Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Answer to the objections from The Retinol Consortium to VKM's document "Risk assessment of vitamin A (retinol and retinyl esters) in cosmetics"

Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics

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Persons working for VKM, either as appointed members of the Committee or as ad hoc experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Assessed by

This opinion has been evaluated and approved by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of VKM.

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Background

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has at request of the Norwegian Food Safety Authority performed a risk assessment of vitamin A in cosmetics (ISBN 978-82-8259-059-4). The assessment was performed by the VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics.

The Norwegian Food Safety Authority forwarded a letter dated December 19th 2012 from The Retinol Consortium to VKM. The headline of the letter was Re: VKM "Risk assessment of Vitamin A (retinol and retinyl esters) in cosmetics". VKM also received the Summary of Dossier on Vitamin A (Retinol, Retinyl acetate and Retinyl palmitate) in cosmetic products (K. Schilling, 2011) sponsored by The German Cosmetic, Toiletry, Perfumery and Detergent Association. In the letter from The Retinol Consortium several objections to the VKM report "Risk assessment of vitamin A (retinol and retinyl esters) in cosmetics" were presented. The objections were evaluated by the VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics in a meeting on March 14th 2013, and later with the members of the working group that drafted the vitamin A risk assessment. The opinion was adopted by VKM's Panel on Food Additives, Flavourings, Processing Aids, Materials in Food and Cosmetics on April 15th 2013.

Terms of reference

The terms of reference was to answer the objections to the VKM risk assessment of vitamin A (ISBN 978-82-8259-059-4) raised by The Retinol Consortium. In addition, it was requested by The Norwegian Food Safety Authority on the meeting March 14th 2013 that VKM should also take into account, if relevant, the Summary of Schilling K. (2011) Dossier on vitamin A (retinol, retinyl acetate and retinyl palmitate) in cosmetic products, sponsored by The German Cosmetic, Toiletry, Perfumery and Detergent Association, 26 October 2011.

Assessment

VKM acknowledge the opinions from The Retinol Consortium and their interest as stakeholders regarding the use of Vitamin A in cosmetic products. In the following, VKM has answered the objections that have been found to be of relevance and which are possible to address within the context of a scientific risk assessment.

General explanatory comments

The risk assessment of vitamin A (retinol and retinyl esters) in cosmetics was prepared by VKM at a request from The Norwegian Food Safety Authority according to the stated terms of reference. The request was to evaluate the potential risk from the total intake of vitamin A from foods, food supplements and cosmetic products in all age groups (including children and adolescents, as well as adults) in the Norwegian population. Because of lack of research data specifically documenting the exact use by consumers of the cosmetic products in Norway (including frequency of use, amounts used per application etc.), the default values in the SCCS's Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation (SCCS, 2012) (hereafter termed SCCS's Notes of Guidance) should be used to estimate exposure from dermal absorption of retinol and retinyl esters from the use of cosmetic products. The risk assessment should consider both systemic and local effects, and

include exposure scenarios to illustrate the influence of potential changes in the maximum authorized concentration levels of the various forms of vitamin A in cosmetics to as yet hypothetical concentrations (worst case scenarios).

Answers to the main objections from The Retinol Consortium as understood by VKM

1) Regarding the assertion that topical administration of vitamin A (retinol and retinyl esters) does not contribute to the systemic burden of exposure of these substances, as opposed to oral administration of these substances

The Retinol Consortium states that "All systemic toxic effects of vitamin A were found to be associated with high plasma levels of retinoic acids, e.g. the embryofetal toxicity of retinyl palmitate. Accordingly, all major investigations (1980s to the present) of the safety of topically or orally applied retinoids in humans have focused on their impact on the plasma level of endogenous retinoids". VKM agrees with this. However, the main question is whether topical applied retinoids can increase the systemic exposure or not. Based on the available literature, VKM does not agree with the statement from The Retinol Consortium that "The absence of systemic effects resulting from topically applied retinoids has been accepted as a fact for more than 20 years".

