

RISK PROFILE

Beta-sitosterol

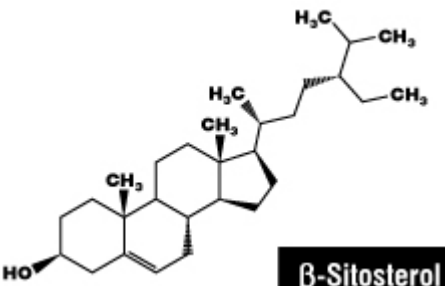
CAS No.83-46-5

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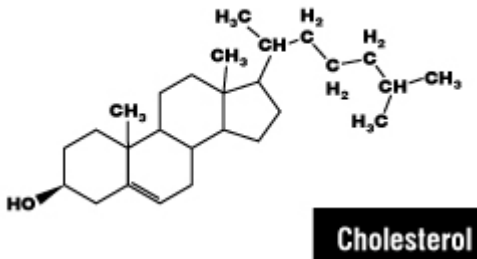
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1. Identification of substance

Chemical name (IUPAC):	Stigmast-5-en-3-.beta.-ol
INCI	Beta-sitosterol
Synonyms	24-Ethylcholest-5-en-3beta-ol; alpha-Dihydrofucosterol; 22,23-Dihydrostigmasterol; 24beta-Ethylcholesterol; 5-Stigmasten-3beta-ol ¹
CAS No.	83-46-5
EINECS No.	201-480-6
Molecular formula	C ₂₉ H ₅₀ O
Chemical structure	 <p>β-Sitosterol</p>

¹ <http://www.chemblink.com/products/83-46-5.htm> (Online Database of Chemicals from Around the World)

	 <p style="text-align: center;">Cholesterol</p> <p>Reference:²</p>
Molecular weight	414.71
Physiochemical properties	Melting point: 139-142 °C Water solubility: Insoluble

2. Uses and origin

Uses	<p>➤ Cosmetic products:</p> <p><i>Functions according to</i></p> <ul style="list-style-type: none"> • CosIng database: <ul style="list-style-type: none"> – <i>Emulsion stabilising</i>: Helps the process of emulsification and improves emulsion stability and shelf-life – <i>Masking</i>: Reduces or inhibits the basic odour or taste of the product – <i>Skin conditioning</i>: Reduces or inhibits the basic odour or taste of the product – <i>Stabilising</i>: Improves ingredients or formulation stability and shelf-life • Other: <ul style="list-style-type: none"> - Anti-inflammatory effect on sensitive, atopic skin³. <p><i>Concentrations of beta-sitosterol being applied</i></p> <p>0.05 – 0.1% beta-sitosterol (SLV, 2004; Annex 1).</p> <p><i>Frequency of use</i></p> <p>The EWG Skin Deep [online] database lists 10 cosmetic products containing beta-sitosterol:</p> <ul style="list-style-type: none"> – sunscreen: makeup (6 products) – moisturizer (4 products)
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² <http://www.covemountainhealth.com/pages/Plant-Sterols-and-Lower-LDL-Cholesterol.html>

³ SLV – Norwegian Medicines Agency (“*enkeltvedtak*”): The claims “anti-inflammatory effect” and “atopic skin” are regarded as medical health claims, and cannot be used for cosmetic products (SLV, 2004). However, the product is not classified as a medicinal product because low content of the ingredient (0.05-0.1%). To be sold and marketed as ingredient in cosmetic products, it must comply with the cosmetics regulation.

