EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Consumer Products

SCCP

OPINION ON

Vitamin K1

phytonadione (INCI name)

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCCP adopted this opinion by written procedure on 28 September 2007

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCP

Questions concerning the safety of consumer products (non-food products intended for the consumer).
In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

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ACKNOWLEDGMENTS

Dr. C. Chambers
Prof. G. Degen
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Keywords: SCCP, scientific opinion, vitamin K1, phytonadione, Directive 768/76/EEC, CAS 84-80-0, 11104-38-4, 81818-54-4

Opinion to be cited as: Opinion of the SCCP on vitamin K1 (phytonadione)

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1. BACKGROUND

Phytonadione (CAS 84-80-0) [INN phytomenadione] with the chemical name 2-methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-1,4-naphthalenedione is used as a skin conditioner in cosmetic products according to the Inventory.

Vitamin K1 is a synonym with phytonadione.

Apparently the current maximum use concentration of vitamin K1 is 2% in EU and 5% in USA.

The basis for this evaluation is a notification made by France to the Commission and the Member States. The French authorities have banned - by a decision dated the 12 January 2006 - the use of vitamin K1 in cosmetic products due to the sensitizing properties of the substance. The ban is based on 5 cases of undesirable effects (allergic reactions) between December 2003 and June 2004 from 3 products and a further 6 cases have been identified between March 2004 and July 2004 from another product containing vitamin K1. The French authorities also refer to 2 cases from Spain and Italy described in the scientific literature accordingly in February and September 2005.

The ban is furthermore supported as vitamin K1 might be used as an injectable therapeutic agent for therapeutic reasons.

The Commission has asked Member States and stakeholders for information.
Only the Belgian Authorities submitted the study "Evaluation of skin sensitisation potential in mice using the local Lymph node assay (LLNA).
The Italian competent authority supports a closer look at the use of vitamin K1, particularly in view of the fact that it is often used in combination with other substances (such as retinol).

2. TERMS OF REFERENCE

1. *Does the SCCP consider that Vitamin K1 [and its oxide] are safe for the consumers when used in cosmetic products taken into account the provided data?*

2. *Does the SCCP recommend any restrictions to their safe use?*

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Phytonadione (INCI name)

3.1.1.2. Chemical names

1,4-naphthalenedione, 2-methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-, (r-(r*,r*-(e)))
2',3'-trans-vitamin K1
2-Methyl-3-[(min 80%E,7RS,11RS)-3,7.11,15-tetrametyl-2-hexadecenyl]-1,4-naphthoquinone
2',3'-trans-phylloquinone
α-phylloquinone
2-methyl-3-phytyl-1,4-naphthoquinone
phytylmenadione
3-phytylmenadione
phytomenadione
antihemorrhagic vitamin

3.1.1.3. Trade names and abbreviations

Aquamephyton	konakion
combinal k1	mephyton
k-ject	mono-kay
kativ n	monodion
kephton	synthex p
kinadion	

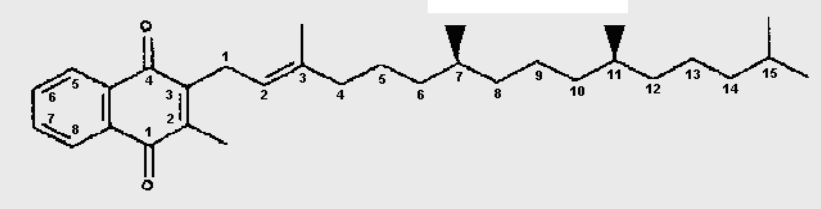
3.1.1.4. CAS / EINECS number

Vitamin K1

CAS	EINECS *
84-80-0	201-564-2 (phytomenadione)
11104-38-4	234-330-3 (vitamin K1)
81818-54-4	279-833-9 (2-methyl-3-(3,7,11,15-tetramethylhexadec-2-enyl)-1,4-naphthoquinone)

* The names in brackets refer only to the EINECS numbers

3.1.1.5. Structural formula



The formula indicates 2'-Trans-7R, 11R-stereoisomer

The Vitamin K1 molecule has two geometrical isomers (cis-trans or *(Z)-(E)* isomers) plus two asymmetric carbon atoms (C7 and C11), each generating two enantiomers (R or S). Thus, there are eight diastereoisomers (four in the ***trans*** and four in the ***cis*** configuration). The name Vitamin K is appropriate only for the 2'-Trans-7R, 11R-stereoisomer (the others are not vitamins), representing 12.5% in an equimolar mixture.

