Australian Government
Department of Health, Disability and Ageing
Australian Industrial Chemicals Introduction Scheme

Retinol and retinol esters

Evaluation statement (EVA00187)

26 June 2026

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Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemicals in this group are retinol and retinol esters, listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation will focus on determining whether the identified health hazards for this group of chemicals are appropriately risk managed for the range of reported industrial uses.

The chemicals in this evaluation will be referred to as follows:

- CAS No. 68-26-8 will be referred to as retinol
- CAS No. 79-81-2 will be referred to as retinyl palmitate
- CAS No. 127-47-9 will be referred to as retinyl acetate
- CAS No. 631-89-0 will be referred to as retinyl linoleate
- CAS No. 7069-42-3 will be referred to as retinyl propionate.

This evaluation will not assess the risk of these chemicals in food or therapeutic goods, as these are not industrial uses under the *Industrial Chemicals Act 2019*.

Summary of evaluation

Summary of introduction, use and end use

Based on available information, the chemicals in this group are used in a range of personal care products (cosmetics), including face creams, body lotions and hand creams available to consumers in Australia.

The chemicals in this group have non-industrial uses, including in food, food supplements and topically applied therapeutic goods. They are also naturally present (as preformed vitamin A) in foods.

Human health

Summary of health hazards

Based on the available data, these chemicals:

- have low acute oral toxicity
- are not likely to be genotoxic.

The available data from studies in animals and humans, indicate that this group of chemicals is expected to cause adverse effects on development of the unborn child. The weight of evidence indicates this is primarily driven by transformation of these chemicals to the biologically active metabolite, retinoic acid.

The teratogenic effects of retinoic acid are well established. Similar teratogenic effects, specifically relating to abnormal development of the spine, deformities of limbs and craniofacial malformations, have been reported in animal studies and observed in humans following exposure to the chemicals in this group. The available data indicate that the type and incidence of teratogenic effects is dependent on the timing at which exposure occurs, with the critical period in early stages of pregnancy. Overall, there is sufficient evidence that the chemicals are human developmental toxicants, warranting classification.

In addition to adverse effects on foetal development, a number of other adverse effects have been associated with excessive vitamin A intake in humans, including hepatotoxicity, changes in lipid metabolism and decreased bone density. Based on the observation of severe liver toxicity in humans including fibrosis and cirrhosis, classification is warranted. Although the severity of effects in the liver could not be determined in the available animal studies, the observed effects including changes in organ weights and lipid accumulation support that the liver is the target organ. Effects were observed at doses in the range of 6–13 mg/kg bw/day.

An internationally recognised tolerable upper intake level (UL) has been set at 3000 µg calculated as retinol equivalents (RE)/day based on teratogenicity. This UL is considered sufficiently protective for adverse effects in liver.

Adverse effects on bone health have also been reported at intake levels ≥ 1500 µg RE/day. Although causality has not been conclusively established, this value has been used internationally as an intake guidance level (GL) for individuals at greater risk of osteoporosis and bone fracture (particularly post-menopausal women).

The available data from studies in animals and humans, suggests these chemicals may have irritation potential, particularly following repeated exposure, but are unlikely to induce skin sensitisation. Cases of skin irritation in humans have been reported following topical application of products containing retinoids. Based on the available data, the retinol esters in this evaluation are at most, slightly irritating to the eye. Limited data are available for retinol. In the available study the chemical caused reversible eye irritation (conjunctival redness > 2).

No inhalation data are available, and limited data are available to evaluate carcinogenicity.

For further details of the health hazard information see **Supporting information**.

Hazard classifications relevant for worker health and safety

The chemicals in this group satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards. The eye irritation classification applies to retinol only.

Health hazards	Hazard category	Hazard statement
Serious eye damage/ eye irritation	Eye Irrit. 2B	H320: Causes eye irritation
Reproductive toxicity	Repr. 1A	H360D: May damage the unborn child
Specific target organ toxicity (repeated exposure)	STOT Rep. Exp. 1	H372: Causes damage to organs through prolonged or repeated exposure

Summary of health risk

Public

Based on the available use information, the public may be exposed to these chemicals in personal care products (cosmetics) by direct application of these products to the skin, hair or lips. Given the widespread use of these chemicals, it is likely a person would use more than one product containing one or more of chemicals per day.

The chemicals are members of the vitamin A group of chemicals. Vitamin A in cosmetic preparations for topical use at concentrations greater than 1% is classified as Prescription only medicines (Schedule 4).

A comparison of estimated exposures, from a range of personal care products that may be used daily, was compared with the tolerable upper intake level (UL) for teratogenicity (3000 µg RE/day) to estimate risks (see **Human health risk characterisation** section). Based on worst-case scenario, when the chemicals are used daily in all products containing these chemicals at 1% RE, aggregate systemic exposures are estimated to be 3 times the UL for teratogenicity. Daily use of a single product type (body lotion) is estimated to exceed the UL alone, by greater than 2-fold.

A guidance level (GL) of 1500 µg RE/day has also been set for a sub-population of individuals at greater risk of osteoporosis and bone fracture, particularly post-menopausal women. Although causality has not been conclusively established, given the prevalence of anti-ageing face cream products containing these chemicals, exposure is likely in this higher risk sub-population and as such, risks were evaluated. Exposure estimates of both aggregate and individual product types (including body lotion and hand cream), also exceed the GL for effects on bone density. Daily use of a face cream alone, containing the chemicals at 1% RE, contributes to 79% of the GL.

In addition, the public is already exposed to these chemicals through their diet and from use of food supplements and topical therapeutic goods.

Given the identified potential systemic health hazards, the evidence indicates that there is a risk to the public that requires management. The risk could be managed by amending the current listing for vitamin A in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) (see **Proposed means for managing risks** section).

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment.

Worker exposure to these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic health effects and potential for eye irritation, these chemicals could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (refer to **Proposed means of managing risk**).

Proposed means for managing risk

Inventory listing

To align the terms of listing with this latest risk assessment, the term of the Inventory listing for retinol, 15-[(9Z,12Z)-9,12-octadecadienoate] (CAS No. 631-89-0; retinyl linoleate), should be varied under section 86 of the *Industrial Chemicals Act 2019* (IC Act) to update the defined scope of assessment.

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling amend the entry for vitamin A in the Standard for the Uniform Scheduling of Medicines and Poisons Standard (SUSMP).

It is recommended that to manage the potential risk associated with the use of these chemicals that the entry:

- restricts use of these chemicals to a lower concentration in cosmetic products.

Consideration should be given to the following:

- The chemicals are used in a wide range of cosmetic products available in Australia.
- Cosmetic products may contain more than one of the chemicals in this evaluation or other retinoids.
- The chemicals are known human teratogens following oral exposure.
- Calculated risk estimates indicate a person could exceed the UL for teratogenicity either through use of multiple products or individual use of body lotion.
- The individual use of certain products (body lotion, hand cream and face cream) results in systemic exposure exceeding or close to the guidance level (GL) of 1500 µg RE/day set for individuals at greater risk of osteoporosis and bone fracture, particularly post-menopausal women.
- The chemicals are restricted to lower concentrations for cosmetic use overseas. Risk estimates for concentration limits in Europe indicate that exposure could constitute up to 51% of the UL based on teratogenicity and 97% of the GL based on bone density.
- The public is also exposed to these chemicals through their diet and from use of food supplements and topical therapeutic goods.

It is recommended that the delegate also consider amending the current entry to clarify the chemicals covered by entry and the concentrations permitted in topical products. There may be benefit in reporting this concentration as ‘retinol equivalents’ rather than Vitamin A. Consideration should be given to the following:

- Retinol equivalents (RE) is the most commonly used unit to measure amounts of vitamin A.
- Current scheduling restrictions for vitamin A in preparations for internal use, refer to retinol equivalents.
- The UL derived for teratogenicity and the GL set for bone density are both referred to in RE units.
- The term vitamin A is commonly referred to in the available literature as comprising of retinol and the family of structurally similar retinoid molecules associated with the biological activity of retinol (such as retinal and retinol esters). From a dietary context, vitamin A is also taken to include provitamin A carotenoids that are dietary precursors of retinol (EFSA 2015; NHMRC 2006).
- The IUPAC–IUB (now IUPAC–IUBMB) Joint Commission on Biochemical Nomenclature (JCBN), recommended that ‘the term vitamin A should be used as the generic descriptor for retinoids exhibiting qualitatively the biological activity of retinol. This term should be used in derived terms such as vitamin A activity, vitamin A deficiency, vitamin A antagonist’ (IUPAC-IUB, 1982).

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement, including recommended hazard classifications, should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Recommended control measures that could be implemented to manage the risk arising from oral, dermal, ocular or inhalation exposure these chemicals include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

These control measures may need to be supplemented with conducting health monitoring for any worker who is at significant risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health.

Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemicals depend on the physical form and the manner in which the chemicals are used.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The Executive Director is satisfied that the identified risks to human health associated with the introduction and use of these industrial chemicals can be managed.

One of the chemicals in this evaluation (CAS No. 631-89-0) contains a defined scope of assessment, as a term of listing on the Inventory. The identified risks and proposed means for managing those risks are applicable to all the retinol esters in this evaluation. As such, the term of listing for the specific chemical is no longer aligned with the latest risk assessment in this evaluation statement. Therefore, a future variation to update the defined scope of assessment as a term of the Inventory listing is necessary to manage the risks from introduction of the chemical (see **Proposed means of managing risk** section).

Note:

1. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.
2. A person introducing these chemicals should be aware of their obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Grouping rationale

The chemicals in this group are retinol and its structurally similar ester derivatives. They are members of the vitamin A group of retinoid chemicals and are sometimes described as preformed vitamin A.

