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Highly refined mineral oils in cosmetics: Health risks are not to be expected according to current knowledge

Updated BfR Opinion No. 008/2018 of 27 February 2018*

The BfR's risk assessment relates to those mineral oil qualities which comply with the purity requirements for pharmaceuticals and for mineral oil authorised as food additives.

Cosmetic products can contain mineral oils. These are complex mixtures of hydrocarbons of different structures and sizes. A distinction should be made between mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH). The latter could potentially contain carcinogenic substances, such as polycyclic aromatic compounds.

According to the EU cosmetics regulation, mineral oils are only permitted in cosmetics if the full refining history is known and the starting material is not carcinogenic, or if the distillate was tested using specific methods (IP346). The IP346 method is an initial test for those mineral oils which are to undergo further purification steps for subsequent use in cosmetic products. This should prevent the use of mineral oils which are of concern to health.

The German Federal Institute for Risk Assessment (BfR) has evaluated the health risks of dermal absorption of MOSH and MOAH from mineral oils via cosmetics. Highly refined mineral oils and microcrystalline waxes, which comply with the purity requirements for pharmaceuticals, are used in cosmetic products for dermal application. The MOAH levels in these mineral oils are reduced through the corresponding technical refinement. As MOSH are hardly absorbed by the skin, the dermal application of cosmetic products containing mineral oils does not result in systemic exposure.

According to the currently available scientific knowledge, no health risks are to be expected for consumers who apply cosmetic products to their skin, in the view of the BfR. Accordingly, there have been no reports up to now of any effects on health through the mineral oil components contained in these cosmetic products, even though they are used over many years and often on a daily basis.

In addition to possible absorption via the skin, oral exposure has to be considered, especially with lip care products, which can also contain mineral oils. As low-viscosity mineral oils can easily be absorbed orally, medium- and high-viscosity mineral oils and microcrystalline waxes are recommended for use in lip care products. Certain highly purified food grade medium- and high-viscosity mineral oils and microcrystalline waxes were subjected to a health risk assessment by the European Food Safety Authority (EFSA) and approved for use in the food sector. Values for acceptable daily intake (ADI) were derived for these mineral oils and waxes by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and by EFSA. Cosmetics Europe, the European trade association for the cosmetics and personal care industry, has advised manufacturers of lip care products only to use those mineral oil fractions for which ADI values apply.

The dose of mineral oils ingested orally via lip care products contributes to less than 10% of the ADI value. If the recommendation of Cosmetics Europe is complied with, no health effects are to be expected from oral intake in the opinion of the BfR.

This opinion replaces Opinion No.014 / 2015 of 26 May 2015

1 Subject of the assessment

The German Federal Institute for Risk Assessment (BfR) has assessed the health risks of mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH) in cosmetic products. To do so, the BfR analysed the occurrence of MOSH and MOAH in various cosmetic products among other tests.

The subject of mineral oil in cosmetic products was discussed several times with the experts and committee members of the BfR Committee for Cosmetics. The BfR also held a discussion with federal institutes and offices as well as authorities of the German federal states in November 2015 on the problems posed by mineral oils, as well as a discussion with experts in November 2016 on MOAH in cosmetic products. The participants were representatives of federal and regional authorities, European institutions, research institutions, universities and trade and industry associations.

BfR-Risk Profile:
Mineral Oil in Cosmetic Products (Opinion No. 008/2018)

A	**Affected groups**	**General population**				
B	**Probability of a health impairment when using mineral oil containing cosmetics (uptake through the skin and mouth, with compliance with the recommendation of Cosmetics Europe)**	Practically excluded	**Unlikely**	Possible	Probable	Certain
C	**Severity of the health impairment when using mineral oil containing cosmetics (uptake through the skin and mouth, with compliance with the recommendation of Cosmetics Europe) [1]**	**No impairment**	Slight impairment [reversible/irreversible]	Moderate impairment [reversible]	Severe impairment [reversible/irreversible]	
D	**Reliability of the available data [2]**	**High: The most important data are available and are free of contradiction**	Moderate: Some important data are missing or contradictory	Low: Numerous important data are missing or contradictory		
E	**Controllability by consumers [3]**	**Control not necessary**	Controllable through precautionary measures	Controllable through avoidance	Not controllable	

Squares highlighted in dark blue indicate the properties of the risk assessed in this opinion (more detailed information on this is contained in BfR Opinion No. 008/2018 of 17 February 2018).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR Opinion. It is not intended for the purpose of comparing risks. The risk profile should only be read in conjunction with the corresponding opinion.

[1] – Line C – Severity of the health impairment when using mineral oil containing cosmetics (uptake via the skin)
The data available to date show no health impairments. There are currently no indications of health effects including cancer through the dermal application or oral intake of cosmetic products containing mineral oils.

[2] – Line D – Reliability of data
Some uncertainties still remain for the health assessment of highly purified, low viscosity mineral oils for humans with regard to the relevance of inflammatory granuloma formation in the liver of exclusively female Fischer 344 rats.

[3] – Line E – Controllability by consumers
The information in this line should not be seen as a recommendation from the BfR; it has a purely descriptive character. The BfR recommends courses of action in its opinion. In accordance with the latest available level of knowledge, no health risks are to be expected for consumers through the dermal uptake of mineral oil containing cosmetics. In this regard, the BfR recommends that data be collected by the federal states (Länder) within the framework of a national monitoring.

2 Result

Mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH) are components of highly refined mineral oil products whose share of polycyclic aromatic compounds has been technologically minimised.

According to Annex II of EU Cosmetics Regulation No. 1223/2009, mineral oils/waxes/distillates are prohibited in cosmetic products except when the refining process is fully known and the starting material is not carcinogenic, or the distillate fulfils the requirements of method IP346, which means that less than 3% weight by weight (w/w) of substances with dimethyl sulphoxide (DMSO) are extractable. This is to prevent the use of mineral oils which can be carcinogenically active in the further purification process.

The IP346 method is based on a method for predicting the carcinogenic potential of a mineral oil in the mouse skin test. This prediction method is based on data of a total of 133 mineral oils tested on mouse skin, of which four were assessed as false-negative using the IP346 method. The false-negative rate lay at 6% (Concawe 2016). Correlations of the content in the DMSO extract with tumour frequency in the mouse skin test showed that tumour frequency increases significantly against the background rate above a value of 3% w/w in the DMSO extract.

In practice, the IP346 method is an initial test for those mineral oils, that for the purpose of being used in cosmetics, are subjected to further purification ssteps, such as catalytic hydrogenation in order to minimise the residual aromatic content. The weight percentage extractable with DMSO is further reduced with each of these purificationsteps. The purified mineral oil fractions used in the cosmetic products fulfils the purity requirements for pharmaceuticals.

The dermal absorption of MOAH depends on the viscosity of the vehicle used; MOAH can in principle become bioavailable via the dermal route, but they are presumably metabolised in the body subsequently before being excreted. Accumulation of MOAH in the body could not be demonstrated.

On the basis of the available data and under consideration of clinical experiences and a lack of epidemiological indications, no health risk can currently be recognised as a result of dermal exposure to cosmetic products containing mineral oils. Health effects through the highly purified mineral oil fractions commonly used in the cosmetics industry have not yet appeared.

There are also no indications at the moment of a health risk to the consumer through dermal absorption of the MOSH fraction in cosmetics. Existing data on skin penetration suggest that higher viscosity oils hardly become systemically available via the dermal exposure route, even though small quantities of shorter chain n-alkanes, which were tested as the model substances for MOSH, are occasionally detected in the epidermis as well as the dermis.