3.1.1.6. Empirical formula

Empirical formula: $C_{31}H_{46}O_2$

3.1.2. Physical form

Clear yellow to golden yellow viscous liquid

3.1.3. Molecular weight

Molecular weight: 450.68 g/mol

3.1.4. Purity, composition and substance codes

/

3.1.5. Impurities / accompanying contaminants

Commercial preparations may contain up to 20% of the biological inactive *cis* isomer.

Ref.: 1

Commercially available phytonadione (phylloquinone) is prepared synthetically and may contain not only 2',3'-trans-phylloquinone (not less than 75%), but also 2',3'-cis-phylloquinone and trans-epoxyphylloquinone (not more than 4.0 percent). Phylloquinone occurs in nature only as the 2', 3'-Trans-7R, 11R-stereoisomer.

Ref.: 2

HPLC chromatograms
Three chromatograms were provided without any explanation or identification of the peaks. After 5 minutes and one hour irradiation with UV several new unidentified peaks appeared on the chromatograms, which were also not described. No information on the nature of UV exposure of the test substance was given

3.1.6. Solubility

500 mg/l	water (22 °C)
500 mg/l	hydrochloric acid 0.1 N (22 °C)
500 mg/l	sodium hydroxide 0.1 N (22 °C))

500 mg/l	glycerine (22 °C)
4500 mg/l	DMSO (dimethyl sulfoxide) (22 °C)
11000 mg/l	methanol (22 °C)
15000 mg/l	acetonitrile (22 °C)
75000 mg/l	ethanol (22 °C)
1 g/l	n-octanol, diethyl ether, acetone, benzene, ethyl acetate, dichloromethane, chloroform, n-hexane, cydohexane, dioxane (22 °C)

Ref.: 3

3.1.7. Partition coefficient (Log P_{ow})

/

3.1.8. Additional physical and chemical specifications

Melting point:	approx. - 20 °C
Boiling point:	140-145 °C
Density:	0.97 g/cm³

3.1.9. Stability

Stable to air and moisture, but decomposes in sunlight. Unaffected by dilute acids, but is destroyed by solutions of alkali hydroxides and by reducing agents.

Ref.: 1

General Comments on physico-chemical characterisation

- The data provided on the physico-chemical characterisation of phytonadione is insufficient.
- No data was provided on 'phytonadione-oxide'
- It is not clear from the submission to which substance the term 'phytonadione-oxide' refers to. It might be phytonadione epoxide, CAS: 25486-55-9; EINECS: 247-022-9

3.2. Function and use

Phytonadione (phylloquinone) is present in plant sources, especially green leafy vegetables. It is also present in small amounts in dairy products. It is synthesised by bacterial flora in the jejunum and ileum. The amount synthesised in the gut contributes significantly towards the daily requirement of the vitamin.

Vitamin K is involved in blood clotting, bone and kidney metabolism. Roles in cell signalling and brain lipid metabolism have also been proposed. Because vitamin K is widespread in the diet and provided by bacteria, deficiency is generally secondary to conditions such as mal-absorption. Newborn babies have low levels of vitamin K, which may result in haemorrhagic disease of the newborn.

There may be decreased utilisation of the vitamin in the production of the vitamin K-dependent clotting factors during any form of acute or chronic liver disease. This is as a result of the destruction of the rough endoplasmic reticulum in the hepatocyte. Patients with hypoprothrombinaemia related to hepatic disorders usually respond to daily parenteral doses of 10 mg of vitamin K for three days. If no response to this treatment is noted this suggests serious hepatocellular damage. (Basu and Dickerson, 1996).

Ref.: 4

The physiological activity of phylloquinone is based on its ability to change between its oxidized (quinone and 2,3-epoxide) and reduced (hydroquinone) forms. The major role of phylloquinone is the post-translational addition of a carboxyl-group into the γ-position of glutamate residues of specific proteins. In this respect, the prime physiological relevance of phylloquinone is the synthesis of coagulation proteins (Ferland, 1998; Olson, 1999 and 2000).