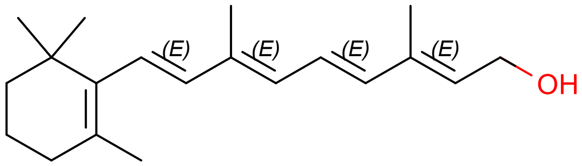
These chemicals have been assessed as a group because they have a common biologically active metabolite (retinoic acid) and similar end uses.

Vitamin A compounds, together with their metabolites and derivatives that exhibit the same properties, are often referred to as retinoids.

The biological activity of different forms of retinoids including retinol, retinol esters, retinaldehyde and retinoic acid is measured using a standardised unit known as retinol equivalent (RE). One RE is defined as the biological activity associated with 1 µg of retinol (CAS No. 38-26-8). Retinol equivalents of 1 mg of different esters are provided in the table below (adapted from SCCS 2016).

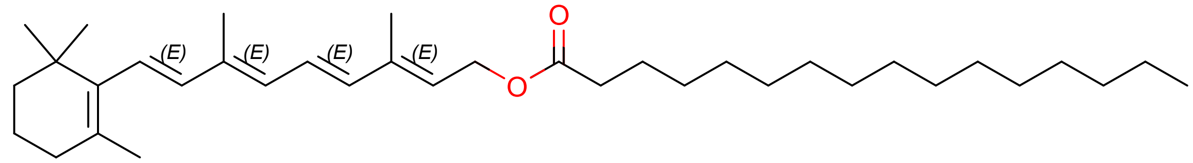
Chemical	Vitamin A activity in retinol equivalents (µg RE)
Retinol (1 mg)	1000 µg RE
Retinyl acetate (1 mg)	870 µg RE
Retinyl palmitate (1 mg)	550 µg RE
Retinyl propionate (1 mg)	840 µg RE
Retinyl linoleate (1 mg)	520 µg RE

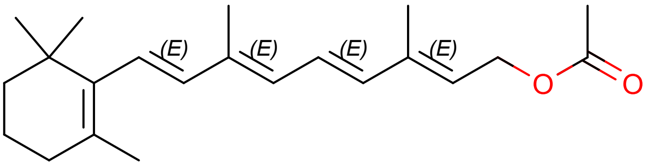
Chemical identity

CAS number	68-26-8
CAS name	Retinol
Molecular formula	$C_{20}H_{30}O$
Associated names	*all-trans*-Vitamin A
Molecular weight (g/mol)	286.45
SMILES (isomeric)	C(=C/C(=C/C=C/C(=C/CO)/C)/C)\C=1C(C)(C)CCCC1C
Structural formula	

CAS number	79-81-2
CAS name	Retinol, hexadecanoate
Molecular formula	$C_{36}H_{60}O_2$
Associated names	Retinol palmitate Retinyl palmitate Vitamin A palmitate
Molecular weight (g/mol)	524.86
SMILES (isomeric)	C(=C/C(=C/C=C/C(=C/COC(CCCCCCCCCCCCCCC)=O)/C)/C)\C=1C(C)(C)CCCC1C

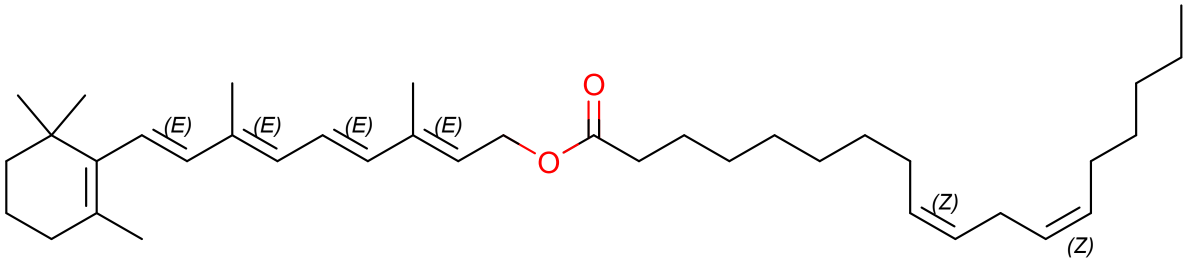
Structural formula



CAS number	127-47-9
CAS name	Retinol, acetate
Molecular formula	$C_{22}H_{32}O_2$
Associated names	Vitamin A acetate Retinyl acetate
Molecular weight (g/mol)	328.49
SMILES (isomeric)	C(=C/C(=C/C=C/C(=C/COC(C)=O)/C)/C)\C=1C(C)(C)CCCC1C
Structural formula	

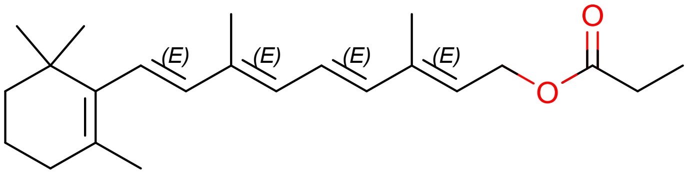
CAS number	631-89-0
CAS name	Retinol, 15-[(9*Z*,12*Z*)-9,12-octadecadienoate]
Molecular formula	$C_{38}H_{60}O$
Associated names	Retinol, linoleate Retinyl linoleate
Molecular weight (g/mol)	548.88
SMILES (isomeric)	C(=C/C(=C/C=C/C(=C/COC(CCCCCCC/C=C\C/C=C\CCCCC)=O)/C)/C)\C=1C(C)(C)CCCC1C

Structural formula



CAS number	7069-42-3
CAS name	Retinol, 15-propanoate
Molecular formula	$C_{23}H_{34}O_2$
Associated names	Retinyl propionate Vitamin A propionate
Molecular weight (g/mol)	342.52
SMILES (isomeric)	C(=C/C(=C/C=C/C(=C/COC(CC)=O)/C)/C)\C=1C(C)(C)CCCC1C

Structural formula



Relevant physical and chemical properties

Chemical	**Retinol**	**Retinyl acetate**	**Retinyl palmitate**	**Retinyl linoleate**	**Retinyl propionate**
Physical form	Pale yellow oil or crystalline solid	Yellow prisms or viscous liquid	Yellow crystalline or amorphous powder		Reddish-brown, oily liquid
Melting point	62-64°C	57-58°C	27-29°C	-	<20°C
Boiling point	421.2°C at 760 mm Hg	440.5°C at 760 mm Hg	607.5°C at 760mm Hg	630.973 ± 34.00 °C at 760mm Hg	453.710 ± 14.00 °C
Vapour pressure	7.5X10-8 mm Hg at 25 °C (Estimated)	-	-	$7.88 \times 10^{-16} \pm 1.85$ mm Hg at 25 °C	$2.02 \times 10^{-8} \pm 1.11$ mm Hg at 25 °C
Water solubility	0.06 nmoL/L (practically insoluble	Insoluble	Insoluble	Insoluble	Insoluble
log K_{ow}	5.68	9.4	15.51 (calculated)	-	9.12 (calculated)

Source: CAS n.d.; EFSA 2013; NCBI n.d.; SCCS 2016.

Introduction and use

Australia

Publicly available information indicate that these chemicals are used as ingredients in personal care products (cosmetics) available for consumers in Australia, at use concentrations potentially up to 1%.

Cosmetic products containing these chemicals, including face cream and serums, moisturiser, nail polish, and lip balm, have been identified on Australian commercial websites.

The chemicals have non-industrial uses in therapeutic goods, including in dietary supplements and topically applied creams (TGA 2026a). They are also naturally present (as preformed vitamin A) in animal-derived foods (NHMRC 2006) and can be used as a nutritive substance in food under the *Australia New Zealand Food Standards Code – Standard 1.3.2 – Vitamins and minerals*.

International

The chemicals in this group are listed in the International Nomenclature of Cosmetic Ingredients (INCI) database (Personal Care Products council n.d.). They are used in a wide range of cosmetic products marketed, or represented, to improve and counteract the appearance of skin aging; these include anti-wrinkle and anti-ageing products (CIR 2008, CIR 2017; DeLima Associates n.d.; EWG n.d; INCI beauty n.d-a; INCI beauty n.d-b; INCI beauty n.d-c; NCBI n.d.; ECHA CHEM n.d.-a; ECHA CHEM n.d-b; ECHA CHEM n.d-c; ECHA CHEM n.d-d; SCCS 2022).

The types of cosmetic products reported to contain these chemicals include:

- body lotion
- face cream and serum
- hand cream
- body wash and bath products
- face wash
- eye cream
- liquid foundation makeup
- deodorant (non-spray)
- nail products
- hair products.

International databases indicate the highest frequency of cosmetic product types containing these chemicals are anti-aging face creams and serums (DeLima Associates n.d.; EWG n.d.; INCI beauty n.d.). Survey data from the United States of America in 2013, indicates that retinol was used in 173 leave-on and 11 rinse-off cosmetic products, while retinyl palmitate was used in 1763 leave-on and 383 rinse-off cosmetic products. Reported concentrations were 0.0001–1.97% in leave-on products and 0.00001–1% in rinse-off products (CIR 2017).

In Europe and Canada, the chemicals are restricted to concentrations that vary based on product type (see **International regulatory status** section).

Existing Australian regulatory controls

AICIS

One of the group members, retinyl linoleate, is listed on the Australian Inventory of Industrial Chemicals (the Inventory) with the following defined scope of assessment as a term of the Inventory listing:

This chemical has been assessed as a component of dermal cosmetic products at concentrations no more than 0.1%. This chemical is not to be used in topical products intended for the eye.

