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Survey and Exposure Assessment of Methylisothiazolinone in Consumer Products

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Survey and Exposure Assessment of Methylisothiazolinone in Consumer Products

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Foreword

The project “Survey and Exposure Assessment of Methylisothiazolinone in Consumer Products” was carried out from July 2013 - October 2014.

This report describes the results of the project including information obtained during the survey, results from chemical analysis of selected consumer products on the Danish market, and an assessment of the exposure of Danish consumers.

Danish Technological Institute (DTI) carried out the project for the Danish Environmental Protection Agency. Participants from DTI were Kathe Tønning (project manager), Sie Woldum Tordrup, Karen Krzywkowski, Bjørn Malmgren-Hansen, Ulla Christensen, Inge Bondgaard Nielsen and Eva Jacobsen.

Jakob F. Schwensen and Jeanne Duus Johansen from the Danish National Allergy Research Centre have contributed to the report with chapter 1.5.1.

A steering group consisting of the following persons followed the progress and results of the project:

- Louise Fredsbo Karlsson, the Danish Environmental Protection Agency
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- Shima Dobel, the Danish Environmental Protection Agency
- Kathe Tønning, Danish Technological Institute

The project was financed by the Danish Environmental Protection Agency.

Conclusion and Summary

Background
Methylisothiazolinone (MI) is a preservative and it is added to many different types of water-based products to prevent microbial growth (e.g., bacteria and mold). MI is found in a wide range of consumer products such as cosmetics, household cleaning products, paint, adhesives, varnish and toys. Recently, there has been a serious global increase in the number of people who are allergic to MI. That has led to the initiation of this project by the Danish Environmental Protection Agency. This report also covers a survey of the use of MI in consumer products, including an assessment of the exposure of Danish consumers to MI.

Recent documentation of the serious allergy causing properties of MI, led to the re-assessment of the safe use of MI by the EU Scientific Committee on Consumer Safety (SCCS) in 2013. The conclusion of the new assessment is that SCCS does not find that it is safe for consumers if 100 ppm[i] MI is used in cosmetic products. For rinse-off products, 15 ppm[ii] is considered a safe concentration of MI, whereas it is not possible to determine a safe concentration for leave-on products on the basis of the available data. SCCS included wet wipes in the category of cosmetic leave-on products. SCCS's assessment of rinse-off products and leave-on hair products is currently under review based on new data.

Objective of the project
The objective of this project was to carry out a survey of consumer products containing MI that are sold on the Danish market, to determine the concentration in selected consumer products, and, finally, to evaluate the exposure of the individual consumer through the products.

Legislation
MI has no harmonised classification, but all suppliers self-classify the substance to be skin sensitizing and give it the danger symbol "irritant" and the risk phrase R43: "May cause sensitization by skin contact". From June 2015, it will be replaced by the hazard pictogram "Warning" and the risk phrase H317: "May cause an allergic skin reaction". The limit for classification and labelling of chemical mixtures containing MI will be 1% (10000 ppm) when the CLP Regulation (Classification, Labelling and Packaging) comes into force in 2015, and the limit for declaring the substance on the label will be 0.1% (1000 ppm). MI, in a three-to-one ratio combination with methylchloroisothiazolinone (MCI) (MCI/MI 3:1), has a harmonized classification. When the combination is used in chemical products in a concentration exceeding 0.0015 % (15 ppm[iii]), the products must also be labelled as sensitizing.

In the EU, cosmetics are subject to the Regulation on Cosmetic Products (Regulation no. 1223/2009), and since 2005 it has been permitted to use MI in concentrations of up to 100 ppm, unless the substance is combined with MCI. When MI is mixed with MCI in cosmetic products in a three-to-one ratio (MCI/MI), the total concentration must not exceed 15 ppm. A recent amendment to the cosmetics regulation means that MCI/MI 3:1 is no longer allowed in leave-on cosmetics as from 16th July 2015.

Detergents and household cleaning products are i.a. subject to the EU Regulation on detergents (Regulation No. 648/2004). According to the Regulation, MI must be declared on the label regardless of the concentration if it is used as a preservative in detergents or cleaning products. In addition, the products are regulated as chemical mixtures, and classified and labelled for their sensitizing effect according to the CLP rules.

[i] ppm indicates "part per million" and 100 ppm corresponds to 0.01%
[ii] ppm indicates "part per million" and 15 ppm corresponds to 0.0015%.
[iii] 15 ppm is the sum of MCI and MI, corresponding to 3.75 ppm MI

Paint, varnish and adhesives come within the category of chemical mixtures and are classified and labelled according to the CLP rules.

Toys are mainly regulated in the Toy Executive Order (Danish Executive Order on Safety Requirements to Toys). Some toys have specific restrictions regarding their chemical content. That is the case for, e.g., make-up or face paint and the like that also come within the Cosmetics Regulation. For the toy category "chemical toys (sets) other than experimental sets" i.a. paint, varnish and adhesives it is a requirement for water-based products that the used preservatives are approved for food and/or cosmetics. With the present Cosmetics Regulation this means that such toys may have a content of MI in a concentration of up to 100 ppm and up to 15 ppm of MCI/MI when they are used together in a three-to-one ratio (MCI/MI). Finger paint (Danish Standards EN 71-7: 2014) may contain a maximum concentration of 0.0008% of MCI/MI when they are used together in a three-to-one ratio, and MI may be added in a maximum concentration of 100 ppm when used without MCI.

Clinical experience with MI

Summarising clinical experience with MI indicates that the frequency of contact allergy to MI is increasing among eczema patients. Especially women who use cosmetic products on a daily basis and certain occupational groups risk developing contact allergy to MI. In recent years, case reports have been presented regarding children who have developed contact allergy to MI after wet wipes have been used. That is problematic, as those children in the future might experience new outbreaks of allergic contact eczema when they are re-exposed to MI, e.g. through water-based paint preserved with MI. Patients who are sensitized to MI have a life-long allergy and repeated exposure to MI will lead to new outbreaks of eczema. Among dermatitis patients, air borne contact allergy has been seen in a few cases often when painting a room. Very often, patients with allergy to MI cannot stay in freshly painted rooms for a very long time after the work has been finished without having an allergic reaction, which indicates that the evaporation of MI is of long duration. Patients can to a certain degree avoid cosmetic products or other consumer products with MI as compulsory declaration helps protect the consumer. However, according to EU legislation on chemical products (CLP), declaration is only required from a content of 1000 ppm (0.1%). From a medical point of view that is problematic, as consumers and e.g. painters are not considered sufficiently protected against allergy to MI when they use products with a high concentration of MI, e.g., paint with a concentration of MI up to 200 ppm.

Survey

The survey of the use of MI has demonstrated that the substance is used in a wide range of consumer products. In general, previous studies in the available literature typically identify the use of MI within cosmetic products, household cleaning products, paint, varnish and adhesives. A few studies comprise investigations of the use of MI in different types of toys, i.a., a survey from 2014 of preservatives in toys that was carried out for the Danish Environmental Protection Agency. Within each product category, the use of MI has spread to many different types of products. In cosmetic products, MI has been identified in i.a. shampoo, conditioner, deodorants (roll-on), wet wipes, cream and hair wax.

Most often, the published surveys have been carried out on the basis of the declaration on the label of the products, and very few comprise chemical analyses of the actual concentration of MI in the products. However, for cosmetic products, the concentration of MI was determined to 52-100 ppm in 12 rinse-off products, 2-96 ppm in three leave-on products and 17-87 ppm in four wet wipes in a study by Lundov *et al* in 2010. The concentration of MI in 19 types of water-based paint was determined to 10-300 ppm, a level that is confirmed by the Danish trade association for coatings and adhesives (DFL).

DFL's (2012) own survey among the members of the association showed that 80 % of paints (water-based paint products for indoor use) contained less than 100 ppm, 19 % contained MI in the interval 100-200 ppm, and the rest contained a higher concentration of MI.

For toys, a recent survey shows that MI was not found in concentrations exceeding the detection limit of 20 ppm in the 11 products that were selected for analysis. The reported areas of application and the use-concentrations in general correspond to information obtained from trade associations and manufacturers. Suppliers of MI recommend the use MI in combination with other preservatives in order to limit its use. The suppliers recommend a concentration of MI in the area of 25-175 ppm, depending on the type of product.

Previous surveys show that the use of MI most often appears in combination with other preservatives. The combination of MI with MCI is still dominating, but others are gaining ground, such as e.g. the combination with other isothiazolinones and phenoxyethanol.

The different rules regarding the declaration and labelling of products depend on the type of product, and that makes it difficult – sometimes even impossible – for the consumer to identify products that contain MI.

In this survey, the greatest number of cosmetic products and household cleaning products were identified when physical shops and internet shops were visited. According to legislation, MI has to be declared for those types of products, and therefore its presence has to be stated on the label. A few products within paint, varnish and adhesives were identified on the basis of information from the manufacturers. Hobby products, some obviously targeted for children, were identified on the basis of information from the manufacturers.

Among the 174 identified products within cosmetics and personal care, the main part were rinse-off products (59%), but leave-on products were also heavily represented among the identified products (41%). 60 products were identified within detergents and household cleaning products, whereas 27 were identified within paint, varnish and adhesives. Finally, seven products were identified within toys and hobby products.

Trade associations as well as manufacturers and importers of products that contain MI confirm that the use of MI is widespread, but also that the preservative and its health-related issues are in focus. In May 2013, the Danish Coatings and Adhesives Association (DFL) carried out a survey among its members concerning the use of MI, and DFL reported that according to the interviewed members MI has a widespread use in water-based paint products. According to the conclusion of the survey, all water-based paint products for indoor use contain MI. Several manufacturers have already phased-out, consider or plan to phase out the substance, while others mention that there is a lack of applicable substitutes. For chemical mixtures, e.g., paint, the need for preservation can reflect production conditions and raw material quality. Stricter requirements to raw material suppliers in these areas might help limit the amount of preservative that is necessary to prevent microbial growth in the product.

Chemical analysis

In cooperation with the Danish Environmental Protection Agency, 31 products were selected for chemical analysis for content of MI. The products were selected within the following four product categories: cosmetics and personal care (22 products distributed on 8 rinse-off products and 14 leave-on products), detergents and household cleaning products (1 product), paint, varnish and adhesives (4 products), and toys and hobby products (4 products). The products were selected with regard to different factors that could influence the development of contact allergy and be crucial to obtaining an overall picture of the exposure of a consumer:

- Products that are expected to have direct skin contact
- Products that are used frequently
- Products that are used by children
- Products with a high concentration of MI
- Products that cover a wide range of product categories and manufacturers

The uncertainty of the analytical results is matrix dependent and the uncertainty for each analysis can be as high as 20% (RSD). Therefore, a limit value is only considered to be exceeded if the average of an analysis in duplicate is more than 20% above the limit value.

Three rinse-off products, preserved with a mixture of MCI and MI in a three-to-one ratio (information from the distributor), turned out to contain 1.8-4.8 mg/kg MI, whereas five rinse-off products preserved with MI without MCI contained 37-71 mg/kg MI.

All of the 14 leave-on products that were analysed were declared to contain MI without MCI and they contained <5-114 mg/kg MI. Two leave-on products do not contain MI above the detection limit (that is 5 and 10 mg/kg, respectively, for the product matrices in question).

One hand washing-up liquid contained 40 mg/kg MI (product is declared with a content of MI and octylisothiazolinone).

Two types of wall paint contained 70 mg/kg and 135 mg/kg MI, respectively. One primer and one adhesive that according to the safety data sheet contain MCI/MI in a three-to-one ratio, contained 21 mg/kg and 13 mg/kg MI, respectively.

Three out of four hobby products contained 3.6-5.8 mg/kg MI, and according to the distributor two of them were preserved with MCI/MI in a three-to-one ratio. One all-purpose glue that according to the manufacturer contained MCI/MI and a concentration of MI < 140 ppm contained 110 mg/kg MI.

Qualitative assessment of analysis results

The content of MI found when analysing selected products is comparable with values reported in previous studies. All cosmetic products in this study comply with the current limit value of 100 ppm MI when the 20% uncertainty of the analysis method is taken into account. Compared to SCCS's new recommendation for a limit value of 15 ppm for MI in rinse-off products and 0 (zero) ppm for MI in leave-on products only five cosmetic products out of the 22 analysed in this project can be regarded as safe.

If the hand washing-up liquid is assumed to be diluted by a factor of 5000 before use, then the analysed concentration of 40 ppm MI in a washing-up liquid will correspond to a use-concentration of 0.008 ppm. That can be compared with limit values for cosmetic rinse-off products where SCCS recommends maximum 15 ppm. Undiluted hand washing-up liquid contains MI in a concentration that exceeds SCCS's recommended limit for rinse-off cosmetics.

Exposure to MI through hobby products, toys, paint, varnish and adhesives cannot be directly compared to the exposure that will take place from cosmetics, but if the consumer's skin is exposed to a product with a concentration of MI that is higher than 15 ppm (which was found in a number of products), then there will be a risk of induction of allergy.

Exposure to MI in paint could be caused by residing in a freshly painted room, because MI evaporates and becomes airborne. This means MI exposure to the skin at the unclothed parts of the body. The contributions of this MI exposure are not included in the exposure assessment, caused by the very few measurements of the MI concentrations, in rooms painted with MI containing paint.

Compared to the current limit value for MI in cosmetics of 100 ppm there is a higher concentration in one of two types of wall paint and one all-purpose glue, where the measurement uncertainty might mean that the content actually is below 100 ppm. For the remaining hobby products, the MI content is below 15 ppm MI. The MI content in the primer and wallpaper adhesive is just above 15 ppm, but below the 100 ppm.

Summary of exposure to methylisothiazolinone (MI) through consumer products

In Table 1, the calculated exposures, expressed as dermal load for a woman and for a three-year-old child, respectively, have been summarised. The contribution from each product shows that the largest exposure is seen when cosmetic leave-on products are used. The dermal load is in general a bit higher for the three-year-olds than for women under the applied assumptions, but it is not believed to be substantially higher. For a woman, the largest individual contribution comes from cosmetics when using a deodorant (750 ng/cm^2/day), while for a three-year-old the largest contribution comes from sunscreen (400 ng/cm^2/day, calculated on the basis of a theoretical content of 100 ppm MI).

Cosmetic products are assumed to be the products that are used most frequently, and that is believed to be decisive for the development of contact allergy. Combined with the relatively high MI concentrations that were determined through chemical analysis, the widespread use of MI in this product category makes it problematic in relation to frequent consumer exposure and subsequent development of contact allergy.

Contributions from the use of “paint, varnish and adhesives” and “cosmetics” are comparable in the calculated dermal load for a woman, whereas hand washing-up liquid only gives a minor contribution to exposure under the applied conditions. The contribution of airborne exposure in freshly painted rooms is not included in the assessment as the data on MI-concentration in such rooms is inadequate.

The calculated dermal exposure from the use of hobby products is not included in this report, as no recognised guideline for choice of parameters for exposure calculations is available today to perform such exposure calculations. Hobby products are not expected to be used every day but at a much lower frequency than for, e.g., cosmetic products and skin contact is not expected to be intentional. However, the appearance of packaging and labelling indicate that the hobby products are intended for children who are more than three years old, and therefore it can in general be expected that the products will be used by children down to the age of three. A high content of MI in these products can therefore be problematic in relation to the development of contact allergy in children.

Product	Woman Dermal load [ng/(cm² x day)]	Three-year-old child Dermal load [ng/(cm² x day)]
Rinse-off cosmetics:		
Liquid hand soap	1.2	3.3
Shower gel	0.8	1.1
Shampoo	4.2	11.5
Conditioner	1.7	4.6
Leave-on cosmetics:		
Cleansing tissue	144	-
Face serum	73.5	-
Wet wipe		135
Moisturiser	114	126
Hand cream	60.6	-
Body lotion	25.7	35.6
Sunscreen	217	400
Deodorant (roll-on)	750	-
Hair wax	47.3	-
Detergents and household cleaning products		
Hand washing-up liquid	0.655	-
Paint, varnish and adhesives		
Wall paint	237	-
Wall and ceiling primer	148	-
Wallpaper adhesive	114	-

TABLE 1
SUMMARY OF DERMAL LOAD DETERMINED IN EXPOSURE SCENARIOS FOR AN ADULT WOMAN AND A THREE-YEAR-OLD CHILD.

On the basis of the 31 analysed products and their calculated exposure, it cannot be expected that all sources of consumer exposure to MI have been included in this survey. For instance, the exposure calculations that comprise wet wipes for facial cleansing and for babies do not include wet wipes for other purposes such as cleaning or intimate hygiene. In general, detergents and household cleaning products received low priority when purchasing products for analysis as, it is assumed, they are normally used in a diluted form. In addition, few analysis data exist in the literature on that type of products. It is possible that this product category might give a higher contribution to the total exposure than what this survey indicates, but exposure is expected to be low due to the very low use-concentration.

Furthermore, some consumer products will also contain other isothiazolinones, e.g., the very potent contact allergen MCI (e.g., liquid hand soap, wallpaper adhesive, wall primer and several hobby products). The trend is that patients who are sensitized in relation to MCI/MI also react to MI, which seems to indicate that the two related compounds MI and MCI both can trigger the allergic reaction. Finally, occupational exposure has not been included in the calculations.

Conclusion

As stated above, a consumer is exposed to MI through many sources. According to the Scientific Committee for Consumer Safety (SCCS) it is not possible based on the available clinical knowledge to determine a safe threshold value for the use of MI for leave-on cosmetics neither with respect to sensitization nor to elicitation of contact allergy. For rinse-off cosmetics, SCCS considers 15 ppm to be a safe concentration of MI with regard to sensitization. From the results of this project, cosmetics are considered to be a major source of exposure to MI as the application frequency is high and MI is currently used in many different cosmetic products. The results also show that MI currently is used in cosmetics in concentrations close to the current limit value of 100 ppm. In relation to the recently published recommendation from the SCCS, these products may constitute a risk. It should be noted that the SCCS may reassess its recommendation on the basis of new data.

The use of other products such as paint, varnish, adhesives and cleaning products is also expected to contribute to the exposure of the consumer. This increases the risk of developing contact allergy from MI, even though the use frequency often is lower in these products. Concentrations of approximately 100 ppm MI have been measured in these types of products. All things considered, consumers are exposed to a wide range of products containing MI in concentrations exceeding 15 ppm. According the recent recommendation from SCCS, this concentration is expected to be problematic in relation to the development of contact allergy from rinse-off cosmetics products.

Konklusion og sammenfatning

Baggrund
Methylisothiazolinon (MI) anvendes som konserveringsmiddel og bruges i mange forskellige typer af vandholdige produkter for at hindre mikrobiel vækst (fx af bakterier og svampe). MI findes i en lang række forbrugerprodukter, såsom kosmetik, rengøringsmidler, maling, lim, lak og legetøj. Det har inden for de seneste år vist sig, at der globalt er en kraftig stigning i antallet af personer, der udvikler allergi over for MI. På baggrund af denne udvikling, har Miljøstyrelsen iværksat nærværende projekt med kortlægning af MI's anvendelse i forbrugerprodukter, der også inkluderer en vurdering af eksponering af danske forbrugere for MI.

De senere års dokumentation for MI's alvorlige allergifremkaldende egenskaber har ført til, at sikkerhedsvurderingen for MI i 2013 er blevet revurderet af EU's Videnskabelige Komité for Forbrugersikkerhed (VKF) (Scientific Committee on Consumer Safety, SCCS). Konklusionen af den nye vurdering er, at VKF ikke anser det for sikkert for forbrugere at anvende 100 ppm[iv] MI i kosmetiske produkter. I kosmetik der er beregnet til at skylle af (rinse-of produkter) anses 15 ppm[v] som en sikker koncentration af MI, mens der for kosmetik, som forbliver på huden (leave-on produkter), ikke kan sættes en sikker koncentration ud fra tilgængelige data. Vådservietter inkluderes af VKF i kategorien leave-on produkter. VKF's vurdering af rinse-off produkter og leave-on hårprodukter er i øjeblikket under revision på baggrund af nye data.

Formål med projektet
Formålet med projektet er at foretage en kortlægning af MI i forbrugerprodukter som sælges på det danske marked, bestemme koncentrationen i udvalgte forbrugerprodukter og endeligt vurdere eksponeringen af den enkelte forbruger igennem forbrugerprodukterne.