Whereas the vitamin K-dependent coagulation proteins are all synthesised in the liver, vitamin K is also essential for the synthesis of a number of proteins produced in extra-hepatic tissues. Examples of the latter group of proteins include:

- the bone Gla-protein, osteocalcin, which is exclusively synthesised by osteoblasts and odontoblasts, and which is a negative regulator of bone formation;
- matrix Gla-protein (MGP), which is synthesised in most soft tissues, but predominantly in cartilage (by chondrocytes) and in vessel wall (by vascular smooth muscle cells) and which is a potent inhibitor of soft tissue calcification;
- growth arrest-specific gene 6 protein (Gas6), which is a ligand for tyrosine kinases and has strong apoptopic activity in cultured cells.

Ref.: 5

Claimed uses for Vitamin K1 as a cosmetic include skin lightening, periorbital hyper pigmentation, treatment of actinic and traumatic purpura and treatment of bruising after laser treatment.
The SCCP is aware of cosmetic products on the market with Vitamin K1 concentrations as high as 8%.
The company that has submitted safety data for this evaluation declares that: "following AFSSAPS recommendations and our own observations…no product […] contains Vitamin K since 1 January 2005". It also stated that from this date, an oxidised form of Vitamin K1 was used instead. No data was provided about the formula of oxidised Vitamin K1.

Ref.: 6

3.3. Toxicological Evaluation

Due to the background of the mandate, this evaluation is focused on skin sensitisation aspects as submitted in the dossier and does not consider general toxicity data.

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

No data submitted

3.3.1.2. Acute dermal toxicity

No data submitted

3.3.1.6. Acute inhalation toxicity

No data submitted

3.3.2 Irritation and corrosivity

3.3.2.1. Skin irritation

No data submitted

3.3.2.2. Mucous membrane irritation

No data submitted

3.3. Skin sensitisation

Murine Local Lymph Node Assay (LLNA) for Vitamin K1

Guideline:	OECD 429
Species/strain:	CBA/J mouse, nulliparous and non-pregnant females.
Group size:	7 groups of 4 animals
Test substance:	vitamin K
Batch:	20040510
Purity:	98.96% (full isomeric composition not clarified, % active ingredient unknown)
Concentrations:	5, 10, 25, 50, 100% in acetone/olive oil (4/1; v/v)
Positive control:	α-hexylcinnamaldehyde (HCA)
GLP:	in compliance

Results
Vitamin K1 was non-irritant in the preliminary test. The highest concentration retained for the main test was the maximal practicable concentration (100%).

In the main test, twenty-eight female CBA/J mice were allocated to seven groups: five treated groups of four animals receiving the test item Vitamin K (isomeric mixture) at the concentration of 5, 10, 25, 50 or 100%, one negative control group of four animals receiving the vehicle (mixture acetone/olive oil (4/1; v/v)), one positive control group of four animals receiving alpha-hexylcinnamaldehyde (HCA) at the concentration of 25%.

Proliferation assay
No lympho-proliferation was noted at any of the test concentrations, while significant lympho-proliferation was observed with HCA at 25%.

The results are presented in the following table:

Treatment	Concentration (%)	Irritation level	Stimulation Index (SI)
Test item	5	non-irritant	1.78
Test item	10	non-irritant	2.10
Test item	25	non-irritant	0.80
Test item	50	non-irritant	0.88
Test item	100	non-irritant	1.67
HCA	25	-	11.18

Conclusion
Under these experimental conditions, Vitamin K1 (isomeric mixture) did not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay.

Ref.: 7

Murine Local Lymph Node Assay (LLNA) for Vitamin Khv(irradiated Vitamin K1)

Guideline: OECD 429
Species/strain: CBA/J mouse, nulliparous and non-pregnant females.
Group size: 7 groups of 4 animals
Test substance: vitamin K(hv)
Batch: 20040510
Purity: 98.96% (full isomeric composition not clarified, % active ingredient unknown)
Concentrations: 5, 10, 25, 50, 100% in acetone/olive oil (4/1; v/v)
Positive control: α-hexylcinnamaldehyde (HCA)
GLP: in compliance

Results
Vitamin K1 was non-irritant in the preliminary test. The highest concentration retained for the main test was the maximal practicable concentration (100%).

In the main test, twenty-eight female CBA/J mice were allocated to seven groups: five treated groups of four animals receiving the test item Vitamin K at the concentration of 5, 10, 25, 50 or 100%, one negative control group of four animals receiving the vehicle (mixture acetone/olive oil (4/1; v/v)), one positive control group of four animals receiving α-hexylcinnamaldehyde (HCA), at the concentration of 25%.

