Scientific Committee on Consumer Safety

SCCS

OPINION ON

Methylisothiazolinone (MI) (P94)

Submission III

(Sensitisation only)

The SCCS adopted this opinion at its 10th plenary meeting

on 25 June 2015 and the final opinion, remaining unchanged, on 15 December 2015

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 Safety (SCCS), 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 Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

Scientific Committee members

Contact
European Commission
Health & Food Safety
Directorate C: Public Health
Unit C2 – Health Information and Scientific Committees
Office: HTC 03/073
L-2920 Luxembourg
SANTE-C2-SCCS@ec.europa.eu

ISSN 1831-4767 ISBN 978-92-79-56129-0

Doi:10.2875/713830 EW-AQ-16-006-EN-N

ACKNOWLEDGMENTS

SCCS Members

Dr. U. Bernauer
Dr. Q. Chaudhry
Prof. P.J. Coenraads
Prof. G. H. Degen (chairperson)
Dr. M. Dusinska
Dr. W. Lilienblum
Dr. E. Nielsen
Prof. T. Platzek
Dr. S. Ch. Rastogi
Dr. Ch. Rousselle
Dr. J. van Benthem

External experts
Prof. A. Bernard
Prof. J. Duus-Johansen
Dr. J. Ezendam
Prof. A. M. Giménez-Arnau (rapporteur)
Dr. E. Mikova
Dr. E. Panteri
Prof. T. Vanhaecke

This opinion has been subject to a commenting period of minimum four weeks after its initial publication. Comments received during this time have been considered by the SCCS and discussed in the subsequent plenary meeting.
Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. Revised opinions carry the date of revision.
In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged. Final opinions carry the date of the finalisation.

Keywords: SCCS, scientific opinion, Methylisothiazolinone (MI) (P94), sensitisation, Regulation 1223/2009, CAS 2682-20-4, EC 220-239-6

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on Methylisothiazolinone (MI) (P94) sensitisation only, 25 June 2015, SCCS/1557/15, final opinion December 2015

TABLE OF CONTENTS

1. BACKGROUND

The Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) adopted two opinions on "Methylisothiazolinone" respectively in March 2003 (SCCNFP/0625/02) and in April 2004 (SCCNFP/0805/04).

The SCCNFP (March 2003 - SCCNFP/0625/02) concluded that the information submitted was insufficient at that time to allow an adequate risk assessment of Methylisothiazolinone to be carried out. The SCCNFP required: more detailed information concerning the physico-chemical properties of Methylisothiazolinone (e.g. LCMS analysis, pH, stability and degradation products); information on the material used in the tests (batch numbers, purity and impurities); an *in vitro* percutaneous absorption study and relevant and adequate genotoxicity/mutagenicity studies.

In response to the opinion of the SCCNFP concerning Methylisothiazolinone, adopted during the 23rd plenary meeting of 18 March 2003 (doc. n° SCCNFP/0625/02), additional information on the physico-chemical properties of the substance, an in vitro percutaneous absorption study and two studies on mutagenicity/genotoxicity were submitted to the SCCNFP for evaluation. In April 2004 the SCCNFP (SCCNFP/0805/04) concluded that the requested data were complete. Methylisothiazolinone was considered non genotoxic/mutagenic.

Methylisothiazolinone (MI) was listed in Annex V/57 of Regulation (EC) No 1223/2009 to be used as preservative at maximum concentration of 0.01% (100 ppm) in cosmetics products.

According to several Member States and a good number of published papers, the sensitisation to MI is becoming an increasing problem all over Europe. In light of this information, the Commission requested to the Scientific Committee (SCCS) a reassessment of the safety of MI when it is used as preservative in cosmetics products at maximum concentration of 100 ppm. The scientific opinion of the SCCS (SCCS/1521/13) on Methylisothiazolinone (P94) Submission II (Sensitisation only) was delivered in March 2014 with the following conclusions:

Current clinical data indicate that 100 ppm MI in cosmetic products is not safe for the consumer. For leave-on cosmetic products (including 'wet wipes'), no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the view of induction of contact allergy. However, no information is available on elicitation.

Recently, the SCCS received a new mandate in order to assess safety of 100 ppm of MI included in rinse off and hair leave on products. Data from Cosmetics Europe concerning the safety of MI in rinse-off and hair leave on products were received in June 2014, new cosmetovigilance data in February 2015 and data on aggregate exposures to rinse-off products in May 2015. The concentration limit of MI to 15 ppm proposed by the SCCS for rinse off products is based on the data available related to the mixture MCI/MI (SCCS/1238/09). New data are submitted trying to demonstrate that 100 ppm included in rinse-off and in leave-on hair cosmetics products is safe for the consumers. The SCCS is requested to give an opinion about the safety of MI at 100 ppm in rinse-off and leave-on hair cosmetic products.

2. TERMS OF REFERENCE

1. On the basis of the data provided, does the SCCS consider Methylisothiazolinone (MI) to be safe for consumers, when used as a preservative in rinse-off products up to concentration limit of 100 ppm from the view of induction of contact allergy?

2. On the basis of the data provided, does the SCCS consider Methylisothiazolinone (MI) to be safe for consumers, when used as a preservative in leave-on hair products up to concentration limit of 100 ppm from the view of induction of contact allergy?

3. Does the SCCS have any further scientific concerns with regard to the use of Methylisothiazolinone (MI) in cosmetic products?

3. OPINION

3.1 Chemical and Physical Specifications

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

INCI methylisothiazolinone

3.1.1.2 Chemical names

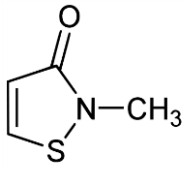
Methylisothiazolinone
IUPAC: 2-Methylisothiazol-3(2H)-one
Other: 2-Methyl-4-isothiazolin-3-one

3.1.1.3 Trade names and abbreviations

3.1.1.4 CAS / EC number

CAS no. 2682-20-4
EC 220-239-6

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

C_4H_5NOS

3.2 Epidemiology of contact allergy to methylisothiazolinone updated

The SCCS Opinion on Methylisothiazolinone published 27 March 2014 includes a complete review of the literature published about Methylisothiazolinone (MI) contact allergy up to that date. The most important data introduced in the 2014 report are the following:

MI alone (without MCI) was introduced as a preservative in industrial products in the early 2000s, and in 2005 it was allowed as a preservative in both leave-on and rinse-off cosmetics at a maximum concentration of 100 ppm (0.01%) (Annex V/57 of the Cosmetic Regulation 1223/2009/ECC; Cosmetic Directive 2005/42/EC).

The first report on contact allergy from MI was published in 1987 (1). After 2000, MI was introduced in industrial products (e.g. paints, adhesives, varnishes and cooling fluids), and

due to its weaker preservative effect was used at higher concentrations than in MCI/MI. Allergic contact dermatitis from MI in occupational settings was reported in 2004 (2) mainly due to exposure to paints (3, 4).