Lovgivning
MI har ingen harmoniseret klassificering, men alle leverandører selvklassificerer stoffet til at være hudsensibiliserende og tildeler det faresymbolet "lokalirriterende" og faresætningen R43: "Kan give overfølsomhed ved kontakt med huden". Fra juni 2015 vil disse blive erstattet af farepiktogrammet "advarsel" og faresætningen H317: "Kan forårsage allergisk hudreaktion". Grænsen for at klassificere og mærke kemiske blandinger med MI er fra ikrafttrædelse af CLP-forordningen for blandinger i 2015 1 % (10.000 ppm), og grænsen for deklarering på etiketten er 0,1 % (1000 ppm). MI i kombination med methylchloroisothiazolinon (MCI) i forholdet 3:1 (MCI/MI) har en harmoniseret klassificering. Når kombinationen anvendes i kemiske produkter over en samlet koncentration på 0,0015 % (15 ppm[vi]), skal produkterne mærkes allergifremkaldende.

For kosmetik, som i EU reguleres under kosmetikforordningen (Forordning nr. 1223/2009), har det siden 2005 været tilladt at anvende MI i koncentrationer op til 100 ppm, hvis ikke stoffet kombineres med MCI. Når MI anvendes sammen med MCI i kosmetiske produkter i forholdet 3:1 (MCI/MI), må den samlede koncentration ikke overstige 15 ppm. En nylig ændring af kosmetikforordningen betyder, at MCI/MI 3:1 fra 16. juli 2015 ikke længere må anvendes i leave-on kosmetiske produkter.

Vaske- og rengøringsmidler er bl.a. reguleret under EU's detergentforordning (Forordning nr. 648/2004). Ifølge forordningen skal MI som konserveringsmiddel i vaske- og rengøringsmidler deklareres på emballagen uanset koncentration. Herudover reguleres produkterne som kemiske blandinger og klassificeres og mærkes for sensibiliserende virkning i henhold til CLP-reglerne.

[iv] ppm angiver "part per million", og 100 ppm svarer således til 0,01 %
[v] ppm angiver "part per million", og 15 ppm svarer således til 0,0015 %.
[vi] 15 ppm er det samlede indhold af MCI og MI, hvilket svarer til 3,75 ppm MI

Maling, lak og lim falder under kategorien kemiske blandinger og klassificeres og mærkes i henhold til CLP-reglerne.

Legetøj reguleres primært under legetøjsbekendtgørelsen (Bekendtgørelse om sikkerhedskrav til legetøjsprodukter). For nogle typer af legetøj stilles der specifikke krav til indholdsstoffer. Dette gælder fx makeup eller fastelavnssminke og lignende, som også er omfattet af kosmetikforordningen. For legetøjskategorien "andet kemisk legetøj (sæt) end sæt til kemiske forsøg", bl.a. maling, lak og lim, kræves for vandbaserede produkter, at de konserveringsmidler, som anvendes, er godkendt til fødevarer og/eller kosmetik. Med de gældende kosmetikregler betyder det, at disse typer legetøj må indeholde MI i en koncentration op til 100 ppm og op til 15 ppm af MCI/MI, når de anvendes sammen i forholdet 3:1 (MCI/MI). Fingermaling (DS/EN 71-7:2014) må indeholde MCI/MI-blandingen i forholdet 3:1 i en koncentration på maksimalt 0,0008 %, og MI må være tilsat i en maksimal koncentration på 100 ppm, når den anvendes uden MCI.

Kliniske erfaringer med MI

Opsummering af kliniske erfaringer med MI tyder på, at hyppigheden af MI-kontaktallergi er stigende blandt eksempatienter. Især er kvinder med daglig udsættelse for kosmetik og visse erhvervsgrupper i risiko for at udvikle kontaktallergi over for MI. Ligeledes er der de senere år præsenteret kasuistikker omhandlende børn med kontaktallergi over for MI efter brug af vådservietter, hvilket er problematisk, da barnet i fremtiden kan opleve genopblussen af allergisk kontakteksem ved genudsættelse for MI fx via vandbaseret maling konserveret med MI. Patienter, der sensibiliseres for MI, har en livslang allergi, hvor genudsættelse for MI vil lede til ny opblussen af eksemet. Luftbåren kontaktallergi er i enkelte tilfælde set hos dermatitispatienter og dette ofte i forbindelse med malerarbejde. Patienter med en allergi over for MI kan ofte ikke opholde sig i nymalede lokaler i en lang periode, efter at arbejdet er udført, uden at reagere allergisk, hvilket tyder på, at afdampningen af MI er langvarig. Patienter kan til en vis grad undgå kosmetik og andre forbrugerprodukter med MI, da lovpligtig deklarering er med til at sikre forbrugeren. I henhold til lovgivningen for kemiske produkter (CLP) er der først krav om deklaration fra et indhold på 1000 ppm (0,1 %). Det er ud fra et lægefagligt synspunkt problematisk, da forbrugeren og fx maleren ikke anses for tilstrækkeligt beskyttet mod allergi over for MI ved anvendelse af produkter med relativt høje koncentrationer af MI, som fx maling med koncentrationer af MI op mod 200 ppm.

Kortlægning

Kortlægningen af anvendelsen af MI har vist, at stoffet anvendes i et bredt udsnit af forbrugerprodukter. Generelt identificerer tidligere studier i den tilgængelige litteratur typisk anvendelse af MI inden for kosmetiske produkter, rengøringsprodukter, maling, lak og lim. Enkelte studier omfatter undersøgelse af anvendelsen af MI i forskellige typer af legetøj, bl.a. kortlægningen fra 2014 af konserveringsmidler i legetøj udført for Miljøstyrelsen. Også inden for de enkelte produktgrupper er anvendelsen af MI udbredt til mange forskellige typer af produkter. I kosmetiske produkter er MI fx identificeret i bl.a. shampoo, balsam, deodoranter, vådservietter, cremer og hårvoks.

Oftest er offentliggjorte kortlægninger foretaget ud fra deklarationen på produkterne, og meget få omfatter kemisk analyse af koncentrationen af MI i produkterne. Med hensyn til kosmetiske produkter er koncentrationen af MI dog bestemt til 52-100 ppm i 12 rinse-off produkter, 2-96 ppm i tre leave-on produkter og 17-87 ppm i fire vådservietter af Lundov *et al* i et studie udført i 2010. Koncentrationen af MI i 19 vandbaserede malinger er bestemt til 10-300 ppm, et niveau der for så vidt kan bekræftes af brancheforeningen, DFL. DFL's (2012) kortlægning blandt foreningens medlemmer viste, at 80 % af malingerne (vandfortyndbare malerprodukter til indendørs brug) indeholdte mindre end 100 ppm, 19 % indeholdte MI i intervallet 100-200 ppm, og den resterende lille del indeholder en højere koncentration af MI. For legetøj viser den nyeste kortlægning på området, at MI ikke findes i de 11 udvalgte produkter til analyse i koncentrationer over detektionsgrænsen på 20 ppm. De rapporterede anvendelsesområder og brugskoncentrationer stemmer generelt overens med informationen indhentet fra brancheforeninger og producenter. Leverandører af MI anbefaler at anvende MI i kombination med andre konserveringsmidler med henblik på at begrænse anvendelsen. Leverandørerne anbefaler en MI-koncentration i området 25-175 ppm afhængigt af produkttype.

De tidligere kortlægninger viser, at anvendelsen af MI oftest ses i kombination med andre konserveringsmidler. Kombinationen af MI med MCI er stadig dominerende, men andre vinder frem, som fx kombinationen med andre isothiazolinoner og phenoxyethanol.

De forskellige regler for deklarering og mærkning af produkter, som afhænger af produkttypen, gør det svært - til tider umuligt – for forbrugeren at identificere produkter, som indeholder MI.

Det største antal produkter er i denne kortlægning identificeret ved besøg i fysiske butikker og ved besøg i internetbutikker for kosmetik og rengøringsmidler. For denne type produkter skal MI ifølge lovgivningen deklareres, og indholdet skal derfor være angivet på emballagen. Enkelte produkter inden for maling, lak og lim blev identificeret ud fra oplysninger fra producenter. Hobbyprodukter, hvoraf nogle tydeligt er målrettet børn, og som kan være legetøj, er identificeret ud fra oplysninger fra producenter.

Af de 174 identificerede produkter inden for kosmetik og personlig pleje var hovedparten rinse-off produkter (59 %), men også leave-on produkter er stærkt repræsenteret blandt de identificerede produkter (41 %). 60 produkter er identificeret inden for vaske- og rengøringsmidler, mens der inden for maling, lak og lim er identificeret 27 produkter. Endelig er der identificeret syv produkter inden for legetøj og hobbyprodukter.

Brancheforeninger samt producenter og importører af produkter, som indeholder MI, bekræfter, at anvendelsen af MI er udbredt, men også at der er fokus på konserveringsmidlet og dets sundhedsmæssige egenskaber. Danmarks Farve- og Limindustri (DFL) har i maj 2013 spurgt sine medlemmer om anvendelsen af MI og kunne oplyse, at MI ifølge de adspurgte medlemmer har en udbredt anvendelse i vandfortyndbare malerprodukter. Ifølge konklusionen af undersøgelsen indeholder alle vandfortyndbare malerprodukter til indendørs brug MI. Flere producenter har allerede udfaset, overvejer eller planlægger at udfase stoffet, mens andre peger på, at der mangler brugbare alternativer. Behovet for konservering kan for kemiske blandinger, som for eksempel maling, afspejle produktionsforhold og råvarekvalitet. Krav til råvareleverandører på disse områder kan være med til at begrænse mængden af konserveringsmiddel, som er nødvendig for at sikre produktet mod mikrobiel vækst.

Kemisk analyse
Der er i samarbejde med Miljøstyrelsen udvalgt 31 produkter til kemiske analyse af indhold af MI. Produkterne er udvalgt inden for de fire produkttyper: kosmetik og personlig pleje (22 produkter fordelt på 8 rinse-off og 14 leave-on produkter), vaske- og rengøringsmidler (1 produkt), maling, lak og lim (4 produkter) samt legetøj og hobbyprodukter (4 produkter). Produkterne er valgt under hensyntagen til forskellige faktorer, som anses for at være af betydning for udviklingen af kontaktallergi og være afgørende for at opnå et samlet billede af eksponering for en forbruger:

- produkterne forventes at have direkte hudkontakt
- produkterne anvendes ofte
- produkterne anvendes af børn
- produkterne har en høj koncentration af MI
- produkterne dækker bredt over forskellige produkttyper og producenter

Usikkerheden på analyseresultaterne er matriceafhængig, og den samlede analyseusikkerhed for det enkelte produkt kan være op til 20 % (RSD). En grænseværdi vurderes således kun overskredet, hvis gennemsnittet af en dobbeltbestemmelse ligger mere end 20 % over grænseværdien.

Tre kosmetiske rinse-off produkter konserveret med kombinationen af MCI og MI i forholdet 3:1 (oplyst af forhandler) har ved de kemiske analyser vist sig at indeholde 1,8-4,8 mg/kg MI, mens fem rinse-off produkter konserveret med MI uden MCI indeholder 37-71 mg/kg MI.

Samtlige 14 analyserede leave-on produkter er deklareret til at indeholde MI uden MCI og indeholder <5-114 mg/kg MI. To leave-on produkter indeholder ikke MI over detektionsgrænsen (for denne type produkter normalt er 0,5 mg/kg, men er hhv. 5 og 10 mg/kg for de pågældende produkter).

Et håndopvaskemiddel indeholder 40 mg/kg MI (produktet er deklareret med MI og octylisothiazolinon).

To vægmalinger indeholder hhv. 70 mg/kg og 135 mg/kg MI. En grunder og en klæber, der ifølge sikkerhedsdatabladet indeholder MCI/ MI i forholdet 3:1, indeholder hhv. 21 mg/kg og 13 mg/kg MI.

Tre af fire hobbyprodukter indeholder 3,6-5,8 mg/kg MI, hvoraf de to ifølge forhandleren indeholder konservering med kombinationen MCI/MI. En hobbylim, der ifølge producenten indeholder MCI/MI og en koncentration af MI <140 ppm, indeholder 110 mg/kg MI.

Kvalitativ vurdering af analyseresultater
MI indhold fundet ved analyse for udvalgte produkter er sammenlignelige med værdier rapporteret i tidligere studier. Alle kosmetiske produkter i dette studie overholder den gældende grænseværdi på 100 ppm MI, når der tages højde for analysemetodens usikkerhed på 20 %. Set i forhold til VKF's nye anbefaling af en grænseværdi på 15 ppm for MI i rinse-off produkter og 0 (nul) ppm for MI i leave-on produkter vil kun fem kosmetikprodukter ud af 22 analyseret i dette studie anses for sikre.

Hvis der for håndopvaskemidlet antages en fortyndingsfaktor på 5000, vil den analyserede koncentration på 40 ppm MI i et opvaskemiddel svare til en brugskoncentration på 0,008 ppm. Dette kan sammenholdes med grænseværdier for kosmetiske rinse-off produkter, hvor VKF anbefaler maksimalt 15 ppm. Ufortyndet håndopvaskemiddel indeholder MI i en koncentration, der ligger over VKF's anbefalede grænse for rinse-off kosmetik.

Eksponeringen af MI igennem hobbyprodukter, legetøj, maling, lak og lim kan ikke sammenlignes direkte med den eksponering, som vil finde sted fra kosmetik, men hvis man får hudkontakt med en flydende formulering med en koncentration af MI på højere end 15 ppm (som er fundet for en række produkter) vil der være en risiko for induktion af allergi.
Eksponeringen fra maling kan dog også ske ved, at man opholder sig i et nymalet rum, da MI i maling fordamper og bliver luftbåren. Der vil således kunne være hudkontakt med de dele af kroppen, der ikke er dækket af tøj. Dette eksponeringsbidrag er der dog ikke medtaget i eksponeringsvurderingen, idet der kun foreligger meget få målinger på rumkoncentrationer efter maling med MI-holdig maling.
I forhold til den nugældende grænseværdi for MI i kosmetik på 100 ppm ses højere niveau for en af to vægmalinger og én hobbylim, hvor måleusikkerheden dog kan betyde, at indholdet reelt ligger under 100 ppm. For de øvrige 3 hobbyprodukter ligger MI-indholdet under 15 ppm MI. MI-indholdet i grunderen og klæberen ligger over 15 ppm, men under de 100 ppm.

Sammenfatning af eksponering for methylisothiazolinon gennem forbrugerprodukter

I **Fejl! Henvisningskilde ikke fundet.** er de beregnede eksponeringer udtrykt som dermal dosis for hhv. en vinde og en treårig opsummeret. Bidrag fra de enkelte produkter viser, at der for de kosmetiske produkter ses den største eksponering ved anvendelsen af produkter, som forbliver på huden. Den dermale dosis er generelt lidt højere for de treårige end for kvinden under de anvendte forudsætninger, men anses ikke for markant højere. Hos kvinden ses det største enkeltbidrag fra kosmetik på anvendelsen af deodorant (750 ng/cm²/dag), mens det største bidrag for de treårige er fra solcreme (400 ng/cm²/dag, beregnet ud fra et teoretisk maksimalt indhold af MI på 100 ppm).

De kosmetiske produkter anses for at være de produkter, som anvendes hyppigst, og dette anses for at være af afgørende betydning for udvikling af kontaktallergi. Dette sammenholdt med tilstedeværelsen af MI, i de relativt høje koncentrationer bestemt ved kemisk analyse, gør anvendelsen af MI så bredt i denne produkttype problematisk i forhold til hyppig forbrugereksponering og følgende udvikling af kontaktallergi.

Bidrag fra anvendelse af "maling, lak og lim"- samt "kosmetik"-produkter er af sammenlignelig størrelse i den udregnede dermale dosis for en kvinde, mens håndopvaskemiddel kun giver et mindre bidrag til eksponering

under de anvendte forudsætninger. Bidrag fra luftbåren eksponering fra nymalede rum er ikke medtaget i vurderingen på grund af utilstrækkelige data om rumkoncentrationer.
Beregning af den dermale dosis for hobbyprodukter er ikke medtaget i denne rapport, da der på nuværende tidspunkt ikke findes anerkendte retningslinjer for valg af parametre til eksponeringsberegning for de udvalgte produkttyper. Hobbyprodukter forventes ikke at blive anvendt hver dag, men i langt lavere frekvens end fx de kosmetiske produkter og hudkontakten med produkter forventes ikke at være intentionel. For hobbyprodukterne giver emballagens udseende og dens mærkning det indtryk, at hobbyprodukterne er tiltænkt både voksne og børn over tre år. Produkterne kan derfor generelt forventes at blive anvendt af børn helt ned til treårsalderen, og et højt indhold af MI i denne type produkter anses derfor at være problematisk i forhold til udvikling af kontaktallergi, hvis det kommer i hyppig og langvarig kontakt med huden.

Produkt	Kvinde - Dermal dosis [ng/(cm² x dag)]	Treårigt barn - Dermal dosis [ng/(cm² x dag)]
Rinse-off kosmetik:		
Flydende håndsæbe	1,2	3,3
Showergel	0,8	1,1
Hårshampoo	4,2	11,5
Hårbalsam	1,7	4,6
Leave-on kosmetik:		
Renseserviet	144	-
Ansigtsserum	73,5	-
Vådserviet		135
Ansigtscreme	114	126
Håndcreme	60,6	-
Bodylotion	25,7	35,6
Solcreme	217	400
Deodorant (roll-on)	750	-
Hårvoks	47,3	-
Vaske- og rengøringsmidler		
Håndopvaskemiddel	0,655	-
Maling, lak og lim		
Vægmaling	237	-
Væg- og loftgrunder	148	-
Tapetklæber	114	-

TABEL 2
OVERSIGT OVER DERMAL DOSIS UDREGNET I EKSPONERINGSSCENARIER FOR EN VOKSEN KVINDE OG ET TRE-ÅRIGT BARN.

Ud fra de 31 analyserede produkter og deraf udregnede eksponeringer for kosmetiske produkter, vaske- og rengøringsmidler og maling, lak og lim kan det ikke forventes, at alle kilder, hvor en forbruger kan komme i berøring med MI, er medtaget i denne undersøgelse. Fx inkluderer eksponeringsberegningerne vådservietter til ansigtsrens og til babyer, mens der ikke indgår anvendelse af vådservietter til andre formål, såsom rengøring eller intimhygiejne. Vask- og rengøringsmidler er generelt prioriteret lavt i forbindelse med indkøb af produkter til

analyse, da det vurderes, at de normalt anvendes i en meget fortyndet form. Der foreligger endvidere meget få analysedata på den type produkter i litteraturen. Det er muligt, at denne produkttype giver et højere bidrag til den samlede eksponering, end det fremgår af denne undersøgelse, men eksponeringen forventes at være lav pga. den normalt meget lave brugskoncentration.

Ydermere vil nogle forbrugerprodukter også kunne indeholde andre isothiazolinoner, fx det meget potente kontaktallergen MCI (fx håndsæbe, tapetklæber og væggrunder samt flere hobbyprodukter), og der er en tendens til, at patienter, som er sensibiliseret i forhold til MCI/MI, også reagerer på MI, dvs. det tyder på, at de to nært beslægtede forbindelser MI og MCI begge kan udløse den allergiske reaktion. Endelig er erhvervsmæssig eksponering ikke inkluderet i beregningerne.

Konklusion

For en forbruger er der som beskrevet i ovenstående rigtig mange kilder til eksponering af MI. På basis af den tilgængelige kliniske viden er det ifølge den videnskabelige komité for forbrugersikkerhed, VKF ikke muligt at sætte en sikker tærskeværdi for anvendelse af MI i leave-on kosmetik, hverken med hensyn til sensibilisering eller med hensyn til elicitering af kontaktallergi. I rinse-off kosmetik anser VKF 15 ppm som en sikker koncentration af MI med hensyn til sensibilisering. Ud fra resultaterne af dette projekt anses kosmetik som en stor kilde til eksponering af MI, da brugsfrekvensen ofte er høj og MI i dag anvendes i mange forskellige kosmetiske produkter. Resultaterne viser også, at der i dag anvendes MI i kosmetik i koncentrationer tæt på den nuværende grænseværdi på 100 ppm. I forhold til den seneste anbefaling fra VKF udgør disse produkter således en risiko. Det skal noteres, at VKF på baggrund af nye data muligvis vil revidere denne anbefaling.