The oral intake of MOSH via lip care products containing mineral oil can lie within the range of dietary MOSH intake. MOSH of a certain chain length range accumulate in the human body. Inflammatory granulomas were detected exclusively in the liver of Fischer 344 rats during experiments after high doses of low-viscosity mineral oils had been administered. These lesions differ morphologically from the non-inflammatory lipogranulomas observed in

the liver of autopsy patients in correlation with increased MOSH levels. Practically no lipogranuloma was found in the liver in another study conducted on autopsy patients with low MOSH levels. The toxicological relevance of the lesions observed in the Fischer 344 rats for humans is doubtful at the moment.

If the recommendation of Cosmetics Europe is complied with only to use mineral oil fractions of food purity qualities in lip care products for which an ADI value was derived by the JECFA or EFSA, no health effects are to be expected through oral uptake. This applies both to the question of granuloma formation in the liver through the MOSH, as well as the lack of indications of mutagenicity or carcinogenicity. Analysis of lip care products in Switzerland and Germany demonstrate, however, that mineral oils which do not comply with this recommendation were also used in a number of products. The BfR advises manufacturers of lip care products to comply with the recommendation of Cosmetics Europe.

3 Rationale

3.1 Risk assessment

A current literature search was conducted in the following databases: DIMDIs databases, ISI/Web of Science, Pubmed, Scopus, ScienceDirect, NTP, Litdoc, Chemici.

3.1.1 Hazard identification

Mineral oils are complex mixtures consisting of saturated aliphatic and cyclic hydrocarbons (MOSH) with different numbers of carbon (C) atoms and mostly alkylated polycyclic and partially hydrogenated aromatic compounds (MOAH). Before being used in cosmetic products, they are technologically processed in such a way, through refining processes such as distillation, extraction and hydrogenation, that the number of potentially carcinogenic aromatic compounds is minimised. The technological purification steps have to be optimised, depending on the origin and composition of the crude oil.

These highly purified mineral oils have various functions in cosmetic products, where they can serve as static inhibitors, plasticisers, skin protection, solvents or viscosity regulators. According to their multiple functions, mineral oils are to be found in skin creams, skin lotions, body and face cleansing agents, sun screens, self-tanning lotions, deodorants and antiperspirants, lip care products, make-up, nail care products, hair gels, skin and eye ointments, Vaseline and baby oil. The concentrations range from 1 to 99%, depending on the product.

The results of the independent analyses conducted by the BfR on the occurrence of MOSH and MOAH in various cosmetic products are presented below.

Characterisation of the mineral oil

The identification and quantification of individual substances is not possible due to the complexity of the mineral oils.Rather, the MOSH and MOAH are each quantified in total separately from each other. The described analytical methods for determining MOSH and MOAH have only existed for a few years and are established in the analysis of vegetable oils, foods and food packaging materials made of cardboard. These methods have also been established in the meantime for the examination of cosmetic products.

Molecular mass distribution

Characterisation per molecular mass distribution allows conclusions on possible mineral oil products and sources of contamination. Several mineral oil products with different molecular mass distributions often occur next to one another in one cosmetic product. The molecular mass range and centring (maximum of the peak hump) are placed in relation to the number of carbon atoms in n-alkanes. Gas chromatographic elution over a non-polar stationary phase is used for this purpose, as the evaporation from a dimethylpolysiloxane is similar to that of distillation evaporation from a mineral oil mixture. This technique is also known as simulated distillation. As the gas chromatographic method actually measures volatility rather than molecular mass, the determined masses deviate somewhat from the real masses:

- For isoparaffins, calibration with regard to n-alkanes tends to underestimate molecular masses somewhat, as iso-alkanes are eluted by up to two C atoms earlier than the n-alkanes
- Cyclic alkanes can also be eluted slightly after the n-alkanes of the same carbon number, i.e. their mass can be slightly overestimated
- The molecular mass distribution of the MOAH is also determined via the retention times of the n-alkanes from the MOSH chromatograms
- As the MOAH chromatograms do not contain any n-alkanes, the absolute retention times are taken. It should be noted here that the C-number of the aromatics can deviate considerably from that of the n-alkanes eluted at the identical retention time. Methylanthracene, for example, contains 15 carbon atoms, but is eluted at n-C21, chrysene (C18) at n-C27 and pyrene (C16) at n-C24.

Analytics of MOSH and MOAH with online LC-GC-FID

MOSH and MOAH are quantified in cosmetic products today by means of HPLC-GC-FID. The biggest problems with the GC-FID method (gas chromatography with flame ionisation detection) used for quantification are the low sensitivity (the detection limit for the undissolved mineral oil peak lies in the range of 50 to 100 ng, which is almost 1000 times higher than for a clean, single signal) and the lack of selectivity. Pre-separation by means of HPLC plays an important role for this reason. This preseparation has to introduce a large aliquot to the GC and isolate the MOSH and MOAH fractions as selectively as possible.

Most of the analyses to date were conducted with online coupled HPLC-GC-FID which combines the advantages of a high separation capacity in pre-separation with high sensitivity (complete transfer to the GC system), extensive exclusion of contamination through manual sample work-up and a high sample throughput. The version with separate MOAH analysis was described for the first time in 2009 (Biedermann et al. 2009a). A further development of the basic method was published recently (Biedermann et al., 2017).

The quantification of MOAH can lead to overestimated results if they are quantified in a sample in the trace range next to a large excess of MOSH (percentage range). This is caused by the carryover of MOSH to the MOAH fraction. This carryover, which is only relevant with MOSH and MOAH concentrations of different orders of magnitude, can be avoided through a two-stage analycal method in which the MOSH are almost removed with simultaneous MOAH enrichment prior to quantification.

Need for standardisation of the analytics of MOSH and MOAH in cosmetics

Standardisation is necessary to guarantee the comparability of the analysis data collected on the occurrence of MOSH and MOAH in cosmetic products. A work group is currently dealing with this within the scope of standardisation work for the collection of official methods in line with Art. 64 of the German Food and Feed Code (LFGB). As the substances to be quantified using online LC-GC-FID analytics have to be vapourable without decomposition and detectable by means of gas chromatography, conventions have to be used for the working range. Current findings show that hydrocarbons can be recorded without discrimination up to a volatility of n-C50 with the appropriate adjustment of the analysis method. The possible discrimination-free recording of higher molecular hydrocarbons would negatively influence the stability of the analysis system. In light of the fact that the comparability of analytical results is being targeted, the quantification of parts of the mineral oil hump in which no discrimination-free quantification is guaranteed should be classed as pointless. Numerous inter-laboratory comparisons as well as the recently completed standardisation of the analytics of MOSH and MOAH in vegetable oils and foods made on the basis of vegetable oils (CEN, 2017) prove that, despite their complexity, the analysis of MOSH and MOAH leads to reproducible results.

Characterisation of ring systems and degree of alkylation in mineral oil aromatics by means of GCxGC analysis

By coupling two consecutive GC separations in which two columns with different separation properties are used (e.g. a non-polar separation column followed by a polar one), the separation of the various ring systems that occur in the mineral oil mixture can be achieved, depending on the degree of processing of the mineral oil. In addition to the ring systems, their degree of alkylation can also be estimated through the position in the chromatogram (Biedermann et al. 2009b). If GCxGC analysis is performed with mass spectrometric detection, qualitative detection of partially hydrogenated ring systems can also be possible if they are present in the sample. The unequivocal identification of individual ring systems in samples of high complexity (high molecular weight, existence of various ring systems, partial hydrogenation) is not always possible, however.In MOAH fractions of individual petrolatum samples there is for instance no structuring in the two-dimensional chromatogram. Due to the great complexity of the mineral oil aromatics, the inability to separate chromatographically into concrete signals for individual compounds and the lack of standard compounds, the identification of individual substances is generally not possible at the moment. With mass spectrometric detection, the identification of structural elements in complex samples is achieved on the one hand through the position in the two-dimensional chromatogram and on the other through the evaluation of characteristic mass numbers for certain ring systems, depending on the degree of alkylation. The identification of the ring systems depending on the examined mineral oil involves uncertainties, as neither the mass numbers (especially if there is hydrogenation of larger ring systems and higher degrees of alkylation) are absolutely specific, nor do any reference standards exist for the various partially hydrogenated compounds with which the identification could be confirmed.