	<ul style="list-style-type: none"> - facial moisturizer/ treatment (2 products) - body wash/ cleanser (1 products) - anti-aging (1 products) <p>The German database 'Codecheck' lists 86 products with beta-sitosterol (Codecheck.info [online]).</p> <p>➤ Food</p> <p>Beta-sitosterol is a naturally occurring phytosterol found in many plants, seeds and fruit; e.g. wheat germ, corn oils, soybeans, rice bran, saw palmetto, and avocados (Kroner [online]). It is often ingested as part of a margarine-like spread.</p> <p>There is no deficiency state of beta-sitosterol or any other phytosterols, but some groups may consume less than recommended (EFSA, 2008).</p> <p>➤ Medicinal products</p> <p>In recent years, beta-sitosterol has been classified as a medicinal drug for treatment of the following conditions:</p> <ul style="list-style-type: none"> - reduce cholesterol levels; associated with risk of heart disease; dosage: 200 – 250 mg beta-sitosterol three times per day, e.g. as margarine spread. - improve symptoms of benign prostatic hyperplasia; oral doses of 125-250 mg daily⁴. <p>EFSA concluded that a cause and effect relationship has been established between the consumption of plant sterols/ stanols and the reduction of blood cholesterol concentrations (EFSA, 2010).</p> <p>However, EFSA concluded that a cause and effect relationship has not been established between the consumption of plant sterols and plant stanols and maintenance of normal prostate size and normal urination (EFSA, 2010).</p> <p>(NTP [online]; Moghadasian & Frohlich,1999)</p> <p>➤ Other products</p> <p>Plant sterols have been found to have immune modulating activity and antitumor activity in animal models and human clinical trials (Bouic, 2001).</p>
<p>Origin</p> <p>Natural (exo /endo) Synthetic</p>	<p><i>Beta-sitosterol</i> is the most abundant phytosterol⁵ (plant sterol); the proportions of sterols in plants are 65% beta-sitosterol, 30% campesterol, and 5% stigmasterol.</p> <p>Phytosterols are substances that are similar in structure to cholesterol and are formed exclusively in plants. They are added to food for their blood cholesterol-lowering properties.</p>

⁴ All but one of four published studies in 1999 found significant benefits of beta-sitosterol in both perceived symptoms and objective measurements, such as urine flow rate (Beth Israel [online]). The daily dosage of beta-sitosterol was reported to be 60 to 135 mg.

⁵ Phytosterols include beta-sitosterol, campesterol, and stigmasterol. These can be found in plants in their free form, esterified, or as glycosides. Stanols are closely related compounds—they are hydrogenated (or saturated) phytosterols(no double bonds in ring structure). These include sitostanol and campestanol (Kroner [online]).

3. Regulation

Norway	Allowed in skin creams only and up till 0,1 % ⁶
EU	No regulation
Rest of the world	No regulation

4. Relevant toxicity studies

Absorption Skin GI tractus	<p>Although structurally similar, about 5% of orally ingested beta-sitosterol is absorbed, as compared to 45-50% of cholesterol (Law, 2000; SCF, 2002a).</p> <p>Absorption of phytosterols appears to be greater during infancy and childhood than during adulthood (5- to 15-fold increase in plasma phytosterols), and in the rare autosomal recessive disease called <i>sitosterolaemia</i> (50 – 100 fold elevated plasma levels). Sitosterolaemia patients are susceptible to premature atherosclerosis (JECFA, 2009; BfR, 2012).</p>
Distribution	<p>In animal studies, beta-sitosterol was found at highest levels in the adrenal cortex, ovary and testis, and liver. Uptake of the radioactively labeled beta-sitosterol fed to rats was highest in the adrenal glands, ovaries and intestinal epithelia prostate gland than in the liver or other genitourinary tissues (e.g., seminal vesicles). (Sanders et al., 2000). See also NTP[online]; JECFA, 2009. Infants fed a vegetable oil-based diet accumulated plant sterols in aortic tissues. (Mellies et al., 1976; cited by Finocchiaro and Richardson 1983 in NTP[online]).</p>
Metabolism	<p>For metabolism, including pharmacokinetics, see NTP[online].</p> <p>The pharmacokinetics of beta-sitosterol in beagle dogs revealed a <i>distribution half-life of 3 hours</i> and a terminal distribution half-life of 129 hours. <i>Absolute bioavailability upon oral administration was 9%</i> (Ritschel et al., 1990).</p>
Excretion	<p>Excretion of absorbed phytosterols and phytosterols predominantly takes place via the bile in the faeces (JECFA, 2009). Phytosterols are believed to decrease the intestinal absorption of cholesterol as well as increasing its excretion in bile and feces (Racette et al., 2010). NTP[online].</p>
Local toxic effects Irritation Sensitivity	<p>Beta-sitosterol is not irritating, as judged from animal experiments; e.g. irritating properties in rabbits, sensitisation potential in the guinea pig maximisation test (SCF, 2002a)</p>
Systemic toxic effects	<p>Plant sterols are capable of interfering, at least to some extent, with the absorption of fat-soluble vitamins, particularly β-carotene; reduced plasma levels of beta-carotenoids (8 – 19%) in response to plant sterols were noted (Hendriks et al., 2003; Ntanios et al., 2002; Law, 2000). Apart from the carotenoid-lowering effect, no other adverse effects were observed in humans with doses up to 3 g/day for three years (Law, 2000).</p>