Public

The chemicals in this group are not specifically listed in the *Poisons Standard – The Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP). However, Vitamin A is listed in Schedule 4 (TGA 2026b), as described:

VITAMIN A for human therapeutic or cosmetic use **except**:
(a) in preparations for topical use containing 1% or less of Vitamin A; or
(b) in preparations for internal use containing 3000 micrograms retinol equivalents or less of Vitamin A per daily dose; or
(c) in preparations for parenteral nutrition replacement.

Workers

The chemicals in this group are not listed on the Hazardous Chemical Information System (HCIS) (SWA n.d.).

No exposure standards are available for the chemicals in this group in Australia (SWA n.d.).

International regulatory status

Exposure standards

No specific exposure standards were identified.

Canada

All the members of this group are listed on the Canadian Cosmetic Ingredient Hotlist: List of Ingredients that are Restricted for Use in Cosmetic Products. The chemicals are only permitted in cosmetic products at maximum concentrations of 0.2% total retinol equivalents (RE) in leave-on products intended for full body application, and 1.0% total RE in other cosmetics (Government of Canada 2025).

European Union

Retinol, retinyl acetate and retinyl palmitate are listed in Annex III of the EU Cosmetic Regulation (EC) No.1223/2009 - List of substances which cosmetic products must not contain except subject to the restrictions laid down. The maximum concentration permitted in cosmetic products is restricted to 0.05% RE in body lotions and 0.3 % RE in leave-on and rinse-off products other than body lotion (EU 2009).

Additionally, under Regulation (EC) No.1223/2009, for any cosmetic product containing retinol, retinyl acetate or retinyl palmitate the following labelling is obligatory:

‘Contains vitamin A. Consider your daily intake before use’.

Human exposure

Public

Chemicals in this group are used in a wide range of cosmetic products (see **Introduction and use** section). Therefore, public exposure to these chemicals is expected from use of these cosmetic products. Oral exposure to these chemicals is expected from use of products applied to the lips. Depending on the type of product, dermal contact with cosmetics products can be limited to specific areas on the body such as the eye region, face, hands, nails or feet, or it can be more extensive, covering large areas of the trunk as well as the face. The duration of exposure for various products may differ substantially; for rinse off products such as soaps or shampoos, exposure might only be for a few minutes, although some residual products can remain. Whereas for leave-on products, the period of exposure could last for several hours. Australian use patterns for the various product categories are assumed to be similar to those internationally.

The public exposure to these chemicals in adults was estimated for scenarios relating to their industrial use in personal care (cosmetic products). In this exposure assessment, the reasonable worst-case approach is used, in which estimates are based on worst-case, but plausible, exposure scenarios.

Adult exposure to the chemicals in cosmetic products (see **Table 1** for details) was calculated as an internal dose (systemic exposure dose) which is proportionate to the use volumes (product amounts), product retention factors (reflecting proportions of product remaining on the skin during normal use) and the dermal absorption of the chemicals. The systemic exposure dose has been calculated as retinol equivalents (µg RE). This will enable comparison with established safety limits (see **Public risk** section) and allow the risk calculations to account for exposure to more than one of the chemicals in the same product. For most product types, the use volumes and product retention factors were determined using values previously established by the SCCS (SCCS 2023). For nail products the product amount is based on values for nail polish established by Netherlands National Institute for Public Health and the Environment (RIVM 2025). Product categories were chosen based on typical identified uses of these chemicals (see **Introduction and use** section). A dermal absorption value of 7.74% was used, based on the value set by the SCCS following a review of an available dermal absorption study (see **Toxicokinetics** section). A default absorption value of 100% was assumed for oral exposure.

The concentration of the chemicals in these products was assumed to be 1% as RE. This is based on the exception for vitamin A in topical products in the Poisons Standard (see **Existing Australian regulatory controls - Public** section) and as a worst case assumes retinol (which has the highest RE of the chemicals in this evaluation) is present at 1%.

Table 1: Daily systemic exposure to retinol and retinol esters (as µg RE/day) from cosmetic products if used at 1% RE.

Product type	Amount (mg/day)	C (% RE)	RF (unitless)	Absorption (%)	Daily systemic exposure (µg RE/day)
Body lotion	7820	1	1	7.74	6053
Face cream	1540	1	1	7.74	1192
Hand cream	2160	1	1	7.74	1672
Deodorant (non-spray)	1500	1	1	7.74	1161
Shampoo	10460	1	0.01	7.74	81
Conditioner	3920	1	0.01	7.74	30
Shower gel	18670	1	0.01	7.74	145
Hair styling products	4000	1	0.1	7.74	310
Lip stick, lip balm	5.7	1	1	100	57
Liquid foundation	510	1	1	7.74	395
Nail products	210	1	1	7.74	163
Total	**-**	**-**	**-**	-	**11257**

Daily systemic exposure = (Amount × C × RF × Absorption x1000 µg RE), rounded to the nearest µg
C = chemical concentration; RF = retention factor; BW = body weight

The highest daily systemic exposures to the chemicals were 6053 µg RE, 1672 µg RE and 1192 µg RE from use in body lotion, hand cream and face cream, respectively. Overall, using the worst-case exposure scenario from use of multiple cosmetic products simultaneously by an individual consumer, the exposure is estimated to be 11257 µg RE/day.

The public will also be exposed to the chemicals through its natural presence in food and their non-industrial uses in food, food supplements and topical therapeutic goods. These uses are outside the scope of this evaluation. Information taken from the 2023 National Nutrition and Physical Activity Survey (ABS 2023) indicate that the usual intake of vitamin A (as retinol equivalents) from food and beverages for adults 18 years and over is:

- 808 µg/day (mean) and 1365 µg/day (95th percentile) for males
- 724 µg/day (mean) and 1214 µg/day (95th percentile) in females.

No information was identified for intake of vitamin A from food supplements. The NNPAS survey indicate that one in 3 people took a dietary supplement in 2023.

Health hazard information

Retinol and retinol esters are a part of group of synthetic and naturally occurring vitamin A compounds also known as retinoids. Retinoids are essential for various physiological functions including vision, growth, proliferation of epithelial tissues, immune functions, bone health and embryonic development.

The biological activities of retinoids, including the chemicals in this group, are due to their conversion to the common active metabolite, retinoic acid. Retinoic acid binds to specific cellular and nucleic acid receptor, leading to upregulation of retinoid receptor genes which results in physiological effects (Kurlandsky et al. 1996; SCCS 2022; Theodosiou et al 2010; VKM 2012). An increased expression of retinol and retinoic acid binding proteins, and retinoic acid metabolising enzymes have been reported following both oral and dermal exposure of the chemicals in this group (Kang et al 1995; VKM 2012).

Toxicokinetics

Information available on dietary intake of these chemicals indicate they are readily absorbed (70–90%) by the intestine following ingestion (EVM 2003; EFSA 2015). Several *in vitro* and *in vivo* investigations on dermal absorption in experimental systems are available. However, most of the studies had deviations from the current testing requirements and guidelines. The available studies in both animals and humans demonstrate that topically applied retinol and retinyl palmitate are absorbed, to some extent, into the epidermis and dermis layers of the skin; although a major portion of the applied dose is not absorbed (Duell et al. 1997; Kang et al. 1995; SCCS 2022, VKM2012). A dermal absorption value of 7.74% was selected by the SCCS following a review of available dermal absorption studies. This was based on an *in vitro* study (freshly biopsied human skin) with retinol (0.3%) in an oil-in-water emulsion. The bioavailable portion after 24 hrs was reported as 4.3%. However, due to study limitations (use of only 2 donors for the 6 replicates), the SCCS calculated bioavailability by adding 2 standard deviations to this mean value.

Due to differences in concentrations and vehicles, limited conclusions can be drawn about the comparative absorption of retinol and retinol esters. Antille et al. (2004) investigated penetration into the epidermis (ex vivo human skin) of 4 topical retinoids, including retinol and retinyl palmitate, in oil-in-water creams at 0.05%. The amounts detected in the epidermis were similar for retinol and retinyl palmitate. This indicates that the dermal absorption value for retinol is likely to be representative for the retinol esters. Studies have demonstrated that the rate of dermal absorption is affected by using different vehicles, skin penetration enhancers and carrier systems commonly used in cosmetic products (SCCS 2022; VKM 2012; Yourick et al., 2008).

Retinoid metabolism is complex and involves many different retinoid forms, including retinol esters, retinal, retinoic acid and oxidised and conjugated metabolites of both retinol and retinoic acid. Ingested retinol esters are hydrolysed to retinol prior to entering the intestinal mucosa. Retinol is then absorbed by enterocytes (intestinal absorptive cells) and bound to cellular retinol binding proteins (CRBPs). The CRBP-bound retinol then undergoes re-esterification, primarily by the enzyme lecithin:retinol acyltranferase (LRAT), and incorporated into chylomicrons (lipoproteins), which are released into general circulation via the lymphatic system. Serum lipases then breakdown these chylomicra, releasing the retinol esters into the general circulation, which are subsequently taken up by stellate (fat storing) cells, primarily in the liver. Approximately 90% of the body’s vitamin A is reported to be stored in the liver this way (EFSA 2013; EFSA 2024; EVM 2003; SCCS 2022).

Mobilisation of these vitamin A stores occurs through hydrolysation of retinol esters by retinol ester hydrolase (REH), to retinol. Retinol is then bound to a specific plasma retinol binding protein (RBP4) and released into circulation. Retinol bound to RBP4 enters target tissues. The mobilisation of vitamin A stores is reported to be highly regulated to ensure homeostatic control of the plasma retinol concentrations.