The first reports from MI contact allergy caused by cosmetics originate from 2010 (5) mainly due to wet wipes for hygiene (baby wipes, moist tissues, moist toilet paper), hair cosmetics (shampoos), facial cosmetics (6, 7), deodorants (8) and sunscreens (9).

Air exposure to MI induced severe cases of airborne allergic contact dermatitis and systemic contact dermatitis, particularly from recently painted walls (10, 11), including a case in a four-year-old child most probably sensitised to MI through baby wipes. Airborne exposures and allergic contact dermatitis from toilet cleaners have also been reported (12).

MI has only recently been tested as a single allergen, separate from MCI/MI in the European baseline series and in the local baseline series in several countries. In the European baseline patch test series, MI is tested at 2000 ppm (0.2%) (17). Reactivity in patients who were patch tested was around 1.5% until 2008 in Denmark (7) but values increased from 0.9% in 2006 to 1.8% in 2008 in Finland (13*)* and very high prevalences were demonstrated in 2011/12 in Leeds (4.6%) (14), London (6%), Coimbra (4.5%) and Leuven, (5.8%), with a very high percentage of reactions found to be actually relevant because the source of the exposure was demonstrated (15).

In Germany, although in selected patients with suspected cosmetic or occupational exposure, MI sensitisation rose from 1.9% in 2009 to 4.4% in 2011, particularly in female patients (188% increase) and in patients with facial dermatitis (200% increase), suggesting that increase in prevalence is most probably related to cosmetic exposure (16). In the US, a similar situation seems to have occurred as MI was considered the allergen of the year 2013 (9).

Contact allergy to MI has been reported in consecutively tested dermatitis patients in Sweden, Denmark, Germany, Finland and the UK. The contact allergy rates reported vary between 0.5% and 6% in 2012. The rates from the UK where noticed in Leeds from 0.6% in 2009 to 4.6% in 2012 (14). In Denmark, an increase from 1.4% in 2009 to 3.1% in 2011 was recorded (11).

Other European countries have recently published their own experiences showing an increased prevalence of contact sensitisation to MI (Figure 1). In Belgium, where in 2012, the sensitisation rate to MCI/MI had increased to 4.5% and that for MI to 6.0%, the latter showed a further increase to 7.2% in 2013. (18) The MCI/MI sensitisation rate increased in the South of Gran Canaria from 3.6% in 2007 to 17.3% in 2012, and when MI was patch tested alone at either 0.05% or 0.2%, the representative sample of this area showed a prevalence of 8.2% (19). The French data from the REVIDAL-GERDA network, with sixteen centres and 7874 patients tested, showed a significant increase in the proportion of MI-positive tests in 2012 and 2011 as compared to 2010 (5.6%, 3.3%, and 1.5%, respectively; $p<0.001$) when patch testing MI at 200 ppm aq. (20). In Finland a clearly increasing incidence of MI contact allergy was found in all clinics providing data (21). It was regarded as an epidemic of contact allergy to MI (see also Figure 1). (22)

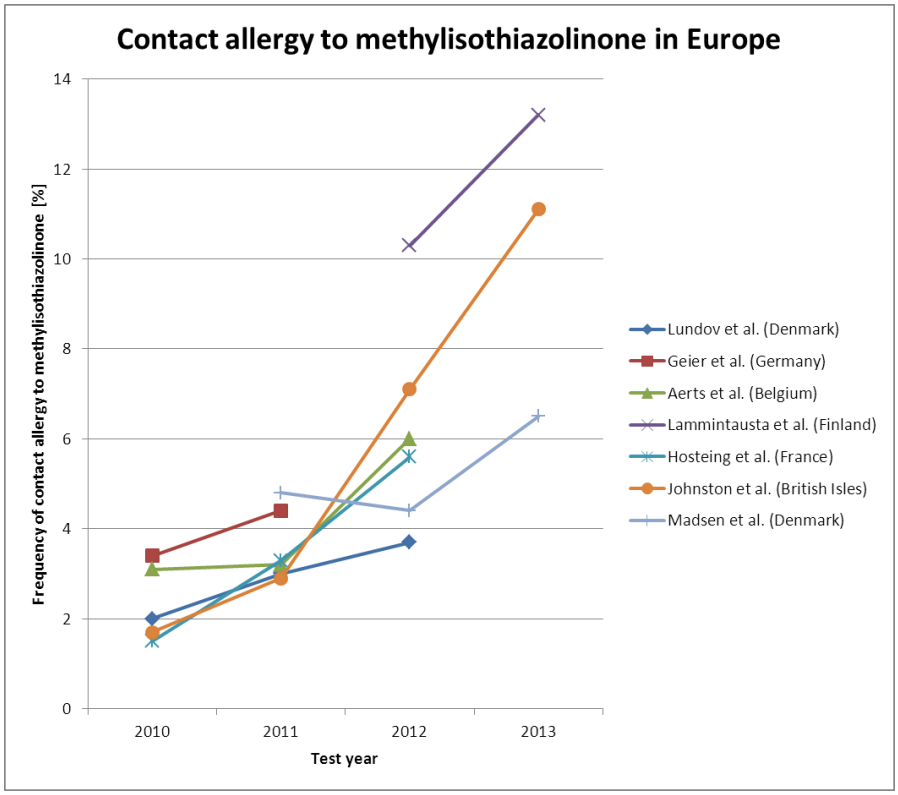


Figure 1. Data from recently published scientific literature concerning changes over time in MI contact allergy among patch-tested patients in different countries, based on refs: 18, 20-23, 29, 30

3.3 (SCCS/1521/13) Opinion on Methylisothiazolinone (P94) and rinse-off products

In the Opinion on MI from March 2014 (SCCS/1521/13), it was concluded that current clinical data indicate that 100 ppm MI in cosmetic products is not safe for the consumer. For leave-on cosmetic products (including 'wet wipes'), no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015) MI is considered safe for the consumer from the view of induction of contact allergy. However, no information is available on elicitation.