Anvendelse af andre produkter som maling, lak og lim samt rengøringsmidler forventes endvidere at bidrage til eksponeringen af forbrugeren. Dermed øges risikoen for udvikling af kontaktallergi, omend brugsfrekvensen af denne type produkter typisk vil være lavere. For enkelte af disse produkter er der målt koncentrationer af MI over 100 ppm.

Samlet set eksponeres man altså som forbruger for en lang række produkter med MI i koncentrationer på over 15 ppm, som ifølge VKFs seneste anbefaling for kosmetiske rinse-off produkter forventes at være problematiske i relation til udvikling af kontaktallergi.

1. Background

1.1 Objective

The objective of this project was partly to identify consumer products on the Danish market that contain MI. In addition, an outline is given of which product categories contain MI, and in which concentrations the substance is used in the various products. Subsequently, selected consumer products identified on the Danish market were analysed for content of MI, and, finally, the exposure of the individual consumer through the consumer products was assessed.

1.2 Function and use of methylisothiazolinone

MI is a preservative and it is added to many different types of water-based products to prevent microbial growth (e.g., bacteria and mold). MI is used in industrial products such as biocides, paint, adhesives, varnish, cleaning agents and detergents as well as in a wide range of consumer products, e.g., cosmetics, household cleaning products, paint, adhesives, varnish and toys (Castanedo-Tardana and Zug 2013). The increasing use of MI in more and more products (and in higher concentrations than when the substance was introduced) (the period from 2000 till 2011)[vii] has led to a serious global increase in the number of people who develop an allergy to MI (Lundov et al. 2013). The development has been so substantial that MI was granted the title of Contact Allergen of the Year 2013 from the American Contact Dermatitis Society (Castanedo-Tardana and Zug 2013). That development has led to the initiation of this project by the Danish Environmental Protection Agency. This report also covers a survey of the use of MI in consumer products, including an assessment of the exposure of Danish consumers to MI.

MI belongs to a group of preservatives that have the common name isothiazolinones, see Fact Box 1. MI has been used as preservative for more than 30 years. Until 2000, MI was only used in combination with another substance, commercially sold as Kathon CG® that contains MCI and MI in a three-to-one ratio. However, MCI is a very potent allergen, and the use of MI, which is believed to be a less potent allergen if MCI is not used together with it, has become more widespread in the past 10-15 years. Earlier, the use of MI as an individual preservative was mainly popular in industrial products and processes, but since 2005, MI has also been used as a stand-alone preservative in cosmetics, which means not in the known combination with MCI. MI does not preserve to the same degree as MCI and therefore higher concentrations of MI are required to obtain the same effect as with the combination of MCI and MI in a three-to-one ratio. In around year 2000, MI was introduced to the market as a stand-alone preservative for preservation in paint and adhesives (Thyssen et al. 2006; Urwin and Wilkinson 2013). Please also refer to chapter 1.6 on legislation and labelling systems.

1.3 Contact allergy – development over recent years

In parallel with the widespread use of MI, an increase has appeared in the reported cases of allergic reactions to MI. From 2006-2010, the prevalence of patients with allergic contact allergy to MI was app. 1.5% in Denmark (37 of 2536 tested dermatological patients) (Lundov et al. 2010). In Germany, in the overlapping period, an increase was seen from 1.9% in 2009 to 4.4% in 2011 (based on 21,274 dermatological patients) (Geier et al. 2012) and there was a corresponding prevalence in Finland of 1.4% and 0.6%, respectively, (out of 10,821 dermatological patients tested with 1000 and 300 ppm MI, respectively, in the period 2006-2008) (Ackermann et al. 2011). However, in the period 2010-2013, the frequency of Danish patients with allergy to MI increased drastically by

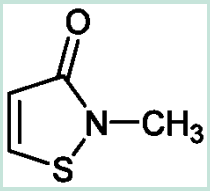
[vii] Data from SPIN – Substances in Preparations in Nordic Countries. Database based on product registers in Norway, Sweden, Denmark and Finland.

2.0% in 2010, 3.0% in 2011 and 3.7% in 2012 (2766 dermatological patients tested in Denmark) (Lundov et al. 2013), and the figure for 2013 is 5.7% (Danish National Allergy Research Centre, 2014)[viii]. During the period 2011/2012, corresponding surveys in a number of European countries (England, Belgium, Portugal) showed a similar increase in allergy to MI; i.a. Urwin and Wilkinson (2013) report a prevalence of 1.8-4.6% in Leeds (2619 tested dermatological patients) (Urwin and Wilkinson, 2013), and Gonçalo and Goossens (2013) reported prevalences of 6.0% in London, 5.8% in Leuven and 4.5% in Coimbra, respectively (Gonçalo and Goossens, 2013). In addition, a new Danish study has shown that exposure to MI down to 5 ppm can cause allergic reactions (Lundov et al., 2011A).

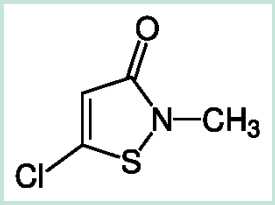
Fact Box 1: Isothiazolinones

Isothiazolinone is a generic term for a group of preservatives that are used to combat bacteria and mold in water-based products such as cosmetics, household cleaning products and paint. The group includes the substances:

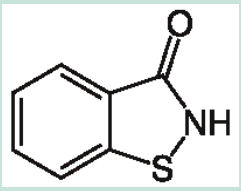
- Methylisothiazolinone (MI, MIT)
- Methylchloroisothiazolinone (MCI, CMI, CMIT)
- Benzisothiazolinone (BI, BIT)
- Octylisothiazolinone (OI, OIT)
- Dichlorooctylisothiazolinone (DCOI, DCOIT)



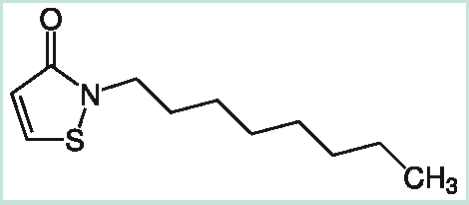
Methylisothiazolinone
CAS no. 2682-20-4



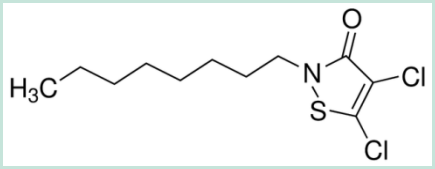
Methylchloroisothiazolinone
CAS no. 26172-55-4



Benzisothiazolinon
CAS no. 2634-33-5



Octylisothiazolinone
CAS no. 26530-20-1



Dichlorooctylisothiazolinone
CAS no. 64359-81-5

In addition to traditional contact allergy, recent years have experienced an increasing number of reported cases of contact allergy after airborne exposure to MI (Lundov et al. 2012). Persons who have stayed in freshly painted rooms, where the paint used was preserved with MI, have developed skin reactions in the areas of the skin that were not covered with clothes. MI remains in the air during and after painting and can therefore come into contact with unprotected skin and in that way cause an allergic reaction. In a few cases, the symptoms were also followed by asthmatic symptoms.

[viii] The figure from 2013 is quoted to be 5.3% on the homepage of the Reseacrh Center but 5.7% this is the coreect figure (personal communication)

1.4 The EU Scientific Committee on Consumer Safety (SCCS)

In 2004, the European Scientific Committee on Consumer Safety (SCCS) assessed that it was safe to use MI in cosmetic products in concentrations of up to 100 ppm (SCCS 2004). In 2009, the SCCS concluded that the use of 15 ppm MCI/MI in a three-to-one mixture was regarded as safe in rinse-off products (SCCS 2009). That assessment has formed the basis of a recent decision to remove MCI/MI in a three-to-one ratio from the positive list for use in leave-on products[ix]. MCI/MI in a three-to-one ratio is now only permitted up to 15 ppm in rinse-off products. The documentation of recent years, concerning the serious allergy causing properties of MI, resulted in SCCS's re-assessment of the MI risk assessment. The conclusion of the new assessment is that SCCS believes it is unsafe for consumers to use cosmetics that contain 100 ppm MI. In rinse-off products, a concentration of 15 ppm MI is regarded as a safe concentration, but for leave-on products a safe concentration cannot be determined on the basis of the available data (SCCS, 2013). According to SCCS, wet wipes belong under the category of leave-on products.[x]

Several cosmetic manufacturers have already announced a voluntary phasing-out of MI. Molton Brown (a British manufacturer of cosmetic products) has told a British internet paper that they will stop using MI from September 2013 (Fletcher, 2013). Beiersdorf, who stands behind Nivea, is cited by the Danish newspaper Politiken to want to phase out the use of MI in all of the company's products in the course of 2014(Guldagger, 2013). Correspondingly, Johnson & Johnson announced in the BBC programme called "Watchdog" that they intend to introduce a MI-free version of their most popular sunscreen on the British market from the summer of 2014 (Watchdog, 2013). In addition, the European trade association Cosmetics Europe recommends all manufacturers to phase out MI in leave-on products including wet wipes by December 2013 (Cosmetics Europe, 2013).

SCCS has, in the autumn 2014, agreed to assess some additional data in order to possibly revise their recommendation with respect to MI in cosmetic rinse-off products and leave-on hair products.

1.5 Methylisothiazolinone and contact allergy

A wide range of chemical substances with low molecular mass can cause contact allergy among humans, and according to the Danish National Allergy Research Centre (Videncenter for Allergi) at least 10% of the Danish population suffers from contact allergy (National Allergy Research Centre, not dated). An allergic reaction can be triggered locally on the skin (appears as eczema) among sensitized people when they are exposed to the allergy causing substance above a certain level. In general, contact allergy is regarded as a threshold effect, and the development of contact allergy is load dependent. In connection with contact allergy, a differentiation is made between the concentration that is needed to sensitize (induction), and the concentration that is needed to trigger an allergic reaction (elicitation) among already sensitized people. Both concentrations are relevant when exposure of consumers has to be assessed in order to protect the consumer against the development of allergy and also to protect against allergic reactions among consumers, who already have developed an allergy. Large variations are often seen from person to person regarding the threshold value for induction and elicitation, and for many substances it is either not possible to determine a threshold value or sufficient data does not exist; therefore a threshold value cannot be determined.

As described earlier, MI is a well-known skin sensitising substance, and the predominant health related problem about MI is its allergy causing potential. In their assessment from 2013, SCCS points out that only one well-described, reliable animal study has been published in which the determination of an induction concentration of MI is stated. The study was based on a LLNA test (local lymph node assay) on mice, where the power of MI, a so-called EC3-value, is determined. The EC3-value is the concentration of the tested substance that results in a triple increase in cell activity compared to a blank specimen. In the study, the EC3-value of MI is compared with the EC3-value of formaldehyde, and the study categorises MI as a very sensitizing substance (SCCS, 2013). However, on the basis of available clinical knowledge, SCCS concludes that a safe threshold value for the use of MI cannot be

[ix] The memberstates have adopted rules on phasing out MCI/MI in a three-to-one ratio from leave-on cosmetics, but the directive has not been publise dyet (September 2014). Information received from the Danish Environmental Agency.
[x] The recommendations of SCCS has not yet (September 2014) led to proposals for changes to limit values for MI in leave-on or rinse-off cosmetic products.

determined for cosmetic products that remain on the skin (leave-on) – neither with regard to sensitization nor elicitation. However, for cosmetics that are rinsed off, SCCS regards 15 ppm to be a safe concentration of MI with regard to sensitization, while a threshold value for elicitation cannot be determined on the basis of available data (SCCS, 2013). Therefore, a health-related assessment of exposure to MI can only be of a qualitative nature.

Skin sensitization and subsequent contact allergy is an immunological process (type IV allergy) that consists of two phases: induction and elicitation. In the first asymptomatic phase, the immune system is affected, whereas subsequent exposure to sufficient amounts of the allergenic substance will develop an immunological reaction with eczema symptoms.
Mechanistically, contact allergy is caused when the allergy causing substance (the allergen) penetrates the epidermis (the outermost layer of the skin), and the substance (or a transformation product) binds covalently to proteins in the body. That reaction results in the creation of a so-called hapten. The haptens are then caught by cells from the immune system (Langerhans cells) that are activated and migrate to the nearest lymph node. That is where the hapten is introduced to other cells in the immune system (the T-cells) and they are also activated so they can recognize the unknown substance if they encounter it again. Cells are now created that can recognise and react to the allergy causing substance if the skin again gets into contact with the substance (Kaplan et al., 2012; OECD, 2012). The creation of haptens and the protein binding properties of a chemical substance is regarded to be one of the most significant factors in the sensitization process and is directly related to the sensitization potential and potency of the substance (Roberts and Aptula, 2008). When a person develops an allergy, an over-reaction takes place in the immune system of the body in the presence of substances that are normally harmless.

A wide range of factors influence the development of contact allergy, i.e. sensitization. The most decisive factors for the development of contact allergy to a substance are:

- Potency of the allergen, i.e., how much substance per area unit is necessary to sensitize a not previously exposed person (WHO, 2008)
- How high a concentration of the allergen a person is exposed to
- How often and for how long the person is exposed to the allergen

Frequent exposure at lower concentrations is regarded to have a greater effect on sensitization than one single exposure at a higher concentration. However, great variations are in general seen from person to person, and in addition to the above-stated factors it is also essential where on the body exposure to a substance takes place, how easily the substance penetrates the skin and if other substances are present that could irritate the skin. In general, the concentration that triggers an allergic reaction in an already sensitized person is lower than the concentration that is required to initially develop the allergy (Lundov, 2010). Decisive factors for the development of contact allergy have been summarised in connection with the exposure assessment in chapter 6, Fact Box 2.

1.5.1 Clinical experience with MI

The preservative MI belongs to the group of isothiazolinones that to varying degrees have demonstrated a favourable anti-microbial effect. Isothiazolinones have been used on a large scale in consumer products as well as in industrial products since the end of the 1970s and the beginning of the 1980s (Law et al., 1984; Flyvholm, 2005). The three most frequently used isothiazolinones in industrial products in Denmark have recently been assessed to be MI, MCI and BIT (Friis et al., 2014).

Methylchloroisothiazolinone/methylisothiazolinone

In the 1980s, a number of isolated occupational and non-occupational cases of contact allergy to the preservative MCI/MI were reported (de Groot et al., 1985; Bruze et al., 1987; Bruze et al., 1990; de Groot et al., 1991). That was followed by reports on an epidemic increase in the prevalence of contact allergy to MCI/MI among patients with contact eczema in several countries (Bjorkner et al., 1986; Hannuksela, 1986; Fransway, 1988; Tosti, 1988; de Groot and Herxheimer, 1989). As the MCI/MI epidemic developed, it became clear that there especially was a connection between exposure to MCI/MI from cosmetics and the observed increase in the prevalence of contact allergy towards MCI/MI (Hannuksela, 1986; Cronin et al., 1988; Menne and Hjorth, 1988). The prevalence of contact allergy towards MCI/MI has through the 1990s and 2000s remained steady at around 2% in Denmark and

Germany (de Groot and Herxheimer, 1989; Wilkinson et al., 2002; Thyssen et al., 2010; National Allergy Research Centre, not dated).

Methylisothiazolinone

MI has been introduced as a stand-alone preservative in industrial products as well as cosmetic products in the last 10-15 years. From year 2000, the industry started using MI in industrial chemical products, e.g., paint and varnish. After the introduction of MI to industrial products, several isolated cases with contact allergy to MI were observed in the years that followed (Isaksson et al., 2004; Thyssen et al., 2006). A Danish case report described four cases of factory workers who had developed MI contact allergy after recent direct skin exposure to various biocides with MI concentrations of 10% during the production of water-based paint (Thyssen et al., 2006). In all four cases, hand eczema was observed, and some also experienced eczema on arms, neck and in the face.

When it became legal to use MI in cosmetics (2005), the first case of non-occupational contact allergy to MI was described in 2010 (Garcia-Gavin et al., 2010). The man in question was middle-aged, and he had developed contact eczema after exposure to wet wipes with a content of MI. Subsequently, a fresh outbreak of eczema was defined after new skin contact to products with a content of MI; soap and paint (Garcia-Gavin et al., 2010). In 2010, a Danish retrospective epidemiological study by Lundov *et al.* for the first time demonstrated that the prevalence of contact allergy to MI was rather high and at the same level as other preservatives that had been used in industrial products as well as consumer products for ages (Lundov et al., 2010). Likewise, a Danish market analysis showed that 19 products out of 1272 (1.9%) cosmetic products contained MI (Lundov et al., 2011A). The 19 products had 74% concentrations of MI above 50 ppm. At the same time, corresponding European studies displayed varying frequencies of consumer products with a MI content (Magnano et al., 2009; Yazar et al., 2011). A Danish market analysis from 2013 demonstrated that the frequency of cosmetics with a MI content had increased from 1.9% to 3.3% (Lundov et al., 2013).

The frequency of contact allergy to MI is increasing in Denmark and at European level. Several studies report an epidemic increase in MI allergy (Lundov et al., 2010; Thyssen et al., 2010; Goncalo and Goossens, 2013; Lundov et al., 2013; McFadden et al., 2013; Uter et al. ,2013; Lammintausta et al., 2014; Madsen and Andersen, 2014A). In Denmark, the frequency of MI contact allergy has according to an epidemiological study from three teaching hospitals increased significantly from 1.8% in 2009 to 4.2% in 2012 (Schwensen et al., 2014). Unpublished data from Gentofte Hospital (Danish teaching hospital) shows that the prevalence of MI contact allergy continued to increase to 5.7% in 2013. The same development is seen at European level, where England, France, Germany, Belgium and Finland report on increases that are similar to an epidemic in the prevalence of MI contact allergy (Goncalo and Goossens, 2013; McFadden et al., 2013; Aerts et al., 2014; Hosteing et al., 2014; Lammintausta et al., 2014).

Allergy to MI caused by non-cosmetic products

MI is presumed to be used frequently by industry, where it especially is used within the paint and varnish industry (Friis et al., 2014). That corresponds with a new Danish and German study; both have found a connection between an occupational group of painters and contact allergy to MI (Uter et al., 2013; Schwensen et al., 2014). In a retrospective cohort of painters who were bothered by eczema, Mose et. al also found that contact allergy to MI was frequently represented (Mose et al., 2012). In addition, it also seems that the broader occupational group of industrial workers is associated with contact allergy to MI, which probably is consistent with the pronounced use of MI in different industrial products, e.g., cutting oil (Schwensen et al., 2014; Friis et al., 2104). An earlier Danish study showed that every third patient among eczema patients with contact allergy to MI had occupational contact eczema (Lundov et al., 2010).

The use of MI in paint is considered to be pronounced and a problem for the painter as well as the consumer in relation to exposure and development of allergy. A new Danish experimental analysis disclosed a rather high and varying content of MI (10-300 ppm) in 19 out of 19 types of tested paint (Lundov et al., 2014). The MI content in paint and other industrial products do not have to be declared before there is a content of 1000 ppm (0.1%). Out of the 19 types of tested Danish paint, only two of the paint product data sheets declared that they contained MI. A corresponding European study headed by the Danish National Allergy Research Centre is currently underway,

where 93% (66 out of 71) of water-based paint purchased in Europe contained concentrations of MI in the interval from 0.7-180 ppm. The lacking declaration of MI in the paint is a problem for the consumer and the painter as it is practically impossible to distinguish between and select paint with or without a content of MI. The painter as well as the consumer who comes into contact with paint has little chance of avoiding allergy or outbreaks of already acknowledged contact allergy to MI by exposure to water-based paint with a content of MI.
Several single cases of eczema after exposure to paint with a MI content are described in the literature (Thyssen et al., 2006; Lundov et al., 2011B; Friis et al., 2012; Kaae et al., 2012; Bregnbak et al., 2013). Lundov et al. was one of the first persons to illustrate that airborne occupational exposure to MI from paint could result in sensitization and the development of allergic contact eczema caused by airborne exposure to MI from a freshly painted room (Lundov et al., 2011). That corresponds to MI in paint being able to evaporate and become airborne, and that steady and measurable air concentrations of MI exist weeks after the paint has been applied (Lundov et al., 2014). In 2012, Kaae et al. described how a 23-year-old woman experienced the first outbreak of face eczema after airborne exposure to MI from a freshly painted room at work. Subsequently, she experienced a fresh outbreak of face eczema after having used a cosmetic cleansing product. (Kaae et al., 2012).