Once inside target organ cells, intracellular retinol can undergo a number of different pathways of metabolism. Retinol can undergo metabolic activation by a 2-step oxidation process, which converts retinol to its active form, retinoic acid. After entering the cell, retinol dehydrogenase (RDH) or alcohol dehydrogenase (ADH) catalyse the oxidation of retinol to retinaldehyde. This first oxidation step of converting retinol to retinaldehyde is reversible. Subsequently, retinaldehyde can be oxidised to retinoic acid by retinaldehyde dehydrogenase (RALDH). This second oxidation step is irreversible (EFSA 2015; EFSA 2024; EVM 2003; Kedishvili 2013; SCCS 2022; VKM 2012; Zasada et al 2019). Oxidation of retinol to all-trans-retinoic acid also occurs in intestinal cells (EFSA 2013).

Cytochrome P450 (CYP) enzymes are reported to catabolise retinoic acid into more water-soluble oxidised and conjugated retinoid forms, which are excreted in faeces and urine.

Limited data are available regarding the metabolic fate of topically applied retinoids. In available human studies no significant increase in plasma levels of retinoids could be detected after repeated topical applications of retinol or retinyl palmitate at low concentrations (SCCS 2016; SCCS 2022; VKM 2012). However, human studies with retinol-based cosmetic products do not provide conclusive information on the toxicokinetics of retinol and its esters after regular skin application (SCCS 2016). Limitations include factors such as the low concentrations of retinoids applied and the smaller area of application compared with values used-by SCCS. In addition, although an increase in plasma levels of retinoids after topical application may not be expected due to the storage capacity and the tightly controlled low-level conversion of retinol to retinoic acid in the skin, it is unclear how this would be impacted with increases to exposure (SCCS 2016; VKM 2012). Topical application is effective in increasing the levels of retinoids in the skin. Studies have demonstrated that the skin has capacity to synthesise cellular RBP and store retinol. Additionally, retinol and retinol esters have been shown to be interconverted in the skin. Topically applied retinol and retinyl palmitate has been shown to trigger biochemical changes (i.e., increased expression of retinol and retinoic acid binding proteins, increased levels of enzymes that metabolise retinoic acid) in the skin. In the study described above, by Antille et al. (2004), application of retinol and retinyl palmitate were shown to increase epidermal levels of retinol and retinol esters but no retinal or retinoic acid was detected. There is a lack of data on the distribution of absorbed retinoids following dermal absorption.

Acute toxicity

Oral

Based on the available data from guideline studies, the chemicals in this group are likely to have low acute oral toxicity.

Several acute oral toxicity studies of retinol, retinyl propanoate or retinyl acetate in mice and rats, conducted similar to Organisation for Economic Cooperation and Development Test Guideline (OECD TG) 401, reported median lethal dose (LD50) values > 2000 mg/kg bw. Sublethal signs of toxicity reported in animals included malaise, decreased motor activity, stupor, muscular weakness, and occasionally changes in gait. Animal mortalities were preceded by convulsions and paralysis (ECHA CHEM n.d.-a; ECHA CHEM n.d. -b, SCCS 2016).

In an acute oral toxicity study, conducted similar to OECD TG 401, retinyl propanoate was administered by gavage to mice (5 animals/sex/dose; strain not specified) at 1717, 2425, 3434 or 4850 mg/kg bw. An LD50 of 1,275 mg/kg bw was reported. However, it is noted that the LD50 may be closer to the limit dose of 2000 mg/kg bw, based on the following mortality rates at each dose: 1717 mg/kg bw (40%); 2425 mg/kg bw (90%); 3434 mg/kg bw (100%) and 4850 mg/kg bw (70%) (ECHA CHEM n.d. d). An LD50 value of 2300 mg/kg bw was reported in similar study in rats (ECHA CHEM n.d.-d). The rat is the preferred species for OECD TG 401.

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

The chemicals are naturally occurring in diet and are commonly used in dietary supplements (NHMRC 2006; TGA 2026a). Acute systemic vitamin A toxicity has reported to occur following ingestion of high dose medications or supplements within a short period typically within hours or days. Reported symptoms include nausea, vomiting, fatigue, abdominal pain (Penniston and Tanumihardjo 2006). In infants, bulging fontanelles linked to an increase in intercranial pressure have been reported at preformed vitamin A intake levels of > 7500 µg RE, as a single dose in infants (SCF 2002).

Corrosion/Irritation

Skin irritation

Based on the available data, the retinol esters in this evaluation are at most slight skin irritants. Although mean scores (based on observations at 24, 48 and 72 hours) of 2.3 or greater were reported in some studies these were not observed in sufficient number of animals to warrant GHS classification (UNECE 2017). No guideline skin irritation studies are available for retinol. There is some evidence of irritation effects, particularly after repeated exposures, in a Buehler assay in guinea pigs (see **skin sensitisation**).

Retinyl propionate

In a skin irritation study, reported as GLP compliant and conducted in accordance with OECD TG 404, retinyl propionate was applied to the skin of New Zealand White (NZW) rabbits (2 males and 1 female) and covered with a semi-occlusive patch for 4 hours. Observations were recorded at 1, 24, 48, 72 hours, 7 and 14 days after patch removal. The following mean scores for individual animals were reported (based on observations at 24, 48 and 72 hours): 2, 2 and 2.3 for erythema and 0, 0 and 0.1 for oedema. Signs of irritation were reversible in all animals within 14 days (ECHA CHEM n.d.-d).

Retinyl palmitate

In a skin irritation study, reported as GLP compliant and conducted in accordance with OECD TG 404, retinyl palmitate was applied to the skin of NZW rabbits (2 female and 1 male) and covered with a semi-occlusive patch for 4 hours. Observations were recorded at 24, 48, 72 hours after patch removal. The following mean scores were reported for individual animals (based on observations at 24, 48 and 72 hours): 1.7 for erythema for all 3 animals and 0 for oedema for all 3 animals. Signs of irritation were reversible in all animals within 14 days. (ECHA CHEM n.d.-c).

Retinyl acetate

In a skin irritation study, reported as GLP compliant and conducted in accordance with OECD TG 404, retinyl acetate was applied to the skin of 3 NZW rabbits (1 female and 2 male) and covered with a semi-occlusive patch for 4 hours. Observations were recorded at 24, 48, 72 hours after patch removal. The following mean scores (based on observations at 24, 48 and 72 hours) were reported for individual animals: 1, 1.7 and 1.7 for erythema and 0 for oedema for all 3 animals. Signs of irritation were reversible in all animals within 14 days. (ECHA CHEM n.d.-b, SCCS 2016).

In a second skin irritation study of retinyl acetate, reported as non-GLP compliant and conducted similar to OECD TG 404, with variations (use of an occlusive dressing and an observation period of less than 14 days) the chemical was applied to the skin of 6 Vienna White rabbits (3 animals/sex) and covered with an occlusive patch for 4 hours. Observations were recorded at 24, 48, 72 hours and 8 days after patch removal. The following mean scores (based on observations at 24, 48 and 72 hours) were reported for individual animals: 2, 2, 2, 2.3, 2.7 and 2.7 for erythema and 0 for oedema for all 6 animals. Signs of erythema and skin scaling were not fully reversible in all animals by the end of the study; however, it was reported that the 8 day observation period was too short for assessment of full reversibility of affects. It is also noted that the chemical was applied to skin under occlusive conditions Signs of oedema were fully reversible in all animals with the 8 days (ECHA CHEM n.d.-b, SCCS 2016).

Eye irritation

Based on the available data, the retinol esters in this evaluation are at most, slightly irritating to the eye. Limited data are available for retinol. In the available study the chemical caused reversible eye irritation (conjunctival redness > 2) warranting classification. Although there is no data on the irritancy potential of the solvent used in this study, this did not negate the need for classification.

Retinol

In an eye irritation study, reported as GLP compliant and conducted in accordance with OECD TG 405, a preparation containing approximately 50% retinol (no data on solvent) was instilled into 1 eye each of 2 male and 1 female NZW rabbits. The eyes were washed out after 24 hours and observed at 1, 24, 48, 72 hours and 8 days. The following individual mean scores (based on observations at 24, 48 and 72 hours) were reported: 0 for corneal opacity for all animals; 0 for iritis for all animals; 2.7, 2.3 and 2 for conjunctival redness; and 1.3, 1.3 and 1.7 for chemosis. Signs of irritation were reported as fully reversible in all animals within 7 days. (ECHA CHEM n.d.-a; SCCS 2016). While the test material was shown to be irritating to the eye, confounding factors such as irritancy potential of the solvent, could not be ruled out with these observations.

Retinyl acetate

In an eye irritation study, reported as GLP compliant and conducted similar to OECD TG 405 with variations (no control, both eyes tested), retinyl acetate was instilled undiluted in the left eye and as a 30% solution in the right eye, of 2 male and 1 female NZW rabbits. The eyes were not washed out, and observations were recorded at 1, 24, 48 and 72 hours. No signs of irritation were observed at 24, 48 or 72 hours in all animals tested with either the undiluted or 30% diluted solution (ECHA CHEM n.d.-b).

In a non-guideline, non-GLP compliant eye irritation study, undiluted retinyl acetate was instilled into 1 eye each of 6 Vienna white, rabbits. The eyes were not washed out, and observations were recorded at 24, 48, 72 hours. No signs of corneal opacity, iritis or chemosis were observed in any of the animals throughout the study. The individual mean scores (based on observations at 24, 48, 72 hours) reported for conjunctival redness were: 0.7, 0.7, 0.7, 1.0, 1.0 and 1.3. This effect was not fully reversible in all animals within 72 hours (ECHA CHEM n.d.-b).

Retinyl palmitate

In an eye irritation study, reported as GLP compliant and conducted similar to OECD TG 405 with variations (no control, both eyes tested), retinyl palmitate was instilled undiluted in the left eye and as a 30% solution in the right eye of 1 male and 2 female NZW rabbits. The eyes were not washed out, and observations were recorded at 24, 48, 72 hours. The following individual mean scores were reported for undiluted administration: 0 for corneal opacity (all animals), 0 for iritis (all animals), 0 for chemosis (all animals), 0; and 0, 0 and 0.1 for conjunctival redness. All signs of irritation (conjunctival redness) were fully reversed within 48 hours. Individual animal data were not provided. No signs of irritation were observed in any animal tested with the 30% diluted solution (ECHA CHEM n.d.-c).