Both *in vivo* and *in vitro* studies demonstrate that topical application is effective with respect to loading the skin with substantial levels of retinoids (see references Boehnlein *et al.,* 1994, Antille *et al.,* 2004 , Kang *et al.,* 1995, Sorg *et al*., 2006 and Fu *et al*., 2007, and text on pages 31-33 in VKM's risk assessment). Furthermore, the topically applied retinol and retinyl palmitate have been shown to trigger biochemical (e.g. increased expression of retinol and retinoic acid binding proteins, increased levels of enzymes that metabolize retinoic acid) and histological (e.g. epidermal hyperplasia, dermal collagen synthesis and degradation) changes in the skin that might be expected from perturbation of previously established retinoid homeostasis (Kang *et al*., 1995; Duell *et al*., 1997; Fu *et al*., 2007). Therefore, in VKM's opinion it is not clear without reasonable doubt that under no circumstances may the retinol or retinyl esters metabolized and/or stored in the skin, as shown above, be transferred into systemic circulation over time, and thereby entail negative systemic effects.

Also taken into account is the difficulty in measuring vitamin A metabolites (free and/or attached to binding proteins) in plasma, and the strong homeostatic regulation keeping the plasma level constant.

VKM has not had access to unpublished reports made by industry (e.g. Renwick and Howes, 1997) or reports which are available only in languages other than English (e.g. Meuling *et al.*, 1995). VKM's opinion is based on the information available in open scientific literature, noticing the limited quality and reporting of the older papers.

2) Use of *in vitro* instead of *in vivo* human data to estimate skin absorption

The other main objection from The Retinol Consortium was that the exposure via cosmetics was estimated using data from an *in vitro* human absorption study, instead of human *in vivo* data. VKM decided not to use human *in vivo* studies not showing significant increase in plasma levels of retinoids after repeated topical application, such as Sass *et al.* (1996) and Nohynek *et al.* (2006), as argued for in the risk assessment (pages 32-34). See also bullet point 1) above. Furthermore, these papers used both lower applied doses and smaller application areas than required by the SCCS's Notes of Guidance. Whether these values are

higher than actual maximum consumer exposure or not, is irrelevant. At present, risk assessment of cosmetic products, such as VKM's risk assessment of vitamin A, is performed according to the SCCS's Notes of Guidance. Cosmetic products are not absolute necessities such as food and drinking water, and therefore the goal of their regulation is to make sure that these products are safe without reasonable doubt.

SCCS's Notes of Guidance describes how to use *in vitro* absorption in human skin in great detail. The use of *in vitro* data is therefore in accordance with the terms of reference. Also, the value of 5.7% dermally absorbed retinol using human skin from the *in vitro* study by Yourick *et al.* (2008) used by VKM, is in fact very similar to the dermal absorption value (5.3%) calculated from the human *in vivo* study by Franz and Lehman (1990) after topical application of retinoic acid. VKM therefore considers the absorption value used to be relevant and appropriate. In addition, when percutaneous absorption data obtained from *in vitro* or *in vivo* human skin are compared, they are found to be approximate when the protocols are matched (Lehman *et al.*, 2011).

Also, the CIR Expert Panel uses *in vitro* absorption data (CIR, 1987; CIR, 2008), as does the German Federal Institute for Risk Assessment (BfR, 2010), in their risk assessments of vitamin A.

3) Overestimation of exposure

The Retinol Consortium claimed that the way the exposure to vitamin A through cosmetics is calculated lead to an overestimation. Under this heading, various points have been addressed.

According to the terms of reference, exposure scenarios were used to estimate exposure to vitamin A. Both standard scenarios and worst case scenarios of exposure to cosmetics were used. The concentrations in the standard scenarios of 0.05% retinol equivalents (RE) in body lotions and 0.3% in face and hand creams were based on information from Gerhard J. Nohynek (L'Oreal R&D, France, personal communication in October 2011) as well as being used by BfR (2010). In the worst case scenarios, the concentration of 0.3% RE in body lotions was based on the maximum allowed concentrations of retinol in Norway. The concentration of 1% RE in face and hand creams was based on information from the Norwegian Medicines Agency, which had already received an application for use of this concentration in cosmetic products from Norwegian cosmetics industry. Since it was of great interest and relevance for The Norwegian Food Safety Authority that the risk assessment took such concentrations into account, the worst case scenarios were included in the terms of reference.

The Retinol Consortium states that "In order to develop a realistic exposure scenario, the VKM Opinion could have referred to the US CIR survey (2008) that showed that baby products do not contain retinol or retinyl palmitate at all, ….". In Norway, creams containing vitamin A (retinol palmitate) are marketed as being safe in use for the whole family, and it is stated in advertisements that it can be used on irritated skin and in the nappy area. Therefore, the CIR survey (2008) does not cover Norwegian conditions.