3.4 New submission

The dossier of data submitted consists of a submission letter entitled 'Industry submission concerning safety of methylisothiazolinone (MI) in rinse-off and leave-on products', dated 12 June 2014, and eight other documents, some of which were submitted later (see below):

Resubmission of comments and data
Re-submission of the comments made by Cosmetics Europe to the draft 2013 Opinion, consisting of:

a. Cosmetic Europe's response to the SCCS Opinion on Methylisothiazolinone, adopted 12 December 2013 (dated 14 February 2014)

b. Hazard characterisation data for Methylisothiazolinone (MI) and Methylisothiazolinone / Chloromethylisothiazolinone (MCI/MI)(Annex I)

c. The Efficacy of Methylisothiazolinone (MI) and Methylchloroisothiazolinone/ Methylisothiazolinone (CMI/MI) and the Microbiological Safety of Cosmetic Products (Annex II)

Submission of new data
Submissions of new data were accepted in 3 rounds, June 2014, February 2015 and May 2015. Data received were:

a. Summary of the data reviewed by the SCCNFP in its opinions on MI from 2003 to 2004.

b. Skin allergy assessment and the Quantitative Risk Assessment.

c. Methylisothiazolinone and the mixture of chlorinated CMI/MI (3:1 ratio) are two different preservatives with different safety and efficacy profiles (dated 26. May 2014)

d. Compilation of cosmeto-vigilance data related to cosmetic products containingMI (submitted February 2015).

e. Assessment of impact on the risk of induction of skin sensitisation from aggregated exposure arising from use of rinse-off cosmetic products containing 100ppm methylisothiazolinone (MI) (submitted May 2015).

3.5 Resubmission of comments from CE for re-consideration

Cosmetics Europe re-submitted a dossier with their previous response to the Opinion of SCCS dated 12 December 2013 consisting of the 3 documents mentioned above.

In the submission letter (dated 12Th June 2014, CE justifies this re-submission with the fact that they do not feel their comments were adequately addressed in the final SCCS Opinion, especially concerning the following points:

- Clinical data in isolation is insufficient to establish safe induction levels for MI.
- MCI is at least one order of magnitude more potent than MI. The animal data and data from Human Repeated Insult Patch Tests are given in the re-submission (annex I) and it is concluded that 'applying identical specific concentration limits to both MCI/MI and MI is not justified based on the available hazard characterization data.'

SCCS comment
The use of MI in cosmetic has caused an unprecedented high rate of sensitised individuals in Europe as reflected by the patch test data from dermatology clinics mentioned above. Clinical data have established that current uses of MI at 100 ppm are unsafe. The risk assessment based on predictive assays using the methods available at the time (SCCS opinion 2004) and later has failed to protect the consumer with regard to induction of contact allergy to MI and allergic contact dermatitis.

Data from humans who have developed contact sensitisation and allergic contact dermatitis through the use of consumer products are highly relevant for risk assessment and should never be disregarded, especially not when risk assessment based on predictive assays has failed. Below, the SCCS comments further on some of these data.

Concerning the difference in potency between MCI and MI, the prediction of potency is based on experimental studies in animals and sometimes humans. These are models that may or may not accurately reflect the true difference between substances. MI has been used since its inclusion in cosmetics in up to 8.8 times higher concentrations (100 ppm) than MCI (11.25 ppm in the mixture MCI/MI 3:1 at 15 ppm). According to the submission, the difference in potency is at least one order of magnitude: the NESIL derived from HRIPTs MCI is 18 times more potent than MI (NESIL MCI: 0.83µg/cm^2 and MI: 15µg/cm^2). Nevertheless, the use of MI in up to 8.8 times higher concentrations than MCI for the past 10 years in cosmetic products has led to the current situation of exceptionally high rates of contact allergy to MI in consumers.

The SCCS also replied to these comments by Cosmetics Europe following the consultation concerning the SCCS Opinion (SCCS/1521/13). In this Opinion it is suggested that MI at 15 ppm in rinse-off products should be safe for the consumer. There is, at present, no data to indicate that a higher level is 'safe' for either induction or elicitation. Therefore, 15 ppm was chosen for safety reasons, as clearly discussed in the Opinion.

3.6 Submission of new data from CE

3.6.1 Quantitative Risk Assessment applied to Methylisothiazolinone in rinse of products and leave-on hair cosmetics

In the submission, Cosmetics Europe applied the Quantitative Risk Assessment (QRA) methodology (24, 25) to predict maximum safe exposure levels, i.e. exposure levels that are assumed not to cause induction of skin sensitisation.

3.6.1.1 QRA methodology

According to the submission, the QRA approach for allergens in consumer products follows the same four fundamental steps as identified for general toxicology risk assessment: a) hazard identification b) dose-response assessment or hazard quantification c) exposure assessment and d) risk characterisation. The induction of skin sensitisation is a threshold-based event; the metric for risk assessment for this toxicological endpoint is accepted to be dose per unit area of skin (or g/cm^2). The key steps of the QRA process are determination of known safe benchmarks, application of sensitisation assessment factors, and calculation of consumer exposure through normal products use. With these parameters, an acceptable exposure level (AEL) can be calculated and compared with the consumer exposure level (CEL). When the AEL exceeds the CEL, it is predicted that induction of skin sensitisation is unlikely to occur.

SCCS comment
The SCCP adopted an Opinion concerning Dermal Sensitisation Quantitative Risk Assessment (Citral, Farnesol and Phenylacetaldehyde) on 24 June 2008 (SCCP/1153/08).

The QRA model mentioned and applied in the new submission is identical with the QRA model assessed in the Opinion (SCCP/1153/08), leading to the following conclusion, as stated in that Opinion:

- The dermal sensitisation QRA model is based primarily on data from experimental sensitisation tests in humans e.g. Human Repeated Insult Patch Tests (HRIPT). There is a lack of in-depth method description, and the experience with this test, its validity, sensitivity and reliability is sparse outside industry. Performing this type of experimental sensitisation tests on humans is considered unethical.

- Epidemiological and experimental data, providing information on sensitisation/elicitation reactions in consumers by the substance evaluated (e.g preservative or fragrance) in marketed products, are not integrated in the dermal sensitisation QRA model. It is of concern that the model operates with multiple product categories without considering risk from aggregated exposures and that scientific consensus has not been achieved concerning the choice of safety factors. Occupational exposures are not considered although they have been identified as an important area of development of the dermal sensitisation QRA.

- The data provided shows that the application of the dermal sensitisation QRA approach would allow increased exposures to allergens, already known to cause allergic contact dermatitis in consumers. The model has not been validated and no strategy of validation has been suggested. There is no degree of certainty that the levels of skin sensitisers identified by the dermal sensitisation QRA are safe for the consumer.

- Identification of safe levels of exposure to existing substances known to cause allergic contact dermatitis in the consumer should be based on clinical data and/or elicitation low effect levels. Currently these are the only methods that have proven efficient in reducing/preventing existing problems of sensitisation/allergic contact dermatitis in the consumer.

The QRA model in the new submission from June 2014 has not been updated or modified concerning any of the points raised above. In the additional submission dated 25 May 2015 the effect of aggregate exposures to MI in rinse–off products on risk of induction of sensitisation by QRA was addressed. See below.

3.6.1.2 Application of quantitative risk assessment to MI

In the submission by CE, the QRA methodology was applied to MI in cosmetic products according to the principles explained above. As stated above, the SCCS has no faith in the model in its current form (SCCP/1153/08), but has nevertheless chosen to comment on substance specific data in this section used in the QRA, as these comments may have relevance for further development of the model and future quantitative risk assessment of MI.