The occupational cases of allergic contact eczema mentioned in the literature indicate that direct skin exposure in rather high concentrations as well as airborne exposure to MI from freshly painted rooms can result in sensitization to MI (Thyssen el al., 2006; Lundov et al., 2011B; Friis el al., 2012; Kaae et al., 2012; Bregnbak et al., 2013). In most cases, the airborne exposure results in eczema on exposed areas of the skin, where uncovered skin has been in direct contact with the airborne allergen and therefore becomes affected by eczema. Repeated exposure e.g. at home, can give rise to generalisation with eczema affection of head, neck, body or possibly the limbs. A Danish case report described a middle-aged woman of 53, who after airborne exposure to MI from a freshly painted room developed serious face eczema and shortness of breath (Lundov et al., 2013). The symptoms improved after treatment with systemic steroid hormones, but several times the patient experienced fresh outbreaks of eczema as a consequence of airborne exposure to MI from paint (Lundov et al., 2013).

An eczema reaction usually decreases after either local or systemic steroid treatment, but it is important to point out that the MI allergy is permanent and fresh outbreaks will occur at reexposure to MI. Besides, MI allergists can experience asthma-like attacks after exposure to MI (Lundov et al., 2011B; Lundov et al., 2013).
No studies exist on the occupational consequences for painters who develop MI contact allergy. However, it is very probable that working as a painter is incompatible with MI allergy under the assumption that more or less all paint in Denmark and Europe contains MI and it is rarely declared on the paint (Lundov et al., 2014).

In Germany it has been uncovered that cosmetologists often are associated with the development of MI allergy (Uter et al., 2103). Overall, the use of MI in cosmetics seems to be the driving force of the epidemic, although it is still a rather small percentage of all cosmetic products that contain MI (Lundov et al., 2010; Lundov et al., 2011A; Lundov et al., 2013; McFadden et al., 2013; Uter et al., 2013; Aerts et al., 2014). However, in Germany and Denmark, a rather high share of patients with MI allergy, 20% and 25%, respectively, have been exposed to MI in water-based paint (Bregnbak et al., 2013; Uter et al., 2013).

Allergy to MI caused by cosmetics
Several European studies indicate that the MI epidemic is driven by consumer related cases among women (Lundov et al., 2010; Geier et al., 2012; McFadden et al., 2013; Hosteing et al., 2014; Schwensen et al., 2014). It has also been uncovered that the percentage share of Danish MI eczema patients with face eczema has increased significantly from 20% in 2009 to 48.7% in 2012 (Schwensen et al., 2014). In the literature, several cases of MI trigger allergy contact eczema have been described among consumers after exposure to cosmetics, wet wipes or paint (Garcia-Gavin et al., 2010; Kaae et al., 2012; Lundov et al., 2013; Vanneste et al., 2013; Alwan et al., 2014). A few case-reports on children have also been described (Aerts et al., 2013; Bregnbak and Johansen, 2013; Madsen and Andersen, 2014B). Two of the cases initially started with contact eczema in the diaper area after the use of wet wipes with a MI content, and in both cases, long-term repeated outbreaks of eczema by airborne exposure to MI from freshly painted rooms was experienced (Aerts et al., 2013; Bregnbak and Johansen, 2013).

MI and cross reactivity to other isothiazolinones

Immunological cross reactivity is the lacking ability of the immune system to distinguish between an allergen and substances that chemically resemble the allergen (Burnett et al., 2010). Therefore, exposure to cross reacting substances to the allergen will trigger allergic contact eczema in the same way as normal exposure to the allergen.

Cross reactivity between isothiazolinones, including MI, have been poorly demonstrated and only few studies exist in the literature with varying results (Bruze et al. 1987; Geier and Schnuch, 1996; Isakson et al., 2008; Schwensen et al., 2014). Contact allergy to MI and MCI/MI is being monitored. To what extent cross reactivity is the issue or if the consumer and the worker merely are exposed to several types of isothiazolinones at a time is unknown (Geier et al., 2012; Bregnbak et al., 2013; Schwensen et al., 2014).

1.6 Legislation and labelling systems

Legislation on classification and labelling of biocides, cosmetics, detergents and household cleaning products, paint and toys will briefly be outlined in the following. In addition, the limit values for MI and MCI/MI for each product type will be summarised for the relevant labelling systems.

1.6.1 Classification and labelling

Dangerous chemical substances and mixtures are classified and labelled to inform and warn the consumer of the hazardous properties of the substances. Chemical substances and mixtures have to live up to the classification and labelling rules that are described in the classification regulation (Regulation No.1075, 2011 (Danish Environmental Protection Agency, 2011)). In 2015, it will be replaced by the CLP Regulation for chemical mixtures (Classification, Labelling and Packaging; Regulation No. 1272/2008) (European Parliament and Council, 2008). The CLP Regulation currently (since 2010) applies to chemical substances. MI has no harmonised classification but all suppliers self-classify the substance to be skin sensitizing and give it the danger symbol “irritant” and the risk phrase R43: : “May cause sensitization by skin contact”. From June 2015, they will be replaced by the hazard pictogram “Warning” and the risk phrase H317: ”May cause an allergic skin reaction”. The limit for classifying and labelling products will be 1% for sensitizing substances when the CLP Regulation comes into force in 2015, and the limit for declaring the substance on the label will be 0.1% and the following sentence must be used: ”Contains [*name of substance*]. Can cause an allergic reaction”. Most manufacturers of chemical products warn the consumers of the allergy danger of MI by putting a label on the packaging if the concentration of MI is 0.1 % (1000 ppm) or more.

On the other hand, if the product contains less than 1000 ppm MI, which often is the case in practice, labelling is not required. Two large European MI manufacturers have given MI a so-called specific concentration limit of 0.1%. That means that some MI containing products that will be marked according to the CLP Regulation for skin subsidizing substances at MI concentrations from 0.1% (1000 ppm) and declared from 0.01% (100 ppm). (Tobiassen, 2014)

When MI is used in combination with MCI in a three-to-one ratio (MCI/MI) in chemical products and if the concentration exceeds 0.0015% (15 ppm), then the products have to be marked as sensitizing according to the list of harmonised classifications. The classification limit was 15 ppm for MCI/MI used in a three-to-one ratio in substances and mixtures and has been applicable since 2004.

Other rules apply to some product categories such as cosmetics and they will be summarised in the following sections.

1.6.2 Biocides

On 1 September 2013, the Biocidal Product Regulation entered into force in the entire EU (Regulation No. 528/2012) (European parliament and council, 2012). The Regulation assumes the regulation at EU level after the Biocidal Directive (98/8/EF) (European Parliament and Council, 1998). The Regulation regulates the marketing and use of biocidal products to protect humans, animals, material or articles against harmful organisms such as pests or bacteria, by the impact of the active substances contained in the biocidal product. The EU legislation will gradually enter into

force and biocide products will according to the Regulation be divided into four main groups: Disinfectants, preservatives, pest control and other biocidal products. Biocidal products will require an approval and only active substances on the list of the European Chemicals Agency (ECHA) of approved active substances may be used in biocide products (ECHA, 2014). In a period of transition, some biocidal products will still be approved by the previous Danish approval rules. In Denmark, there is currently no obligation to get preservatives such as MI approved, and therefore no limits exist for the use of MI in consumer products in general. MI is currently not included on ECHA's list of approved active substances, but is at the moment being assessed in four different product categories: preservatives for products during storage (PT6: In can preservatives), preservatives for liquid cooling and processing systems (PT11), slimicides (PT12) and working or cutting fluid preservatives (PT13), which all belong under the main group: preservatives (Tobiassen, 2014).

1.6.3 Cosmetics

Cosmetics are harmonised in the EU, which means that the same rules apply in all EU countries. Cosmetics are regulated by the Cosmetics Regulation (Regulation No. 1223/2009) (European Parliament and Council, 2009) that entered into force in July 2013. All cosmetic products that are marketed within the borders of the EU must state information about the ingredients. According to the Regulation, cosmetic products are defined as "*'any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours"* (European Parliament and Council, 2009).

Cosmetics comprise products such as toothpaste, cream, deodorants, make-up, soap, shampoo, hair dye and play cosmetics etc. There are rules regarding which names the ingredients used in cosmetics must be declared under. The names are known as INCI names (International Nomenclature of Cosmetic Ingredients). Ingredients must not be declared with other names and must always be spelled in the same way. The INCI name for MI is "methylisothiazolinone", and the content of MCI must be declared as "methylchloroisothiazolinone".

Since 2005, it has in the EU been legal to use MI alone, i.e., not in combination with other isothiazolinones, in concentrations up to 100 ppm in cosmetics (SCCS, 2013). When MI is used together with MCI in cosmetics in a three-to-one ratio (MCI/MI), the total concentration must not exceed 15 ppm. That limit has been valid for cosmetics in the EU since 1989. A recent amendment to the cosmetics regulation means that MCI/MI 3:1 is no longer allowed in leave-on cosmetics as from 16th July 2015.

Cosmetic products marked with the blue wreath from Asthma-Allergy Denmark must not contain MI. Cosmetic products that are ecolabelled with the Nordic Ecolabel must not contain MI, whereas soap, shampoo and conditioner marked with the European Ecolabel may contain MI in concentrations up to 100 ppm. Marking cosmetic products with the European Ecolabel so far only comprises rinse-off products and it is expected (at the end of 2013) that the group of products will expand to, i.a., products for shaving when the document criterion are updated (Nordic Ecolabel, 2013).The European Ecolabel has no criterion for the marking of leave-on products. The objective of the two ecolabels (the Nordic Ecolabel and the European Ecolabel) is to favourably affect consumption and production in a more environmentally-friendly direction and in that way obtain a cleaner environment and increased health (Ecolabel, not dated). However, focus is mainly on sparing the environment, and neither the European Ecolabel nor the Nordic Ecolabel are decidedly health labels.

1.6.4 Detergents and household cleaning products

Detergents and household cleaning products are subject to a number of different statutory requirements, i.a., the EU Regulation on detergents (Regulation No. 648/2004) (European Parliament and Council, 2004). According to the Regulation, preservatives in detergents and household cleaning products must be declared on the label regardless of the concentration (enclosure VII of the regulation) (Danish Environmental Protection Agency, not dated).

In addition, detergents and household cleaning products come under the CLP Regulation with regard to classification and labelling, and when using MI and MCI/MI the products must be classified and labelled for sensitizing effects according to the CLP Regulation, see chapter 1.6.1.

Detergents and cleaning products marked with the blue wreath of Asthma-Allergy Denmark may not contain MI. Products with the Nordic Ecolabel or the European Ecolabel are permitted to contain up to 100 ppm MI, however hand washing-up detergents with the Nordic Ecolabel may contain up to 1000 ppm.

1.6.5 Paint, varnish and adhesives

Earlier, MI appeared in combination with MCI as preservative in paint, varnish and adhesives, but ever since around year 2000, the substance has also been used as stand-alone preservative or in mixtures with other preservatives than MCI.

According to the CLP Regulation for classification and labelling, paint has to be labelled if it contains more than 15 ppm in a MCI/MI mixture (three-to-one ratio). MI alone is classified as sensitizing by most companies, which means that products are marked when the concentration of MI is 1% or more. Products with a MI concentration below 1% are not marked, but the substance is declared from 0.1%, please refer to chapter 1.6.1.

Ecolabelled paint (the European Ecolabel and the Nordic Ecolabel) may contain up to 500 ppm isothiazolinones and a maximum content of MI of 200 ppm. Today, there is no labelling scheme for paint that can guarantee the consumer a MI-free product. Due to airborne contact allergy, demonstrated in paint containing MI, Asthma-Allergy Denmark has decided to include paint as a new product category in their declaration scheme (April 2014). The criteria stipulate that paint marked with the blue wreath must not contain MI (Asthma-Allergy Denmark, 2013).

1.6.6 Toys

Toys are mainly regulated in the Danish Executive Order on Toys (Executive Order on Safety Requirements to Toys). According to the Toy Order, toys are defined as *"products that solely or partly are made or intended to be used by children under the age of 14 during play"* (Order no. 13 of 10/01/11). The Toy Order entered into force in 2011, but the requirements concerning the use of chemicals in toys did not enter into force until July 2013 (Danish Safety Technology Authority, 2011).

For some toys, there are requirements to the declaration of certain ingredients. In addition, there can be limits to which type of preservative may be used and in which concentrations. That is e.g. the case for make-up or fancy dress make-up and the like that are regulated by the Toy Order as well as the Cosmetics Regulation described in chapter1.6.3, finger paint and paint, varnish and all-purpose glue (that are regarded as toys). Standards exist for finger paint (Danish Standard EN 71-7:2014) (Danish Standard, 2014) and for some types of paint, varnish and adhesives (Danish Standard EN 71-5:2013) (Danish Standard, 2013). It is not a requirement that the toy standards have to be met, but it is expected that toys that meet the harmonised standards also meet the requirements in the Toy Order. Toys that do not observe the harmonised standards are subject to EC type examination. In addition, toys must not contain substances in concentrations that constitute a hazard.

For the toy category "Chemical toys (sets) other than experimental sets" that comprise e.g. paint, varnish and all-purpose glue (regarded as toys) (Danish Standard EN 71-5: 2013) (Danish Standard, 2013) it must be met water-based paint, varnish and all-purpose glue that the preservatives that are used have to be approved for food and/or cosmetics. However, substances only approved for cosmetic rinse-off products may not be used for this type of toy. According to the current cosmetic regulation of MI that means that water-based paint, varnish and all-purpose glue that are considered to be toys according to the standard can contain MI in a concentration of up to 100 ppm.

For finger paint (Danish Standard EN 71-7: 2014) (Danish Standard, 2014) it is required that preservatives must be chosen from Annex B of the standard DS/EN 71-7:2014. Annex B lists the MCI/MI mixture in a three-to-one

ratio with a content of maximum 0.0008%. A maximum concentration of 100 ppm MI may alternatively be added, when it is used without MCI.

For other toys such as slime and play dough, there are no requirements to content of preservatives. All preservatives can therefore be used as long as they are not considered hazardous for children playing with the toys.

For hobby products, the Danish trade organisation called Joint Council for Art and Hobby Articles (Fællesrådet for formnings- og hobbymaterialer (FFFH)) has developed its own A-labelling system that set requirements to the ingredients of various types of hobby products (finger paint, dry colours, wet colours, varnish and glue, play dough, molten metal, clay, gypsum and gypsum gauze as well as make-up colours). In some cases, the requirements to the contents are more rigorous compared to legislation. The scheme has a list of preservatives that are accepted in some of the product categories, where it is specified that maximum 100 ppm MI and 15 ppm MCI/ MI (in a three-to-one ratio) may be used (as on November 2013).

The Nordic Ecolabel sets requirements to the combination of MCI/MI (in a three-to-one ratio) that must not exceed a concentration of 15 ppm, and to isothiazolinones (including MI) that are limited to a content of maximum 500 ppm. If a Nordic Ecolabel writing utensil is considered (such as ballpoint pens or speed markers), then MI must not be used, if the product is intended for children.

2. Survey

2.1 Delimitation

This survey focused on consumer products that are marketed in Denmark or sold on Danish/ Danish-language internet pages, whereas the search for information on concentration levels and their dissemination in different product categories was not limited to Danish products as the available data was very limited. However, the identification of products for analysis solely comprised products marketed in Denmark or sold on Danish/Danish-language internet pages.

2.2 Procedure

The survey was carried out in the period from July-December 2013.

Initially, searches were carried out in the available literature, and contact was taken to a number of trade associations, companies, research centres and organisations to collect information on the use of MI in consumer products. A number of retail shops were subsequently visited, and in addition information was sought in selected internet shops.

2.2.1 Information and internet search

A number of MI studies already exist: studies that to a larger or smaller degree comprise a survey of the use and in some cases analysis of the content of MI in specific products and product groups. In connection with this project, information mainly comprises articles written in the light of scientific research (i.a., found by searching on the words methylisothiazolinone, isothiazolinone, contact allergy etc. via PubMed, ScienceDirect and others). To a certain degree, articles from other periodicals and newspapers of interest have been included (e.g., *Politiken, Astma-Allergi Bladet* and the periodical of the Danish Consumer Council called *Tænk*).

A general internet-based search was carried out with search words such as methylisothiazolinon(e), allergy and consumer products (and similar Danish search words) to obtain an understanding of the consumers' access to knowledge and to get an impression of the current development. The manufacturers' websites were visited to obtain information on products through safety data sheets (SDS) and other technical data sheets. Initially, social media were screened to investigate the MI activity in these media types. Furthermore, methylisothiazolinone was searched for in available databases on chemicals in consumer products to identify products/product categories where MI is used.

2.2.2 Database search

A search was carried out in the public part of the SPIN database, which is based on information from the product files from the Nordic countries. A search was also carried out on the database of the Danish Environmental Protection Agency on surveys of chemical substances in consumer products.

2.2.3 Contact to trade associations, companies and manufacturers

In connection with the survey, contact was taken to different trade associations with regard to collecting information about their knowledge of the distribution and use of MI. MI is used in a wide range of products and therefore contact was taken to a number of different trade associations:

- Joint Council of the Danish Toy Trade (LF)
- The Nordic Association of Toy Manufacturers (Nordic Toys)
- Joint Council of Art and Hobby Articles (FFFH)
- The Trade Association SPT (cosmetics, personal care, detergents and household cleaning products)
- Danish Coatings and Adhesives Association (DFL)
- The Federation of Danish Building Industries (building materials)

The trade associations were initially contacted by phone and when relevant an inquiry was sent to the members through the trade association regarding participation in the survey. The members were asked to fill-in a questionnaire regarding their use of MI (see example in Appendix 1). In addition, direct contact was established to a number of relevant companies over the telephone to obtain a more detailed understanding of the use of MI in specific products.

Two MI manufacturers in the EU were contacted in connection with the survey. They were asked about their knowledge of the use of MI regarding identification of product categories and their recommendations regarding the use of MI within different product categories. Furthermore, they were asked about the intervals of the use-concentrations of MI in different product categories.

2.2.4 Contact to knowledge centres and interest groups

Asthma-Allergy Denmark, the Danish National Allergy Research Centre and the Information Centre on Environment and Health were contacted to obtain information about their work and knowledge of problems concerning the use of MI in Denmark.

2.2.5 Shop visits

Shop visits were carried out to identify products where MI is declared on the label. Shops that were visited physically in connection with the project include department stores, supermarkets, a chemist, a health food shop, a pharmacy, a hairdresser, toy shops, DIY markets and paint dealers. In general, the staff was contacted on arrival to the shop and the objective of the project was presented. Details concerning the individual products were registered during the visit. Besides visiting the physical shops, a number of internet based shops were visited, including grocery stores and dealers of cosmetic products.

2.3 Results of the survey

2.3.1 Information and internet search

A number of previous surveys were identified. They were reviewed to identify product categories and available analytic determinations of the content of MI in each category.

A Swiss survey of the use of MCI/MI in substances and products for public or commercial use (that were registered in the Swiss product file) identified 3644 products with MCI/MI in 1999, and in the following two years the number of products increased to 4161 and 4843 registered products, respectively. The use of MCI/MI was registered within the product groups of paint, varnish, coatings, adhesives, sealants and household cleaning products (Reinhard et al., 2001). Already in 2001, the study addressed cases of airborne contact allergy due to

MCI/MI, and experimental tests documented the presence of MCI in the air immediately after painting and 42 days after painting (Reinhard et al., 2001).

Magnano *et al.* (2009) surveyed the use of MCI/MI and MI in household cleaning products and detergents (hand washing-up liquid, detergents, softener, household cleaning sprays and universal cleaning products) on the Italian market. Out of 291 products, 35.7% contained MCI/MI and 10.3% contained MI (Magnano et al., 2009). It was not specified, to which degree MI was combined with other preservatives than MCI in the last-mentioned group of products.

A Swedish survey identified MCI/MI and MI in cosmetics (2008) and household cleaning products (2010) in 20 shops in Stockholm. The cosmetic products that were investigated are within the groups of shampoo, conditioner, liquid soap and wet wipes. Out of 204 products, 22% contained the mixture of MCI/MI (3:1) and 0.5% MI. Household cleaning products (97 investigated products) comprise washing-up liquid and universal cleaning products and 9% contained MCI/MI and 16% contained MI. In the household cleaning products, four different types of isothiazolinones (with MI as the most frequently used) were found, and 28% of the products contained one or more isothiazolinones. (Yazar et al. 2011)

In the period from 2000-2010, a Belgian survey of dermatological patients procured information on ingredients that are present in the allergy causing cosmetic product (if it was identified in the patient case). The study is divided into two periods: 2000-2005 and 2006-2010. In these two periods, MCI/MI and MI are identified in the product types of skin care, hair products, body care, sunscreen, facial cleanser, products for intimate hygiene, deodorants and shaving products. Out of 621 products, in which the allergy provoking product was identified, 54 products contained MCI/MI and 23 products contained MI. To which degree MI is combined with other preservatives than MCI in the 23 products does not appear from the survey. All products with MI were found in the period from 2006-2010, whereas six of the 54 MCI/MI containing products were found from 2000-2005 (Travassos et al., 2011). Therefore, the survey confirms the increased use of MI during the specified period.

