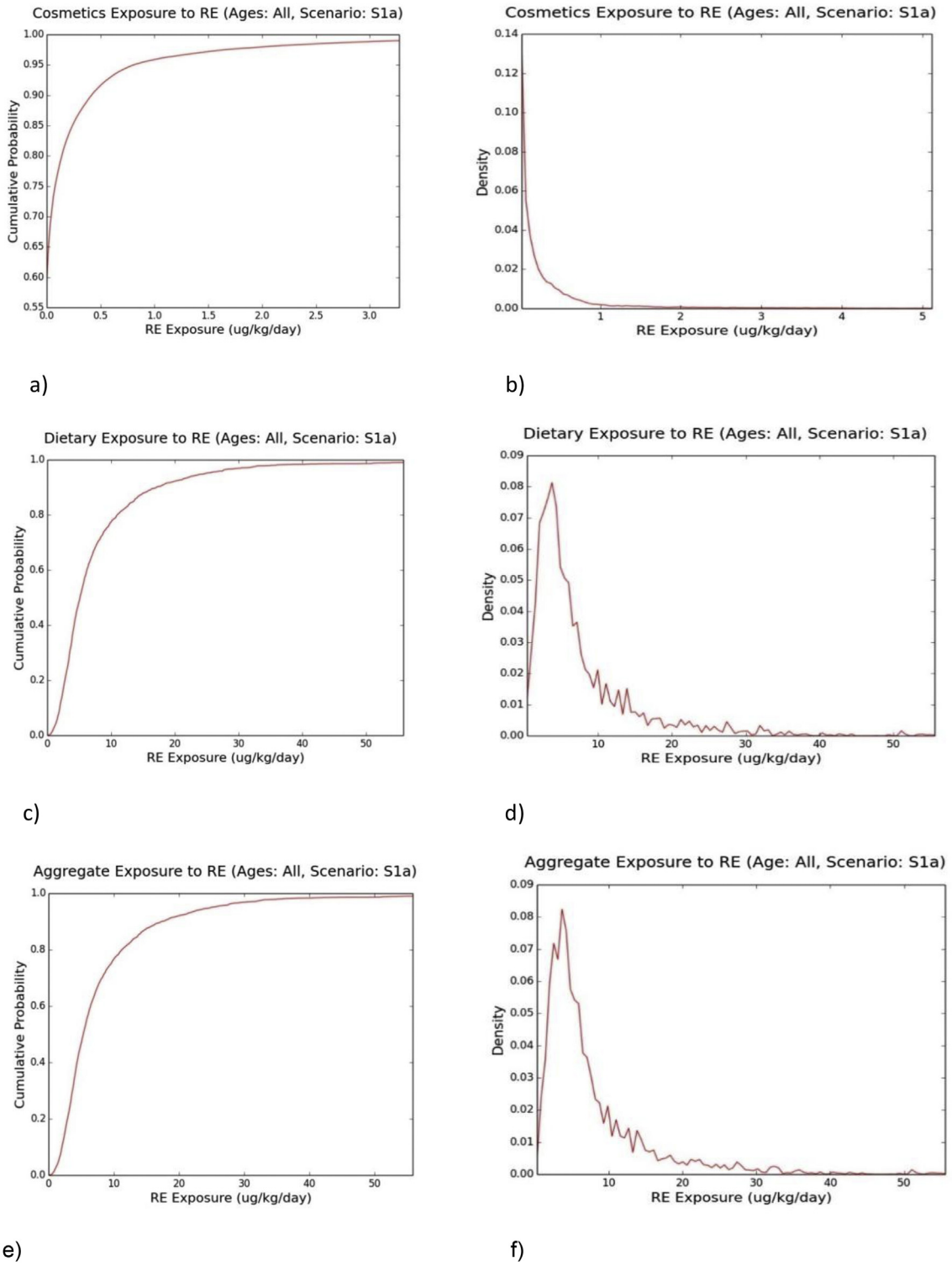


Fig. 4. European Population: Cumulative probability (a,c,e) and probability density functions (b,d,f) graphs are shown above for scenario S1a. Cosmetics exposure (a,b), dietary exposure (c,d) and aggregate exposure (e,f) are shown. * EU Tolerable Upper Intake Limit (3000 μg/day; 45 μg/kg/day internal exposure dose (IED).

sources ranged from 422 (Granada, Spain) to 1715 μg/day (Malmö, Sweden), whereas for women the range was 241 (Ragusa, Italy) to 1219 μg/day (Umea, Sweden).