The maximum permitted amount of MI in cosmetic products is 100 ppm. The consumer exposure to 100 ppm (0.01%) MI is calculated by multiplying the amount of product used per day by 0.01% and is expressed as dose/surface area (i.e. µg/cm^2). The range of products for which suitable exposure data have been identified, along with the amount of product used, is listed in Table 1 (Annex I of this Opinion).

According to the submission, No Expected Skin Sensitisation Level (NESIL) is a benchmark that is derived from animal and human data through the application of a Weight of Evidence (WoE) approach using all relevant data.

For the determination of a WoE NESIL for MI, the data from 5 Human Repeat Insult Patch Tests (HRIPT) and 4 local lymph node assays (LLNA) were considered. In the HRIPTs, no positive responses were observed up to an exposure level of 15 µg/cm^2 MI in water. Sensitisation was induced at exposures of 20 and 25 µg/cm^2. Based on these data, CE concludes that MI can be considered to be a strong sensitiser.

In the LLNA, MI had EC3 values between 0.4% (100µg/cm^2) and 11% (2750µg/cm^2) depending on the vehicle used. The EC3 values indicate that MI is a strong sensitiser.

Taking all of the data together, since the HRIPT threshold is the lowest no observed effect level (NOEL) available, it shall, according to the submission, take precedence in deriving the NESIL for use in the QRA. Therefore, the WoE NESIL for MI is 15µg/cm^2. A summary of the considered HRIPT studies (26) conducted on MI is given in the submission as table 2 and reproduced below:

Vehicle, Dose Volume, Patch Size	**Induction Concentration (ug/cm^2)**	**Challenge Concentration**	**Positive Responses**
Water; 0.2ml, 4 cm^2	200ppm (10 µg/cm^2)	200ppm	0 / 100
Water; 0.2ml, 4 cm^2	300ppm (15 µg/cm^2)	300ppm	0 / 98
Water; 0.2ml, 4 cm^2	400ppm (20 µg/cm^2)	400ppm	1 / 116
Water; 0.2ml, 4 cm^2	500ppm (25 µg/cm^2)	500ppm	1 / 210
Water; 0.2mL,4 cm^2	600ppm (30 µg/cm^2)	600ppm	0 / 214

Table 2: Summary of the HRIPT studies conducted on MI (from the submission)

SCCS comment

In the submission, the NESIL is determined to be 15 µg/cm^2 by WoE approach based on data from HRIPT given above and as table 2 in the submission.

The sensitivity and predictivity of the HRIPT does not only depend on the choice of concentration for induction, but also the choice of challenge concentration.

It can be seen from table 2 above (from the submission) that not only the induction concentrations varied between experiments, but also the challenge concentration of MI. The high dose induction group has been challenged with a high dose (max 600 ppm) and the low dose induction group with a low dose (min 200 ppm). It is a general principle in patch testing that the maximal concentration that can be tolerated without causing skin irritation should be used for demonstrations of sensitisation (27).

This means that the lower levels in these experiments, which seemingly cause no induction, are not put to a sufficient test at challenge and that induction may have occurred but may not have been revealed. The NESIL for MI may be lower than 15 µg/cm^2, as the experiments have not been performed in a way so that conclusions on no-effect levels can be made.

The SCCS also has comments regarding AEL/CEL ratio and predicted risk from rinse-off products and stay-on hair cosmetics.

In the submission table 3 (reproduced in Annex 1), 20 products categories are green: ranging from an AEL/CEL of 1.0 (body lotion and after-sun cream) to 140.6 (shower gel).

According to the submission product, categories with an AEL/CEL >1 are unlikely to cause induction. This would also mean that body lotion and after-sun cream lotion with an

AEL/CEL of 1 should have been coloured red in the table 3 as these products are likely to induce sensitisation.

According to the submission 100 ppm is safe for use concerning induction of sensitisation in rinse-off products and stay-on cosmetics as the AEL/CEL is above 1.

The AEL/CEL is calculated in the following way with data used for shower gels:
AEL= NESIL (15 µg/cm^2) /SAF (100)= 0.15 µg/cm^2
CEL= 0.0011 µg/cm^2 (table 2- Annex 1)
AEL/CEL= 0.15 µg/cm^2/0.0011 µg/cm^2 = 136 (incorrectly given as 140.6 in the submission (table 3-Annex 1).

A product with an AEL/CEL of 1.1 is in theory unlikely to cause induction. This means that the QRA model predicts that not only 100 ppm (0.01%) in a shower gel is unlikely to cause induction but also 1.2% MI (12000 ppm). For shampoos 0.18% (1800 ppm) is the predicted maximum concentrations unlikely to induce sensitisation and for hairstyling products 0.03% (300 ppm) given an AEL/CEL ratio of 1.1.

The data provided show that the application of the dermal sensitisation QRA approach to rinse-off products would allow increased exposures to MI, a strong allergen already known to cause many cases of allergic contact dermatitis in consumers. This alone makes it difficult to have confidence in the model in its current version.

The comments above also apply to stay-on hair cosmetic products. Furthermore, it is not clear if the QRA model for stay-on hair cosmetics in the original submission (June 2014) also takes exposure to the hands into account. Hands are bound to be exposed to the hair products either during application or by touching the hair unintentionally.

3.6.1.3 Assessment of aggregate exposure in the QRA

In the new submission by CE (May 2015), aggregate exposures to a number of rinse-off products such as shower gels and shampoos are calculated. Aggregate exposure is calculated using an interim/pragmatic approach in which the CEL is calculated for different body parts relevant for MI exposure by rinse-off products, e.g. hands, face, scalp and the rest of the body. Aggregate exposure is the sum of the exposure level estimated for the individual products used on the respective body part. In all cases concerning aggregate exposures to rinse-off cosmetic products yields an AEL:CEL ratio greater than 1. The following AEL:CEL ratios were reported:

- Hands = 2.1
- Face = 1.8 (females) and 5.3 (males)
- Scalp = 8.8
- Rest of the body = 140.

CE considers it an interim assessment of impact of aggregate exposures and concludes that the risk of induction from aggregate exposure to rinse-off products is very low.

SCCS comment
The SCCS assessed the QRA in 2008 and pointed to several shortcomings in the model including the lack of considerations of aggregate exposures. The SCCS is aware that updating of the QRA model is currently ongoing in industry. The QRA presented by CE is using the same approach, except the aggregate exposure assessments, as defined in the initial QRA approach. Hence, the criticism raised previously by the SCCS (SCCP1153/08) is the same. Furthermore, the aggregate exposure assessment, which is presented as an interim approach, needs to be evaluated and accepted by the SCCS before it can be applied to specific substances.