The values used to estimate exposure to retinol and retinyl esters from the use of cosmetics were based on consumer exposure figures in SCCS's Notes of Guidance (Table 3), according to the terms of reference. These numbers were the 90th percentile, and VKM acknowledge that this fact could have been mentioned in the risk assessment. However, these were the only numbers available to calculate the exposure from the use of cosmetics, since mean levels were not given.

The use of accumulated maximized exposure parameters (term used by The Retinol Consortium) and assumptions in risk assessments is the usual approach when specific data on actual human exposure is lacking, as was the case here. VKM does not claim to present new data, so the worst case scenarios included in the terms of reference in the risk assessment represent a hypothetical risk. On the other hand, with the coming changes in regulation of cosmetic products these scenarios were of great interest for The Norwegian Food Safety Authority since they had already received applications on use of higher concentrations. However, VKM's main focus was not the worst case estimates, acknowledging that they represent overestimations for most consumers actually having a different use on one or more points than included in the scenarios. This was discussed in detail in the Chapter 5 Uncertainty.

4) Is the information available sufficient to conclude on photocarcinogenesis
The Retinol Consortium comments that 'The VKM Opinion states that retinyl palmitate could be photo-carcinogenic in mice….'. It is not stated in the VKM vitamin A risk assessment that vitamin A cause photocarcinogenesis. It is referred to studies that may indicate that retinol and retinyl palmitate could be photocarcinogenic in mice, however, it is specified that these results do not provide sufficient information to conclude this. Therefore, VKM also claimed that more data was needed before the relevance of these mice studies for humans could be decided. The *in vitro* data were mentioned to discuss plausible mechanisms for potential photocarcinogenic effects. Potential positive effects of retinoids in skin cancer prevention were also addressed in the risk assessment (see page 35), although the terms of reference requested a risk assessment, not a risk-benefit-assessment, of vitamin A.

5) Weighing the risk in accordance to previous risk assessments
Although referring to previous risk assessments, when receiving a request for a risk assessment from the Norwegian Food Safety Authority, VKM always performs an independent risk assessment, based on available literature and its own expertise and judgment. Therefore, the comment from The Retinol Consortium that the conclusions from the CIR Review (CIR, 1987; CIR, 2008) should be given appropriate weight in the overall safety evaluation is in VKM's opinion not justified. Also, the approach used by VKM in this risk assessment is basically similar to the approach previously used by BfR (2010).

6) Use of the weight of evidence approach
The Retinol Consortium states that the weight of evidence approach was not used by VKM. VKM is well aware of the fact that there are several documents written by various organizations and authors describing this approach in theory. However, at present there is no agreement between different institutions on a coherent way of applying this approach in practice. It can be observed that various groups of authors claim to use this approach in very different ways. Therefore, VKM do not find this comment justified.

Comments related to the Summary of Dossier on vitamin A (retinol, retinyl acetate and retinyl palmitate) in cosmetic products (K. Schilling 2011) sponsored by The German Cosmetic, Toiletry, Perfumery and Detergent Association, 26 October 2011

VKM did not have access to the whole dossier, and therefore not the references, only the summary. In this summary, it is referred to *in vitro* studies of absorption of vitamin A in human skin, as VKM has used in their risk assessment of vitamin A. It is stated that the most

appropriate such study found a dermal bioavailability of 4.3%, which is not very different from the value of 5.7% used by VKM. It is also referred to 'a standard risk assessment approach based on EU/SCCS exposure estimations for cosmetic products using reliable *in vitro* penetration data'. Obviously, the industry is well aware of the normal use of human *in vitro* data for estimating dermal absorption of substances in cosmetic products. Therefore, their comment claiming that VKM should have used human *in vivo* data instead of human *in vitro* data in their risk assessment is not understandable and not justified.

In light of the mentioned uncertainties, VKM's conclusions based on the estimated exposure in the standard scenarios are not substantially different from the conclusions in this summary, i.e. that the use of topically applied vitamin A is safe as a cosmetic ingredient under the use conditions of 0.05% RE in body lotions and 0.3% RE in hand and face creams. However, according to the terms of reference, VKM's risk assessment of vitamin A also included worst case scenarios representing a new (hypothetical) situation with increased levels of vitamin A in cosmetic products. The sources of overestimations in these scenarios were clearly stated in the risk assessment.

Conclusion

VKM does not find the objections from The Retinol Consortium to be pertinent and of such a nature that a revision of their risk assessment is warranted.

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