The exposure estimate in cosmetics by the Norwegian Scientific Committee for Food Safety was a deterministic estimate - using exposure values from the SCCS Notes of Guidance (SCCS - for leave on products for two scenarios: a standard scenario (0.05% RE for body lotion and 0.3% RE for face cream and hand cream) and the worst case scenario (0.3% RE for body lotion and 1% RE for face cream and hand cream). For the standard and worst case scenarios, respectively, they estimated an absorbed retinol dose of 856 μg/day and 3446 μg/day (14 μg/kg bw/day and 57 μg//kg bw/day and assuming 60 kg bodyweight). These deterministic estimates from the Norwegian authorities grossly overestimate exposure to RE from cosmetics; firstly, they assume that all body lotion, hand cream and face cream that a consumer uses contains RE, which is very unrealistic, and secondly, they assume

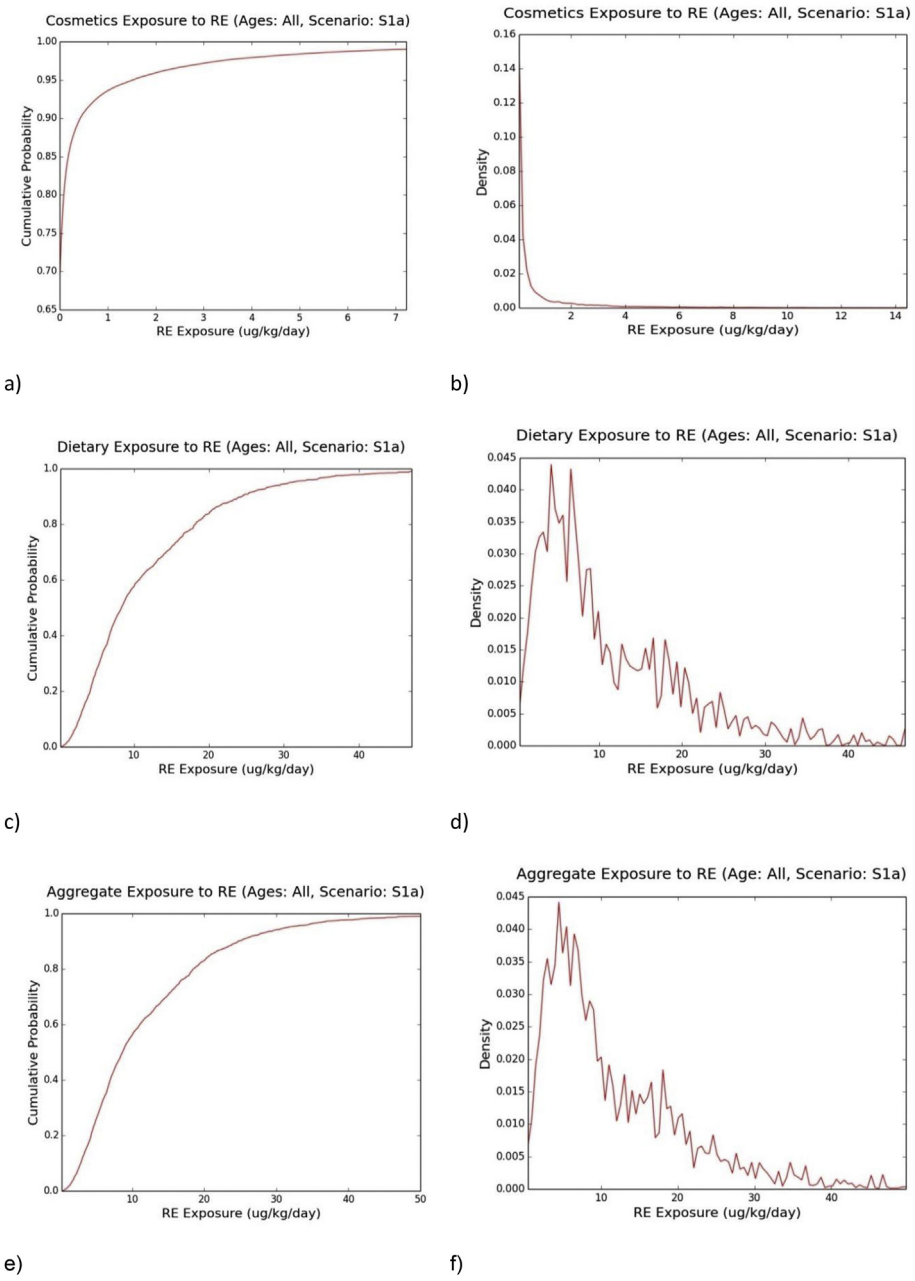


Fig. 5. USA Population: Cumulative probability (a,c,e) and probability density functions (b,d,f) graphs are shown above for scenario S1a. Cosmetics exposure (a,b), dietary exposure (c,d) and aggregate exposure (e,f) are shown. * EU Tolerable Upper Intake Limit (3000 μg/day; 45 μg/kg/day internal exposure dose (IED).

that everyone used P95 usage amounts for each of the three products on each occasion.