<u>Mineral oil in cosmetic products</u>

Definitions, general, purification

Mineral oil products used in cosmetic preparations must be declared accordingly on the product, e.g. using the INCI designations *paraffinum liquidum* (medicinal white mineral oil), *paraffin* (paraffin waxes), *cera microcristallina* (microcrystalline wax) or *petrolatum* (white or

yellow Vaseline, petroleum jelly). In mineral oils and waxes used in cosmetic products, the length of the carbon chains varies between C15 and C100+; these are strongly lipophilic mixtures with an octanol/water partition coefficient (log $K_{o/w}$) greater than 7 (Petry 2017).

The complex mineral oil mixtures contained in various cosmetic products consist of saturated hydrocarbons (MOSH) as well as aromatic and sometimes partially hydrogenated aromatic hydrocarbons (MOAH). From a chemical point of view, the saturated hydrocarbons are chain- and ring-shaped hydrocarbons, whereas the MOAH fraction comprises a complex mixture of mainly alkylated aromatic hydrocarbons. The identification of individual substances is not possible.

The percentage of MOAH contained in the crude oil (usually 15 to 30%) can be reduced considerably in the product, depending on the industrial process used to process the crude oil. This means that the distillation steps for mineral oils that are intended to use for cosmetics are followed individually or in combination by extractions, chemical modifications and hydrogenations. Only fractions which have successfully passed the IP346 test are subjected to these subsequent purification steps. The IP346 method is therefore an initial test for those mineral oils which are to be subjected to further purification steps for use in cosmetic products. Using the techniques outlined above, highly refined mineral oil raw materials are produced whose residual levels of aromatic compounds are minimised and which satisfy the purity requirements of the European Pharmacopoeia.

The purification steps lead to a step-by-step reduction in the proportion extractable with DMSO in line with the IP346 method and thereby in MOAH levels too. This is substantiated by data presented at the BfR within the scope of the experts' discussion in November 2016 and the consumer protection forum in December 2017. These data were collected along the processing stages between a mineral oil proven not to be carcinogenic after testing with the IP346 method and the mineral oil end product assigned for use in cosmetic products. It should be noted here that both the weight percentage extractable with DMSO in line with the IP346 method, as well as the mutation index (MI) in the modified Ames test decrease significantly. In this way, levels in the DMSO extract of 0.2% and an MI of 0.02 are reported for the final quality of a low-viscosity medicinal white oil after the last purification steps. An MI of < 1 measured in the modified Ames test means that the tested fraction is not mutagenic.

Data on the technologically achievable MOAH residue levels in highly purified mineral oil end products were also discussed. This depends on each C number range or the molecularity of the various mineral oil end products. Accordingly, there are reports of MOAH residue levels of below 250 ppm (0.025%) for a low-viscosity medicinal white oil and residue levels in the range from 1 to 1.7% for the highly molecular crystalline waxes. This comparatively high residue level of MOAH can be explained by the fact that the considerably higher molecularity of the microcrystalline waxes in line with the higher C number range produces considerably longer alkyl chains. The aromatic and partially hydrogenated ring structures contained in the MOAH fraction are therefore substituted by long alkyl chains which contribute accordingly to the weight percentages of the MOAH fraction. The percentage of aromatic molecule parts is low, however.

Mineral oil findings to date in cosmetic products for dermal application

The BfR analysed 19 mineral oil-containing cosmetic products from various product groups and four Vaselines for MOSH and MOAH mineral oil components. Paraffinum liquidum, petrolatum (synonym: Vaseline), cera microcristallina and paraffin were declared either individu-

ally or in combination. MOSH and MOAH were quantified per LC-GC analysis in all cosmetic products. The highest MOAH levels with values between approx. 1% and 4.5% were determined in four cosmetic products (one hair wax, two care creams, one foot balsam). It was conspicuous that petrolatum was listed as the sole mineral oil constituent or in first place in the INCI list in these samples. Comparable MOAH levels of between 1.7% and 5% were also determined in the four tested Vaselines. All other cosmetic products containing mineral oils had MOAH levels of between 0.007% and 0.3%.

More thorough analyses of the MOAH fraction were conducted per GCxGC-ToF-MS by way of example on two samples. Clear indications were found in both of these samples that the substituted two and three-ring aromatics they contained had been partially hydrogenated.

Petrolatum (synonym: Vaseline) is a mixture of at least two different mineral oil components, of which at least one is an oil and at least one a wax. It is possible that not only low-aromatic, i.e. pharmaceutical qualities are used in the manufacture of petrolatum but also technical qualities. This would explain why the addition of petrolatum to a cosmetic product leads to a MOAH content in the upper single digit percentage range.

MOSH and MOAH were generally not detectable in ten analysed cosmetic products without any mineral oil-based constituents. Individual samples showed minimal traces of MOAH ranging from 4 to 400 ppm which could possibly have come from vegetable oils, formulation aids or process contaminants.

In the meantime s everal of the regional authorities responsible for monitoring the market have developed the capability of determining MOSH and MOAH in cosmetic products and analysing samples from the German market. The data available to the BfR confirm the findings of MOAH levels up to the single digit percentage range in Vaseline and several cosmetic products for dermal application.

Findings in lip care products

Kantonales Labor Basel conducted examinations in 2012, 2014 and 2016 in which lip care and other products were tested for their MOSH content and volatility ranges. Data on MOAH were only collected in the test series conducted in 2016 in which levels of up to 4.5% were reported (Kantonales Labor Basel Stadt 2012, 2014a, 2014b, 2016; Niederer et al., 2015).

The examination of more than 200 lip care products from the Swiss market (Niederer et al., 2015) showed that the mineral oil quality used in numerous products did not comply with Recommendation No. 14 of Cosmetics Europe (Cosmetics Europe 2014). This recommendation proposes that only those mineral oils be used in lip care products for which an ADI value (acceptable daily intake) for their use in foods was derived within the scope of a risk assessment. Analysis of more than 40 lip care products from the German market by the BfR and a regional authority responsible for monitoring the market confirm the test results of Niederer et al. (2015). The BfR determined MOSH levels ranging from 8.3 to 73.9% in 19 mineral oil-containing lip care products from the German market. In addition to this, MOAH levels of up to 3.9% were quantified in these samples, which is comparable with the samples from the Swiss market.

3.1.2 Hazard potential

Acute toxicity

The acute toxicity of distillates is low; a single oral dose of 5 g/kg bw of 100% *Paraffin*, for example, showed no adverse effects in rats (CIR 1984).