Observations in humans

Cases of mild to moderate skin irritation have been reported following repeated topical application of cosmetic products containing the chemicals in this group (CIR 1987; VKM

2012). However, limited to no information is available on other chemicals contained in these products.

For all topical retinoids the skin irritation effect is dose-dependent, and the adverse effect may be avoided at low concentrations (VKM 2012). Human patch tests (*in vivo* studies) of retinol and retinyl palmitate reported that these chemicals were not irritating to skin at concentration up to 1.6% and 0.6%, respectively.

Retinol was applied to the skin of adult volunteers, at concentrations of 0.4, 0.8 and 1.6% in an ethanol and propylene glycol vehicle (10 adults per group), then covered with an occlusive patch for 4 days. Observations were recorded after patch removal and assessed for signs of erythema. Mean scores were less than 2 (out of a maximum score of 10) for all retinol treatment groups and did not differ significantly from the vehicle control group (Kang et al.,1995).

Retinol and retinyl palmitate were applied to skin of adult volunteers at concentrations of 0.1, 0.3 and 0.6% in an ethanol and propylene glycol or butylated hydroxytoluene vehicle (8 adults per group), then covered with an occlusive patch for 4 days. The chemicals were reported as not irritating to the skin, with erythema not observed at any test concentration (Duell et al.,1997).

Sensitisation

Skin sensitisation

Based on the weight of evidence from the available data, the retinol esters in this evaluation are not likely to be skin sensitisers. A positive response in at least 30% of animals was not observed in any available guinea pig maximisation test (GPMT) studies with retinol esters. The evaluation of available data for retinol was difficult due to a decreasing irritation threshold after repeated topical administration. Although the sensitisation potential cannot be ruled out, data are not sufficient to warrant classification. No clear evidence of skin sensitisation in humans exposed to low concentrations of the chemicals has been identified.

Retinol

In an *in vivo* skin sensitisation study reported as GLP compliant and conducted in accordance with OECD TG 406 (Buehler test), 0.5 ml of a 25% retinol solution in a Lutrol E 400 vehicle, was applied to the skin of 20 female Harlan guinea pigs on days 0, 7 and 14 (induction phase). Control animals were applied vehicle only. Observations were recorded after 24 and 48 hours at each application. No signs of skin irritation were observed after the first induction. However, after the second and third induction applications, discrete or patchy to intense erythema, swelling and scaling were observed in all test group and 3 control animals.

Animals were challenged with a 10% retinol solution in Lutrol E 400, which was applied 2 weeks after the last induction exposure. This was followed by a second challenge 7 days later with a either a 5% or 10% retinol solution in Lutrol E 400.

After the first challenge, similar skin reactions were reported in 17/20 test group animals and 3/10 non-induced control group animals. After the second challenge, positive skin reactions were reported in:

- 16/20 test group and 8/20 control group animals challenged with a 5% retinol solution

- 19/20 test group and 14/20 control group animals challenged with a 10% retinol solution.

Due to the skin reactions noted in test group and control group animals, a third challenge was performed 3 weeks later with a 2.5% retinol solution using a different vehicle (Miglyol 812). Positive responses were reported in 19/20 test group animals and 5/20 control group animals. No reactions were reported in vehicle only control group animals throughout the study (ECHA CHEM n.d.-a; SCCS 2016).

The SCCS, in its review of this data, commented that the decreasing irritation threshold due to repeated topical application, and the use of different vehicles, hampered evaluation of the study. However, the potential for retinol to induce skin sensitisation could not be ruled out (SCCS 2016).

In an open epicutaneous test (OET) in guinea pigs with retinol, inflammatory skin reactions were observed during induction and challenge. These consisted of erythema and swelling, partially with open eczematous appearance, noted in a varying degree and incidence dependent on the induction pre-treatment and the respective applied challenge application. However, results were deemed inconclusive and most likely due to irritation (SCCS 2016).

Retinyl acetate

In a guinea pig maximisation test (GPMT), reported as GLP compliant and conducted according to OECD TG 406, intradermal induction was performed on 20 female Himalayan white spotted guinea pigs using 5% retinyl acetate in olive oil and topical induction with 30% of the chemical. The animals were then challenged with topical application of 10% retinyl acetate in olive oil, 2 weeks and 4 weeks after the intradermal induction. After the first challenge exposure, slight erythema and oedema were reported in 3/20 and 4/20 test group animals at 24 and 48 hours, respectively; these effects were also reported in 5/10 control group animals. No skin reactions were noted in any test group or control group animals after the second challenge exposure (ECHA CHEM n.d.-b; SCCS 2016).

Retinyl palmitate

In a guinea pig maximisation test (GPMT), reported as GLP compliant and conducted according to OECD TG 406, intradermal induction was performed on 20 female Himalayan white spotted guinea pigs using 5% retinyl palmitate in olive oil and topical induction with 100% of the chemical. The animals were then challenged with 30% retinyl palmitate in olive oil, 2 and 4 weeks after intradermal induction. After the first challenge exposure, slight erythema was reported in 4/20 and 2/20 animals at 24 and 48 hours, respectively. No skin reactions were observed in any animal after the second challenge (ECHA CHEM n.d.-c; SCCS 2016).

Retinyl propionate

In a GLP compliant, guinea pig maximisation test (GPMT) conducted according to OECD TG 406, intradermal induction was performed on 10 male and 10 female Himalayan white spotted guinea pigs using 5% retinyl propionate in olive oil and topical induction with 100% of the chemical. The animals were then challenged with 30% of retinyl propionate in olive oil 2 weeks after intradermal induction. Spontaneous mortality was reported in 1 female in the test group. Erythema was reported 24 hours after challenge, only in 1/19 animal which resolved within 48 hours after challenge exposure (ECHA CHEM n.d.-d).

Observation in humans

The chemicals are widely used in topically applied product and while mild to moderate skin irritation effects have been reported, no clear evidence of skin sensitisation in humans has been identified (SCCS 2016).

In a non-guideline study, 14 adult female volunteers were maintained on a vitamin A poor diet and treated topically for 21 days with creams containing 0.30% retinol or 0.55% retinyl palmitate. After approximately 1 week of topical application, skin reactions (rash, itching) at treatment sites were reported in 9/14 and 4/14 subjects treated with retinol and retinyl palmitate, respectively. For 1 subject from the retinol group, moderate to severe reactions were reported and treatment was discontinued for 4 days. In all subjects, skin reactions were reported to either stabilise or subside after approximately 10 to 12 treatment days. It was reported that irritation reactions were transient and mild in retinyl palmitate group compared to moderate reaction observed in retinol group. The chemicals were not considered to induce skin sensitisation based on this study (CIR 2013, VKM 2012,).

In a 21 day cumulative irritation study, 26 volunteers applied 0.2 ml of facial moisturiser containing 0.5% retinyl propionate occlusively for approximately 24 hours per day. No signs of skin reactions were reported (CIR 2013).

In another study, 33 volunteers were instructed to apply a facial moisturiser containing 0.3% of retinyl propionate twice daily for 28 days. One subject was reported to have mild erythema and pruritus after using the moisturiser for one week. Another subject experienced a severe sinus infection. No other effects were reported (CIR 2013).

In silico

The chemicals except retinol have structural alerts for skin sensitisation via protein binding based on the mechanistic (and endpoint-specific) profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox). The alerts included protein binding via an SN2/nucleophilic substitution and acylation. Simulated autoxidation metabolites (including retinol) had alerts for skin sensitisation via protein binding. The alerts for the metabolites included protein binding via Michael addition and acylation.

Simulated metabolites (skin metabolism simulator) of retinol have alerts for skin sensitisation via protein binding. The alerts for the metabolites included protein binding via Michael addition and Schiff base formation.

These chemicals fell out of the defined applicability domains in all skin sensitisation models in OASIS TIMES (LMC 2022). The applicability domain gives an indication of the reliability of predictions based on the structural, molecular features or mechanistic information of the QSAR model.

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 2.2 was utilised to estimate the skin sensitisation potential of the chemicals. The chemicals are not predicted to be skin sensitisers (Lhasa Limited).

Repeat dose toxicity

In addition to adverse effects relating to developmental toxicity (**See Reproductive and developmental toxicity**) a number of other adverse effects have been associated with excessive vitamin A intake in humans, including hepatotoxicity, changes in lipid metabolism and decreased bone density. A 2002 review by the European Commission Scientific Committee on Food (SCF) of available data on preformed vitamin A (retinol and retinol esters), identified lowest doses reported to produce these different effects (SCF 2002). An EFSA review in 2024 analysed new evidence relating to these effects.

Key human data from these reviews and information from available animal data from studies conducted according to or similar to OECD TG are summarised below.

Based on the observation of severe liver toxicity in humans including fibrosis and cirrhosis, classification for Specific Target Organ Toxicity – Repeated exposure Category 1 is warranted according to GHS criteria. Although the severity of effects in the liver could not be determined in the available animal studies the observed effects including changes in organ weights and lipid accumulation support that the liver is the target organ. Effects were observed at doses in the range of 6–13 mg/kg bw/day.