Proliferation assay
No lympho-proliferation was noted at any of the test concentrations, while significant lympho-proliferation was observed with HCA at 25%.

The results are presented in the following table:

Treatment	Concentration (%)	Irritation level	Stimulation Index (SI)
Test item	5	non-irritant	1.02
Test item	10	non-irritant	0.64
Test item	25	non-irritant	0.80
Test item	50	non-irritant	1.10
Test item	100	non-irritant	1.10
HCA	25	-	8.54

Conclusion
Under our experimental conditions, the test item Vitamin K hv did not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay.

Ref.: 8

Comment
The batch and the analytical certificate provided was that for the non-irradiated form of Vitamin K (isomeric mixture). No data about the isomeric composition of the test substance in both tests are provided. Therefore, no conclusion can be made regarding the sensitising potential by LLNA vitamin K1, either irradiated or non-irradiated before use.

3.3.4. Dermal / percutaneous absorption

No data submitted

3.3.5. Repeated dose toxicity

3.3.5.1. Repeated Dose (28 days) oral / dermal / inhalation toxicity

No data submitted

3.3.5.2. Sub-chronic (90 days) oral / dermal / inhalation toxicity

No data submitted

3.3.5.3. Chronic (> 12 months) toxicity in mice

No data submitted

3.3.6. Mutagenicity / Genotoxicity

3.3.6.1. Mutagenicity / Genotoxicity *in vitro*

No data submitted

3.3.6.2. Mutagenicity / Genotoxicity *in vivo*

No data submitted

3.3.7. Carcinogenicity

No data submitted

3.3.8. Reproductive toxicity

3.3.8.1. One generation reproduction toxicity

No data submitted

3.3.8.2. Teratogenicity

No data submitted

3.3.9. Toxicokinetics

No data submitted

3.3.10. Photo-induced toxicity

3.3.10.1. Phototoxicity / photoirritation and photosensitisation

***In vitro* assessment of phototoxic potential using human reconstructed epidermis**

Guideline: /
Tissue: human reconstituted epidermis [SKINETHIC™]
N° of chambers: 6
Test substance: vitamin K1 phytonadione
Batch: 03.581
Purity: /
Concentrations: 100% and diluted to 10 and 1% in paraffin oil
GLP: /

A toxicity assay was carried out using SKINETHIC cultures (0.63 cm^2 epidermis). The test product was tested as supplied (i.e, 100%) and diluted to 10 and 1% (v/v) in paraffin oil. Reconstituted epidermis (REp) was treated overnight (approximately 18h). The toxic effect was assessed by using the MTT assay. No significant cytotoxicity was observed in epidermis. Taking into account these results, the test substance was to be applied undiluted on the culture surface, for a 24h incubation period prior to UV exposure.

Test product (6.3µl /epidermis) was applied directly onto the surface of tissues. Control and treated REps were incubated at 37°C for 24 hr and subsequently washed with HBSS. REps were irradiated with UV_A dose 6 J/cm^2 (3 biopsies/UV_A dose), while 2 REps of each experimental group were kept at room temperature in the dark during UVA exposure (dark control). After further incubation at 37° C for 24h, viability was assessed by a MTT test.

Results

	CONTROL		TREATED	
	0	6 J/cm2	0	6 J/cm2
OD_{570} (mean) St. Dev.	0.899 0.005	0.871 0.008	0.861 0.011	0.323 0.011

	CONTROL		TREATED	
	0	6 J/cm2	0	6 J/cm2
Viability	100%	97%	100%	38%
Cytotoxicity		3%		62%

Conclusion
Vitamin K1 (phytonadione) can be considered as phototoxic *in vitro*.

Ref.: 9

Comments
In this study, no positive controls were used. The isomeric composition of the test compound was not reported.
The method which was used is not a validated *in vitro* method for the assessment of phototoxic potential. The 3T3 NRU Phototoxicity test (OECD 432) should have been used instead.

3.3.10.2. Phototoxicity / photomutagenicity / photoclastogenicity

No data submitted

3.3.11. Human data

Patch tests with two isomers of Vitamin K were applied on the back of 107 healthy volunteers. No reaction was observed after 48 and 72 hours (only statement, no data provided).

Ref.: 10

Comment
References 11 and 12 describe a therapeutic use of vitamin K and were considered not relevant for risk assessment.