Subchronic and chronic toxicity

Oral application

The toxicity of highly refined mineral oils and mineral waxes was tested on rats in feeding studies with repeated administration via feed. The administration of low- and medium-viscosity mineral oils and paraffin waxes at levels of up to 2% via feed led to high MOSH concentrations in the mesenterial lymph nodes and liver of female Fischer 344 rats (Baldwin et al., 1992; Firriolo et al., 1995; Smith et al., 1996; Scotter et al., 2003; Griffis et al., 2010; McKee et al., 2012). With subchronic exposure with a level in feed of 2%, the MOSH concentration in the liver was in the range of 980-9200 ppm (low- and medium-viscosity mineral oils) and 2700-19800 ppm (paraffin waxes) respectively. The tissue concentrations were considerably lower for highly viscous mineral oils and microcrystalline waxes (Smith et al., 1996). Compared to female Fischer 344 rats, male Fischer 344 rats and female CRL:CD and Sprague-Dawley rats showed a significantly lower accumulation of MOSH in the examined tissues (Baldwin et al., 1992; Firriolo et al., 1995; Griffis et al., 2010).

The time progressions of the MOSH concentration in the liver of female Fischer 344 rats observed in subchronic and chronic studies (Trimmer et al., 2004; Barp et al., 2017a) indicate that steady-state concentrations have been reached. The MOSH accumulation in the liver was reversible. Accordingly, a monoexponential decrease in the MOSH concentration was shown in the recovery phase (phase after discontinuation of treatment) (Trimmer et al., 2004). From studies with recovery phases (Trimmer et al., 2004; Smith et al., 1996; Barp et al., 2017a), it was possible (under the assumption of a monoexponential decrease) to derive half-lives of 60-190 days for low-viscosity mineral oils, 91-122 days for medium- and high-viscosity mineral oils, 20-30 days for paraffin waxes and 23-50 days for a MOSH mixture with a broad molecular mass distribution. It can be estimated from these elimination half-lives how long it would take with daily MOSH exposure until the MOSH concentration in the liver reaches a steady state. If 5 half-lives are used as the basis for achieving 97% of the equilibrium concentration, steady-state level would be reached with Fischer 344 rats in 100 days to 2.6 years, depending on the type of product administered.

Mineral oils and waxes which caused high MOSH concentrations in the liver of female Fischer 344 rats in subchronic studies resulted in terms of magnitude to comparably high values in the mesenterial lymph nodes (Baldwin et al., 1992; Firriolo et al., 1995; Smith et al., 1996; Scotter et al., 2003; Griffis et al., 2010; McKee et al., 2012). The MOSH concentrations in the fat tissue, on the other hand, were lower by one order of magnitude than those in the liver (Smith et al., 1996; Barp et al., 2017a). A subchronic study with the administration of a MOSH mixture with a broad molecular mass distribution showed a more or less linear increase in the MOSH concentration in fatty tissue (Barp et al., 2017a). This study did not provide any indication that accumulation in fatty tissue is reversible, because the MOSH levels in the fat tissue did not decrease after the treatment was discontinued.

The high MOSH concentration in the tissue of female Fischer 344 rats was accompanied among others by the formation of microgranulomas in the mesenterial lymph nodes, as well

as granulomatous changes in the liver. Subchronic studies showed an increase in incidence and severity of the microgranulomas in the mesenterial lymph nodes for light white oil and certain low-viscosity mineral oils and paraffin waxes (Baldwin et al., 1992; Firriolo et al., 1995; Smith et al., 1996; Scotter et al., 2003; Griffis et al., 2010; McKee et al., 2012). For the mesenterial lymph nodes these studies as well as chronic studies with medium- and high-viscosity mineral oils (Trimmer et al., 2004) produced no indications of accompanying inflammatory reactions, necrosis or other lesions. Based on these findings and due to similar reaction patterns observed with other highly molecular, poorly soluble substances, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) classified the histopathological changes in the mesenterial lymph nodes as not adverse (JECFA 2012). The CONTAM panel of the European Food Safety Authority (EFSA) observed the microgranulomas in the mesenterial lymph nodes as a non-specific, adaptive alteration which is of little concern from a toxicological point of view (EFSA 2012).

After subchronic exposure to high doses of low-viscosity mineral oils and paraffin waxes, granulomas began to form in the liver of female Fischer 344 rats, with an accompanying inflammatory reaction, so-called epitheloid cell granulomas (Baldwin et al., 1992; Firriolo et al., 1995; Smith et al., 1996; Scotter et al., 2003; Griffis et al., 2010). For medium- and high-viscosity mineral oils and microcrystalline waxes, on the other hand, subchronic and chronic studies produced no indications of treatment-related granulomatous changes in the liver of female Fischer 344 rats (Trimmer et al., 2004; Shoda et al., 1997; Smith et al., 1996; Scotter et al., 2003). These are the qualities of mineral oils and waxes that Cosmetics Europe recommends for use in lip care products. The lesions in male Fischer 344 rats were less severe compared to the reaction of female animals (Baldwin et al., 1992; Smith et al., 1996). In general, these treatment-related effects could not be observed in other rat strains and in dogs (Shubik et al., 1962; Firriolo et al., 1995; Griffis et al., 2010; Smith et al., 1995).

In humans, so-called lipogranulomas were detected in the liver, spleen, lymph nodes and other organs in connection with deposits of MOSH (Fleming et al. 1998; Carlton et al. 2001). Only a very few studies exist on histopathological findings with information on MOSH concentrations in individual human tissues and organs. Boitnott and Margolis (1970) examined liver samples of 60 autopsy patients and observed MOSH concentrations ranging from <100 to 5,000 ppm. Lipogranulomas in the form of multiple accumulations of oil droplets which were easily recognisable in the routine examination occurred with MOSH concentrations higher than 600 ppm. Barp et al. (2014) examined tissue samples from 37 autopsy patients (25-91 years old). The MOSH concentrations in the liver were almost log-normally distributed with a median of 71 ppm and a 95th percentile (P95) of 521 ppm (maximum: 901 ppm; BfR, unpublished data). Chromatographical analyses of MOSH in the liver showed a molecular mass distribution between C18 and C45 (Barp et al. 2014). Practically no lipogranulomas were found (Barp et al., 2017b). In addition to this, the study provided no indications of a statistically significant increase in the MOSH concentration in the liver with increasing age (BfR, unpublished data).

Additional analyses of tissue samples from 37 autopsy patients (Barp et al., 2014;BfR, unpublished data) showed median MOSH concentrations in the mesenterial lymph nodes, subcutaneous fatty tissue and spleen of 166 ppm, 87 ppm and 28 ppm (P95: 518 ppm, 406 ppm, 277 ppm) respectively. Statistical analysis of age dependency showed a 1.2-fold increase of the mean MOSH concentration in the subcutaneous fatty tissue per decade of age (BfR, unpublished data). In another study, the MOSH concentrations in biopsy samples of subcutaneous fatty tissue taken from 142 pregnant women (aged 19-47) during caesarean delivery were examined (Concin et al., 2008/2011). The median MOSH concentration in fatty tissue was 55 ppm (P95: 120 ppm). Statistical analysis of age dependency showed a 1.4-fold in-

crease in the mean MOSH concentration in subcutaneous fatty tissue per decade of age (BfR, unpublished data). The age-dependent increase in the mean MOSH concentration indicates accumulation of MOSH in fatty tissue over time. It should also be taken into account here, however, that older generations were exposed in younger age to a greater extent to mineral oils via food than younger generations, which helps to explain the extent of the increase in addition to accumulation over time.

Inflammatory granulomatous alterations in the liver of Fischer 344 rats are an adverse effect which was so far observed exclusively in this specific rat strain. From a morphological-histological point of view, however, the epitheloid cell granulomas observed here differ from the non-inflammatory lipogranulomas observed in humans (Trimmer et al., 2004; Smith et al., 1996; Griffis et al., 2010; Carlton et al., 2011; Fleming et al., 1998; Fleming & Carrillo, 2018; Miller et al., 1996; Adenuga et al., 2017). In its opinion prepared in 2012 on low- and medium-viscosity mineral oils, the JECFA concluded that the available data are not sufficient to draw conclusions on the relevance of the effects observed in Fischer 344 rats for humans (JECFA, 2012). Similarly, the EFSA CONTAM panel arrived at the conclusion in its opinion of 2012 that the information currently available is insufficient to regard the granulomatous changes in the liver of the Fischer 344 rat as specific to this strain of rat. There continues to be a need for clarification here in the view of the BfR.