3.7 Use test with rinse-off products in MI sensitised consumers.

In the submission letter (dated 12 June 2014), a paragraph is devoted to the subject of performing a use test study – also called ROAT study - in sensitised consumers.

A negative use test study with a rinse-off product would confirm safety concerning not only elicitation, but also induction. CE states that: 'The cosmetics industry is studying different possibilities to further confirm the safety of MI-preserved rinse-off products in MI-patch test positive consumers'.

SCCS comment
In the meantime a use test study in MI sensitised consumers has been performed and published in February 2015 (28). Here 19 MI-allergic subjects and 19 controls without MI allergy applied 2 liquid hand soaps five times per day on areas of 5*10 cm on the ventral side of their forearms. One soap contained 100 ppm MI, the maximum allowed concentration in cosmetics, and was used by 10 allergic subjects and all controls. Another liquid soap with 50 ppm MI was used by 9 allergic subjects. As the negative control, all subjects used a similar soap that did not contain MI. The repeated open applications (ROAT) proceeded for up to 21 days or until a positive reaction occurred. The study was conducted in a randomised and blinded fashion. Ten (10) out of 10 MI-allergic subjects developed positive reactions to the soap with 100 ppm and 7 out of 9 reacted to the 50 ppm soap, while none of the 19 controls had a positive reaction during 21 days of application ($p=0.0001$). The authors concluded that rinse-off products preserved with 50 ppm MI or more are not safe for consumers. A no-effect level was not determined (28).

The results of this study do not support safety of MI in rinse-off products at either 100 ppm or at 50 ppm for elicitation or induction.

3.8 Compilation of cosmetovigilance data related to cosmetic products containing Methylisothiazolinone (MI)

Five major manufacturers of cosmetic products from the Cosmetics Europe MI Task Force collated all reported undesirable events associated with products containing MI and products from the same categories without MI for a period of five years and 6 months (1 January 2009 – 30 June 2014). The categories for which data were identified were: rinse-off products (face wash, shampoo, conditioner, and shower products), hair leave-on products (hair styling products), skin leave-on products (face wipes, deodorants, face care, baby wipes, after-shave products).

The causal relationship of each reported event to the product was assessed using a 5-level scale and was assigned to one of the following categories: "very likely", "likely", "not clearly attributable", "unlikely" and "excluded", in accordance with the causality assessment method recommended by the European Commission. Undesirable events given a causality assessment "likely" and "very likely" were considered as undesirable effects**;** they were further assessed by a qualified assessor and those which were compatible with the symptoms and chronology of allergic contact dermatitis and skin irritation were given the respective designation.

Reporting rates were calculated as the number of undesirable events (separately for MI-containing and non-MI-containing products) per millions of units sold for the time period considered. Overall 'industry rates' were calculated by dividing the sum of all reported undesirable events by the sum of all units sold by the five companies during the five years

and six months (in millions). The results are reported separately for leave-on skin products, rinse-off skin and hair products and leave-on hair products.

Once leave-on products were assessed there was an approximately 5-fold difference in confirmed undesirable effects (allergic contact dermatitis and skin irritation) between leave-on skin products containing MI and leave-on skin products without MI. There was no increase in reporting rates for rinse-off products containing MI (0.71) as compared to rinse-off products without MI (2.0). No increase in reporting rates for leave-on hair products containing MI (0.09) was observed as compared to leave-on hair products without MI (0.15). It is concluded in the report that the reporting rates are generally low for both MI-containing and non-MI-containing products.

SCCS comment

The submission does not provide detailed information about methodology or data concerning numbers and types of the adverse events, the number of products in each category from each company or the number of adverse events disregarded. It only provides end results as given above. It is therefore not possible to assess the data.

A number of recent peer-reviewed scientific papers from different countries address the same question as the cosmetovigilance study by CE concerning product types involved in allergic contact dermatitis to MI (18, 20, 30). They all show that rinse-off products play a role in allergic reactions in consumers diagnosed with MI contact allergy.

A restropective, nationwide and multicentre French report-based study (20) involved an analysis of all cases reported by French doctors belonging to the REVIDAL-GERDA group and performing patch tests from 2010 to 2012. Sixteen centers participated in the study and 7874 patients were tested. MI-positive tests rose from 1.5% in 2010 to 5.5% in 2012. Tests were clinically relevant in 80.2% to 90.3% of cases. Information about the products used was available for 83.7% (247/295) of MI-positive patients. Cosmetics accounted for 73.1% of causative products. Among the cosmetics that were specified, the majority were rinse-off, mainly soaps, particularly industrial soaps, toilet products, and hair products (20).

A study from Belgium (18) reviewed the medical charts of patients who were investigated between 2010 and 2012 by members of the Belgian Contact and Environmental Dermatitis Group for MCI/MI and MI allergy. All together 8680 patients were patch tested for MCI/MI allergy and 5979 with MI alone, and 373 (4.3%) and 324 (5.4%), respectively, turned out positive. The youngest patient was 2 years of age. Cosmetics were allergen sources for MI and or MCI/MI in 53.7% to 61.3% of cases. Although the exact cosmetic was reported only for a subgroup of patients, some specific leave-on products were mentioned including wet wipes and deodorants. Also a considerable number of rinse-off products were involved (e.g. shampoos), but the specific number was not given (18).

In Germany (30), contact allergy surveillance data collected by the Information Network of Departments of Dermatology in the years 2009–2012 were analysed. For 602 MI-positive patients, their own products had been patch tested (altogether, 4933 different products causing a total of 372 positive patch test reactions). In particular, leave-on products caused a high proportion of positive patch test reactions to the tested products. In total 5.6% out of the MI positive patients without fragrance allergy was positive to liquid soaps/shower gels and 3.9% to shampoo. In comparison 7.5% were positive to face cream and 17.5% to moisturisers. Patch tests with rinse-off products may be quite non-sensitive for detecting sensitisation to any of their ingredients including MI, as the product is diluted before testing (30).

These studies differ from the CE cosmetovigilance study in methodology as the consumer (patient) with an adverse reaction to a cosmetic product has been seen by a dermatologist

and also patch tested. This means that a diagnosis can be made and a causal relationship to product types established. The studies do not offer a comparison with other preservatives.

In addition to these studies RIVM in the Netherlands took a multi-stakeholder approach entailing spontaneous reports from consumers, general practitioners and dermatologists regarding undesirable effects to cosmetic products. The four most frequently reported cosmetic products involved in undesirable reactions were moisturisers, make-up, hair care products and soaps. Dermatologists reported more cases than consumers of undesirable effects of hair care products (predominately shampoos, constituting 82% of the products) and soaps (bath and shower products). The most commonly reported allergens in the patients were isothiazolinones (23%), whereof almost half were found have a causal link between the undesirable effect and the cosmetic product, however no direct link was made between the specific allergens and product types in the report (31).