Animal data

In a 90 day dietary exposure study, reported as non-GLP compliant and conducted similar to OECD TG 408, Sprague-Dawley (SD) rats (20 animals/sex/dose) were administered retinyl acetate in feed at 28, 112 or 318 ppm. All animals (including a control group) were fed a basal diet containing average dietary background levels of 2.5–3.4 mg RE/day. Intake of the test substance was reported to decrease during the study. Average weekly intake was calculated as 1.62–3.07, 6.40–12.57 and 18.55–35.79 mg/kg bw/day in females and 1.43–3.32, 5.77–12.97 and 15.98–36.74 mg/kg bw/day in males administered 28, 112 and 318 ppm in diet, respectively. No clinical signs of toxicity, changes in body weights or mortality were observed in any treatment group animals. An NOAEL of 28 ppm was reported (corresponding to 1.43-3.32 mg/kg bw/day in males and 1.62-3.07 mg/kg bw/day in females), based on slightly increased activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the plasma (males only) and lipid accumulation in the Kupffer cells of the liver (both sexes), at higher doses. Numerical values are not reported, and reversibility of effects was not assessed (ECHA CHEM n.d.-b).

In a 90 day dietary exposure study, reported as non-GLP compliant and conducted similar to OECD TG 408, SD rats (20 animals/sex/dose) were administered retinyl acetate in feed at 27,108 or 307 ppm. All animals (including a control group) were fed a basal diet containing average dietary background levels of 2.5–3.7 mg RE/day. Average weekly intake was calculated as 1.54–3.19, 5.87–12.97 and 17.32–37.56 mg/kg bw/day in males and 1.70–2.94, 6.83–11.52 and 19.51–33.07 mg/kg bw/day in females (27, 108 and 307 ppm diet groups, respectively). No clinical signs of toxicity, changes in body weights or mortality were observed in any treatment group animals. An NOAEL of 27 ppm was reported (corresponding to 1.54–3.19 mg/kg bw/day in males and 1.62–3.07 mg/kg bw/day in females), based on effects observed at higher doses, including increased plasma triglyceride levels, increased alkaline phosphatase(ALP) and ALT, lipid accumulation of the Kupffer cells and decrease of the intrahepatocellular lipid droplets, and increased absolute and relative liver weights. Numerical values are not reported, and reversibility of effects was not assessed (ECHA CHEM n.d.-b).

In a 90 day dietary exposure study, reported as non-GLP compliant and conducted similar to OECD TG 408, SD rats (20 animals/sex/dose) were administered retinyl acetate in feed at 66, 263 or 746 ppm. All animals (including a control group) were fed a basal diet containing average dietary background levels of 2.5 mg RE/day. Average weekly intake was calculated as 3.16–7.41, 12.64–29.76 and 36.67–87.06 mg/kg bw/day in males and 3.94–7.71, 15.59–31.26 and 45.11–88.68 mg/kg bw/day in females (66, 263 and 746 ppm diet groups, respectively). No clinical signs of toxicity, changes in body weights or mortalities were observed in any treatment group animals. An NOAEL of 66 ppm was reported (corresponding to 3.16–7.41 mg/kg bw/day in males and 3.94–7.74 mg/kg bw/day in females). This was based on effects observed at higher doses, including increased plasma triglyceride levels, hypercholesterolemia (females), increased ALP (males), high potassium levels (females), lipid accumulation of the Kupffer cells and decrease of the intrahepatocellular lipid droplets, and increased absolute and relative liver weights. Numerical values are not reported, and reversibility of effects was not assessed (ECHA CHEM n.d.-b).

In a 14 day oral toxicity study, mice (5 animals/sex/dose; strain not specified), were administered retinyl propionate via gavage at the following reported doses 24.25, 48.5, 97.0, 194.0 or 388.0 mg/kg bw/day, daily. All animals from the 164 and 388 mg/kg bw/day died after 13 and 7 doses, respectively. Reported signs of toxicity included weight loss, ataxia, respiratory depression, piloerection and hair loss (ECHA CHEM n.d-d). No other details are available.

In 10 month, oral toxicity studies in rats (10 animals/group; strain and sex not specified) and dogs (3 animals/group; breed and sex not specified) were administered retinyl palmitate, 5 days/week for 10 months. Rats were administered the chemical at 5.5, 13.8 or 27.5 mg/kg bw/day by gavage. Dogs were administered 0.6, 2.8 or 13.8 mg/kg bw/day by oral capsules. No adverse effects or mortalities were reported in either the rats or dogs. Body growth and haematological values were reported to be with normal limits for both species (CIR 1987).

Observation in humans

Liver

Vitamin A toxicity in humans has been associated with pathological effects observed in liver, including hepatic steatosis, fibrosis, and cirrhosis. Hepatic steatosis is observed in the early stages resulting from disrupted lipid homeostasis and triglyceride accumulation due to excessive retinoid metabolism. Oxidative stress, inflammation, and stellate cell activation contribute to fibrosis and cirrhosis (Pestalardo et al. 2025).

Chronic toxicity also leads to portal hypertension, hepatomegaly, and impaired liver function, manifesting as abdominal pain, jaundice, and ascites. In many cases, the hepatotoxicity is reversible after the withdrawal of vitamin A. However, in some patients the liver disease progresses after vitamin A withdrawal, from steatosis or fibrosis into micronodular cirrhosis, development which can be fatal. In a case study review of 41 patients diagnosed with a vitamin A-induced hepatic pathology at various levels of severity, 9 (22%) were reported to have died in less than 2 years following diagnosis and disease progression was demonstrated in 3 others (SCF 2002).

Based on case reports of individuals consuming high doses of preformed vitamin A for several years, an intake of 7500 µg RE/day taken over 6 years was identified by the SCF as the lowest reported dose to cause hepatotoxicity (SCF 2002). A subsequent review of available data by the European Food Safety Authority (EFSA) noted that the available evidence is insufficient to characterise the dose–response relationship between the vitamin A intake and liver damage, and that hepatotoxicity occurring at lower than 7500 µg RE/day cannot be ruled out (EFSA 2024).

Bone

Studies have reported that large doses of vitamin A can interfere with calcium and bone metabolism leading to abnormalities such as hypercalcemia, ligamentous calcification, bone pain and osteoporosis. Vitamin A intake at > 1500 µg RE/day has been reported to increase the risk of fractures and reduce bone mineral density. Cases of self-reported increase in fractures had been reported in individuals with vitamin A intakes of over 2000 µg RE/day (Blomhoff 2001; EVM 2003; SCF 2002; VKM 2012). The SCF noted that that further evidence would be required to demonstrate a true cause-effect relationship between vitamin A intake and adverse effects on bone density. However, it was indicated that intake greater than 1500 µg RE/day might pose a risk. An EFSA review in 2024 noted that 'evidence from prospective observational studies in humans on the relationship between the intake of preformed vitamin A at levels below the current UL of 3000 µg RE/day and these endpoints are conflicting'. EFSA concluded that 'the evidence that has become available since the assessment of the SCF (2002) does not support the association between preformed vitamin A at intakes ≤ 3000 µg RE/day and impaired bone health' (EFSA 2024).

Changes in lipid metabolism

Several reports suggest that retinol increases plasma triacylglycerol concentrations in humans (SCF 2002). In a randomised controlled trial (n=2297) changes in lipid metabolism, (2-3% increase in blood serum cholesterol) were reported following a daily dose of 7500 ug RE/day for approximately 4 years (SCCS 2016). Effects on lipid metabolism were considered to be a minor change only but could represent an increase in risk (SCF 2002).

Genotoxicity

Based on the weight of evidence and available data, the chemicals in this group are not likely to have genotoxic potential. Mostly negative results (including negative results in all guideline studies) are reported in the *in vitro* studies. Genotoxic effects were also not observed in the available non-guideline *in vivo* study.

In vitro

Negative results were reported for retinol, retinyl palmitate and retinyl acetate in the following in *vitro studies*.

Retinol:

- Bacterial reverse mutation assays conducted similar to OECD TG 471 in Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 and Escherichia coli WP2 uvrA with and without metabolic activation at concentrations up to 1250 µg/plate (ECHA CHEM n.d.-a).
- Non guideline mammalian gene mutation assay in the hypoxanthine-guanine phosphoribosyl transferase (Hprt) locus in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 25 and 50µM/plate respectively.
- Non-guideline, *in vitro* mammalian chromosome aberration study, in human lymphocytes without metabolic activation at concentrations up to 28.7 µg/ml for retinol (ECHA CHEM n.d. -a).
- Non -guideline, *in vitro* mammalian chromosome aberration study, in Chinese hamster lung V79 cells with and without metabolic activation at concentrations up to 32 µg/ml for retinol (ECHA CHEM n.d. -a).
- Several non-guideline, *in vitro* sister chromatid exchange assays in Chinese hamster V79 cells with and without metabolic activation at concentrations ranging from 16-50 µg/ml (CIR1987; ECHA CHEM n.d. -a).

- Non-guideline, *in vitro* unscheduled DNA synthesis assay in primary rat hepatocytes without metabolic activation at concentrations up to 14.3 µg/ml (ECHA CHEM n.d. -a).

Retinyl palmitate:

- Bacterial reverse mutation assay conducted in similar to OECD TG 471 in Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at concentrations up to 3300 µg/plate (ECHA CHEM n.d.- b, c).

Retinyl acetate:

- Bacterial reverse mutation assay conducted in similar to OECD TG 471 in Salmonella typhimurium TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at concentrations up to 750 and 3300 µg/plate (ECHA CHEM n.d.- b, c).
- *In vitro* micronucleus test (OECD TG 487) in Chinese hamster V79 cells *without* metabolic activation at concentrations up to 31.6 µg/mL.
- Several non-guideline, *in vitro* sister chromatid exchange assays in Chinese hamster V79 cells with and without metabolic activation at concentrations ranging from 16-50 µg/ml (CIR1987, ECHA CHEM n.d. -a).

Positive results were reported in a non-guideline, in vitro sister chromatid exchange assays in Syrian hamster M3E3/C3 cells, without metabolic activation at concentrations up to 24 µg/ml of retinol (ECHA CHEM n.d. -a).