In Denmark, the National Allergy Research Centre carried out a survey of cosmetic products containing MCI/MI and MI in 2010. Eight shops were visited and 1272 declared cosmetic products were gone through for content of MCI/MI and MI. Leave-on as well as rinse-off products were included. 132 products with MCI/MI were found while 19 products were found with MI (without MCI). The products are distributed on 12 rinse-off products, three leave-on products and four wet wipes. The products were analysed for MI with a content of 52-100 ppm in rinse-off products, 2-96 ppm in leave-on products and 17-87 ppm in wet wipes (Lundov et al., 2011A).

Lundov *et al.* (2014) identified and analysed 19 types of water-based paint and found a concentration of MI in the interval of 10-300 ppm (Lundov et al., 2014). In most of the paint that was analysed during the survey, MI was combined with either MCI, benzisothiazolinone or both. The concentration of all three types of isothiazolinone was determined in the survey and the results show that some paint has a MI content that is four to 18 times higher than the MCI content. That might indicate that pure MI had been added to products that already contained a MCI/MI mixture (in a three-to-one ratio).

In general, previous surveys typically comprise cosmetic products and most often the surveys were carried out on the basis of the declarations on the products. The surveys show that MI often is used in combination with other substances. The combination with MCI still dominates, but others are gaining ground such as the combination with other isothiazolinones or phenoxyethanol. A few surveys include household cleaning products and there are few references to MI in paint. On many products there is no duty to declare at the typical use concentration, and therefore information on the label concerning the content of MI will not be available to consumers. Even for declared products, few studies exist in the literature that was gone through regarding the chemical analysis of use-concentrations of MI.

Internet-based databases on consumer products exist on the American website EWG.org (identifies 2.816 cosmetic products (out of >74,000) and 347 household cleaning products (out of >2,000) with MI). The main part of the identified cosmetic products containing MI fall within rinse-off products (e.g., shampoo, conditioner and

shower gel), but leave-on products are also represented with many products (e.g., hair products and cream) (Environmental working group, not dated). The Household Products Database also identifies many products (728) that contain MI within cosmetics, household cleaning products, Do-It-Yourself products and pet products (U.S. Department of health & human services, not dated).

Consumer operated initiatives for instance appear on Facebook, where an open, common page dedicated to isothiazolinones has been established (”Allergy to Isothiazolinone, Methylisothiazolinone and Chloroisothiazolinone”). 1161 people ”liked” the page (December 2013), and the page is used by consumers to e.g. share experience and knowledge concerning the content of MI in products. The various categories of products and the distribution of products under each category, stated partly in databases on consumer products and partly in the social media, are in agreement with the identified product types of this survey.

2.3.2 Database search

The SPIN database has information on chemical substances registered in products that are marketed in Scandinavia. The database is based on data from product registers in Norway, Sweden, Denmark and Finland where companies have a duty to register the use of chemical substances in products for professional use that can cause health, environmental or occupational hazards[xi]. In the Danish product register products must be registered if they are produced in amounts ≥100 kg/year, and if the product contains at least one substance that is classified as dangerous in a concentration of at least 0.1% or 1% (depending on the classification of the substance). There is no duty to register consumer products in the product register. Furthermore, the SPIN database only shows pooled, non-confidential information. Therefore, the SPIN registrations will not give a complete overview of the use of MI in the Danish market, but they show the development within products for professional use.

SPIN states the use of MI in 22 applications, and the areas of paint, varnish and adhesives comprise the majority of the reported products in Denmark (2011), whereas use in detergents and household cleaning products come in second; please refer to outline of the ten most frequently reported applications in Table 3.

No.	Application	Number of products	Tons MI
59	Paint and varnish	861	0.3
9	Household cleaning products	125	<0.1
61	Surface treatment products for non-metal	113	<0.1
10	Colouring agents	106	<0.1
2	Adhesives	68	0.2
39	Non-agricultural pesticides and preservatives	49	1.3
20	Fillers	36	0.1
55	Others	35	<0.1
31	Impregnation materials	31	0.1
50	Surface-active agents	30	<0.1

TABLE 3: PRODUCTS FROM THE SPIN DATABASE THAT CONTAIN MI. THE NUMBER OF PRODUCTS AND TONS MI, REGISTERED IN DENMARK IN 2011, IS GIVEN FOR THE TEN MOST FREQUENT APPLICATIONS (22 REGISTERED IN TOTAL) ARRANGED ACCORDING TO THE NUMBER OF REGISTERED PRODUCTS.

It is also possible to follow the development in the use of MI by looking at the number of products and tons of MI within the registered applications over a number of years. In Table 4, the development in number of products in the SPIN database containing MI from 2000-2011 appears for Denmark and Scandinavia, respectively. In the

[xi] www.spin2000.net

course of the period, there was a general increase (almost a doubling in the period 2000-2011) in number of products as well as tons of MI for Denmark and in total for Scandinavia. That increase is reflected in the increased prevalence of contact allergy as described in chapter 1.5.1. The largest increase appears from 2000 to 2001, where MI is introduced as preservative without combination with MCI within industrial products. However, the values in general seem to fluctuate, and no clear trend in the consumption of MI can be seen from the SPIN reports for Denmark or Scandinavia. Reports on tons of MI in 2005 and 2006 seem unrealistically high (due to Norwegian and Finnish reports), but can unfortunately not be explained.

Year	DK - Number of products	DK - Tons MI	Scandinavia – Number of products	Scandinavia – Tons MI
2000	841	4.20	2913	31.9
2001	1200	4.90	3388	50.1
2002	1321	5.50	3744	84.6
2003	2165	4.80	4849	58.8
2004	2334	3.40	5100	51
2005	1721	3.20	4636	459.5
2006	1805	1.50	4993	348.8
2007	1963	1.50	5227	73.9
2008	1807	2.30	4337	37.6
2009	1779	4.40	5374	78.1
2010	1824	11.60	5952	78.6
2011	1614	9.40	5774	81.9

TABLE 4: DEVELOPMENT FROM 2000-2011 IN PRODUCTS WITH MI REGISTERED IN THE SPIN DATABASE. THE NUMBER OF PRODUCTS AND TONS OF MI REGISTERED IN DENMARK AND SCANDINAVIA, RESPECTIVELY, IS INDICATED. THE HIGH NUMBER FROM SCANDINAVIA IN 2005-2006 IS DUE TO HIGH REGISTRATIONS MAINLY FROM FINLAND AND NORWAY DURING THAT PERIOD.

In the database of the Danish Environmental Protection Agency covering chemical substances analysed in consumer products during surveys carried out for the Danish Environmental Protection Agency, four surveys were registered where MI was identified in consumer products: Face paint and theatre make-up, liquid hand soap, glass and porcelain dye and decorative liquid. The related reports were examined, but very little information was found on MI. In the survey of face paint and theatre make-up no reference was found to MI or MCI/MI in the report (Petersen et al., 2002). The survey of products with decorative liquid identified two products with a content of MCI/MI out of 16 purchased products. The two products were a paper scale (one liquid) and a torpedo (decoration with two liquid phases), respectively. On the basis of the analysed data, the concentration ratio between MCI and MI in the products cannot be calculated to a three-to-one ratio, but the concentration of MCI (20-140 ppm) exceeds the concentration of MI that only appears in very low concentrations (2-40 ppm) (Lundskov et al., 2003). Analyses for MI were not carried out in the survey of glass and porcelain dye, but it was merely noted that MCI/MI in a three-to-one ratio is frequently used in such products (Mikkelsen et al., 2005). The survey of liquid hand soap identified four products with MCI/MI out of 50, but analyses were not carried out of MCI/MI in connection with the survey (Larsen et al., 2006).

A recent survey of preservatives in toys published by the Danish Environmental Protection Agency in 2014 has not yet been included in the database (Poulsen and Nielsen, 2014). In this study, the use of MI was identified when the following products were surveyed: acrylic paint, finger paint, adhesives, soap bubbles and hobby paint. However, in a subsequent chemical analysis of 11 selected products, MI does not exist above the detection limit of the applied analysis of 20 ppm.

2.3.3 Trade associations, companies and manufacturers

Several of the six trade associations that were contacted had knowledge of the problem related to MI. A number of the trade associations agreed to facilitate contact to their members and ask them to participate in a questionnaire survey concerning the use of MI. 24 companies were contacted in that way. Nine completed the questionnaire and six out of the nine confirmed the use of MI in their products. None of the six companies use MI as the sole preservative, but they use a combination of several substances such as, e.g., MCI/MI.

In May 2013, the Danish Coatings and Adhesives Association (DFL) carried out a survey among its members concerning the use of MI, and DFL reported that according to the interviewed members MI has a widespread use in water-based paint products. According to the conclusion of the survey, all water-based paint products for indoor use contain MI. 80% contain less than 100 ppm, 19% contain MI in the interval of 100-200 ppm, and the remaining part contains a higher concentration of MI (Dahl, 2014). The challenge of the trade is i.a. that a large proportion of MI in the final products originates from the raw materials, and the Danish manufacturers are very dependent on large foreign manufacturers in this respect. DFL also pointed out that the concentration of MI that is necessary in the members' products depends more on the quality of the raw materials than on the type of product. DFL informs that the manufacturers of paint and of hobby products continuously invest work and efforts to reduce MI content in paints. They have succeeded in - if not completely to phase out – to minimize the use of MI in their products. DFL reports that a new decision among its members, who delivers decorative paints, implies to follow recommendation from the European trade organisation, CEPE about voluntary declaration of MI in products containing 15 -100 ppm. The products will be declared "contains Methylisothiazolinone". From 1st June 2015 products containing >100 ppm MI will be declared on the label as consequence of self-classification of MI from 1000 ppm and according to the CLP Regulation for skin sensitising substances (EUH208). The primary aim with the voluntary declaration is to give information to the already sensitized part of the population so that they can make an informed choice. Several of the questioned trade associations asked for possible alternatives, as they currently have no knowledge of applicable substitutes on the market that they can recommend to members who want to phase-out MI.

A larger Danish paint manufacturer confirms the information from DFL about the widespread use of MI within the trade. However, he does point out that the stated concentrations typically are calculated theoretic maximum concentrations of MI based on the addition to raw materials and during production. The manufacturer has experienced that the concentration of MI is reduced during the production process, and therefore the actual concentration in the products is often lower than the added amount. The manufacturer points out that a concentration of MI of 300 ppm often is not exceeded as the product's total MAL-code will be negatively influenced if the concentration of MI is increased further. However, the manufacturer also informs that there are actual plans regarding the phasing-out of MI within the next year due to the problems with allergic reactions. The vapour pressure of MI is higher than that of benzisothiazolinone (BI), which also is used in paint. A higher vapour pressure means that MI to a higher degree will evaporate from paint than BI will, so the MI concentration in the air will be higher. In addition, rooms are today often aired less after painting as there are less obnoxious smells from the paint compared to earlier, and that gives a risk of air-borne contact allergy. The problem could be solved by improving the raw material quality of the products supplied to the paint industry. Improved cleanliness in the production process can reduce microbial contamination and the result would be a reduced need for preservatives. However, that would be an expensive change, and as many of the raw material suppliers in this trade are large international companies the real possibility of putting forward demands is probably limited.

A larger Danish toy manufacturer confirms the use of MI in confined aqueous solutions in toys, where direct skin contact with the liquid during normal use is not possible. That means that toys such as, e.g., lava lamps or decoration items containing liquids where contact with the liquid only takes place if the object is damaged can contain MCI/MI or MI. The use of MCI/MI in such products had previously been confirmed in the survey carried out by Lundskov *et al.* (2003), please refer to chapter 2.3.2. According to the manufacturer, they neither accept MCI/MI nor MI in their products that e.g. comprise soap bubbles, finger paint or slime toys where direct contact with the liquid during normal use takes place.

Several of the contacted companies and organisations mention that they do not know alternatives within the approved preservatives where the preserving ability lives up to the requirements for their products. That applies widely to paint, hobby products and cosmetics. One single larger manufacturer of ballpoint pens has also mentioned the lack of alternative preservatives, and stresses the extensive process connected with the introduction of a new preservative (i.a. as a consequence of the new biocide regulation) as a limiting factor in the substitution of problematic preservatives, including MI.

Two large manufacturers of MI confirm the demand and sale of MI to be used in the product categories that were identified in connection with this survey. No further product categories were identified by the manufacturers. One manufacturer points out that their recommendation regarding the use of MI solely concerns combinations with other preservatives to obtain the best preserving effect and synergy between the used preservatives. That is confirmed by the other manufacturer, who, however, points out that MI in some mixtures can be adequate on its own. The combination with other preservatives is recommended partly to avoid an overconsumption of one single preservative, and partly to obtain sufficient microbial control at the lowest possible concentration of preservative. Sufficient microbial control cannot always be obtained by using one single substance or can be cheaper by combining several different substances. The manufacturers recommend a MI concentration range of 25-175 ppm depending on the type of product.

2.3.4 Organisations

The Danish Information Centre for Environment and Health (Informationscenter for Miljø og Sundhed) (closed at the end of 2013) and Asthma-Allergy Denmark both points out that consumers contact them particularly regarding MI and allergic reactions to paint. However, both organisations refer consumers to the National Allergy Research Centre.

2.3.4.1 Danish National Allergy Research Centre

Currently, the National Allergy Research Centre reports an increase in the number of allergic reactions to MI in Denmark, which gives cause for concern. The Centre has followed the development in reactions to MI from 2006 and up to today through patch tests carried out on patients referred to Gentofte Hospital (Danish Hospital) because of allergic reactions. During the period 2009 to 2013, the hospital witnessed an increase from 1.4% to 5.7% in the number of patients who react to MI, which according to the Research Centre is a substantial increase. The results of an investigation of MI where, i.a., 60 cosmetic products were identified on the Danish market that were preserved with MI alone, have just been published (Lundov et al., 2013). Among dermatitis patients, air borne contact allergy has been seen in a few cases often when painting a room. Very often, patients with allergy to MI cannot stay in freshly painted rooms for a very long time after the work has been finished without having an allergic reaction, which indicates that the evaporation of MI is of long duration. A study of the evaporation of, i.a., MI from painted surfaces under controlled conditions demonstrated that the substance can be detected in the air for up to 42 days after painting (Lundov et al., 2014). MI can be detected in the air already a few hours after the application of paint. The concentration was highest the first couple of days after application, but the release of MI continued in a relatively low concentration during the entire measuring sequence. During the study, 19 types of paint were purchased on the Danish market and analysed, and a MI content of 10-300 ppm was found. In addition to MI, the analyses also showed a BI and MCI content.

2.3.5 Shop visits

Nine physical shops were visited in connection with this survey; one shop did not wish to participate in the investigation. One Danish grocery shop was visited as an online shop where a number of declarations were directly available on the website for the benefit of the consumers. A smaller number of online shops that deal with cosmetic products were also visited.

In the shops that were visited, products were as a starting point identified on the basis of the declaration. Especially in connection with products with no requirements regarding declaration at low concentrations of MI, contact was taken to the staff in the shops, and they were asked if they could help identify products with MI. However, the staff in the visited shops was not able to identify products with MI, but referred to the websites of the manufacturers for further information.

That is why only products within the categories of cosmetics and household cleaning products were identified in the visited shops; MI must be declared on those types of products.

2.3.6 Identified product categories

In the survey, a total of 268 products containing MI were identified. The products are distributed in four defined product categories and an outline appears in Table 5

Product category	Number of products	Product subgroup
Cosmetics and personal care	174	**Rinse-off (103):** Shampoo (42) Shower gel (30) Conditioner (19) Liquid hand soap (7) Shaving foam (5) **Leave-on (71):** Cream (25) Hair products (20) Facial cleanser (8) Other personal care (8) Deodorant (5) Wet wipes (3) Make-up (2)
Detergents & household cleaning products	60	Hand washing-up liquid (17) Liquid detergent (11) Other cleaning products (11) Toilet bowl cleanser (8) Car shampoo (4) Wetting agent (3) Cleaning tissues (2) Vinyl cleaner (2) Floor cleaner (2)
Paint, varnish and adhesives	27	Paint and primer (16) Adhesives (8) Varnish, mordants & others (3)
Toys and hobby products	7	Textile, window, hobby and glitter paint (5) Glue (2)
Total	268	

TABLE 5: PRODUCT OVERVIEW THAT SHOWS THE CATEGORIES OF THE IDENTIFIED PRODUCTS AND THEIR SUBGROUPS. THE NUMBER IN PARENTHESIS FOR EACH SUBGROUP DENOTES THE NUMBER OF PRODUCTS IDENTIFIED IN THE SUBGROUP THAT CONTAINED MI.

According to the declaration, the major part of the 268 identified products with MI contain other preservatives in combination with MI, such as other isothiazolinones (MCI, benzisothiazolinone and octylisothiazolinone), phenoxyethanol (PE) or parabens. According to the survey, the most frequently utilized method for preservation of the identified products was to combine several preservatives, and the MCI/MI combination is the most frequent, but the combination of MI/PE is also used frequently. One product was identified where nine different preservatives were used in the same product.

For cosmetics, the starting point was the declaration of contents on each product, where the qualitative occurrence of MI was declared. The same is the case for household cleaning products, whereas the content of MI in other products such as paint, adhesives and toys was identified from other available sources, including safety data sheets. Often they can be found on the websites of the manufacturers or by direct contact. Concentrations far

below 1000 ppm are typically used to obtain the preserving effect in e.g. paint, and therefore it is not necessarily a demand according to the labelling and classification rules (see previous chapter 1.6.1) that the MI content has to be stated on the safety data sheet of the product, and only a few manufacturers choose to do that.

2.4 Summary of survey

This survey has shown that MI is used in a wide range of consumer products. In general, previous studies in the available literature identify the use of MI within cosmetic products, household cleaning products, paint, varnish and adhesives. Few studies comprise the use of MI in different types of toys, i.a., the survey from 2014 of preservatives in toys carried out for the Danish Environmental Protection Agency. Within the individual product categories, the use of MI has also spread to many different types of products. In cosmetic products MI was identified in shampoo, conditioner, deodorants, wet wipes, cream and hair wax.

Most often, surveys were carried out on the basis of the declaration on the products, and very few comprise chemical analyses of the actual concentration of MI in the products. However, Lundov *et al* (Lundov et al., 2011) determined the concentration of MI in cosmetic products to 52-100 ppm in 12 rinse-off products, 2-96 ppm in three leave-on products and 17-87 ppm in four wet wipes. The concentration of MI in 19 types of water-based paint was determined to 10-300 ppm (Lundov et al., 2014), a level that is confirmed by the Danish Coatings and Adhesives Association (DFL). DFL's (2012) own survey among the members of the association showed that 80 % of paints (water-based paint products for indoor use) contained less than 100 ppm, 19 % contained MI in the interval 100-200 ppm, and the rest contained a higher concentration of MI.
For toys, the newest survey in the field shows that MI does not exist in concentrations exceeding the detection limit of 20 ppm (Poulsen and Nielsen, 2014) in the 11 products that were selected for analysis. The reported use-concentrations in general correspond with the information obtained from trade associations and manufacturers. Suppliers of MI recommend to combine MI with other preservatives in order to limit the use. The suppliers recommend a MI concentration in the range of 25-175 ppm, depending on the type of product.

The surveys show that the use of MI most often takes place in combination with other preservatives. The combination with MCI is still predominant, but others are gaining ground such as the combination with other isothiazolinones and phenoxyethanol.

The different rules regarding declaration and labelling of products depend on the type of product, and that makes it difficult – sometimes even impossible – for the consumer to identify products that contain MI. Non-existing labelling on a number of consumer products that contain MI means that it in reality is impossible for a consumer to opt out products with MI.