⁶ Regulation to be removed 11 July 2013

	<p>No other side effects or biochemical anomalies have been observed in randomized trials or plant sterol margarines, in earlier studies testing 3g/day for 3 years, or in animal studies testing proportionately higher doses (citations in Law, 2000).</p> <p>SCF concluded that 3 g/day of plant sterols represents an upper limit for safe use of these substances (SCF, 2002a).⁷</p>
Acute	The acute toxicity for beta-sitosterol administered intraperitoneally (i.p.) to mice is >3000 mg/kg (>7.23 mmol/kg) (NTP [online]).
Repeated dose	Short term (60 days) s.c. exposure of male and female albino Wistar rats to beta-sitosterol at 2 mL/kg/day (0.0048 mmol/kg/day) did not produce gross or microscopic lesions either in the liver or the kidney. All clinical biochemical parameters were in the normal range except for serum protein and serum cholesterol; serum cholesterol was markedly depleted in both sexes in a dose dependent manner. Male Fischer CD rats fed 0.2% beta-sitosterol in the diet for 28 weeks experienced no adverse effects (NTP [online]).
Mutagenicity /genotoxicity	No evidence for genotoxicity of phytosterols or phytostanols and their esters (JECFA, 2009).
Carcinogenicity	No indication of potential for carcinogenicity (JECFA, 2009).
Reprotoxicity / teratogenicity	No changes in reproductive parameters (JECFA, 2009).
Other effects	Plant sterols as independent risk factor for cardiovascular disease? (see section 6 (VKM, 2005; JECFA, 2009; BfR, 2012)).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	<p>Risk assessment using "acceptable daily intake" (ADI):⁸</p> <p>In 2009, JECFA established a group ADI of 0- 40 mg/kg bw (2.4 g per day for a 60 kg person) for the group of phytosterols, phytostanols and their esters, expressed as the sum of phytosterols and phytostanols in their free form. This was based on an overall NOAEL of 4200 mg/kg bw/day, using the combined evidence from several short-term (90-day) studies of toxicity and applying a safety factor (SF) of 100 (JECFA, 2009).</p> <p>ADI (human dose) = NOAEL (experimental dose) /Safety factor ADI = 4200 /100 = approx. 40 mg /kg bw /day beta-sitosterol. This equals 2.4 g per day for a 60 kg person.</p> <p>Note that the value derived by JECFA (2.4 g per day) differs from the threshold value of 3 g per day as outlined in the opinion of the SCF</p>
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⁷ JECFA (2009) established a maximum limit of 2.4 g per day for a 60 kg person based on ADI of 40 mg/kg bw.

⁸ JECFA (2009) performed risk decisions on systemic toxicity of beta-sitosterol using the concept of the "acceptable daily intake (ADI)" derived from an experimentally determined "no-observed-adverse-effect level (NOAEL)." The ADI is commonly defined as the amount of a chemical to which a person can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. The ADI concept has often been used as a tool in reaching risk management decisions (e.g., establishing allowable levels of contaminants in foodstuffs and water.)