In vivo

In a non-guideline, mammalian erythrocyte micronucleus study, 6 male mice (ddyY strain) were administered retinyl palmitate in olive oil at 37.5, 75, 150, 300 mg/kg bw by intraperitoneal injection as either a single dose or 4 doses separated by 24 hour intervals. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups (CIR 1987).

In silico

The parent chemicals do not have structural alerts for DNA binding based on the mechanistic (and endpoint-specific) profiling functionality of the OECD QSAR Toolbox version 4.5 (OECD 2022). Simulated metabolites (*in vivo* rat metabolic simulator) of the chemicals have a structural alerts DNA binding via AN2, alpha,beta-unsaturated carbonyls, H2 acceptor, Schiff base formation and aldehyde reactions.
The chemicals were predicted to be non-genotoxic using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.31.1) and the expert rule-based system (including NEXUS METEOR simulated metabolites), DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (version 2.6), (Lhasa Limited).

Carcinogenicity

Insufficient data are available to evaluate this endpoint.

In a photocarcinogenicity study in hairless mice (SKH-1 strain), increased incidences and multiplicities of squamous cell neoplasms of the skin exposed to simulated solar light upon topical application of a cream containing retinyl palmitate compared to a control cream were reported (NTP 2012). However, extrapolation of these results from hairless mice to humans were considered inappropriate due to substantial differences in skin physiology, barrier function, and susceptibility to ultraviolet radiation (VKM 2012)

Reproductive and development toxicity

Based on the available data, the chemicals in this group are expected to cause adverse effects on development, warranting hazard classification. The teratogenic potential of this group of chemicals in both humans and animals has been widely reported and reviewed internationally. The weight of evidence from available studies indicate that this is primarily driven by transformation of these chemicals to the biologically active metabolite, retinoic acid.

The teratogenic effects of retinoic acid are well established. Retinoic acid binds to specific retinoic acid receptors (RARs), leading to upregulation of retinoid receptor genes which results in physiological effects. It has been reported that RARs show specific spatio-temporal patterns of expression, particularly during embryonic development. This suggests that retinoic acid signalling is involved in most, if not all, morphogenetic and patterning processes (COT 2022; Kurlandsky et al. 1994; Theodosiou et al. 2010; VKM 2012, SCF 2002).

Similar teratogenic effects, specifically relating to abnormal development of the spine, deformities of limbs and craniofacial malformations, have been reported in animal studies and observations in humans following exposure to the chemicals in this group. A 2002 review by the SCF, of available data on preformed vitamin A (retinol and retinol esters), indicated that teratogenic effects (birth defects) similar to those observed following exposure to retinoic acid or other retinoids have been documented in cases of women who had ingested vitamin A during the early stages of pregnancy (SCF 2002). The SCF found the series of data to confirm the link between excessive vitamin A intake and teratogenesis in humans, which it considered to be well documented in animals including rodents and non-human primates. It has also been indicated that the type and incidence of teratogenic effects depended on the timing at which exposure occurs, with the critical period in early stages of pregnancy. Subsequent international reviews have cited the 2002 SCF opinion, similarly, acknowledging the teratogenic potential of these chemicals in humans (COT 2022; EFSA 2006; EFSA 2015; EFSA 2024; EVM 2002; EVM 2003; SCCS 2016; VKM 2012). Overall, there is sufficient evidence that the chemicals are human developmental toxicants and as such a classification of Reproductive toxicity Category 1A; May damage the unborn child, is warranted.

Key studies relevant to the conclusions of this evaluation are summarised below.

Animal data

In a non-guideline study, a single oral dose of retinyl palmitate (CAS No. 79-81-2) was administered by gavage at 100, 300 or 1000 mg/kg bw to pregnant Riv:TOX rats (22–40 animals/group) on gestational day (GD) 10. All animals (including a control group) were also administered a dietary background level of the chemical at 5 mg/kg feed, over the preceding 6 weeks. Dams were euthanised on GD 11 or GD 21, and morphological assessment of conceptus was undertaken. A dose-dependent increase of the number of congenital malformations was reported, including the frequency of embryos at GD 11 with an open cranial neural tube (8.7% at 100 mg/kg bw, 23.8% at 300 mg/kg bw, 63.4% at 1000 mg/kg bw), compared with embryos from control group animals (1.5%). At GD 21, the high dose group showed an increase in late resorptions and a decrease in live foetuses per dam. Both the medium and the high dose groups had a high incidence of foetuses with malformations (71% and 97%, respectively), which included cleft palate, malformations of the jaw, ears and eyes, and spina bifida; all commonly related to delayed neural tube closure (COT 2022; Piersma et al. 1996).

Similar effects were reported in a second experiment from the above study. Groups of pregnant Riv:TOX rats administered different dietary background levels of retinyl palmitate (1.5, 5, 15, or 50 mg/kg feed) were administered a single oral dose of the chemical on GD 10 at either 0 or 1000 mg/kg bw (14–17 animals/group). Dams were euthanised on GD 11 or GD 21, and morphological assessment of conceptus was undertaken. The increase in delayed neural tube closure, post-implantation loss and the incidence of malformations was similar across the diet groups treated with 1,000 mg/kg bw (COT 2022; Piersma et al. 1996). Maternal effects were not reported, and a lowest observed adverse effect level (LOAEL) or no observed adverse effect level (NOAEL) could not be established from either experiment in this study. It is noted that morphological assessment was only undertaken for live foetuses. Therefore, the occurrence of lethal malformations may be underrepresented in the reported data.

In a non-guideline study, pregnant Swiss-Webster mice (6–10 animals/group) were administered retinol (CAS No. 68-26-8) as a single oral dose at 0 (control groups) or 75 mg/kg bw (treatment groups) by gavage on either GD 7, 8, 9, 10 or 11. Dams were euthanised on GD 18 and morphological assessment of foetuses was undertaken. Teratogenic effects were observed in foetuses from treatment groups in the absence of maternal toxicity. The incidence and types of malformations appeared to relate to timing (GD) of treatment with the chemical. Treatment on GD 8 was reported to produce the highest incidence of embryonic deaths, whereas treatment on GD 10 was reported to not significantly increase the number of malformed foetuses compared with controls. Treatment on GD 7, 8 or 9 induced malformations of the palate, jaw, ears, eyes and head, while treatment on GD 11 induced forelimb development abnormalities. The incidence of unossified sternabrae was reported to be significantly increased in foetuses from dams exposed to the chemical on GD 9, compared with the control group (CIR 1987).

In a non-guideline study, pregnant Swiss albino mice (10-12 animals/group) were administered a single intraperitoneal (i.p.) injection of retinyl palmitate (CAS RN 79-81-2) at 15000 IU/kg (equivalent to 3.0 mg/kg bw), or 2 i.p. injections of the chemical in one day, 10 hours apart, at 10000 or 15000 IU/kg (equivalent to 2 doses of 3.0 mg/kg bw or 2 doses of 4.5 mg/kg bw, respectively, administered in one day). Doses were administered on GD 9, 10, 11 or 12, coinciding with the timing of limb morphogenesis in mouse embryos. Dams were euthanised on GD 18 and morphological assessment of conceptus was undertaken.

A treatment-related and dose-dependent increase in the incidence of foetal limb malformations was reported, with 9 (3.2%) observed following one dose of 3.0 mg/kg bw/day, 49 (17.5%) at 2 doses of 3.0 m/kg bw and 65 (23.9%) at 2 doses of 4.5 m/kg bw. Limb malformations included micromelia (abnormally short limbs), absence of fingers or toes, and an increased cleft between metacarpal or metatarsal bones. A higher frequency of foetal limb malformations was observed in the GD 10–11 groups; the combined incidence across GD10 and 11 were 7 (5.2%) for the single 3.0 mg/kg bw dose group, 33 (23.9%) at 2 doses of 3.0 m/kg bw and 44 (40.0%) at 2 doses of 4.5 m/kg bw. An increase in the number of absorbed embryos was also observed in the GD 10–11 groups, comparative to the control group. Additional malformations were observed in foetuses from the highest maternal exposure group (2 i.p. injections of 4.5 mg/kg bw). These included mandibular hypoplasia (underdeveloped jaw), exencephaly (neural tube defect) and cleft palate (CIR 2013; Rezaei et al. 2009). It is noted that assessment of gross malformations was only undertaken for live foetuses.

In a non-guideline study in pregnant Cynomolgus monkeys (8–29 animals/group depending on dose), retinyl palmitate (CAS No. 79-81-2) was orally (nasogastric gavage) administered at 2.25, 6, 12 or 24 mg/kg bw/day (equivalent to 7500, 20000, 40000 and 80000 IU/kg bw/day) either once daily on GD 16–27, once daily on GD 16–25 then twice daily on GD 26 and 27. The period of exposure was based on an established sensitive period for induction of retinoid embryopathy in monkeys, which occurs during key stages of embryogenesis (gastrulation and neurulation) in this species (Gong et al., 2023; Hendrickx et al. 2000). The dosing regime was not expected to impact results. All animals, including controls, were additionally exposed to vitamin A via their daily food intake. The study was conducted across 2 laboratories with results combined. Foetal growth and development were monitored periodically using ultrasound. Maternal weights were recorded weekly throughout the study. Foetuses were surgically removed between GD 98 and GD 102 for examination.

Signs of maternal toxicity were reported in animals from the 2 highest dose groups (12 and 24 mg/kg bw/day), including erythema, skin rash, epistaxis, rhinorrhoea, swollen eyelids, gingivitis, lip lesions, and alopecia; these were reported as mild to severe signs of hypervitaminosis A. Maternal body weight gain was delayed in animals from the 2 highest dose groups compared to the control group. However, the mean maternal weights of the treated groups were comparable to the control group by the end of the observation period. At the highest dose, moderate to severe decreases in food intake were observed sporadically, which recovered after the cessation of treatment. No signs of maternal toxicity were observed in animals from the 2 lower dose groups (2.25 and 6 mg/kg bw/day).