In this survey, the greatest number of cosmetic products and household cleaning products were identified when physical shops and internet shops were visited. According to legislation, MI has to be declared for those products, and the presence of MI has to be stated on a label. A few products within paint, varnish and adhesives were identified on the basis of information from the manufacturers. Hobby products, of which some were clearly aimed at children and can be toys, were identified on the basis of information from the manufacturer. However, the use of MI and MCI/MI in other toys than hobby products was confirmed partly by a manufacturer who was contacted in connection with this survey (solely accepted in products where liquid containing MI does not come into contact with the skin), and partly in connection with the survey of preservatives in toys carried out for the Danish Environmental Protection Agency (Poulsen and Nielsen, 2014).

Among the 174 identified products within cosmetics and personal care, the main part were rinse-off products (59%), but leave-on products were also heavily represented among the identified products (41%). 60 products were identified within detergents and household cleaning products, whereas 27 were identified within paint, varnish and adhesives. Finally, seven products were identified within toys and hobby products.

Trade associations as well as manufacturers and importers of products that contain MI confirm that the use of MI is widespread, but they also confirm that the preservative and its health-related issues are in focus. Several

manufacturers have already phased-out, consider or plan to phase out the substance, while others mention a lack of applicable substitutes. For chemical mixtures, e.g., paint, the need for preservation can reflect production conditions and raw material quality. Stricter requirements to raw material suppliers in these areas might help limit the amount of preservative that is necessary to prevent microbial growth in the product.

3. Choice of products for analysis

Based on the survey results, a list of 31 consumer products was prepared in cooperation with the Danish Environmental Protection Agency for chemical analysis of the content of MI. According to the information collected during the survey, the selected consumer products all contain MI and they are available on the Danish market.

The products were selected according to a number of prioritised criteria that i.a. were assessed to have an impact on consumer exposure:

- *Product expected to be in direct contact with the skin*
  Contact allergy is a local effect and skin contact is a condition for sensitization. Cosmetic leave-on products have higher priority than rinse-off products and household cleaning products as the products remain on the skin for a longer period of time and a larger amount of MI is expected to be absorbed in the skin.

- *Products that are used frequently (daily or several times a day)*
  Frequency is a decisive factor for the development of contact allergy. That is why products that are used several times a day receive higher priority than products that are not used frequently. That will also be taken into account when assessing exposure to the products.

- *Products that are used for/by children*
  Products aimed at children have high priority as the development of contact allergy at an early age can lead to lifelong allergy that will result in recurring inconvenience and in worst case in the development of a chronic disease that can influence the working capacity and quality of life.

- *Products with a high concentration of MI*
  The development of contact allergy is load dependent, meaning that the risk of developing contact allergy increases when a higher concentration of the substance is used. Therefore, products without MCI have higher priority than products with MCI/MI, as it is expected that the concentration of MI is higher than if MCI also is present. That is why products such as paint have high priority; according to the survey results they can contain a high concentration (up to 300 ppm).

- *Products covering a wide range of products, various manufacturers and different price ranges*
  The analysis results will be used to assess the exposure of a consumer to MI. Products from different product categories have high priority in order to obtain an improved total impression of the exposure among individual consumers, who in worst-case use many different products that contain MI. In order to cover the individual product groups as widely as possible different manufacturers and products have been chosen in the high as well as the low end of the price scale.

The products were selected within the following four product categories, and the number of products within each category is shown in parenthesis:

- Cosmetics and personal care (22)
- Detergents and household cleaning products (1)
- Paint, varnish and adhesives (4)
- Hobby products (4)

The majority of the products identified in this survey belong to the category of cosmetics and personal care (65% of the identified products). Frequent application and direct skin contact are also expected to occur most frequently in that category. Among cosmetics and products for personal care, 14 leave-on products (that remain on the skin) and eight rinse-off products (that are rinsed off the skin) were chosen. Sunscreen with MI was not identified during shop visits carried out in the survey phase (in physical and internet shops), and therefore no sunscreen was chosen for analysis. However, the selection of sunscreen was limited due to the time of year (shop visits took place from September-December). With the exception of one wet wipe, no products containing MI within cosmetics and personal care were identified during the survey that were directly aimed at children. As far as possible, products that appeal to a wide target group (the family) and that also are expected to be used for children, rather than products aimed specifically at women or men, were chosen. In addition, many different products were chosen within each category with only few representatives of each in order to give broad coverage. Especially in connection with moisturisers and other products for the face, products were chosen from various price ranges.

In the course of the survey, 60 products were identified within detergents and household cleaning products (22% of the identified products). In relation to exposure, detergents and household cleaning products can be compared with the rinse-off products within cosmetics and personal care. Only a minor part of the product is expected to remain on the skin in connection with use and therefore exposure is expected to be substantially lower for that product group than for, e.g., leave-on cosmetics. In addition, household cleaning products are not expected to be used as frequently as products within cosmetics and personal care. Hand washing-up liquid gives direct skin contact and is used frequently by many consumers. The concentration of MI is not expected to be higher than for, e.g., rinse-off soap products within cosmetics and personal care. However, hand washing-up liquid is normally diluted before use and the concentration of MI is therefore expected to be lower during exposure of the consumer. A single hand-washing up liquid has therefore been chosen for chemical analysis.

Among the 27 identified products within paint, varnish and adhesives (10% of the identified products) where the content of MI is confirmed on the basis of the safety data sheets on the supplier's website or information from the National Allergy Research Centre, four products were chosen. Paint products are not expected to be used very often, but on the other hand there are examples of a MI content of up to 300 ppm compared to the cosmetic products where the limit is 100 ppm. One wall primer was chosen as one of the four products (product no. 13), as it can be used for walls as well as ceilings, and its use on ceilings is expected to give higher skin exposure.

In the survey, seven products were identified within toys and hobby products. Some of the products are, e.g., due to the appearance of the packaging clearly aimed at hobby work carried out by children and they are marked with the CE-mark (that indicates that the manufacturers regard them as toys). Other products are not directly aimed at children, but nevertheless it must be assumed that they might be used by children for hobbies. Four hobby products were selected for analysis. The three of them are CE-marked (product no. 27, 30, 31), and two clearly aim to attract smaller children (packaging with glitter, pirates and princesses – product no. 30 and 31). On two of the four products it is stated that the product is not recommended for children under the age of three (product no. 27 and 31). In addition, three of the products carry the A-label from the Danish Joint Council of Art and Hobby Articles (FFFH) (product no. 15, 27 and 31), see chapter1.6.6.

Table 6 gives an outline of the products that were chosen for analysis.

Product description	Product category	Product No.
Liquid hand soap	Cosmetics and personal care (rinse-off)	22
Liquid hand soap	Cosmetics and personal care (rinse-off)	20
Shower gel	Cosmetics and personal care (rinse-off)	4
Shower gel	Cosmetics and personal care (rinse-off)	5
Shampoo	Cosmetics and personal care (rinse-off)	17
Shampoo	Cosmetics and personal care (rinse-off)	16
Conditioner	Cosmetics and personal care (rinse-off)	19
Conditioner	Cosmetics and personal care (rinse-off)	6
Wet wipes (baby)	Cosmetics and personal care (leave-on)	23
Wet wipes (face)	Cosmetics and personal care (leave-on)	28
Wet wipes (face)	Cosmetics and personal care (leave-on)	2
Facial cleanser	Cosmetics and personal care (leave-on)	3
Moisturiser	Cosmetics and personal care (leave-on)	7
Moisturiser	Cosmetics and personal care (leave-on)	18
Face serum	Cosmetics and personal care (leave-on)	24
Hand cream	Cosmetics and personal care (leave-on)	26
Body lotion	Cosmetics and personal care (leave-on)	21
Deodorant (roll-on)	Cosmetics and personal care (leave-on)	1
Deodorant (roll-on)	Cosmetics and personal care (leave-on)	8
Hair wax	Cosmetics and personal care (leave-on)	9
Hair wax	Cosmetics and personal care (leave-on)	25
Hair wax	Cosmetics and personal care (leave-on)	10
Washing-up liquid	Detergents	11
Wall primer	Paint, varnish and adhesives	13
Wall paint	Paint, varnish and adhesives	12
Wall paint	Paint, varnish and adhesives	29
Wallpaper adhesive	Paint, varnish and adhesives	14
All-purpose glue	Hobby products	27
Textile paint	Hobby products	30
Glass paint	Hobby products	31
Hobby paint	Hobby products	15

TABLE 6: OUTLINE OF CONSUMER PRODUCTS CHOSEN FOR CHEMICAL ANALYSIS OF MI.

3.1 Summary of choice of products

In cooperation with the Danish Environmental Protection Agency, 31 products were selected for chemical analysis of the content of MI. The products were selected within the four product categories: cosmetics and personal care (22 products comprising 8 rinse-off products and 14 leave-on products), detergents and household cleaning products (1 product), paint, varnish and adhesives (4 products) as well as toys and hobby products (4 products). The products were chosen in consideration of whether or not they can be expected to come into direct contact with the skin, how frequently they are used, if they are used by children, if they have a high concentration of MI, cover several different types of products and manufacturers; all of the above factors are regarded as essential to the development of contact allergy and they are decisive in order to obtain a general impression of the exposure of a consumer.

4. Chemical Analyses

31 consumer products from the product categories of ”cosmetics and personal care”, “detergents and household cleaning products”, “paint, varnish and adhesives” and “hobby products and toys” were chosen for analysis of their content of MI. The 31 products were divided into five groups, and within each group the products are believed to have comparable product matrices. Therefore, products within the same group were extracted and analysed according to the same method.

4.1 Description of analysis method

The content of MI in the products was determined through analysis in true duplicate by gas chromatography with mass spectrometric detection (GC-MS); see the details of the analysis in Table 7.

The removed subsamples were extracted with 10-30 ml dichlormethane added internal standard of o-terphenyl (30 min. on shaking table), and then the analyses were carried out by GC-MS.

Equipment	Agilent GC (7890A) with MSD (5975C)
Column	Agilent CP-Wax 57 CB, 25 m x 1.2 µm
Injector	Without split: 250 °C
Temperature application	35-200 °C, 20 °C per min.
Mass spectrophotometer	Scan mode

TABLE 7: GC-MS CONDITIONS USED FOR THE CHEMICAL ANALYSES.

4.2 Validation of the quantitative analysis method

A validation of the applied method for determination of MI was carried out, and the below parameters were investigated and documented.

Analyses of a reference standard with a known content of MI were carried out to identify the retention time and mass spectrum. The mass spectrum was compared with the mass spectrum from the MS library from NIST[xii]. The reference standard was prepared on the basis of an analysis chemical from Sigma-Aldrich with a purity of >98% (Fluka batch no. 1364155).

O-Terphenyl was added as internal standard to compensate for possible variations in the extraction and during the GC-MS analyses.

Linearity in the range of measurement was determined by analysis of the reference standard at five different concentration levels on two different days. The linearity fit was acceptable with R^2>0.99.

The detection limit was calculated to 0.5 mg/kg on the basis of the deviation on a reference with a content corresponding to the lowest calibration point analysed on different days.

[xii] National Institute of Standards and Technology

Blank specimens were included on all analyses runs, and no substances were detected with interference with MI in any of the blank specimens.

Recovery was investigated by spiking selected samples with a known amount of MI. Spiking of a product was carried out for each of the different types of product matrices (referred to in Roman numerals in the following). The average recovery of six determinations of each product can be seen in Table 8.

Sample/ product [Product matrix]	Recovery %	Standard deviation %
26 Cream [I]	82	4.1
23 Wet wipes [II]	90	6.6
10 Hair wax [III]	100	3.2
11 Hand washing-up liquid [IV]	110	3.7
13 Paint [V]	120	1.5

TABLE 8: RECOVERY PERCENTAGE OF MI IN THE FIVE PRODUCT MATRICES FOR CHEMICAL ANALYSIS. THE MATRICES ARE REFERRED TO WITH ROMAN NUMERALS FROM I-V. THE RESULT IS AN AVERAGE OF THE SIX DETERMINATIONS.

The uncertainty of the analysis method was determined on the basis of the following:

- The relative standard deviation of six repeated measurements on a control sample containing MI.
- The relative standard deviation of six determinations of five selected products.

Without regard to the recovery percent, the uncertainty of the analysis method was determined to 15% (relative standard deviation, RSD), which therefore is the expected deviation of the results of an analysis in duplicate.

The recovery percent reflects that the uncertainty of the analysis results is matrix dependent, and that the total analysis uncertainty of each product can be up to 20% (RSD).

Therefore, a conservative RSD of 20% is used to estimate the analysis results. A limit value is only regarded as exceeded if the average of the analysis in duplicate is more than 20% above the limit value.

4.3 Results of the chemical analyses

The results of, the average of the analyses in true duplicate and the standard deviation are reported in Table 9-12 after grouping into the categories ”cosmetics and personal care”, ”detergents and household cleaning products”, ”paint, varnish and adhesives” and ”toys and hobby products”.

4.3.1 Cosmetics and personal care

The content of MI was analysed in 22 cosmetic products within cosmetics and personal care, see Table 10. Three of them contain the combination of MCI/MI in a three-to-one ratio, cf. the declaration (refer to the last column in Table 10), while the other 19 products contain MI but not MCI, however, often in combination with one or several other preservatives.

An amendment to the cosmetics regulation was recently adopted, which means that MCI:MI in a three-to-one-ratio, may no longer be used in leave-on cosmetic products from the 16. July 2015., The three-to-one ratio of

MCI/MI is still permitted in rinse-off products after the 16. July 2015 with a total concentration of 15 ppm (European Parliament and Council, 2009), and therefore products preserved with that mixture can contain up to 3.8 ppm MI. The chemical analyses demonstrated that the two liquid hand soaps and one conditioner, on which MI/MCI had been declared, contained 3.8 mg/kg, 4.8 mg/kg and 1.8 mg/kg MI, respectively (product no. 22, 20 and 6).

In the other analysed cosmetic products, the permitted limit for MI is 100 mg/kg. In the rinse-off products, the MI levels are 61-71 mg/kg for shower gel (n=2, product no. 4 and 5), 37-55 mg/kg for shampoo (n=2, product no. 16 and 17) and 59 mg/kg for conditioner (n=1, product no. 19).

Among 14 leave-on products where the permitted limit of MI is 100 mg, three different wet wipes were analysed and the content of MI was found to be <5 mg/kg, 77 mg/kg and 105 mg/kg, respectively, (product no. 2, 23 and 28); the content is stated per mass of liquid per wet wipe, see Table 9.

The other facial products (facial cleanser, face serum and two moisturisers) contained between <10 mg/kg and 72 mg/kg (product no. 3, 24, 7 and 18), while the content of MI is determined to 23 mg/kg and 51 mg/kg for a hand cream and a body lotion (product no. 26 and 21), respectively.

The two analysed roll-on deodorants and the three hair waxes contained 88-100 mg/kg MI (product no. 1 and 8) and 56-114 mg/kg MI (product no. 9, 25 and 10), respectively.

As mentioned, the total analysis uncertainty of the individual product can be up to 20% (RSD). Therefore, a limit value is only regarded as exceeded if the average of an analysis in duplicate is more than 20% above the limit value. Therefore, none of the analysed samples were assessed to exceed the limit values.

	Determination of gram liquid per wet wipe		
Sample/ Product [product matrix]	g liquid per wipe	Average (g)	Standard deviation (g)
2 Wet wipes (face) [II]	4.0 4.5	4.3	0.3
23 Wet wipes (baby) [II]	4.4 4.5	4.4	0.05
28 Wet wipes (face) [II]	3.6 4.0	3.8	0.3

TABLE 9: WEIGHT OF LIQUID PER WET WIPE FOR THE THREE ANALYSED WET WIPES.

Sample no./Product [Product matrix]	MI (mg/kg)	Average MI (mg/kg)	Standard deviation (mg/kg)	Combination of MCI/MI* (3:1)
22 Liquid hand soap [IV]	3.7 3.9	3.8	0.2	Yes
20 Liquid hand soap [IV]	4.8 4.8	4.8	0.0	Yes
4 Shower gel [IV]	72 70	71	1.5	No
5 Shower gel [IV]	62 61	61	0.9	No
17	58	55	3.4	No

Sample no./Product [Product matrix]	MI (mg/kg)	Average MI (mg/kg)	Standard deviation (mg/kg)	Combination of MCI/MI* (3:1)
Shampoo [IV]	53			
16 Shampoo [IV]	40	37	5.0	No
	33			
19 Conditioner [IV]	61	59	2.0	No
	58			
6 Conditioner [IV]	1.6	1.8	0.2	Yes
	1.9			
23 Wet wipes (baby) [II]	74	77	4.4	No
	81			
28 Wet wipes (face) [II]	97	105	11	No
	113			
2 Wet wipes (face) [II]	<5	-	-	No
	<5			
3 Facial cleanser [I]	71	72	2.3	No
	74			
7 Moisturiser [I]	<10	-	-	No
	<10			
18 Moisturiser [I]	37	41	5.4	No
	45			
24 Face serum [I]	47	51	5.9	No
	55			
26 Hand cream [I]	24	23	0.8	No
	23			
21 Body lotion [I]	46	51	6.4	No
	55			
1 Deodorant (roll-on) [I]	105	100	5.9	No
	96			
8 Deodorant (roll-on) [I]	87	88	2.3	No
	90			
9 Hair wax [III]	117	114	4.4	No
	111			
25 Hair wax [III]	57	56	1.8	No
	55			
10 Hair wax [III]	102	96	8.3	No
	90			

TABLE 10: CONTENT OF MI IN COSMETIC PRODUCTS DETERMINED BY CHEMICAL ANALYSIS.

<: BELOW THE DETECTION LIMIT THAT WAS INCREASED FOR SAMPLE 2 AND 7 BECAUSE OF INTERFERENCE FROM THE PRODUCTS.

-: NOT RELEVANT

*DECLARED ON THE LABEL

4.3.2 Detergents and household cleaning products

One hand washing-up liquid was analysed and it contained 40 mg/kg MI (product no. 11), see Table 11. According to the declaration, the product contains MI as well as octylisothiazolinone (OI) as preservative.

Sample/ Product [Product matrix]	MI (mg/kg)	Average MI (mg/kg)	Standard deviation (mg/kg)	Combination of MCI/MI (3:1)*
11 Hand washing-up liquid [IV]	41 39	40	1.5	No

TABLE 11: CONTENT OF MI IN DETERGENTS AND HOUSEHOLD CLEANING PRODUCTS DETERMINED BY CHEMICAL ANALYSIS. *DECLARED ON THE LABEL.

4.3.3 Paint, varnish and adhesives

Two types of wall paint were analysed and turned out to contain 70 mg/kg and 135 mg/kg of MI (product no. 12 and 29), respectively, see Table 12. According to the analyses, a wall primer and a wallpaper adhesive contained 21 mg/kg and 13 mg/kg MI (product no. 13 and 14), respectively. According to the data safety sheet these products contain MCI/MI and benzisothiazolinone as preservative (see last column in Table 12).

Sample/ Product [Product matrix]	MI (mg/kg)	Average MI (mg/kg)	Standard deviation (mg/kg)	Combination of MCI/MI (3:1)*
12 Wall paint [V]	136 134	135	1.6	Not informed
29 Wall paint [V]	69 70	70	0.8	Not informed
13 Wall primer [V]	21 21	21	0.1	Yes
14 Wallpaper adhesive [V]	13 13	13	0.0	Yes

TABLE 12: CONTENT OF MI IN PAINT, VARNISH AND ADHESIVES, DETERMINED BY CHEMICAL ANALYSIS. *ACCORDING TO SAFETY DATA SHEET.

4.3.4 Toys and hobby products

According to the manufacturers, three of the four analysed hobby products contained the combination MCI/MI (three-to-one ratio); see the last column in Table 13. One of them, a glue that has an A-label from the Danish Joint Council of Art and Hobby Articles (FFFH) (see chapter 1.6.6 on A-labelling) contained 110 mg/kg MI, cf. the chemical analyses (product no. 27). The manufacturer of this product has reported that they add MCI/MI in a concentration < 0,0015 % (15 ppm). MI is also added to the product through the binding agent, which is preserved with both MI and MCI/MI. According to the manufacturer, the total content of MI is <0,014 % (140 ppm), of which a smaller part is added as MCI/MI (<0,0015 %). Therefore, the analysed amount agrees with the information given by the manufacturer.