3.9 DISCUSSION

In the previous Opinion on MI from March 2014 (SCCS/1521/13), it was concluded that no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated for leave-on cosmetic products. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015 %) MI was considered safe for the consumer from the view of induction of contact allergy, while no data were available concerning elicitation.

The present SCCS Opinion addresses safety concerns regarding the use of MI at 100 ppm in rinse-off and leave-on hair cosmetic products. The arguments to defend this concentration used by Cosmetic Europe are based on the results of a QRA including new data on aggregate exposures and the information obtained from the cosmetovigilance system. According to the QRA methodology, rinse-off and leave-on hair cosmetic products are considered safe with a low risk of inducing contact sensitisation. The data obtained from the cosmetovigilance system established by Industry do not show an excess of adverse events due to MI in rinse–off and leave-on hair cosmetic products compared to products without MI.

Nevertheless, the most recently published peer-reviewed literature shows an increase in contact allergy to methylisothiazolinone in Europe. New data from Belgium, Gran Canaria, France, Germany, Finland and the United Kingdom demonstrate an extraordinary increase and high rate of contact allergy to MI. In some countries, the increase has more than tripled in just a few years and has reached epidemic proportions. New cases are also seen in very young children of 1-2 years of age, which is unusual for contact allergy.

The QRA for induction of contact sensitisation has previously been evaluated by the Scientific Committee (SCCP1153/08), which amongst others concluded that: 'The model has not been validated and no strategy of validation was suggested. There is no confidence that the levels of skin sensitizers identified by the dermal sensitisation QRA are safe for the consumer.' The QRA model used in this new submission about MI in rinse-off and leave-on hair cosmetic products is similar to the QRA previously evaluated by the SCCP.

The QRA data provided specifically on MI in the current submission predict that 100 ppm (0.01%) MI is unlikely to induce sensitisation in rinse-off products and stay-on hair cosmetics. However, this QRA approach does predict that even higher concentrations of MI - up to 12.000 ppm (1.2%) - in such products would be unlikely to induce sensitisation. The fact that the QRA model permits such high levels of a strong sensitiser in rinse-off products seriously questions its predictions and makes it difficult to have confidence in the presented QRA model, as also highlighted in the Opinion SCCP1153/08. Aggregate exposure is not considered in the first submission of QRA data from June 2014, but in an additional

submission from Cosmetics Europe from May 2015, QRA interim data considering aggregate exposures to rinse-off products were provided.

The SCCS is aware that the QRA model is currently being updated. All the criticism raised in Opinion SCCP1153/08 needs to be addressed and the new model needs to be assessed and scientifically accepted before it can be applied to specific substances. The aggregate exposure model also needs to be evaluated and accepted by the SCCS before it can be applied to specific substances.

Predictive models are important to avoid adverse health effects in humans from cosmetic ingredients. However in situations where the adverse health effects have already occurred in humans, it is appropriate to consider the epidemiological data as these represent the relevant end-point at which preventive actions are to be directed. Such data exist from dermatology clinics and as cosmetovigilance data, either as spontaneous reports or active surveillance.

The cosmetovigilance system established by industry is based on spontaneous reports primarily from consumers and rarely supported by dermatological assessment or allergy testing, which makes the causality assessment difficult and subject to variation among companies. Such cosmetovigilance data may be useful in indicating a problem with certain ingredients or specific products, but is in general of limited value in establishing safety or disproving a problem. The data submitted by Cosmetics Europe lacked details in reporting, such as numbers of adverse reaction to different product types, and could thus not be assessed.

Cosmetovigilance data have recently been published from several countries (2014-2015). A multi-stakeholder approach was taken by The Netherlands entailing spontaneous reports from consumers, general practitioners and dermatologists. Dermatologists reported more cases than consumers of undesirable effects of hair care products (predominately shampoos) and soaps (bath and shower products). The most commonly reported allergens in the patients were isothiazolinones, but this study did not allow to causally link the specific allergens to certain product types.

In Belgium and France, all data on MI contact allergic patients from multiple dermatological centers were reviewed. In the Belgium study it was concluded that although the exact cosmetic was reported only for a subgroup of patients, a considerable number of rinse-off cosmetics (e.g. shampoos) were involved. No distinction was made between MI and/or MCI/MI. In the French study concerning MI allergy, the majority of causative products were rinse-off, mainly soaps, particularly industrial soaps, toilet products, and hair products. In a German multi-centre study patients had been tested with their own cosmetic products. Stay-on cosmetic products were clearly more often positive in MI allergic patients than rinse-off products. Nevertheless, rinse-off products also gave reactions. Testing of rinse-off products requires dilution and may make the test less sensitive in picking up allergies. These data represent consumers who have been exposed sufficiently to develop the disease allergic contact dermatitis. This may be caused by one product or multiple products simultaneously or in sequence.

There is no doubt from the clinical data as presented in the previous and present Opinion that stay-on cosmetic products, especially wet wipes, are important causes of MI allergy. This is also acknowledged by CE in their submission and they have advised their members to discontinue the use of MI in such products. Rinse-off cosmetic products also play a significant role in allergic contact dermatitis to MI according to recent epidemiological studies. This is supported by a new use test study performed in patients sensitised to MI, where a soap preserved with 100 ppm or 50 ppm MI used five times a day elicited allergic reactions in all or almost all sensitised patients and not in controls. This study may not directly show that rinse-off products are implicated in induction of contact allergy to MI, but may indicate a role. It is generally accepted that concentrations/doses of allergens, which

do not elicit reactions, would also be safe for induction in the majority of individuals e.g. The Nickel Directive (Nickel Directive (76/769/EEC - now 94/27/EEC)) and the recent REACH regulation of chromium VI in leather (regulation EU 301/2014, which adds a Chromium VI restriction to Annex XVII of regulation 1907/2006 (REACH)) are based on this principle. Thus as almost all the participants in the use test study developed allergic contact dermatitis to a soap with 100 ppm or 50 ppm, the result of this study do not support safety of MI at current use concentrations in terms of induction.

In the scientific Opinion (SCCS/1521/13) on methylisothiazolinone (MI), the conclusion concerning safe use of MI in rinse-off products at 15 ppm was based on bench-marking to the experience with the use of the mixture MCI/MI at 15 ppm for the past 30 years. In the new submission, industry submits that MCI and MI are very different in their sensitising potency and therefore imposing identical concentration limits is not warranted.

In the current Opinion it is highlighted that MI has been used in up to 8.8 times higher concentrations than MCI for the past 10 years in cosmetic products, which has led to the current situation of high rates of contact allergy to MI in consumers. There are, at present, no convincing data to indicate that a higher level is 'safe' for either induction or elicitation. Therefore, 15 ppm was chosen for safety reasons given in the previous Opinion (SCCS/1521/13).