There have been unspecified adverse skin reactions reported from the topical use of vitamin K containing products (6 case reports in France, 2 in Belgium, 1 in Spain and 1 in Italy). The product manufacturer considered these adverse reactions to be secondary to the use of the products on injured skin, which is not recommended. The estimated frequency was 2.5 to 4 cutaneous intolerance for 100 000 sold products (Vitamin K1, 1 and 2%).

Ref.: 13

The French authorities, in a report of the Commission de cosmétologie, noted 11 cases of adverse effects after topical application of Vitamin K1 containing products in France, including the 6 cases reported in the cosmetovigilance report from the manufacturer (Ref. 13). Amongst these, two cases were reported with products containing oxidised Vitamin K1.

Ref.: 14

Contact dermatitis due to topical cosmetic use of Vitamin K1

A 27-year-old woman developed dermatitis of the face, particularly in the periorbital area. For 4 months, she had used a cosmetic treatment of the face to decrease periorbital hyper-pigmentation, Auriderm K2® cream, a mixture containing vitamin K1 and retinol. Patch tests showed a positive reaction to Auriderm K2® cream. Patch tests with the ingredients of the

cosmetic cream were positive to vitamin K1 2% pet. (D2+/ D3++) and *trans*-vitamin K 2% pet (D2+/D3+++).

This was the first report of allergic contact dermatitis due to vitamin K1 from topical cosmetic use.

Ref.: 17

A 45 year old woman developed a severe eczematous reaction on her face where she had been applying a clarifying cream. A repeated open application test (ROAT) on her forearm was positive. Patch testing of the cream's ingredients showed positive reactions to vitamin K1. At 1% and 10% in petrolatum; controls were negative.

Ref.: 16

2 cases of eyelid dermatitis cause by Vitamin K1 in a cosmetic cream (Ureadin® facial contour) were reported in women using the cream for 3-4 weeks. Patch tests to the Ureadin® cream (+++) and Vitamin K1 (+++) were positive but the cream without the vitamin was negative; 15 control subjects showed no reactions.
The patch test preparation of vitamin K1 was 1 mg/ml aqueous.

Ref.: 20

Eczematous hypersensitivity from aqueous vitamin K injection

A case was reported of an eczematous reaction following injection with vitamin K1 for treatment of warfarin-induced hypoprothrombinemia.

Ref.: 18

Type IV hypersensitivity to vitamin K

The day after intramuscular injection of vitamin K1 (phytomenadione) into her thigh, a 27-year-old-woman with normal liver function developed a relapsing and remitting eczematous reaction localized to the injection site, and later a further eczematous reaction under an adhesive dressing (Duoderm®). On patch testing, she was positive to vitamin K1 and cross-reacted to vitamin K4; she was also positive to colophonium and to ester gum rosin, the dressing adhesive. Recurrent angioedema persisted for several months and, 2 years later, symptoms were still occurring over the injection sites. Structure-activity relationships among vitamin K allergens are discussed.

Ref.: 19

Between 1964 and 1994, at least 52 patients with cutaneous adverse effects of vitamin K were described in the European and North American literature, with 94 cases in the Japanese literature. A review of the details of these patients, primarily from therapeutic use of Vitamin K1, is given and 2 new therapeutic use cases reported. Adverse effects were seen not only in patients with liver-function disturbances but also in patients without liver diseases, and occur mostly after intramuscular or subcutaneous administration of vitamin K1, independent of the total dose. Patch and intracutaneous tests often give positive reactions. The mechanism of action was considered in many patients to be a delayed-type hypersensitivity reaction.

Intramuscular and subcutaneous injections of Vitamin K1 have induced three types of cutaneous reactions:

- 10-14 days after injection eczematous reactions. The allergic mechanism was confirmed in several patients by intradermal and/or epicutaneous testing. There were positive patch test reactions with Vitamin K1; Vitamin K3 was negative

- Scleroderma-like patches at site of former injection several months or year after injection. Sensitization was proven in 4 patients by intradermal tests.
- Urticaria

Additionally, 5 individuals exposed to vitamin K1 in the occupational setting and who developed contact dermatitis on their hands and faces are recorded.