Treatment-related and dose-dependent increases in foetal malformations and increase in abortions were reported to be statistically significant ($p \leq 0.0001$) (see **Table 2)**. Malformations were primarily observed in the craniofacial region. Malformations of the thymus and heart were observed in single foetuses.

Table 2: Developmental toxicity of retinyl palmitate in cynomolgus macaques (adapted from Hendrickx et al. 2000)

Dose Group (mg/kg bw/day)	No. of animals treated	No. of abortions	No. of malformations
0 (Control)	15	1 (7%)	0/14 (0%)
2.25	25	1 (4%)	0/24 (0%)
6	26	5 (19%)	1/22* (5%)
12	8	3 (38%)	2/6* (33%)
24	29	19 (66%)	5/11* (45%)

* Includes one nonviable foetus available for examination.

The NOAEL and LOAEL for developmental toxicity were reported to be 2.25 mg/kg bw/day (equivalent to 7500 IU/kg bw/day) and of 6 mg/kg bw/day (equivalent to 20000 IU/kg bw/day), respectively, based on abortions and malformations (COT 2022; Hendrickx et al. 2000).

Observations in humans

A number of prospective cohort studies and case-control studies investigating teratogenic effects relating to exposure to preformed vitamin A are available. EFSA concluded that 3 of these studies had low risk of bias:

- A prospective case study (Rothman et al. 1995).
- Two case-control studies (Botto et. al 2001 and Johansen et al. 2008).

The prospective study assessed pregnancy outcome data relative to daily vitamin A intake of 22748 pregnant women. The study cohort was originally recruited between 1984 and 1987 to evaluate risk factors for neural-tube defects. Among these women, 339 had infants with birth defects, and 121 of those infants had abnormalities in structures derived from the cranial neural crest. For defects linked to cranial neural crest tissue, infants born to women who reported to consume more than 15000 IU/day of preformed vitamin A (4500 µg of retinol equivalents (RE) per day) from food and supplements had a prevalence rate 3.5 times higher than those whose mothers consumed 5000 IU/day (1500 µg RE/day) or less (95% confidence interval (CI)). When vitamin A intake from supplements alone was considered, infants of women who consumed more than 10000 IU/day (3000 µg RE/day) had a prevalence rate 4.8 times higher than those whose mothers consumed 5000 IU/day or less (95% CI). A smoothed regression curve suggested a threshold of about 10000 IU/day (3000 µg RE/day) of supplemental vitamin A. The authors observed that a higher frequency of defects occurred among infants whose mothers reported to consume high levels of vitamin A before the seventh week of pregnancy, which covers the period of embryonic development in humans (EFSA 2024; Findlay et al. 2007; Rothman et al. 1995).

The case-control study by Botto et al. investigated the relationship between maternal intake of vitamin A and cardiac outflow tract defects (n=126). Retinol intakes from supplements > 3000 µg RE/day were associated with a higher risk of transposition of great arteries (EFSA 2024). The Johansen et al study investigated association between maternal intake of vitamin A from diet and supplements and risk of having a baby with an orofacial cleft (n=535). No increased risk of orofacial cleft or categories thereof were observed for high intakes of either retinol (> 3398 µg RE/day) or total vitamin A (> 3763 µg RE/day) (EFSA 2024).

In a multicentre prospective study, data for 311 infants born to mothers reported to be exposed to vitamin A at ≥ 10000 IU/day (≥ 3000 µg RE/day) during the first 9 weeks of gestation were evaluated for the presence of major structural malformations. The median dose of vitamin A was 50000 IU/day (range, 10000-300000 IU/day). Among the infants born, 3 infants were reported to have a major malformation. No congenital malformations were reported among 120 infants exposed to more than 50,000 IU/day of vitamin A. The authors concluded that while no evidence was found of an association between major structural malformations and intake of ≥ 3000 µg RE/day, there were potential limitations in the study. This included the information source being mail or telephone interviews with mothers or their doctors (Mastroiacovo et al. 1999). This study was determined by EFSA to have a high risk of bias (EFSA 2024).

A range of case-controlled retrospective studies estimated the intake of vitamin A in mothers of malformed infants, comparative to control subjects. These studies differed in their classification of malformations, statistical power, and the quality of data on vitamin A consumption. Most studies found no association between moderate vitamin A intake (approximately 3000 µg RE) and foetal malformations. In addition, very few women reported consuming high levels of vitamin A, which substantially reduced the ability of these studies to detect any meaningful effect (Azais-Braesco and Pascal 2000; COT 2022).

A range of epidemiological studies have analysed the effects of topical retinoid exposure in pregnant population, including prescription medicines. Among them is a recent Nordic cohort study conducted by Refsum et al. (2026). This is the largest cohort study that has analysed topical retinoid use during pregnancy. Consistent with the previous studies, the study does not show a significant increase in risk of congenital malformations. The study examined the risk of malformations in pregnancies from the therapeutic use of retinoids primarily adapalene (a third generation retinoid) and tretinoin (all-trans retinoic acid) used at very low-concentration (0.025%–0.1%). Therefore, the relevance of these findings for cosmetic uses of retinoids is uncertain. Furthermore, the authors acknowledged several limitations that may have led to an underestimation of the true risk, including the potential for use of retinoid-containing cosmetics in the control group. The authors concluded that a safety precaution to avoid topical retinoid use in pregnancy remained justified (Refsum et al. 2026).

Human health risk characterisation

Critical health effects

A tolerable upper intake level (UL) of 3000 µg RE/day was derived by the SCF in 2002 based on teratogenicity potential. The UL is considered as the maximum level of total chronic daily intake of a nutrient (from all sources) unlikely to pose a risk of adverse human health effects (EFSA 2006; SCF, 2002). Subsequent international reviews support that this UL is still appropriate (SCCS 2016; EFSA 2024; VKM 2012)

Although teratogenicity is only relevant to women of child-bearing age, the SCF considered the UL to be appropriate for men, infants and children, as it is considerably lower than the intake level of 7500 µg RE, at which adverse effects have been reported in those populations. This includes hepatotoxicity and adverse effects on lipid metabolism in adults and bulging fontanelles in infants (SCF 2002).

Exposure to vitamin A has been associated with effects on bone density. Reviews of this data conclude that further evidence is required to demonstrate a true cause-effect relationship; however, 1500 µg RE/day has been regarded internationally as a guidance level (GL) for individuals at greater risk of osteoporosis and bone fracture, particularly post-menopausal women (EFSA 2015; SCCS 2016; VKM 2012).

For assessing the risk from exposure to cosmetic products containing this group of chemicals, the points of departure are best represented by the UL of 3000 µg RE/day and GL of 1500 µg RE/day.

Public risk

To characterise the risk to human health associated with systemic exposure to the chemicals the calculated systemic exposure doses (see **Public exposure** section) were compared to the UL for teratogenicity and GL for bone density effects (see **Table 3**).

For most personal care products, the estimate of systemic exposure to the chemical was less than 50% of the UL, indicating a low health risk to the public from the individual use of these products. However, the exposure estimates for use in body lotion alone at a concentration of 1% resulted in exposure twice the UL. Exposure estimates for use scenarios of body lotion and hand cream also individually exceeded the GL for effects on bone density. Use of the chemicals at 1% concentration in a face cream alone is estimated to result in systemic exposure contributing to 79% of the GL.

In addition, given the widespread use of these chemicals, it is likely a person would use more than one product containing one or more of chemicals per day. The worst-case scenario when the chemicals are used daily in all products results in a combined daily systemic exposure of 11257 µg RE. This is over 3 times the UL and 7 times the GL. A person using only face cream and hand cream have systemic exposure contributing to 95% of the UL and nearly twice the GL.

Table 3- Contribution of worst-case daily systemic exposure to this group of chemicals from cosmetic products as a percentage of the UL and GL

Product type	Daily systemic exposure (µg RE/day)	% of UL based on teratogenicity	% of GL based on bone density
Body lotion	6053	202	404
Face cream	1192	40	79
Hand cream	1672	56	111
Deodorant (non-spray)	1161	39	77
Shampoo	81	3	5
Conditioner	30	1	2
Shower gel	145	5	10
Hair styling products	310	10	21
Lip stick, lip balm	57	2	4
Liquid foundation	395	13	26
Nail products	39	5	11
Total	**11257**	**371**	**742**

Daily systemic exposure, calculated as µg RE/day for a 60 kg adult; UL = upper intake level of 3,000 µg RE/day; GL = guidance level of 1,500 µg RE/day.

The SCCS reviewed the risk of the chemicals in cosmetic products at concentrations of 0.05% in body lotion and 0.3% RE for other leave-on and rinse-off products. The SCCS estimated that exposure *via* all cosmetic products (including lip products) may lead to daily systemic dose of 24.3 RE µg/kg bw/day (SCCS 2016). This is equivalent to 1458 µg RE for an adult of 60 kg (SCCS 2016). This exposure equates to 51% of the UL based on teratogenicity and 97% of the GL based on bone density.

In a re-review of the chemicals safety in 2022 the SCCS concluded that the chemicals are safe in cosmetics at the concentrations of 0.05% Retinol Equivalent (RE) in body lotion, and 0.3% RE for other leave-on and rinse-off products. However, it noted that the contribution to overall public exposure from cosmetics may be of concern for consumers with the highest exposures from other sources (food and food supplements). The SCCS considered it ‘beyond the scope of the SCCS to suggest maximum concentration limits that take into account contributions from other sources e.g. food, food supplements’ (SCCS 2022).

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