	<p>and EFSA (SCF, 2002a; JECFA, 2009; BfR, 2012).</p> <p>We assume a systemic NOAEL dividing the NOAEL obtained via feeding studies with the bio-availability of 5 %. Hence, the systemic NOAEL to be used estimating the margin of safety (MoS) is (4200 x 0.05 =) 210 mg/Kg bw day.</p>
Exposure cosmetic products	<p><i>Illustrative example:</i></p> <ul style="list-style-type: none"> • Body lotion <p>Systemic exposure dose (SED) was estimated for different cosmetic product types according to COLIPA data (SCCS [online]), using 0.1% beta-sitosterol as an illustrative example⁹:</p> <p>0.1 % beta-sitosterol (cream, body lotion) Calculated relative daily exposure of product: 123.20 mg/kg bw/day Concentration of ingredient in the product: 0.1% = 0.001 Dermal absorption (SCCS default value): 100% = 1</p> <p>SED = A (mg/kg bw/day) x C(%) / 100 x DAp (%) / 100 = 123.20 mg/kg bw/day x 0.001 x 1 = 0.123 mg/kg bw/day</p> <p>This corresponds to a systemic exposure of 0.123 x 60 = 7.4 mg /day (60 kg person) and 0.123 x 74 = 9.1 mg / day (74 kg person) i.e. average: 8.3 mg /day (adult person)</p>
Margin of Safety (MoS)	<p>MoS for body lotion: NOAEL systemic = 4200 x 0.05 = 210 mg/kg bw/day (JECFA, 2009; BfR, 2012) SED = 0.123 mg/kg bw/day MoS = (NOAEL/SED) = 210 / 0.123 = 1707</p> <p>SCF established a safety threshold of 3 g/day for oral uptake of phytosterols, whereas JECFA estimated a threshold of 2.4 g beta-sitosterol per day for a 60 kg person in food (SCF, 2002; JECFA, 2009).</p> <p>Based on the information that about 5% of orally ingested beta-sitosterol is absorbed (Law, 2000), the systemic exposure of 3 g beta-sitosterol from diet and supplements amounts to: 3 g * 0.05 = 150 mg.</p> <p>Thus, a daily exposure of 8.3 mg (average) beta-sitosterol from cosmetic products represents approx. 5% of the threshold levels derived from oral intake: 8.3 (mg/day) / 150 (mg/day).</p>

6. Other sources of exposure than cosmetic products

Food stuffs	<p>To date the safety of phytosterols/phytostanols has been reviewed on several occasions (SCF, 2000, 2002a, 2002b, 2003, 2004; JECFA, 2009; BfR, 2012).</p> <p>Typical diets provide approximately 250 mg phytosterols per day in US, about 200 mg /day in UK and Netherlands, and approx. 300</p>
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⁹ The current Norwegian regulation allows a maximum concentration of 0.1% beta-sitosterol.