For cosmetic products, especially for lip care products, it is important, that animal studies with oral administration did not show any indications of granuloma formation in the liver for medium- and high-viscosity mineral oils and microcrystalline waxesAcceptable daily oral intake doses (ADI) were defined by the JECFA and EFSA for microcrystalline waxes and highly refined white oils in food quality with medium- and high-viscosity on the basis of these data and other data on genotoxicity and carcinogenicity (JECFA 2002 and 2012; EFSA 2009 and 2013a, 2013b). These are the qualities that should be complied with for lip care products according to the recommendation of Cosmetics Europe.

Dermal application

Rodent studies on subchronic toxicity after dermal application of mineral oils consistently showed no indications of adverse effects. Highly purified white oil was included as a control in several studies on C3H mice with life-long exposure to mineral oil products (Biles et al. 1988; McKee et al. 1986; 1989; 1990; McKee and Lewis 1987). In these cases, a complete autopsy was conducted in each instance. There were no indications of any kind of histopathological changes in the internal organs. In Fischer 344 rats and white New Zealand rabbits, there were no indications either of histopathological (F344, rabbits), haematological or cutaneous changes (rabbits) after repeated, long-term, topical application of white oils (NTP 1992; Johnson & Johnson Consumer Products, non-published data, quoted in Nash et al. 1996).

Carcinogenicity

Dermal application

The carcinogenicity of a mineral oil mixture is related to its content of aromatic hydrocarbons. The modified Ames test (Blackburn et al. 1984) and skin tests on mice have shown that all mineral oils are mutagenic or carcinogenic if they are not subjected to a treatment intended to minimise the content of aromatic hydrocarbons (Cruickshank and Squire 1950). Epidemiological studies (IARC 2012) prove that dermal exposure in the work place to untreated or

only slightly treated mineral oils can lead to skin cancer. This means that the carcinogenicity of mineral oils depends on the type and intensity of purification steps, i.e. on the degree of refining (Chasey, McKee 1993).

The MOAH fraction contains a mixture of primarily alkylated and partially hydrogenated but also unsubstituted aromatic hydrocarbon compounds with different numbers of ring systems. This mixture cannot be clearly characterised and varies depending on the mineral oil. According to the current state of knowledge, where carcinogenicity is present, it is caused by polycyclic aromatic hydrocarbons containing 3 to 7 aromatic rings. In this context, unsubstituted polycyclic aromatic hydrocarbons (PAH) in particular were thoroughly investigated and some of these PAHs have been classified as carcinogenic and mutagenic by the International Agency for Research on Cancer (IARC), EFSA and in accordance with the CLP regulation (EFSA 2008; JECFA 2006; IARC 2010).

On the other hand, the existing data on the carcinogenic potential of alkylated and partially hydrogenated aromatic hydrocarbon compounds are insufficient. The small number of studies on alkylated PAHs shows that alkylation can have an impact on the carcinogenic activity of the compounds. For example, the application of the PAHs phenanthrenes and anthracenes on mouse skin has shown that they are non-carcinogenic, but multiple methylation of the respective compound significantly increases the incidence of skin tumours (LaVoie et al. 1981, 1982, 1985). The position of the methylation in the PAH ring systems is relevant in this context. It is currently not possible to perform a general assessment of partially hydrogenated aromatic hydrocarbons with respect to their carcinogenic potential because literature data for this substance group are only available on a small number of individual substances, such as tetralin and partially hydrogenated dibenz[*a,h*]anthracene as well as partially hydrogenated ananthrenes, benzanthracenes and partially hydrogenated 3-methylcholanthrene (Lijinski 1965, 1972). Carcinogenic and non-carcinogenic effects were identified here for the different hydrogenation products, depending on the degree of hydrogenation. However, the results for individual substances can not be extrapolated the overall MOAH fraction. As yet, there are no studies on the carcinogenicity of MOAH fractions.

Due to the complexity and variability of the composition of the MOAH fraction and the lack of a lead substance for assessing carcinogenicity, the carcinogenic potential of the entire mineral oil as a mixture is classified according to the valid CLP regulation (Regulation (EC) No. 1272/2008). It is regulated that mineral oils containing less than 3 % w/w of substances extractable with DMSO should not be classified and labelled as carcinogenic (IP346 method). The weight percentage of substances extractable with DMSO hereby represents an indirect measure of the content of PAHs in the mineral oil.

The basis for the classification as a carcinogen is the correlation of the percentage of DMSO-extractable substances determined using the IP346 method and the tumour rate in mice determined by dermal carcinogenicity tests (CONCAWE 1994, 2016). In these dermal lifetime carcinogenicity studies, the undiluted test material was applied to the backs of the laboratory animals.

During these mouse skin tests, undiluted mineral oils which had undergone different distillation and purification processes and thus reflect varying degrees of refining were tested in order to cover the wide range of different mineral oil compositions that are used in many technical sectors. These *in vivo* studies were performed on two mouse strains with different sensitivity (CF1 and C3H) with dermal application several times per week for up to two years (CONCAWE 1994). The study design varied with respect to the doses applied and the frequency of application per week.

The existing mouse skin tests originate from a time when there were no standardised guidelines on test procedures and quality assurance. However, the literature data indicate good validity of the experimental data collected in the animal studies on dermal carcinogenicity, because the maximum tolerable dose determined by the relevant preceding dose-finding studies was applied to the two mouse strains and the tumour development stages and tumour incidences were established for the skin and partly also for internal organs in comparison with negative and positive control groups (Biles et al. 1988; Chasey and McKee 1993). Although no dose response data can be derived from these studies, the *worst case* is represented by applying the maximum tolerable dose.

In the CONCAWE report (1994), a tumour rate of ≥ 4% ("cut-off") was defined as the threshold value for the carcinogenic effect of a mineral oil in the mouse skin test, which is above the typical spontaneous background rate in untreated control animals of the mouse strains used. The tumour rate of 4% as the threshold for the carcinogenic effect of a mineral oil is statistically founded and assumes a sample size of 50 animals. Using the exact test by Fisher as a basis, there is a p-value of 0.056 for a tumour rate of 10% (5 of 50 animals) assuming that there are no animals with tumours in a control group of the same size. This is close to the usual significance threshold of 0.05. In light of the fact that the spontaneous tumour rate determined from historical data was < 1%, Concawe defined the threshold value as ≥ 4% (Concawe, 1994, 2016). Alternatively, when using the exact binomial test and a spontaneous tumour rate of 0.3% (McKee et al. 1990), 2 or more tumour cases out of 50 animals result in a one-tailed test into a p-value < 0.05 . The threshold value of ≥ 4% tumour rate for the classification of a mineral oil as carcinogenic in the mouse skin test is thus confirmed.

Taking into account further data published since 1994, there is a data set of 133 mineral oils tested on mouse skin, *in vivo* 59 were positive and 74 were negative (CONCAWE 2016). Using the IP346 method, four mineral oils were assessed as false-negative (false-negative rate 6%) and seven were assessed as false-positive (false-positive rate 11%) (sensitivity: 93%, specificity: 91%) (Concawe 2016). One of the false-negative predicted mineral oils was a solvent-refined mineral oil refined, which represents the lowest purification level and is simply a starting material for further processing. Here, the tumour rate was 10%. With two other mineral oils that were subjected to additional hydrogenation, the tumour rate was 5%. The fourth sample with a tumour incidence of 4% was a mixture of solvent-refined mineral oils. Furthermore, it no mutagenicity was demonstrated for these mineral oils in the modified Ames test, as is the case for other carcinogenic mineral oil mixtures.