Ref.: 15

3.3.12. Special investigations

No data submitted

3.3.13. Safety evaluation (including calculation of the MoS)

Not applicable

3.3.14. Discussion

According to the applicant, since 2005 vitamin K has been replaced in their products by "oxidised" Vitamin K. The applicant claims that "oxidised" Vitamin K is photo-stable in contrast to Vitamin K, which is considered to produce sensitising by-products after UV irradiation. However, experimental data to support this is absent from the submission.

The dossier presented to the SCCP is incomplete and does not permit a proper evaluation of Vitamin K1 or "oxidised" Vitamin K1.

For "oxidised" Vitamin K1, the chemical identity of the substance has not been specified and no experimental data on the sensitising potential or other toxicological endpoints has been provided.

The LLNA test performed on UV irradiated Vitamin K, which should contain sensitising photo-degradation products, was negative.

There are a number of clinical case reports concerning cutaneous sensitisation to Vitamin K1. Although the risk of such allergy is small, Vitamin K1 can be a life-saving therapeutic agent. In cases of pre-existing sensitisation caused by topical application of Vitamin K1 in cosmetics, an individual might not be able to receive Vitamin K1 therapeutically.

4. CONCLUSION

Because of the inadequate nature of the dossier submitted, the SCCP is unable to provide an adequate safety evaluation for the use of vitamin K1 (phytonadione) and its "oxide" in cosmetic products. However, as such use may cause cutaneous allergy, individuals so affected may be denied an important therapeutic agent.

5. MINORITY OPINION

Not applicable

6. REFERENCES

1. Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989, p. 1580
2. IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-present. (Multivolume work)., p. V76 424 (2000)
3. HSDB - Hazardous Substances Data Bank (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB)
4. Expert Group on Vitamins and Minerals. Revised review of vitamin K. doc. n° EVM/01/09, revised aug 2002
5. Scientific Committee on Food. Opinion on the Tolerable Upper Intake Level on Vitamin K. doc. n° SCF/CS/NUT/UPPLEV/32 Final. 4 April 2003.
6. AURIGA International, letter to Mrs J. Meunier. Service Denrées alimentaires, aliments pour animaux et autres produits de consommation. Brussels,11 July 2006
7. Sire G. Vitamin K. Evaluation of skin sensitization potential in mice using the local lymph node assay. CIT, France. Study number 31769 TSS, 26 January 2007
8. Sire G. Vitamin K hv. Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA). CIT, France. Study number 31771 TSS; 26 January 2007
9. Boue-Grabot, M., Halaviat, B. Vitamine K1 Phytonadione. *In vitro* assessment of phototoxic potential using human reconstructed epidermis. Bio HC, France. Report PTC_E 03.581. 13 July 2006
10. Heenen M. Rapport sur les réactions d'irritation observées après la pose de patch tests de 2 isomères de la vitamine K. ULB, Brussels. Ref. adm/heenen/1102. 21.11.2002
11. Cesarini J.P. Rapport d'essai clinique du protocole Auriderm k5® sur les plaies provoquees, standardisees chez l'homme. Unpublished report. 5.10.1999.
12. Cesarini J.P. Rapport d'essai clinique avec Auriderm® K5. unpublished report. 27.02.1999
13. AURIGA International. Cosmetovigilance. unpublished report
14. Avis de la Commission de cosmetology n° 25. France. 29 September 2005
15. Bruynzeel I., Hebeda CL, Folkers E., Bruynzeel DP. Cutaneous hypersensitivity reactions to vitamin K: 2 case reports and a review of the literature. Contact Dermatitis. 1995 Feb; 32(2):78-82
16. Serra-Baldrich E., Dalmau J., Pla C., Muntanola A.A. Contact dermatitis due to a clarifying cream. Contact Dermatitis 2005 53(3), 174-175
17. Veneziano L., Simonetta S., Voudouris S., Tosti A. Contact dermatitis due to topical use of vitamin K. Contact Dermatitis 2005. 52(2), 113-114
18. Keough G.C., English J.C., Meffert J.J., Eczematous hypersensitivity from aqueous vitamin K injection. Cutis 1998 Feb; 61(2): 81-83
19. Sommer S., Wilkinson S.M., Peckham D., Wilson C. Type IV hypersensitivity to vitamin K. Contact dermatitis 2002. 46(2), 94-96
20. Ruiz-Hornillos FJ, Prieto A, De Castro FJ et al. Allergic contact dermatitis due to vitamin K1 contained in a cosmetic cream. Contact Dermatitis 2006. 55: 246-247