	<p>mg/day (upper limit 680 mg) in Finland. The intake is estimated to be up to 40% higher in vegetarians.</p> <p>JECFA concluded that the dietary exposure of free phytosterols and phytosterols would typically be less than 30 mg/kg bw/day (i.e. approx. 2 g per day for a 60 kg person). This is fairly close to the estimated ADI of 40 mg/kg bw/day.</p> <p>A daily intake of 1.5 to 2 g of plant sterols was recommended for cholesterol-lowering in package labelling of MultiBene foods (SCF, 2004).</p> <p>Although concerns have been raised that ingestion of high levels of plant sterols reduce the absorption of the fat-soluble vitamins and carotenoids, at typical use levels no effect on vitamins A, K and D has been reported. However, β-carotene levels are lowered up to 19% in some studies (Law, 2000; Drugs.com [online]).</p> <p>A majority of consumers do not seem to be aware of the importance to consume sufficient fruit and vegetables to prevent a reduction in plasma carotenoids levels (EFSA, 2008). The potential β-carotene lowering effect should be communicated to the consumer, together with appropriate dietary advice regarding the regular consumption of fruits and vegetables (SCF, 2004).</p> <p>However, "No serious concern can be deduced regarding the role of β-carotene as a vitamin A precursor, except in situations where vitamin A requirements are greater than normal as in pregnancy, lactation or infancy" (SCF, 2002).</p> <p>Thus, the overall assessment is that the safety of phytosterol-containing foods is acceptable given appropriate labeling, dietary advice on carotenoid intakes from the diet and observing a maximum 3 g/day intake (Law, 2000; SCF, 2004; VKM, 2005).</p> <p>According to national dietary intake data (NORKOST), the average estimated intake of phytosterols from margarine (yellow fat spread) is 2 g (95 percentile: 4 g/day). As a worst case scenario, VKM estimated that ingestion of fortified milk and yoghurt (with the same amount of phytosterols as margarine) would give intake as high as 8 g/day (95 percentile) phytosterols (VKM, 2005). The committee remarked that increasing the number of products containing phytosterols would give increased risk for consumption of more than 3 g/day.</p>
Pharmaceuticals	<p>At a recommended daily dose of 2 g, dyslipidemic patients can reduce LDL-C by 10% to 15%, projected to reduce heart disease risk by 25% (Rideout et al., 2012; JECFA, 2009; BfR, 2012).</p>
Other sources	
Adverse side effects - from uses other than cosmetics	<p>In 2009, JECFA reported that "to date, there is no convincing evidence for an association of elevated phytosterol levels and increased risk for cardiac heart disease (CHD)" (JECFA, 2009).</p> <p>However, there is currently an on-going discussion in the EU working group or Novel Food related to cardiovascular risks of phytosterols for healthy people who consume fortified foods with these substances in high amounts over longer periods.</p> <p>BfR has assessed a recent study from Netherlands, which indicates</p>

	<p>that consumption of food containing plant sterols has unwanted effects on human retinal microvessels (Kelly et al., 2011).</p> <p>Review of experimental, animal and human studies revealed that “it is not yet possible to conclude whether phytosterols is neural, anti-atherogenic or pro-atherogenic” and that “the evidence from human epidemiological investigations does not favor use of phytosterols to reduce clinical cardiovascular endpoints and atherosclerosis (Lottenberg et al., 2012). Thus, although a positive association of plant sterol plasma concentrations and cardiovascular disease is suggested, it remains unclear whether slightly elevated serum plant sterols are involved in arteriosclerotic processes or whether they are only markers of the absorption of cholesterol (BfR, 2012).</p> <p>1-2% of men taking beta-sitosterol for benign prostatic hyperplasia have experienced slight gastrointestinal upset (Gerber, 2002, cited in Kroner [online]).</p> <p>In older studies with <i>parenteral</i>¹⁰ application, some estrogenic activity of phytosterols was reported (SCF, 2000), raising some concerns that estrogenic activity may result from <i>oral</i> uptake of phytosterols. However, phytosterols (incl. beta-sitosterol and stigmasterol) have failed to show estrogenic activity <i>in vitro</i> (e.g. the estrogen receptor binding assay) and <i>in vivo</i> (e.g. uterotrophic assay) (JECFA, 2009; Hendriks, et al., 2003).</p>
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¹⁰ Intravenous, subcutaneous, and intramuscular injections are all parenteral routes of administration.

7. Assessment

Beta-sitosterol is a naturally occurring phytosterol. A major source of human exposure in the general population is the diet, typically in seeds, nuts and vegetable oils (estimated range: 150 – 400 mg). In consumer groups with high intake of fortified foods (novel foods) containing beta-sitosterol, often in the form of margarine spread (two or three portions), daily doses of 2 g of free phytosterols are common.

As a cosmetic ingredient, beta-sitosterol is registered in the Cosing database (cf. Decision 96/335/EC, 8th May 1996), with functions such as “masking”, “skin conditioning” and “stabilising”.

General toxicity:

SCF determined that oral ingestion of phytosterols (containing from 50 – 80% beta-sitosterol) is safe given that total ingested levels do not exceed 3 g per day (SCF, 2000; SCF, 2002)¹¹.