The IP346 method represents a prediction method for determining the carcinogenic potential of a mineral oil for dermal contact. It should be noted that no data currently exist on the extent to which the content in the DMSO extracts determined using the IP346 method correlate with the content of MOAH. It is known that DMSO extracts the unsubstituted and low alkylated aromatic compounds very well, while the extraction efficiency is significantly lower for highly alkylated and possibly partially hydrogenated aromatic compounds, i.e. discrimination exists for the latter (Natusch 1978). Furthermore, there are no toxicological studies with mineral oils which allow conclusions to be made on the content of MOAH. Nevertheless, it can be stated that the *in vivo* mouse skin test for carcinogenicity of mineral oils includes all constituents and the IP346 method provides good correlation with these *in vivo* results, despite different extraction efficiency.

The IP346 method was developed in the 1980s at a time when there were no OECD guidelines on conducting carcinogenicity studies, which means that the method cannot meet today's requirements for developing such tests. From the present point of view, we would

question, for example, the number of animals, the variability of the mouse strains and the definition of 4% tumour incidence in the *in vivo* test as the "cut-off", as well as the lack of chemical characterisation of the tested mineral oil mixtures. At the time, the study design of the mouse skin test was chosen to allow a yes/no statement to be made regarding carcinogenicity. *Worst case* conditions were selected in order to achieve reliable results. The maximum tolerable dose identified by pre-testing was applied to particularly sensitive mouse strains, in some cases over their whole lifetime. In the meantime, the definition of the 4% cut-off value for tumour incidence in the *in vivo* test has been statistically confirmed. From today's perspective, the IP346 test represents a valid initial test for mineral oils that are then subjected to additional purification processes before being used in cosmetics.

Oral application

Lip care products can be ingested orally. For lip care products containing mineral oils, Cosmetics Europe recommends only using mineral oils for which ADI values have been derived (Cosmetics Europe 2014). For this reason, the following statements focus on these mineral oil qualities.

JECFA and EFSA have evaluated highly purified medium- and high viscosity white oils and microcrystalline waxes , approved their use in the food sector and derived ADI values (EFSA 2009, 2013a, 2013b, JECFA 2002). The white oils and waxes approved as food additives are characterised by physico-chemical parameters such as viscosity, molecular mass range and lower C number range and need to correspond to purity requirements according to food laws. To comply with these purity specifications, the crude oils used were subjected to a various purification steps such as distillation, solvent extraction, hydrocracking, treatment with oleum and hydrogenation (EFSA 2009 and 2013a, 2013b). Furthermore, the degree of purity analougous to pharmceuticals was tested. Chemical characterisation did not take place.

EFSA evaluated the carcinogenicity of the approved white oils with oral consumption based on the study of Trimmer et al. (2004). In two-year feeding studies, medium- and high-viscosity white oils were administered up to a dose of 1200 mg/kg body weight per day to Fischer 344 rats. Histopathological examination was performed on 48 different tissues including the liver, spleen, kidneys, bone marrow, and reproductive organs. Neither medium- nor high-viscosity white oils of food grade were found to be carcinogenic *in vivo* (Trimmer et al. 2004, EFSA 2009, 2013a).

There are no oral carcinogenicity studies for microcrystalline waxes (EFSA 2013b). According to the JECFA, no carcinogenic effects could be detected in a two-year feeding study on Sprague-Dawley rats with paraffin waxes of similar viscosity (dose up to 5800/mg body weight and day) (Shubik et al. 1962). Taking into account the results for medium- and high-viscosity white oils (Trimmer 2004), EFSA concluded that there are no indications of carcinogenic potential for food-grade microcrystalline waxes (EFSA 2013b).

In synopsis, it can be stated that food-grade white oils compliant with the legal limit value for benzo[*a*]pyrene (BaP) showed no indications of carcinogenic potential in either oral or dermal animal studies (Trimmer et al. 2004).

Dermatotoxicity

The toxicity and sensitisation potential of mineral oil products in the skin are low. In rabbits, treatment with a petrolatum-paraffin wax mixture resulted in slight eye irritation (CONCAWE

1999). In humans, a patch test under non-occlusive conditions with a petrolatum-paraffin wax mixture resulted in a mild erythema (CONCAWE 1999). Furthermore, a patch test study with 80,000 patients showed that medicinal white oils demonstrate no sensitisation potential in human skin (Schnuch et al. 2006).

3.1.3 Exposure

For consumers exposure to MOSH and MOAH results primarily from oral intake via food as well as inhalation from the air (DFG 2008). Dermal absorption is also possible. For cosmetic products, dermal exposure is particularly significant, as well as indirect oral exposure (hand-to-mouth contact, hand-to-food contact). Oral intake is also relevant for lip care products.

Dermal penetration and absorption

Studies on dermal absorption or penetration of MOSH were performed with radioactively traced aliphatic hydrocarbons. When pig skin *in vitro w*as treated over a period of 24 hours with ^{3}H-docosane (C22; 3 mg/cm²) or ^{14}C-hexadecane (C16; 5 mg/cm²) in petrolatum, poly-decene ($C_{10}H_{20})_x$, mineral oil, soybean oil or cosmetic w/o creme, the radioactively traced hexadecane was found in the *stratum corneum* at between 97.6% (w/o creme) and 99.3% (petrolatum), in the epidermis below the *stratum corneum* at between 1.2% (w/o creme) and 0.4% (petrolatum) as well as in the dermis at between 1.1% (w/o creme) and 0.3% (petrolatum); the distribution for docosane was similar. The dermal absorption, but not the transport into the receptor fluid, depended on the vehicle used (Brown et al. 1995). In guinea pigs *in vivo* that were treated over a period of 48 hours with ^{14}C-hexadecane (C16, without vehicle, dissolved in heptane), docosane (C22) or mineral oil as vehicle, an average of 3-15% of the radioactive tracer was found in the epidermis, but only 0.1% was found in the dermis and a total of 0.1% in other tissues (liver, kidney). No radioactivity was detectable in blood (Rossmiller and Hoekstra 1966a). The uptake of ^{14}C-hexadecane via the skin showed a significant dependency on the vehicle; from a carbon chain length of C22 onwards, the uptake decreased. In a further in vivo test on hairless mice, ^{3}H-docosane in undiluted petrolatum or 1% petrolatum in propylenglycol:ethanol (7:3 v/v) was applied for 2.5 hours to the skin, which had been pre-treated with acetone.. It can be assumed that skin pre-treated with acetone has a restricted barrier function, because during the corresponding test 10% of the ^{3}H-docosane dissolved in petrolatum penetrated the deeper skin layers. However, ^{3}H-docosane was not detectable in the blood here either (Brown et al. 1995). A summary of the different studies on skin penetration of mineral oils and waxes used in cosmetic products was recently published by Petry (Petry et al. 2017).

It is known that unsubstituted PAHs are absorbed via the skin and become bioavailable, whereby the absorption rate decreases with an increasing number of rings. Studies on the dermal uptake of unsubstituted PAHs also showed that these depend strongly on the vehicle used. Studies with radioactively traced BaP have proven that radioactive BaP can be detected in the blood after a 6-hour treatment of CF1 mice *in vivo* with 0.1% ^{14}C-BaP in low viscosity oils or 0.1% ^{3}H-BaP in oils or bitumen (viscosity range between 32 cSt and 69 x 10^{6} cSt). The blood levels for BaP decreased with increasing viscosity of the vehicle (Potter et al. 1999).