4. CONCLUSION

1. On the basis of the data provided, does the SCCS consider Methylisothiazolinone (MI) to be safe for consumers, when used as a preservative in rinse-off products up to concentration limit of 100 ppm from the view of induction of contact allergy?

The information provided does not support the safe use of MI as a preservative in rinse-off cosmetic products up to a concentration limit of 100 ppm from the view of induction of contact allergy.

For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the point of view of induction of contact allergy.

2. On the basis of the data provided, does the SCCS consider Methylisothiazolinone (MI) to be safe for consumers, when used as a preservative in leave-on hair products up to concentration limit of 100 ppm from the view of induction of contact allergy?

The information provided does not support the safe use of MI as a preservative in leave-on hair cosmetic products up to a concentration limit of 100 ppm from the point of view of induction of contact allergy.

3. Does the SCCS have any further scientific concerns with regard to the use of Methylisothiazolinone (MI) in cosmetic product

The concerns and opinions raised in SCCS Opinion SCCS/1521/13 (12 December 2013 with revision 27 March 2014) remain. The results of the recent Scandinavian study do not support safety of MI in rinse-off products at either 100 ppm or at 50 ppm for elicitation or induction.

5. REFERENCES

1. Bruze M, Dahlquist I, Fregert S, Gruvberger B, Persson K. Contact allergy to the active ingredients of Kathon CG. Contact Dermatitis. 1987 ;16(4):183-8.

2. Gruvberger B, Bruze M. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. Dermatitis. 2004;15(4):201-5.

3. Thyssen JP, Sederberg-Olsen N, Thomsen JF, Menné T. Contact dermatitis from methylisothiazolinone in a paint factory. Contact Dermatitis. 2006; 54(6):322-4.

4. Mose AP, Lundov MD, Zachariae C, Menné T, Veien NK, Laurberg G, Kaaber K, Avnstorp C, Andersen KE, Paulsen E, Gotthard Mortz C, Sommerlund M, Danielsen A, Thormann J, Kristensen O, Kristensen B, Andersen BL, Vissing S, Nielsen NH, Johansen JD. Occupational contact dermatitis in painters: an analysis of patch test data from the Danish Contact Dermatitis Group. Contact Dermatitis. 2012; 67(5):293-7.

5. García-Gavín J1, Vansina S, Kerre S, Naert A, Goossens A. García-Gavín J1, Vansina S, Kerre S, Naert A, Goossens A. Methylisothiazolinone, an emerging allergen in cosmetics? Contact Dermatitis. 2010;63(2):96-101.

6. Lundov MD1, Thyssen JP, Zachariae C, Johansen JD Prevalence and cause of methylisothiazolinone contact allergy. Contact Dermatitis. 2010;63(3):164-7.

7. Lundov MD, Krongaard T, Menné TL, Johansen JD Methylisothiazolinone contact allergy: a review.Br J Dermatol. 2011;165(6):1178-82.

8. Amaro C, Santos R, Cardoso J. Contact allergy to methylisothiazolinone in a deodorant. Contact Dermatitis. 2011;64(5):298-9.

9. Castanedo-Tardana MP1, Zug KA Methylisothiazolinone. Dermatitis. 2013; 24(1):2-6.

10. Aerts O, Cattaert N, Lambert J, Goossens A Airborne and systemic dermatitis, mimicking atopic dermatitis, caused by methylisothiazolinone in a young child. Contact Dermatitis. 2013; 68(4):250-1.

11. Lundov MD, Zachariae C, Menné T, Johansen JD. Airborne exposure to preservative methylisothiazolinone causes severe allergic reactions. BMJ. 2012; 4:345

12. Lundov MD, Menné T. Airborne exposure to methylchloroisothiazolinone and methylisothiazolinone from a toilet cleaner. Contact Dermatitis. 2013; 68(4):252-3.

13. Ackermann L, Aalto-Korte K, Alanko K, Hasan T, Jolanki R, Lammintausta K,Lauerma A, Laukkanen A, Liippo J, Riekki R, Vuorela AM, Rantanen T. Contact sensitisation to methylisothiazolinone in Finland--a multicentrestudy. Contact Dermatitis 2011; 64; 49-53

14. Urwin R & Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new "epidemic". Contact Dermatitis 2013; 68: 253–5

15. Gonçalo M, Goossens A. Whilst Rome Burns: The Epidemic of Contact Allergy to Methylisothiazolinone. Contact Dermatitis 2013; 68: 257-258

16. Geier J, Lessmann H, Schnuch A, Uter W. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? Contact Dermatitis 2012; 67: 334-41

17. Bruze M, Engfeldt M, Gonçalo M and Goossens A. Recommendation to include methylisothiazolinone in the European baseline patch test series. (On behalf of the European Society of Contact Dermatitis (ESCD) and the European Environmental and Contact Dermatitis Research Group (EECDRG)). Contact Dermatitis 2013; 69: 263-271

18. Aerts O, Baeck M, Constandt L, Dezfoulian B, Jacobs MC, Kerre S, Lapeere H, Pierret L, Wouters K, Goossens A. The dramatic increase in the rate of methylisothiazolinone contact allergy in Belgium: a multicenter study. Contact Dermatitis 2014; 71: 41-48

19. Liuti F, Hernandez Hernandez Z, Borrego Hernando L. Increased sensitisation to Kathon CG (methylchloroisothiazolinone plus methylisothiazolinone) in the South of Gran Canaria, Spain. Actas Dermosifiliogr 2014; 105:882-883

20. Hosteing S, Meyer N, Waton J, Barbaud A, Bourrain JL, Raison-Peyron N et al. Outbreak of contact sensitisation to methylisothiazolinone:an analysis of French data from the REVIDAL-GERDA network. Contact Dermatitis 2014; 70: 262-269

21. Lammintausta K, Aalto-Korte K, Ackerman L, Alanko K, Berry P, Hasan T et al. An epidemic of contact allergy to methylisotiazolinone in Finland. Contact Dermatitis 2014; 70: 184-185

22. Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy- a growing epidemic. Contact Dermatitis. 2013;69:271-5.

23. Madsen JT, Andersen KE. Further evidence of the methylisothiazolinone epidemic. Contact Dermatitis. 2014; 70: 246-247

24. Basketter DA, Clapp CJ, Safford BJ, Jowsey IR, McNamee P, Ryan CA, Gerberick GF. Preservatives and skin sensitisation quantitative risk assessment. Dermatitis. 2008 Jan-Feb;19(1):20-7.