The chemical analyses showed a content of MI of 3.6 mg/kg and 5.3 mg/kg for the two other hobby products that were preserved with the MCI/MI-mixture (product no. 30 and 15). According to the manufacturer, the content was 9.8 mg/kg and 3 mg/kg, respectively. The product with the highest content of MI is A-labelled and exceeds the limit value that according to the labelling system is app. 3.8 mg/kg for MI when using the MCI/MI combination in a three-to-one ratio. According to the manufacturer this is due to lack of update in connection to change in recipe of the binding agent. The binding agent is now replaced with a binding agent with a lower content of MI, so that the product is in compliance with the limit value of the A-label.

One paint for window glass contained 5.8 mg/kg MI, cf. the chemical analyses (product no. 31).

Sample/ Product [product matrix]	MI (mg/kg)	Average MI (mg/kg)	Standard deviation (mg/kg)	Combination of MCI/MI (3:1)
27[1)] Glue [V]	125 100	110	17	Yes[2)]
15 Hobby paint [V]	5.5 5.1	5.3	0.3	Yes
30[1)] Textile paint [V]	3.8 3.3	3.6	0.3	Yes
31[1)] Window paint [V]	6.1 5.4	5.8	0.5	Not informed

TABLE 13: CONTENT OF MI IN HOBBY PRODUCTS DETERMINED BY CHEMICAL ANALYSIS.
1) THE PRODUCTS ARE CE-MARKED AND CAN THEREFORE BE DEFINED AS TOYS BY THE MANUFACTURER. [2)] THE MANUFACTURER HAS REPORTED A CONTENT OF MI OF <140 MG/KG.

4.4 Summary of the results of the chemical analyses

For three cosmetic rinse-off products that were preserved with a combination of MCI and MI in a three-to-one ratio, cf. the declaration, the chemical analyses showed that they contained 1.8-4.8 mg/kg MI, which agrees with the information that it is a mixture of MCI/MI. The five other rinse-off products were preserved with MI without MCI and contained 37-71 mg/kg MI. All 14 analysed leave-on products were declared to contain MI without MCI. They contained <5-114 mg/kg MI. Two leave-on products did not contain MI above the detection limit (which in general is 0.5 mg/kg for the cosmetic products but 5 and 10 mg/kg respectively for the two products in question) The analysed hand washing-up liquid contained 40 mg/kg MI (the product was declared to contain MI and octylisothiazolinone).

Two types of wall paint contained 70 mg/kg and 135 mg/kg MI, respectively. One primer and one adhesive that according to the data safety sheet contained MCI/MI in a three-to-one ratio contained 21 mg/kg and 13 mg/kg MI, respectively.

Three out of four hobby products contained 3.6-5.8 mg/kg MI, of which the two according to the manufacturer were preserved with MCI/MI in a three-to-one ratio. One all-purpose glue that according to information from the manufacturer contained MCI/MI with a MI concentration of <140 ppm is analysed to a content of 110 mg/kg MI.

By assessment of the results from the analysis, a conservative relative standard deviation (RSD) of 20% is used. Therefore a limit value will only be exceeded if the average value of the double determination exceeds 20% of the limit value.

5. Qualitative assessment of the analysis results

This chapter compares the information on use-concentrations, collected during the survey, with the analytical data obtained for the selected products. In addition, the concentration level in each product is evaluated in relation to the SCCS assessment of MI, published in 2013.

5.1 Assessment of cosmetics and personal care

The chemical analyses that were carried out on the 22 selected products within cosmetics and personal care show a concentration of MI in rinse-off products in the interval of 37-71 ppm, in leave-on products in the interval of 23-114 ppm and in the analysed wet wipes in the interval of 77-105 ppm. The concentrations agree with the analyses previously carried out by Lundov *et al.*, where 52-100 ppm MI in 12 cosmetic rinse-off products, 2-96 ppm in three cosmetic leave-on products and 17-87 ppm in four wet wipes were found (Lundov et al., 2011).

When an uncertainty of 20% is considered, then all cosmetic products analysed in this survey are regarded to be within the current limit for the MI content of 100 ppm for cosmetic products.

The use of MI in cosmetic products with regard to sensitizing potential was reassessed by SCCS in 2013. The conclusion of the new assessment was that SCCS does not find it safe for consumers to use 100 ppm MI in cosmetic products. In rinse-off cosmetics, 15 ppm is regarded as a safe concentration of MI with regard to sensitisation, while a safe concentration cannot be given for leave-on cosmetics on the basis of the available data (SCCS, 2013). SCCS have included wet wipes under the category of leave-on products.

Only three out of the eight analysed rinse-off products had a concentration of MI below 15 ppm. These products will generally be regarded as safe in relation to the latest recommendation on MI from SCCS (see Table 14). The three products were preserved with the MCI/MI mixture in a three-to-one ratio. Two leave-on products contain MI below the detection limits, respectively 5 and 10 ppm. The two products were according to the declaration conserved with only MI.

Sample/Product [matrix]	MI content Average mg/kg	Combination of MCI/MI (3:1)	Category
22 Liquid hand soap [IV]	3.8	Yes	Rinse-off
20 Liquid hand soap [IV]	4.8	Yes	Rinse-off
4 Shower gel [IV]	71	No	Rinse-off
5 Shower gel [IV]	61	No	Rinse-off
17 Shampoo [IV]	55	No	Rinse-off
16 Shampoo [IV]	37	No	Rinse-off
19 Conditioner [IV]	59	No	Rinse-off
6 Conditioner [IV]	1.8	Yes	Rinse-off
23 Wet wipes (baby) [II]	77	No	Leave-on
28 Wet wipes (face) [II]	105	No	Leave-on
2 Wet wipes (face) [II]	-	No	Leave-on
3 Facial cleanser [I]	72	No	Leave-on
7 Moisturiser [I]	-	No	Leave-on
18 Moisturiser [I]	41	No	Leave-on
24 Face serum [I]	51	No	Leave-on
26 Hand cream [I]	23	No	Leave-on
21 Body lotion [I]	51	No	Leave-on
1 Deodorant (roll-on) [I]	100	No	Leave-on
8 Deodorant (roll-on) [I]	88	No	Leave-on
9 Hair wax [III]	114	No	Leave-on
25 Hair wax [III]	56	No	Leave-on
10 Hair wax [III]	96	No	Leave-on

TABLE 14
OUTLINE OF ANALYSIS RESULTS FOR THE SELECTED PRODUCTS WITHIN COSMETICS & PERSONAL CARE AND CATEGORISATION AS RINSE-OFF OR LEAVE-ON PRODUCT, RESPECTIVELY.

5.2 Assessment of detergents and household cleaning products

The concentration of MI in the analysed hand washing-up liquid was determined to 40 ppm. The retention of a hand washing-up liquid on the skin could be expected to be comparable with a cosmetic rinse-off product, but normally it is used in a diluted version. As it is anticipated that the product is used in a solution that has been diluted 5000 times, then the real use-concentration will be 0.008 ppm. SCCS's assessment of the safe use of MI is based on cosmetic products, but if a parallel is drawn between the theoretically calculated concentration of MI of 0.008 ppm in washing-up water and the new recommendation from SCCS, where the solution is regarded to be comparable with a cosmetic rinse-off product, then that product could probably be regarded as safe to use (SCCS, 2013). The content of MI in undiluted washing-up liquid does exceed SCCS's recommended max limit of 15 ppm for rinse-off products.

5.3 Assessment of paint, adhesives and varnish

The concentration of MI in the analysed paint and adhesives was 13-135 ppm. That agrees very well with the concentration interval of 10-300 ppm determined by Lundov *et al.* for 19 types of water-based paint (Lundov et al., 2014). Moreover, that level is also confirmed by the Danish trade association for coatings and adhesives (DFL). DFL's (2012) survey among the members of the association showed that 80 % of paints (water-based paint products for indoor use) contained less than 100 ppm.

In their assessment from 2013, SCCS concludes that a concentration of MI of 15 ppm or more is not safe in relation to induction of allergy in rinse-off cosmetics. However, exposure to paint, adhesives and varnish cannot be directly compared with exposure to cosmetics, but if the skin gets into contact with paint, adhesives or varnish with a concentration of MI that is higher than 15 ppm, then there might be a risk of induction of allergy based on the opinion from SCCS.

The contribution of airborne exposure in freshly painted rooms is not included in the report, as there is only one single study containing data on concentration of MI in the air after painting.

5.4 Assessment of toys and hobby products

The products that were analysed in this survey within the category of toys and hobby products were analysed to contain 110, 5.3, 3.6 and 5.8 ppm MI, respectively. One all-purpose glue contained 110 ppm MI, which corresponds to the given information from the manufacturer of a MI content of < 140 ppm. For toys, a recent survey shows that MI was not found in the 11 products selected for analysis in concentrations above the detection limit of the applied method (20 ppm) (Poulsen and Nielsen, 2014).

In their assessment from 2013, SCCS concludes that a concentration of MI of 15 ppm or more is not safe in relation to induction of allergy in rinse-off cosmetics. However, the exposure to toys and hobby products cannot be directly compared with exposure to cosmetics, but if your skin is in contact with toys or hobby products that have a concentration of MI higher than 15 ppm, , then there might be a risk of induction of allergy based on the opinion from SCCS.

5.5 Summary of qualitative assessment

The analysed values for the chosen products are comparable with the values reported in previous studies. All cosmetic products analysed in this study observe the current limit value of 100 ppm MI, when the 20% uncertainty of the analysis method is considered. Compared to the new recommendation of SCCS regarding a limit value of 15 ppm for MI in rinse-off products and 0 (zero) ppm for MI in leave-on products, only five cosmetic products out of the 22 that were analysed in this project are regarded as safe.

If the hand washing-up liquid is assumed to be used with a dilution factor of 5000, then the analysed concentration of 40 ppm will correspond to a use-concentration of 0.008 ppm. That can be compared with the limit values of cosmetic rinse-off products where SCCS recommends maximum 15 ppm.

The exposure of MI through hobby products, toys, paint, varnish and adhesives cannot be directly compared with the exposure that will take place from cosmetics, but if a consumer's skin is in contact with a liquid mixture with a concentration of MI that is higher than 15 ppm (which was found in a number of products), then there will be a risk of induction of allergy.

Compared to the current 100 ppm limit value of MI in cosmetics, a higher level was seen in one of the two types of wall paint and in one all-purpose glue. However, the measuring uncertainty might indicate that the content in reality is below 100 ppm. For the other 3 hobby products, the MI content was below 15 ppm MI. The MI content in the primer and the adhesive were above 15 ppm, but below 100 ppm.

6. Exposure assessment

As previously described, MI is a known skin sensitizing substance and MI's allergy causing potential is its dominating health-related problem. Skin sensitization and resulting contact allergy is an immunological process (type IV allergy) that consists of two phases: Induction (also known as sensitization) and following elicitation (provocation that triggers the allergic reaction). Decisive factors for the development of contact allergy are described in Fact Box 2.

In connection with contact allergy, a distinction is made between the concentration required to sensitize and the concentration required to trigger an allergic reaction in a person who already is sensitized. In 2013, MI was assessed by SCCS for sensitization. On the basis of the available clinical knowledge in 2013, SCCS concluded that a safe threshold value cannot be determined for the use of MI in cosmetic leave-on products; neither with regard to sensitization nor with regard to elicitation. However, in rinse-off products SCCS regards 15 ppm to be a safe concentration of MI with regard to sensitization, while the available data does not determine a threshold value for elicitation. (SCCS, 2013). The following assessment of exposure to MI from consumer products will therefore have a qualitative nature.

In the following chapters, exposure scenarios will be set up and the applied models will be described. Choice of parameters will be listed and justified. Chapters will follow with the estimated exposure levels, determined for each of the four product categories identified in the survey: "cosmetics and personal care", "detergents and household cleaning agents", "paint, varnish and adhesives" and "toys and hobby products". The individual exposure levels calculated on the basis of the scenarios that were set up will then be assessed qualitatively in relation to the consumer.

6.1 Outline of exposure scenarios

MI is used as preservative in a number of different product categories and within them an assessment was carried out of the exposure to MI. In this report, focus is on dermal exposure, which is the most substantial source for exposure to MI through the identified and analysed consumer products.

Sensitization is a local effect, where parameters such as duration and frequency of exposure as well as concentration and potency of the allergen in the product are essential to the development of allergy, see Fact Box 2. Regarding the development of allergy, exposure expressed as a dermal load (the amount of MI per skin area (mg/cm^2)), has proven be of great importance (WHO, 2008), which is why it was used in this project to calculate the exposure to MI.

Fact Box 2: Factors of importance to the development of contact allergy

Mechanistically, contact allergy is caused when the allergy causing substance (the allergen) penetrates the epidermis (the outermost layer of the skin), and the substance (or a transformation product) binds covalently to proteins in the body. That reaction results in the creation of a so-called hapten. The haptens are then caught by cells from the immune system (Langerhans cells) that are activated and migrate to the nearest lymph node. That is where the hapten is introduced to other cells in the immune system (the T-cells) and they are also activated so they can recognize the unknown substance if they encounter it again. Cells are now created that can recognise and react to the allergy causing substance if the skin again gets into contact with the substance (Kaplan et al., 2012; OECD, 2012). The creation of haptens and the protein binding properties of a chemical substance are assessed to be one of the most important factors in the sensitization process and are directly related to the sensitization potential and potency of the substance (Roberts and Aptula, 2008).

Factors of importance to the development of allergy:

- Potency of the allergen, i.e. how much substance per area unit is necessary to sensitize a not previously exposed person
- How high a concentration of the allergen a person is exposed to
- How often the person is exposed to the allergen
- How long the person is exposed to allergen
- If the skin at the same time is exposed to other skin sensitizing substances

There are great differences from person to person regarding how high a concentration of an allergen is required to sensitize and elicitise, but in general the concentration that causes an allergic reaction in an already sensitized person is lower than the concentration required to initially develop the allergy.

As far as possible, the exposure scenarios were developed according to the REACH guideline: *"Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.15 - Consumer exposure estimation"*, edition 2.1 from October 2012 (ECHA, 2012) and the guidelines for assessing the cosmetic ingredients described by the SCCS (in *"The SCCS's Notes of Guidance for testing of cosmetic substances and their safety evaluation"*, 8th edition from 2012) (SCCS, 2012).

Exposure scenarios were set up for an adult woman and a three-year-old child. Women are expected to be exposed to MI through consumer products to a higher degree than men, especially as women have a larger consumption of cosmetic products. Three-year-old children were chosen for the exposure assessment as that age group is expected to be exposed to MI through many different kinds of products (e.g. hobby products, wet wipes and other cosmetic products, including sunscreen).

Exposure was assessed in the light of realistic worst-case scenarios, i.e., under the assumption of a consumption that is based on a frequent use of a given product and on the use of rather large amounts of the product. Some of the identified products that contain MI are expected to be used rarely or seasonally. The dermal load of MI was determined on a daily basis (mass per area unit per day) and the exposure level for each product was assessed qualitatively.

A number of default values are defined to calculate estimates within many product categories to standardise the exposure assessments, and as far as possible they have been used. For cosmetic products a starting point was

taken in the Notes of Guidance from SCCS (SCCS, 2012), in the following called ”SCCS's guidelines”. For the other consumer products parameters reported in product specific ”Fact Sheets” were used. They have been published by the Dutch research institute called RIVM[xiii] that ensures that the exposure assessments are performed in a transparent and standardized way. The parameters reported in the ”Fact Sheets” form the basis of calculations carried out with the software ConsExpo. ConsExpo was developed by RIVM and used to predict human exposure through consumer products based on mathematical models and standard values. This report takes a starting point in ”Fact Sheets” concerning product related parameters for household cleaning products (Prod'homme de Lodder et al., 2006), paint products (Bremmer and van Engelen, 2007), Do-It-Yourself products (ter Burg et al., 2007) and toys (Bremmer and van Veen, 2002). The use of parameters from ”Fact Sheets” corresponds with the recommendations in the recently published ”Existing Default Values and Recommendations for Exposure Assessment” from Scandinavia (Nordic Council of Ministers, 2011), as the parameters are based on European data.

Correspondingly, the default values are used for parameters that are not product related such as the surface area of the body or parts of it. The applied defaults values are described in detail below. For the worst-case scenario an immediate and 100% transfer of MI from the product/product layer to the skin was assumed. Finally, the exposure assessments (as far as possible) were based on the measured concentrations of MI in the products that were analysed in connection with this survey. In cases, where several similar products were analysed, the highest concentration found in the exposure calculations was used and a product number was given.

6.1.1 Calculation formulae

The formulae used for the exposure calculations take their starting point in the formulae recommended in ECHA's guideline for exposure scenarios, R. 15 (ECHA, 2012).

Cosmetics and personal care: For products that are applied directly on the skin (e.g., cosmetic products), the dermal load was calculated, L(der), on the basis of the following formula (”instant application”-model):

$$L(der) = 1000 \times Q(prod) \times Fc(prod)/A(skin) \qquad \text{(formula R.15-3)},$$

where:

L(der):	substance amount per skin area per application	[mg/cm²]
Q(prod):	applied amount of product	[g]
Fc(prod):	weight fraction of substance in the product	[g/g]
A(skin):	area of exposed skin	[cm²]

This report determines the dermal load of MI per day, i.e. the amount of MI per skin area in one day. The default values of the product amounts used in the calculations are based on a daily load as stated in SCCS's guidelines (i.e., a daily frequency is included).

Correspondingly, the calculation took a retention factor (an estimate of the fraction of the product that is expected to stay on the skin) into consideration in order to obtain the actual amount of the product, which a given skin area is exposed to. If a cosmetic product that will be cleaned or washed off immediately after use (a rinse-off product) is in question, then the retention factor will be lower than for a product that remains on the skin (a leave-on product).

Detergents and household cleaning products: When exposure takes place by dipping (parts of) the body into a liquid that contains MI (e.g., during washing-up by hand), the dermal load is determined on the basis of the concentration of MI in the liquid, C(der):

$$C(der) = RHO(prod) \times Fc(prod) \times 1000/D \qquad \text{(formula R.15-5)}$$

[xiii] Rijks Instituut voor Volksgezondheid & Milieu (RIVM), The National Institute for Public Health and the Environment, Holland

Then the dermal load is calculated:

$$L(der) = C(der) \times TH(der) \quad \text{(formula R.15-6)},$$

where:

C(der):	concentration of substance on the skin	[mg/cm^3]
RHO(prod):	density of the product before dilution	[g/cm^3]
Fc(prod):	weight fraction of substance in the product	[g/g]
D:	dilution factor	[-]
TH(der):	thickness of product layer on the skin (default 0.01 cm)	[cm]

Paint, varnish and adhesives: In connection with the exposure scenarios for paint and Do-It-Yourself products, the dermal load was calculated on the basis of the following formula ("constant rate" model (Bremmer and van Engelen, 2007)):

$$L(der) = R \times t \times Fc(prod)/A(skin),$$

hvor:

R:	rate by which the skin is exposed	[mg/min]
t:	application period	[min]
Fc(prod):	weight fraction of substance in the product	[g/g]
A(skin):	area of exposed skin	[cm^2]

Toys and hobby products

According to the REACH-guidance about consumer exposure estimation (ECHA 2012) the dermal exposure is calculated on the basis of formula R.15.3 when products are applied directly on the skin (see the formula in the above part "Cosmetics and personal care"). In this calculation it is assumed that the entire load of product that is smeared on the body potentially is absorbed. It might be possible to make the calculation of exposure for toys and hobby products based on this formula but at the time for preparation of this report there was no clear guidance how to set the standard values for the exposure of the specific types of products in this report. In a report about preservations in toys published by the Danish Environmental Protection Agency in 2014 (Poulsen and Nielsen 2014) adjusted values for calculation of exposure from some types of toys are used. Those are based on values for finger paint stated in RIVM's Children Toys Fact Sheet (Bremmer and van Veen 2002). A similar calculation method of the dermal exposure for the hobby products could be considered in the present evaluation, although using a moderated quantity of product and also a retention factor. However, it was assessed that the uncertainty of the results would be considerable which is why a more simple comparison of concentrations was preferred. It is expected that the European trade organization, FEICA[xiv] during 2015 will make a proposal to more product specific and appropriate exposure scenarios for different types of glue (including hobby glue).

6.1.1.1 Choice of values for body areas

For all calculations, an area of the body or relevant body parts are used, based on the newest values from the American environmental protection agency, US EPA, as recommended in a new publication from *Norden* (Nordic Council of Ministers, 2011). Although the average American weighs more and therefore also has a larger body area than the average European, the figures are assessed to be typical of today as they are based on analyses of the most recent data (NHANES[xv] 1999-2006), while European data mainly is based on older data, typically the 1997 edition of "Exposure Factors Handbook" (U.S. EPA, 1997). In addition, the weight of adult Europeans is increasing and is approaching the body weight and surface area of the average American.