When human skin was treated *in vitro* with 0.1% ^{14}C-BaP, dissolved in low- and high-viscosity mineral oils or in bitumen, BaP was detectable in the receptor fluid, depending on the viscosity of the oil in this case also (Potter et al. 1999). However, there are no studies of this kind to date on alkylated polycyclic and partially hydrogenated aromatic compounds.

Apart from these studies with radioactively traced individual substances, a large number of microscopic-histological studies have been published in which mineral oil and other oils were detected in the *stratum corneum* but not in deeper skin layers after dermal application. These studies are not discussed separately in this opinion because the methods used were not suitable for detecting low levels of hydrocarbons and therefore cannot allow any reliable statement on bioavailability.

Gastrointestinal resorption

MOSH ingested orally follow the route of intestinal resorption of dietary fats. They are resorbed by the small intestine primarily into the lymphatic system and only to a -lower extent into the liver portal vein (Albro and Fishbein 1970; Albro and Thomas 1974; Savary and Constantin 1967; Vost and Maclean 1984). Tests in rats and pigs with oral administration of different white oils (dissolved in olive oil or contained in feed) at low doses resulted in resorption rates of 20-88% (Tulliez 1986; Halladay et al., 2002). It can be deduced from the molecular mass distribution of MOSH in the liver that MOSH are resorbed up to approximately C40 (female Fischer 344 rats) or C45 (humans) (Barp et al., 2014; 2017a).

Unsubstituted or mono-methylated PAHs are resorbed after their uptake in the digestive tract via the lymphatic system and the hepatic portal vein (Harris et al. 2013, 2016; Ramesh et al. 2004; Lindstrom et al. 1987; Laher et al. 1984; Laher and Barrowman 1987, 1998). 2-3 ring systems are resorbed faster and more comprehensively than 5-6 ring systems (IARC 2010; Chang 1943; Rahman et al. 1986).) There is a lack of experimental data on gastrointestinal resorption for more complex mixtures of highly alkylated and partially hydrogenated aromatic compounds (MOAH). As MOAH have structural characteristics of PAHs and MOSH as well as similar physico-chemical properties, , it has therefore to be assumed that they can be resorbed via the gastrointestinal tract in a comparable manner.

Uptake of MOSH from cosmetic products

To clarify the extent to which cosmetic products contribute to an accumulation of MOSH in the human body, the correlation between the use of different cosmetic products and the MOSH concentration in subcutaneous fatty tissue was studied in 142 pregnant women (Concin et al. 2011). The use of cosmetic products was determined by means of a questionnaire. A multiple linear regression analysis showed a statistically significant correlation between increased MOSH levels in fatty tissue and the use of sunscreen during pregnancy, but no correlations were found with the use of creams for preventing striae, of breast creams, or creams used for medical reasons. Questions on the use of cosmetics in daily life were also asked: in this context, significant correlations were found with the use of hand cream and lipstick, but not with the use of body lotions, face cream or sunscreen (Concin et al. 2011).

Overall, these results pose the question of the extent to which the dermal absorption of MOSH from cosmetic products contributes to an accumulation in the body. In studies on dermal penetration with radioactive tracers, no radioactivity was detected either *in vitro* in the receptor fluid or *in vivo* in the blood. Even though the observation period did not exceed 48 hours here, systemic availability of MOSH via the dermal exposure route hardly seems to occur. On the one hand, it is obvious that MOSH can accumulate in the body, particularly through absorption via the gastrointestinal tract. On the other hand, there are no clear findings that cosmetics can make a relevant contribution to this accumulation via dermal absorption. It is surprising, for example, that the use of sunscreen in pregnancy could contribute to

an accumulation of MOSH in fatty tissue, but not the use of face cream or body lotion. The situation with lipstick is different, in that oral uptake can be assumed here which could contribute to overall exposure. A possible oral uptake could also explain why a correlation exists between the use of hand cream and sunscreen and higher MOSH concentrations in the fatty tissue. For example, MOSH could be transferred from hands to food and consumed in this way. Hand-to-mouth contact represents another possibility of oral intake. More detailed analyses of the data set from Concin et al. (2011) by the BfR indicated that the levels of MOSH in fatty tissue were, on average, 2.2. times higher in women who used lipstick as well as hand cream and sunscreen than in woman who did not use any of these products.

Oral uptake of MOSH from lip care products

On the basis of animal studies on oral uptake, white oils and waxes with low-viscosity or low C-number range (JECFA 1995, 2012) have been considered as potentially problematic, because their accumulation in Fischer 344 rats indicated that they could lead to inflammatory granulomatous processes in the liver, for example.

According to Recommendation No. 14 from Cosmetics Europe (2014), only those mineral oil hydrocarbons for which an ADI value has been derived should be used in lip care and oral care products. This refers to food-grade mineral oils and microcrystalline waxes that have a carbon chain length of at least 25 C-atoms (at 5% boiling point), a molecular mass of at least 480 Da (Dalton) and a viscosity value of at least 8.5 centistokes (cSt). This restriction relates to statements from JECFA (2002, 2012) which defined an ADI of 10 mg/kg body weight for mineral oils of medium-viscosity. For high-viscosity mineral oils (from 28 C-atoms, 500 Da and 11 cSt) and microcrystalline waxes (from 25 C-atoms, 500 Da and 11 cSt), the ADI derived by JECFA is 20 mg/kg body weight (JECFA 2002). EFSA has defined a group ADI of 12 mg/kg body weight for medium and high-viscosity mineral oils (EFSA 2009, 2013a). Long-chain substances with a carbon number over 35 are considered to have poor oral bioavailability (EFSA 2012). The ADI values were derived for mineral oil qualities that meet the purity specifications for use in food and have gone through corresponding purification steps to minimise the aromatic contents.

However, analyses performed in Switzerland and Germany on approximately 240 lip care products showed that, in many products, more than 5% of the MOSH were shorter-chained, i.e. contained fewer than 25 C-atoms. These low-molecular mass MOSH (< C25) were detected at levels significantly higher than recommended by Cosmetics Europe. With these products, the consumers also had oral exposure to these more strongly accumulating MOSH.

According to the SCCS Notes of Guidance (2015), 57 mg of lipstick is applied per day. In the "worst case" scenario, these are completely ingested. Based on the MOSH contents between 8.2% and 74% determined by the BfR in lip care products on the German market, a daily external intake dose of MOSH of between 0.08 and 0.7 mg/kg body weight is calculated, which is within the range of the estimated daily intake of 0.03 to 0.3 mg/kg body weight estimated by EFSA for food (EFSA 2012). For this reason, lip care products can make a relevant contribution to the total exposure to MOSH.

However, the extent of analysis of the examined lip care products from the German market is small and not representative. Representative monitoring data would be necessary for the evaluation in order to clarify how much mineral oil is contained in lip care products on the German market and how these mineral oil mixtures are composed.

3.1.4 Risk characterisation

Dermal uptake

According to current data, there are no inherently conclusive and robust indications that MOSH from cosmetic products make a relevant contribution via dermal uptake to the accumulation of MOSH in the body.

According to EU Cosmetics Regulation 1223/2009, for cosmetics containing mineral oils with possible MOAH contents, the mineral oil products must be tested for carcinogenicity before they are used in cosmetic products. Another test for mutagenicity of mineral oils is the modified Ames test. An MI < 1 means that there is no mutagenic potential.