25. QRA Technical Guidance Dossier 2006 and updated information booklets can be found on the RIFM website. http://www.rifm.org/publications

26. Politano VT, Api AM. The Research Institute for Fragances Materials´human repeated insult patch test protocol. Regulatory Toxicology and Pharmacology 2008; 52:35-38

27. Bruze M, Svedman C, Andersen KE, Bruynzeel D, Goossens A, Duus Johansen J, Matura M, Orton D, Vigan M on behalf of the ESCD. Contact Dermatitis 2012; 66:131-136

28. Yazar K, Lundov MD, Faurschou A, Matura M, Boman A, Johansen JD, Liden C. Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: A Repeated Open Application study. Br J Dermatol 2015: Accepted

29. Johnston GA, contributing members of the British Society for Cutaneous A. The rise in prevalence of contact allergy to methylisothiazolinone in the British Isles. Contact Dermatitis 2014:70(4):238-40

30. Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitisation. Contact Dermatitis 2013 69, 231–238

31. Salverda JG, Braqt PJ, de Wit-Bos L et al. Results of cosmetovigilance survey in The Netherlands. Contact Dermatitis 2013: 68:139-14842

ANNEX I

Product type	Product exposure (g per day)	Product surface area (cm2)	Product exposure data (µg/cm2)	Exposure data source	Consumer exposure level (µg/cm^2)
Shower gel	18.67	17500	0.011	a	0.0011
Facial wash (liquid)	1.6	565	0.028	a	0.0028
Hand wash soap - bar	4.8	840	0.057	b	0.0057
Shaving products (male)	2	305	0.066	b	0.0066
Shampoo	10.46	1440	0.073	a	0.0073
Hair conditioner rinse off	14	1440	0.097	b	0.0097
Hand wash soap - liquid	20	840	0.238	a	0.0238
Facial cleaning lotion	1.54	565	0.273	c1	0.0273
Facial toning lotion	1.54	565	0.273	c1	0.0273
Face mask (PVA)	1.54	565	0.273	c1	0.0273
Face mask (non-PVA)	1.54	565	0.273	c1	0.0273
Hair conditioner leave on	4	1440	0.278	c2	0.0278
Hair styling products	4	1010	0.396	a	0.0396
Body lotion	7.82	15670	0.499	a	0.0499
After sun cream lotion	7.82	15670	0.50	a	0.0499
Eye shadow	0.02	24	0.83	a	0.0833
Make-up remover	5	565	0.88	a	0.0885
Liquid foundation	0.51	565	0.90	a	0.0903
concealer	0.51	565	0.90	c3	0.0903
Mouthwash	21.62	216.8	1.00	a	0.0997
Sunscreen lotion/cream/trigger	18	17500	1.03	a	0.1029
Toothpaste	2.7	216.8	1.25	a	0.1245
Eyeliner	0.005	3.2	1.56	a	0.1563
After shaving cream	1.6	775	2.065	c1	0.2065
Men's facial care	1.6	775	2.065	b	0.2065
baby nappy area Cleansing lotion	0.55	220	2.50	b	0.2500
Hand cream	2.16	860	2.512	a	0.2512
Face cream (women)	1.54	565	2.726	a	0.2726
Face mask (overnight treatment)	1.54	565	2.726	c4	0.2726
Deodorant aerosol spray (excluding propellant)	0.69	200	3.45	a	0.3450
nappy area protection cream	1.32	220	6.00	b	0.6000
Semi-permanent hair dyes (and lotions)	35	580	6.034	a	0.6034
Deodorant body spray (ethanolic)	1.43	200	7.15	a	0.7150
Deodorant non-spray	1.51	200	7.55	a	0.7550
Deodorant cosmetic pump spray	1.51	200	7.55	c5	0.7550
Lipstick, lip salve	0.057	4.8	11.88	a	1.1875
Diaper rash cream	2.64	220	12.00	b	1.2000
Facial wipes	NA	NA	13.00	c6	1.3000
Moist toilet tissue,	NA	NA	13.00	c6	1.3000
Mascara	0.025	1.6	15.63	a	1.5625
Baby wipes	NA	NA	21.00	c6	2.1000
Nail varnish product	0.25	11	22.73	b	2.2727

Table 1: Summary of source consumer exposure data to product and product containing 100 ppm MI for use in quantitative risk assessment.

The following hierarchy of exposure data was used:

a) SCCS notes of Guidance

b) QRA Technical Guidance dossier for fragrance ingredients (IFRA)

c) Where no exposure data was available, surrogate data was derived from the technical expertise of the Cosmetics Europe companies:

c1) surrogate exposure: face cream with 10% retention factor applied.

c2) surrogate exposure: styling aids

c3) surrogate exposure: foundation

c4) surrogate exposure: face cream

c5) surrogate exposure: non-spray deodorant

c6) surrogate exposure: deposition from film of liquid

Product type	Consumer exposure level to MI (µg/cm^2)	Product specific SAF	AEL / CEL ratio
Shower gel	0.0011	100	140.6
Facial wash (liquid)	0.0028	100	53.0
Hand wash soap - bar	0.0057	100	26.3
Shaving products (male)	0.0066	300	7.6
Shampoo	0.0073	100	20.7
Hair conditioner rinse off	0.0097	100	15.4
Hand wash soap - liquid	0.0238	100	6.3
Facial cleaning lotion	0.0273	100	5.5
Facial toning lotion	0.0273	100	5.5
Face mask (PVA)	0.0273	300	1.8
Face mask (non-PVA)	0.0273	100	5.5
Hair conditioner leave on	0.0278	100	5.4
Hair styling products	0.0396	100	3.8
Body lotion	0.0499	300	1.0
After sun cream lotion	0.0499	300	1.0
Eye shadow	0.0833	300	0.6
Make-up remover	0.0885	100	1.7
Liquid foundation	0.0903	100	1.7
concealer	0.0903	100	1.7
Mouthwash	0.0997	100	1.5
Sunscreen lotion/cream/trigger	0.1029	300	0.5
Toothpaste	0.1245	100	1.2
Eyeliner	0.1563	300	0.3
After shaving cream	0.2065	300	0.2
Men's facial care	0.2065	300	0.2
baby nappy area Cleansing lotion	0.2500	300	0.20
Hand cream	0.2512	100	0.6
Face cream (women)	0.2726	100	0.6
Face mask (overnight treatment)	0.2726	100	0.6
Deodorant aerosol spray (excl. propellant)	0.3450	300	0.1
nappy area protection cream	0.6000	300	0.08
Semi-permanent hair dyes (and lotions)	0.6034	100	0.2
Deodorant body spray (ethanolic)	0.7150	300	0.1
Deodorant non-spray	0.7550	300	0.1
Deodorant cosmetic pump spray	0.7550	300	0.1
Lipstick, lip salve	1.1875	300	0.04
Diaper rash cream	1.2000	300	0.04
Facial wipes	1.3000	100	0.1
Moist toilet tissue,	1.3000	300	0.04
Mascara	1.5625	300	0.03
Baby wipes	2.1000	300	0.02
Nail varnish product	2.2727	100	0.1

Table 3: The QRA outcome for 100 ppm MI in a range of cosmetic products