In the SCCS Opinion for vitamin A, a deterministic aggregate exposure estimate for cosmetics alone was calculated, leading to an estimated systemic exposure dose (SED) of 24.3 μg RE/kg/day (with lipstick products) and 21.3 μg RE/kg/day (without lipstick products). We propose that the current study where exposure is modelled using probabilistic approaches in Creme Care and Cosmetics using subject-based usage data and occurrence data on RE in products provides a much more refined, scientifically robust and realistic exposure estimate that is more relevant for safety assessment. Taking the worst case scenario 2b calculations for cosmetics exposure, yields values of 3.2 μg/kg/day (Europe) and 3.8 (USA) μg/kg/day, significantly lower than the Scientific Committee on Consumer Safety, 2017 estimates from a deterministic approach.

The occurrence data is used to model exposure more accurately by considering that RE are only added to a certain portion of cosmetic and personal care products, as opposed to assuming that the ingredients are always present in a given category, which leads to a significant overestimation of exposure. This methodology is standard in the area of food exposure assessment; in Europe, exposure to food additives is assessed using a tiered approach with the use of occurrence data (Bemrah et al., 2008; Le Donne et al., 2017; Mistura et al., 2013; Martyn et al., 2016). In these studies, the use of probabilistic modelling with concentration and occurrence data enabled relevant population samples to be modelled capturing variability in the formulations of products. Moreover, we can be confident in these data as Mintel GNPD data examined over the last 10 years (2007–2016)(Fig. 2) show that the use of RE in cosmetic and personal care products is either stable or decreasing, which suggest that it is unlikely that we would see an increase in the occurrence beyond current levels in the future. Nevertheless, we have been conservative in the approach here by rounding values up to the

Table 9
Qualitative (tier 1) evaluation of the influence of uncertainties on the estimate of exposure.

Assumption	Direction and Magnitude of Uncertainty	Comments
Frequency of use data from the Kantar diary (France, Germany, Spain and Great Britain) for cosmetic products of interest (excluding eye shadow, mascara, face powder, blusher, eyebrow pencil, make up remover, eye cream) representing frequency of use data for these products amongst all EU citizens.	+/−	Good quality data, with low potential to cause overestimation or underestimation
Frequency of use data from the Netherlands (Biesterbos, 2012) for eye shadow, mascara, face powder, blusher, eyebrow pencil, make-up remover representing frequency of use data for these products amongst EU and US citizens.	+/−	Good quality data, with low potential to cause overestimation or underestimation
Frequency of use data from P&G for eye cream representing frequency of use data for these products amongst EU and US citizens.	+/−	Good quality data, with low potential to cause overestimation or underestimation
Frequency of use data from the Dutch (DNFCS), Irish (IUNA), and UK (NDNS) dietary surveys representing frequency of use data for foods amongst EU citizens.	+ +/− -	Sufficiently representative data but there may be some gaps in knowledge for specific countries which could mean these data overestimate or underestimate and average for the EU population
Amount per use data from the Cosmetics Europe studies for cosmetics and additional data from the CTFA and Biesterbos studies for certain cosmetics representing amount per use data for these products amongst EU and US citizens.	+ +/− -	Sufficiently representative data but there may be some gaps in knowledge for specific countries which could mean these data overestimate or underestimate and average for the EU population
Amount per use from the Dutch (DNFCS) Irish (IUNA), and UK (NDNS) national dietary surveys representing amount per use data for food amongst EU citizens.	+ +/− -	Sufficiently representative data but there may be some gaps in knowledge for specific countries which could mean these data overestimate or underestimate and average for the EU population
Amount per use from NHANES dietary surveys representing amount per use data for food amongst US citizens.	+ +/− -	
The Mintel GNPD database contains a comprehensive list of cosmetic products sold across the European Union and North America	+/−	Good quality data, with low potential to cause overestimation or underestimation
Occurrence from the GNPD database is representative of the likelihood of consumer use of cosmetic products.	+/−	Good quality data, with low potential to cause overestimation or underestimation
Reported concentrations by BfR, 2014, CIR 1987, 2008; Fiume and Heldreth (2017),Ries and Hess (1999); VKM, 2012 and internal databases in P&G are representative of products available on the market.	+ +	Conservative estimates have been used, therefore exposures are likely to be moderately overestimated
The potential for brand loyalty (Arcella et al., 2003), e.g. to always buy the same product containing a high % of ingredient.	–	High end users and upper end concentrations have been included, but 100% high end use by an individual is not assumed.

* Key to direction and magnitude.
+, + +, + + + = uncertainty likely to cause small, medium or large over-estimation of exposure.
-, - -, - - - = uncertainty likely to cause small, medium or large under-estimation of exposure.

nearest 5%. We appreciate that the currently available databases are only available commercially, which makes regulatory scrutiny of modelling approaches more challenging than if occurrence data were available in the public domain.