In practice, the IP346 method constitutes an initial test to be followed by additional purification steps such as hydrogenation to minimise the residual aromatic compound levels. These further purification steps result in progressively lower DMSO-extractable levels and lower MI values. At the 17th BfR Consumer Protection Forum, values for DMSO extracts of < 0.2 weight percentage and an MI value of 0.02 were reported for the final purification step of a low-viscosity white oil that is used in cosmetic products. Therefore, there were no indications of carcinogenicity or mutagenicity. The technologically achieved MOAH residual levels were < 250 ppm for a low-viscosity white oil. The purified mineral oil fractions used in the cosmetic products thus meet the purity requirements for pharmaceuticals.

Overall, based on the current scientific literature and the very prevalent and long-term use of such products on the skin with at the same time a lack of clinical and epidemiological evidence, no health risk for the consumer can be derived from the dermal application of cosmetic products containing mineral oils.

Oral intake

With values of up to 0.7 mg/kg body weight, the daily oral exposure to MOSH through lip care products containing mineral oils is within the range of the intake through food determined by EFSA and can therefore make a relevant contribution to total exposure and accumulation. However, a comparison with the ADI value for medium- and high-viscosity mineral oils (ADI = 12 mg/kg body weight per day, EFSA 2009, 2013a) and the ADI value for microcrystalline waxes (group ADI = 20 mg/kg body weight per day for high viscosity mineral oils and microcrystalline waxes, JECFA 2002) makes it clear that the oral intake of MOSH via lip care products contributes to less than 10% of these ADI values. This also applies when consumption through food is considered additionally. The prerequisite for this comparison is that no low -iscosity mineral oils were used in lip care products.

MOSH can accumulate in tissue and have even been detected in various human tissues. In principle, the accumulation of foreign substances in the human body is undesired, but is not considered per se as an adverse effect. The relevance of the inflammatory granulomas in the liver, only detected up to now in feeding studies with low-viscosity mineral oils on female Fischer 344 rats, to humans is not clear. There is a need for clarification here. By way of contrast, feeding studies do not indicate any formation of granulomas in the liver for medium- and high-viscosity mineral oils and for microcrystalline waxes.

Taking into account the observed formation of granulomas, JECFA and EFSA derived ADI values for specific highly purified medium- and high-viscosity mineral oils and microcrystalline waxes and approved them as food additives. Through the specification of minimum val-

ues for the C-number at the 5% boiling point and for the viscosity, the proportion of the critical low-viscosity mineral oils with a low C-number, for which no ADI value was derived, was minimised in the approved fractions. Recommendation No. 14 from Cosmetics Europe addresses this and recommends that only those mineral oils for which ADI values have been derived be used.

For this reason, no risk regarding formation of granulomas in the liver can be expected from the oral uptake of MOSH through lip care products which comply with the recommendation of Cosmetics Europe. However, if oils containing increased fractions of low-molecular hydrocarbons with C<25 are used, there are some uncertainties, because the relevance of the granulomas induced in Fischer 344 rats for humans is unclear and is a subject of discussion.

The mineral oil fractions for which an ADI value was defined are not only characterised by specific physico-chemical requirements, they must also meet particular purity requirements. This relates, for example, to certain purification processes and the corresponding purity specifications for food. These food-grade medium- and high-viscosity white oils were not carcinogenic in *in vivo* tests. There are also no indications of carcinogenicity in food-grade microcrystalline waxes. Accordingly, no carcinogenic effects can be expected if the qualities and purity grades approved for food additives are used in lip care products.

In synopsis, it can be stated that no adverse health effects can be expected if Cosmetics Europe Recommendation No. 14 is complied with, i.e. with regard to the use of mineral oil fractions in lip care products with an ADI value which meet the associated specifications for physico-chemical properties, as well as purity requirements.

3.2 Assessments by expert committees

Discussions in the BfR Committee for Cosmetics

The question of a health assessment of MOSH and MOAH in cosmetic products, particularly with regard to the occurrence of skin cancer, was discussed in the 15th, 16th and 17th meetings of the BfR Committee for Cosmetics (BfR 2016a, 2016b, 2017).

The minutes have been published on the BfR website.

- http://www.bfr.bund.de/en/bfr_committee_for_cosmetics-744.html

Assessments by international expert bodies (Health Canada, ECHA, IARC)

In the recent past, mineral oils that are also used in cosmetic products have been toxicologically assessed by various bodies. Statements exist on pharmaceutical white oil (paraffinum liquidum) in particular, which consider dermal exposure in addition to oral exposure (Health Canada 2015, ECHA 2015, IARC 2012). All of these statements come to the conclusion that highly processed mineral oil products (white oils) do not pose a risk to health; this also applies to cosmetics.

The evaluation by the Canadian health authority "Health Canada" is of particular significance because mineral oils in cosmetic products were specifically examined. In their assessments, the experts agree that the carcinogenic potential decreases with an increasing degree of refinement. Although this evaluation relates primarily to unsubstituted PAHs in mineral oil, the absence of epidemiological findings also highlights the health safety of medicinal white

oils, according to Health Canada. In agreement with this, EFSA (2012) confirmed the existing ADI values for the oral intake of white oil in the framework of a re-assessment of food-grade mineral oil fractions (mineral oil (P100, P70 and P70(H) and microcrystalline wax) and classified this group with a low priority for re-assessment.

In addition to white oil, petrolatum (CAS No.: 8009-03-8), for example, is also used as an ingredient in cosmetic products. In the case of petrolatum too, the full refining process must be known and the raw material must not be carcinogenic. Petrolatum is a complex hydrocarbon mixture of soft wax and paraffin in different proportions. Petrolatum consists mainly of saturated crystalline and liquid hydrocarbons with a chain length of more than C25. Aside from petrolatum, which meets the pharmaceutical purity requirements, there is also technical petrolatum with deviating characteristics (e.g. a higher PAH content). In the risk assessment of petrolatum, Health Canada assumed that the petrolatum used in cosmetic products is a mixture consisting of medicinal white oil and medicinal wax. Under these purity specifications, polycyclic aromatic 3-7 ring systems should have been almost completely eliminated from the end product petrolatum through the extensive refining. This was confirmed for the 16 unsubstituted EPA PAHs by corresponding analyses in a selection of cosmetic products. Only traces of the EPA PAHs or none at all could be detected. For this reason, the Canadian authority comes to the conclusion in its assessment that the use of petrolatum in cosmetic products is safe for consumers. MOAH were not specifically addressed in this assessment.

3.3 Recommendations for action/measures

The EU Cosmetics Regulation provides clear guidelines on the use of distillates or products manufactured from mineral oil mixtures, particularly with respect to excluding potentially mutagenic and carcinogenic properties. In addition, the manufacturer/supplier must ensure that its products do not pose a risk to the health of consumers.

Moreover, for lip care products Recommendation No. 14 from Cosmetics Europe, the European trade association for the cosmetics industry, also applies. BfR recommends that manufacturers comply with this Cosmetics Europe recommendation in order to guarantee that only mineral oil fractions and purity grades are used as ingredients for which JECFA/EFSA have derived an ADI value.

Additional information on the subject "Mineral oil" at the BfR website:

Frequently asked questions to the BfR on mineral oil in cosmetic products

Frequently asked questions to the BfR on the migration of mineral oil from packaging materials to foodstuffs

17th BfR Consumer Protection Forum "Mineral oil at the focus of consumer health protection" on the current state of discussion from 7 to 8 December 2017

- Conference transcript (in German)
http://www.bfr.bund.de/cm/343/mineraloel-im-fokus-des-gesundheitlichen-verbraucherschutzes-abstracts.pdf

- Live stream
http://bfr.westream.biz/media/

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