Cosmetics:

Local:

No irritating or local adverse effects of beta-sitosterol have been reported (JECFA, 2009; SCF, 2002). SCF reported that oil-derived beta-sitosterol was not irritating, as judged from animal experiments (irritating properties in rabbits, sensitisation potential in the guinea pig maximisation test). Likewise, Pierre Fabre reported lack of irritating properties for Trixera (0.05% beta-sitosterol) in animal tests and “Human Repeated Patch Test” (Pierre Fabre, 2003).

Post-marketing survey data also demonstrated absence of significant local adverse effects of beta-sitosterol (Pierre Fabre, 2003).

Systemic:

JECFA established a group ADI of 0-40 mg/kg bw for the group of phytosterols, phytostanols and their esters, expressed as the sum of phytosterols and phytostanols (free forms). The estimate was based on an overall NOAEL of 4200 mg/kg bw/day derived from several short term (90 day) studies in rodents, and ADI was derived by applying a safety factor of 100 to NOAEL. This amounts to a threshold of 2.4 g beta-sitosterol per day for safe use in a 60 kg person by oral ingestion.

In order to establish safety guidelines in cosmetics, we used leave-on body lotion to represent the largest possible exposure area. 0.1% beta-sitosterol was used as an illustrative example to estimate the daily systemic exposure dose (SED) of the ingredient in cosmetics. The resulting daily exposure of beta-sitosterol was 8.3 mg (on average), which is approx. 5% of the daily safety threshold established for oral uptake via the diet (SCF, 2000; 2002).¹²

Food:

The overall assessment from SCF is that the safety of phytosterol-containing foods is acceptable given appropriate labeling, dietary advice on carotenoid intakes from the diet and observing a maximum 3 g/day intake.¹⁰

Medicinal products:

Beta-sitosterol has been used as a (oral) drug in the treatment of hyperlipoproteinemias in doses of 2 - 6 g /day.

Total exposure:

As described above, the main source of human exposure to beta-sitosterol is the “background” diet (range: 150 – 400 mg). In addition, “novel” foods fortified with plant sterols (often in the form of

¹¹ JECFA established a value of 2.4 g per day for a 60 kg person, based on an ADI of 40 mg/kg bw (JECFA, 2009).

¹² Based on a bioavailability of 5% (oral ingestion); see section 4.

margarine spread), typically contains two or three portions to achieve 2 g of free phytosterols, totaling approx. 2.4 g.

This is within the safety threshold established by SCF (SCF, 2000; 2002; 2004) and JECFA (2009), concurred by an EFSA report in 2008, which stated that: "In general there seems so far to be little over-consumption of food products with added plant sterols" (EFSA, 2008). However, the estimated intake via the food of 30 mg/Kg bw day outdoes as much as 75 % of the established ADI (40 mg/Kg bw day). The difference of 10 mg/Kg bw day between the estimated intake and the ADI is not much taking into consideration all the uncertainty of the data laid to ground. .

Cosmetic products represent only 5.5% of maximum recommended dietary oral intake (3 g). However, the total systemic exposure (food + cosmetics) amounts to $(1.5 + 0.1 \Rightarrow) 1.6 \text{ mg / Kg bw day}$ and applying a systemic NOAEL of 210 mg/Kg bw day this means that the "total" MoS is only marginally higher than 100; 131.

Conclusion

We conclude that beta-sitosterol does not present a safety concern when used as an ingredient in cosmetic products at the current maximum allowed use levels (i.e. 0.1%).

We are of the opinion that the following limitations would secure safe use of beta-sitosterol in cosmetic products:

- Ought not to be used in other products than skin creams
- Maximum concentration in ready to use products: 0.1%

Remarks:

Lottenberg et al. (2012) concluded that "it is not yet possible to conclude whether phytosterols are neutral, antiatherogenic or proatherogenic".

Doubts on the safety of phytosterols for *healthy people* who consume these substances *regularly* in high amounts over *longer periods* have been raised (BfR, 2012). This includes infants and children (see section 4), as there is evidence for greater absorption of phytosterols during infancy and childhood than during adulthood (5- to 15-fold increase in plasma phytosterols), as well as accumulation of plant sterols in aortic tissues.

8. References

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9. Annexes

Annex 1: Examples of uses for beta-sitosterol in cosmetic products