In the European population, our study shows that the mean internal aggregate exposure to vitamin A from the realistic scenario S1a is 8.6 ± 0.04 μg/kg bw/day, which is well below the GL. The diet is the biggest contributing factor in aggregated exposures above the GL at P95 in high-end exposed post-menopausal women (P95 27.3 ± 0.3 μg/kg bw/day). The internal exposure to RE from the use of all cosmetic products in the realistic scenario is low (P95 of the realistic scenario is 0.80 ± 0.01 μg/kg bw/day for all countries combined, all age groups), and provides only a very small fraction of the total internal aggregate exposure of 25.0 ± 0.20 μg/kg bw/day across all age groups (approximately 3% at P95).

In the more conservative scenarios for the European population, where it is assumed that the concentration of RE in the cosmetic products is higher than exists realistically today – fixed at 0.3% in all cosmetics (S2a), or that more cosmetic products on the market contain RE (S1b), or that both of these assumptions are true (S2b), the resulting mean internal aggregate cosmetics exposures are respectively higher: S2a 1.71 ± 0.03 μg/kg/day, S1b 1.56 ± 0.03 μg/kg/day, 2b 3.22 ± 0.03 μg/kg/day. The internal aggregate exposure from all sources (age groups combined) in this most conservative scenario (S2b) is 25.3 ± 0.2 μg/kg/day, which is still well below the UL, and only slightly above the GL.

In the USA population, our study shows that the mean internal aggregate exposure to vitamin A from the realistic scenario S1a is 12.2 ± 0.04 μg/kg/day, which is well below the GL. However, the contribution from the diet in all age groups at P95 of the distribution, at 30.9 ± 0.15 μg/kg/day (leading to an aggregate of 31.6 ± 0.14 μg/kg/day), is above the GL for people at greater risk of osteoporosis and bone breakage, but still below the UL (45 μg/kg/day). The highest value for P95 in post-menopausal women reaches 41.9 ± 1.3 μg/kg/day for the most conservative S2b scenario (this is above the GL and below the UL). This reflects the higher use of vitamin A-containing dietary supplements by post-menopausal women in the USA compared to Europe. The internal exposure to RE from the use of all cosmetic products in the realistic scenario is low (P95 of the realistic scenario is 1.52 ± 0.03 μg/kg/day for all age groups), and provides only a very small fraction (4.8%) of the total internal aggregate.

Vitamin A is also an essential micronutrient to keep the body healthy and the World Health Organisation specify a recommended daily intake (RDI) of 8.5 μg/kg/day to avoid vitamin A deficiency. EFSA (2015) has specified a population reference intake (PRI) (the level of (nutrient) intake that is adequate for virtually all women in a population group) of 11 μg/kg/day (650 μg/day). The data from this study would suggest that on average, particularly younger women (age 18–44) in Europe fall short of the WHO RDI, whereas women in the USA, on average are exposed to levels around the EFSA PRI.

In any exposure assessment there are always uncertainities in the data and in the past decade, the European Foods Standards Agency (EFSA, 2006) have proposed methods to make such uncertainties more transparent in the reporting of an exposure assessment. Several factors might influence the uncertainty of our aggregate exposure assessment and using the EFSA approach, uncertainties around factors of the data we can identify have been documented with the direction of the effect (overestimation/underestimation potential) noted (Table 9).

The current assessment does not include the potential of brand loyalty, which is defined as the tendency of consumers to purchase and consume the same products repeatedly (EFSA, 2006), and which could in theory result in a high exposure level by individuals who regularly use products that contain a high concentration of the ingredient of interest. This is a source of uncertainty in the current analysis and it is possible that the estimated exposure for brand-loyal individuals who are regular consumers of products containing high concentrations of RE may be underestimated (Arcella et al., 2003). However, on balance, this aggregate exposure model was designed to adopt conservative approach that is still likely to present an overestimate of exposure, including the use of the high end point estimates of concentration data and the rounding up of occurrence data to the next highest 5%.

Overall, this study confirms that exposure to vitamin A from cosmetic products is very low (2–5%) in relation to total estimated exposure to vitamin A in European and North American women. The conservative aggregate exposure estimates to retinoids, derived in this project from the diet, dietary supplements, and from cosmetics is below the UL, which supports the lack of a teratogenicity concern from current uses. By far the major source to aggregate exposure to vitamin A is from diet, including the use of supplements and estimated exposure is greater in the North American population than the European population. While there is a potential concern for total exposure to vitamin A in North American women at risk of osteoporosis and bone breakage (i.e., 95th percentile aggregate exposure was greater than the GL), the conservative nature of the aggregate exposure scenarios in this manuscript should be considered. In addition, recent epidemiological evidence has called into question the association between high serum retinol concentrations and bone fracture (Holvik et al., 2015).

Acknowledgments

This work was funded by Procter & Gamble.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.05.057.

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