For the exposure scenario of an adult woman, values for the lower quartiles were used for the total body area as well as for the area of body parts as stated in total for women ≥21 years (see table 7-13 in Exposure Factor Handbook from 2011 (U.S. EPA, 2011)). By choosing the lower quartile for body area a higher exposure will be

[xiv] The Association of the European Adhesive & Sealant Industry
[xv] National Health and Nutrition Examination Survey (NHANES), USA

calculated compared to the use of a mean value. That procedure is used by RIVM[xvi] in connection with their recommendations for exposure scenarios for specific product categories defined by RIVM in "Fact Sheets". RIVM uses the quartile (lower or upper) that gives the highest exposure and thereby represents a realistic worst-case scenario (Bremmer et al., 2006).

For children, the age groups change at three years of age, and data was given for the groups 2-<3 years and 3-<6 years. The 5th percentile for the group 3-<6-year-old children was chosen for the total body area for three-year-old children (girls and boys together, see table 7-9 in Exposure Factor Handbook (U.S. EPA, 2011)), which gives a conservative estimate of the dermal load determined as the amount of MI per skin area. The percentage of the individual body parts only vary a little between the age groups 2-<3 years and 3-<6 years and an average of the mean values for the two age groups is used in the calculations (see table ES-1 in Exposure Factor Handbook (U.S. EPA, 2011)). The applied surface areas are shown in Table 15.

Area (cm^2)	Adult woman (≥21 years)	Three-year-old children (boys and girls)
Total	16600	6100
Head	1110	500 (8.2% of total)
Hands	820	293 (4.8% of total)
Armpits	200[a]	-
Torso	-	2507 (41.1% of total)

a) Value from the guidelines of SCCS (SCCS, 2012).

TABLE 15
APPLIED VALUES FOR THE TOTAL BODY AREA AND OF RELEVANT BODY PARTS FOR ADULT WOMEN AND THREE-YEAR-OLD CHILDREN. VALUES ARE BASED ON (U.S. EPA 2011), IF NOTHING ELSE IS INDICATED.

6.1.2 Exposure scenarios for cosmetic products

For the cosmetic products, the exposure scenarios were set up based on the SCCS guidelines and according to their recommendations the newest values from Cosmetics Europe (the European trade association for cosmetics, previously Colipa) were used for the applied daily amount of cosmetic products that are described in detail in two publications from Hall et al. All in all, the publications cover 11 product categories and the consumer pattern was investigated among the European population (men and women from 17-74 years of age) during the periods 2003-2005 (body lotion, deodorant, moisturiser, shampoo, lipstick and toothpaste) (Hall et al., 2007) and 2005-2008 (mouth wash, shower gel, liquid foundation, hand cream and hair styling products) (Hall et al. 2011). It is assessed that the 11 product categories in total cover app. 95% of the estimated consumption of cosmetic products in the EU (Hall et al,. 2011). The reported applied daily product amounts have been estimated on the basis of a probabilistic analysis of the values that European consumers have reported regarding frequency and applied amount of given cosmetic products. The values are collected in table 3 in the guidelines of SCCS (SCCS, 2012) together with the values for some additional products where the estimated daily amount was determined by multiplying the values of the maximum amount applied each time and the most common application frequency.

In addition, table 3 in the SCCS guideline also gives retention factors that are used to take into account that certain cosmetic products are cleaned or washed off, which makes the exposure amount substantially smaller than the total content in the applied amount used (SCCS, 2012).

[xvi] RijksInstituut voor Volksgezondheid & Milieu (RIVM), The National Institute for Public Health and the Environment, Holland - et hollandsk forskningsinstitut , der er en uafhængig styrelse under Dutch Ministry of Health, Welfare and Sport.

Furthermore, table 2 in the SCCS guideline shows the area/s of the body that is/are expected to be exposed when using a certain cosmetic product (SCCS, 2012).

6.1.2.1 Adult women's exposure through cosmetic products

Some products do not have a recommended amount, e.g. for the face serum that was analysed for content of MI in this survey. In that case, exposure was calculated on the basis of the maximum daily product amount of 0.8 g per day that is recommended on the label by the manufacturer.

In connection with wet wipes for facial cleansing, the measured weight of the liquid per wet wipe is used (3.8 g, product no. 28, see Table 9), and the application frequency is fixed at twice daily (morning and evening). In addition, a retention factor of 0.1 is used according to a recommendation from a guide covering the assessment of biocide-containing products (ICHP, 2002) on the assumption that 0.5 ml liquid remains on the skin after using a wet wipe, and the assumption that the average weight is 5 g per wet wipe (Gosens et al., 2014).

During the survey, no sunscreen was found on the Danish market that contained MI (perhaps due to the time of year the survey took place). However, there has been focus on the MI content particularly in sunscreen (Watchdog, 2013) and as rather large amounts of sunscreen are used periodically, sunscreen was included in the exposure calculations. As worst-case, it is assumed that sunscreen contains the maximum permitted amount of MI of 100 ppm. In the SCCS guideline it is assumed that an adult uses 18 g of sunscreen per day (SCCS, 2012). That is below the recommendations from the Danish Cancer Society that recommends what corresponds to 66 g per day for an adult (based on a consumption of 20 g/m^2 and two applications per day) (Danish Cancer Society, 2013). The Danish Environmental Protection Agency recommends a daily amount of 36 g per day and that amount was used in the following calculations.

For liquid hand soap, the survey only identified products that were preserved with a mixture of MCI and MI in a three-to-one ratio, and not only with MI. The highest measured concentration in the analysed liquid hand soaps was used in the exposure calculations. It is possible that liquid hand soap preserved with MI (without MCI) with a substantially higher concentration of MI exists, but none were identified in connection with this survey.

Product	Product amount, Q(prod) [g/day]	Application frequency (applications per day)	Exposure area, A(skin) [cm²]	Retention factor, F [-]	Contact area
Rinse-off:					
Liquid hand soap	20	10	820	0.01	Hand area
Shower gel	18.67	1.43	16600	0.01	Total body area
Shampoo	10.46	1	1375	0.01	Hand area + 0.5 x head area
Conditioner	3.92	0.28	1375	0.01	Hand area + 0.5 x head area
Leave-on:					
Cleansing wipes	7.6[a]	2	555	0.1	0.5 x head area
Face serum	0.8[b]	1[b)]	555	1	0.5 x head area
Moisturiser	1.54	2.14	555	1	0.5 x head area
Hand cream	2.16	2	820	1	Hand area
Body lotion	7.82	2.28	15490	1	Total body area – head area
Sunscreen	36	2	16600		Total body area
Deodorant (roll-on)	1.5	2	200	1	Armpits
Hair wax	4	1.14	965	0.1	0.5 x hand area + 0.5 x head area

a) Based on weight determination of product with two daily applications.
b) Manufacturer's recommendation for maximum daily use.

TABLE 16
PARAMETRES USED TO ESTIMATE THE EXPOSURE OF ADULT WOMEN TO MI THROUGH THE USE OF COSMETIC PRODUCTS. VALUES ARE FROM THE SCCS GUIDELINES, MAINLY TABLE 2 AND 3, IF NOTHING ELSE IS INDICATED.

6.1.2.2 Three-year-old children's exposure through cosmetic products

In connection with the survey, no cosmetic products were identified (with the exception of wet wipes) that were especially aimed at children. However, cosmetic products aimed at the family, such as liquid hand soap, moisturiser, body lotion, sunscreen, shampoo, conditioner and shower gel can also be used for children, and therefore the relevant analysed products are used in the exposure calculations for a three-year-old, see Table 17.

Recommendations from SCCS concerning the consumed amounts of different cosmetic products are related to adult consumers. Values for the daily applied amounts of shower gel, shampoo and conditioner for three-year-olds were fixed at half of the amount an adult uses. That is in agreement with a survey of a two-year-old's exposure to

chemical substances that was carried out for the Danish Environmental Protection Agency in 2009 (Tønning et al., 2009). Correspondingly, half the amount of the value of an adult daily consumption of moisturiser and body lotion was used. However, the applied daily amount of liquid hand soap was fixed at the same amount as for adults, as small children frequently get their hands washed.

The recommendations for the contact area of cosmetic products for adults are used in the scenarios for children, however, "hands" was removed from the contact area in connection with shampoo and conditioner as somebody helps a child wash their hair at that age.

The recommendation from the Danish Cancer Society, concerning the consumed amount of sunscreen, corresponds to 24 g per day for a three-year-old (based on a consumption of 20 g/m^2 and two applications per day (Danish Cancer Society, 2013)). It is assumed that the recommendation from the Danish Cancer Society is observed to a higher degree for small children than for adults, and the application frequency for children who bathe and play with water can also amount to more than twice a day. In the worst-case scenario for three-year-old children, the exposure to MI through sunscreen is therefore calculated with a consumption of 24 g per day. During the survey, no sunscreen was found on the Danish market with a content of MI, and therefore the exposure calculation is based on the worst-case assumption that the applied sunscreen contains the maximum permitted amount of MI of 100 ppm.

Parameters from an article published in 2014 by RIVM (Gosens et al., 2014) were used to calculate the exposure to MI in wet wipes for children using diapers; the article estimated the total exposure of 0-3 year-olds to parabens. A user frequency of five times a day is given (in connection with diaper change) and, in addition, a retention factor of 0.1 is used as recommended by a technical guide concerning exposure to biocide-containing products (ICHP, 2002). Half of the area of the torso is used as contact area (corresponding to the area for crutch, behind, upper thighs and lower part of the stomach). The average weight of liquid per wet wipe, determined in connection with analysis, was used for the calculation (4.4 g, product no. 23, see Table 9).

For liquid hand soap, the survey only identified products that had been preserved with a mixture of MCI and MI in a three-to-one ratio and not MI alone. As in the calculation for women, the highest measured concentration in the analysed liquid hand soaps were used, although it is probable that products preserved with a higher concentration of MI (without MI) can occur.

The parameters used to estimate the exposure of three-year-old children to MI through cosmetic products can be seen in Table 17..

Product	Product quantity Q(prod) [g/day]	Application frequency (applications per day)	Exposure area A(skin) [cm²]	Retention factor, F [-]	Contact area
Rinse-off:					
Liquid hand soap	20	10	293	0.01	Hand area
Shower gel	9.34	1.43	6100	0.01	Total body area
Shampoo	5.23	1	250	0.01	0.5 x head area
Conditioner	1.96	0.28	250	0.01	0.5 x head area
Leave-on:					
Wet wipes	22[a]	5	1254	0.1	0.5 x torso[b]
Moisturiser	0.77	2.14	250	1	0.5 x head area
Body lotion	3.91	2.28	5600	1	Total body area – head area
Sunscreen	24.4	2	6100	1	Total body area

a) Based on weight determination of product with five daily applications.
b) Parameters from (Gosen et al., 2014).

TABLE 17
PARAMETRES USED TO ESTIMATE THE EXPOSURE OF A THREE-YEAR-OLD TO MI THROUGH THE USE OF COSMETIC PRODUCTS. VALUES ARE BASED ON THE SCCS GUIDELINES (VKF 2012), IF NOTHING ELSE IS INDICATED.

6.1.3 Exposure scenarios for detergents and household cleaning products

Parameters for estimation of the daily exposure to MI when washing up by hand were found in RIVM's Cleaning Products Fact Sheet (2006) (Prud'homme de Lodder et el., 2006) according to the recommendations from *Norden* 2012 (Nordic Council of Ministers, 2011), see Table 18. As mentioned earlier, the values are based on top quartiles of consumer data.

When choosing products for analysis, the cosmetic products received higher priority than detergents and household cleaning products as it is assumed that there is a more frequent and higher exposure from cosmetics (especially leave-on products). As cosmetic products are expected to contribute with the most substantial exposure to MI, only one detergent and household cleaning product was selected for analysis. The exposure calculation for detergents and household cleaning products is based on that one value.

Product	Product amount, Q(prod) [g]	Product volume, V [cm³]	Frequency, f [pr. day]	Layer thickness of product, TH(der) [cm]
Washing-up liquid	7	5000	1,17	0,01

TABLE 18
PARAMETERS USED FOR ESTIMATING ADULT WOMEN'S EXPOSURE TO MI THROUGH THE USE OF CLEANING AGENTS. VALUES ARE FROM (PRUD'HOMME DE LODDER ET AL., 2006).

6.1.4 Exposure scenarios for paint, varnish and adhesives

Parameters for estimating exposure to MI during Do-It-Yourself work such as painting and priming were found in RIVM's Paint Products Fact Sheet (Bremmer and van Engelen, 2007), while the parameters that are relevant for the application of wallpaper adhesive comes from RIVM's Do-it-yourself Products Fact Sheet (ter Burg et al., 2007). The applied parameters appear in Table 19 and are explained below.

Product	Contact rate, R [mg/min]	Application period, t [min]	Exposure area, A(skin) [cm²]	Contact area
Wall paint	30	120	820	Hand area
Wall and ceiling primer	60	120	820	Hand area
Wallpaper adhesive	30	240	820	Hand area

TABLE 19
PARAMETRES USED FOR ESTIMATION OF THE EXPOSURE TO MI FOR A WOMAN THROUGH PAINT, VARNISH AND ADHESIVES. THE VALUES ARE FROM RIVM'S FACT SHEETS (BREMMER AND VAN ENGELEN, 2007; TER BURG ET AL., 2007).

The level of dermal exposure when applying water-based wall paint with a paint roller or brush is described by the "constant rate" model in ConsExpo. Parameters connected with painting walls are the contact rate that is defined as the rate by which the product is added to the skin (mass per time unit) and the application period (painting period) that does not include preparation and tidying-up. It is anticipated that mainly the hands are exposed to paint when a wall is painted. In RIVM's "Fact Sheet" it is estimated that 20-40% of the total dermal exposure is on hands when painting a wall and as worst-case the highest value of 40% is used in the calculation.

The blocking primer (product no. 13) that was purchased for analysis of MI can be used to treat ceilings as well as walls. The greatest skin exposure is expected when painting a ceiling and therefore that situation is used as worst-case scenario (as for paint it is based on the "constant rate" model). The primer has a viscosity that can be compared to paint and the contact rate during ceiling work is determined to 60 mg/min cf. RIVM's Paint Products Fact Sheet (Bremmer and van Engelen, 2007). As worst-case it is assumed that the hands are exposed to 80% of the skin exposure (for low viscose products a hand exposure of >80% of the total skin exposure is stated (Bremmer and van Engelen, 2007)). When priming a ceiling, the application time is evaluated to be comparable with the application time when painting walls.

Dermal exposure when using wallpaper adhesive is also described by means of the "constant rate" model and relevant parameters were found in RIVM's Do-it-yourself Products Fact Sheet (ter Burg et al., 2007). The application period, meaning the paperhanging itself minus tidying-up etc. where no essential skin contact is assumed amounts to four out of six working hours. As the wallpaper adhesive is a finished product and ready to

use, exposure from ”mixing and loading” has not been included, which would have been necessary if the wallpaper adhesive had been purchased as a powder that has to be mixed with water before use.

The contribution of airborne exposure in freshly painted rooms is not included in the assessment, as the available data on MI-concentration in such rooms are insufficient for calculation.

6.1.5 Exposure scenarios for toys and hobby products

The selected products are regarded as either being directly aimed at smaller children or it is very likely that they will be used for hobbies by smaller children. For women, exposure to this type of product is expected to take place when participating in hobby work together with smaller children. However, at the time for preparation of the report product no specific methodology for estimating exposure for these types of products was available. Parameters for estimating exposure to MI when using toys and hobby products could have been modified the values based on values from RIVM's Children's Toy Facts Sheet (Bremmer and van Veen, 2002) (cf. recommendation from *Norden* 2012 (Nordic Council of Ministers, 2011)).
It is necessary to adjust the parameters as product types that are directly comparable are not included in the Fact Sheet from RIVM. Moreover, it is considered relevant to introduce a retention factor for calculating the dermal exposure for the hobby products chosen for analysis in this survey. RIVM's Facts Sheet describes the exposure of children to different types of toys, including various hobby products. However, it was assessed that the uncertainty of the results would be considerable which is why the calculation of the dermal dose regarding hobby products is not included in this report. It is expected that the European trade organization, FEICA during 2015 will make a proposal to more product specific and appropriate exposure scenarios for different types of glue (including hobby glue).

6.2 Calculation of exposure to methylisothiazolinone through consumer products

The exposure levels to MI through product categories that have turned out to contain MI were calculated on the basis of realistic worst-case scenarios. The concentration of MI was determined through analysis of selected products from these product categories and the highest measured value was applied when estimating the product's contribution to the total dermal load of MI through consumer products. Regarding toys and hobby products it was decided not to make calculation of exposure, since there was no clear guidance how to set the standard values for the exposure of the specific types of products included in this report.

6.2.1 Calculation of exposure through cosmetic products

Exposure through cosmetic products was calculated on the basis of realistic worst-case scenarios with the application of values for MI content determined through chemical analysis of selected products. Sunscreen has no analytic determination and therefore a worst-case scenario of a content of 100 ppm MI was used. In addition, a worst-case assessment was carried out on the basis of application of the maximum permitted values in cosmetic products, and a corresponding worst-case calculation based on the limit values that are recommended for cosmetic products by SCCS's assessment of MI from 2013, which means maximum 15 ppm in rinse-off products and 0 (zero) ppm in leave-on products (SCCS, 2013).

6.2.1.1 Calculation of adult women's exposure through cosmetic products

Exposure for adult women to MI through cosmetic products is calculated based on the models and parameters selected and explained in the previous chapters.. The results appear in Table 20.
The dermal load is calculated on the basis of the suggested maximum content by SCCS in 2013 and is based on the application of MI without MCI. rAapplication of the combination MCI/MI is permitted up to 15 ppm in cosmeticsat the time for this reports preparation , leading to a correspondingly lower (MCI/MI in a three-to-one ratio) MI content. From the 16th July 2015 leave-on products (cosmetic product) that contain MCI:MI in a three-to-one-ratio must no longer be on the marked.

Product	Weight fraction of MI (analysis data) [ppm] <sample no.>	Based on analysis data	Dermal load [ng/(cm² x day)] Based on maximum permitted content (100 ppm)	Based on recommended maximum content (15 ppm) (SCCS, 2013)
Rinse-off:				
Liquid hand soap	4.8 <20>	1.2	24.4	3.7
Shower gel	71 <4>	0.8	1.1	0.2
Shampoo	55 <17>	4.2	7.6	1.1
Conditioner	59 <19>	1.7	2.9	0.4
SUM (rinse-off)		**7.8**	**36.0**	**5.4**
Leave-on:				
Cleaning wipes	113 <28>	144	137	0
Face serum	51 <24>	73.5	144	0
Moisturiser	41 <18>	114	278	0
Hand cream	23 <26>	60.6	263	0
Body lotion	51 <21>	25.7	50.5	0
Sun screen	100[a]	108	108	0
Deodorant (roll-on)	100 <1>	750	750	0
Hair wax	114 <9>	47.3	41.5	0

a) No analysis data and therefore the maximum permitted content of 100 ppm were used.

TABLE 20
CONTRIBUTION OF COSMETIC PRODUCTS TO ADULT WOMEN'S EXPOSURE TO MI.

Calculation example – shampoo (adult woman):
L(der) = (10^6 µg/g x 10.46 g/day x 0.01 x 55 x 10^{-6}))/(820 cm² + 0.5 x 1110 cm²) = 0.004 µg /(cm² x day)

For a woman's exposure to MI, the greatest contribution was estimated to come from leave-on products where the dermal concentration typically is higher than for the rinse-off products. Among the leave-on products the largest dermal load comes from exposure to deodorant (where other allergen substances, e.g., perfume, also can appear). The same is seen for the calculation of exposure to products with 100 ppm (as a theoretical maximum) where the dermal concentration in leave-on products is greater than for rinse-off products. In their report from 2013, SCCS recommended a maximum MI of 15 ppm for rinse-off products and 0 (zero) ppm for leave-on products, which gives a much lower dermal load for the individual products, and therefore the recommendation is expected to give

a substantial reduction in exposure within cosmetics, if it is implemented. However, there might still be a smaller MI contribution from products preserved with a combination of MCI and MI (in a three-to-one ratio).

Sensitization is a local effect and therefore the sum of exposure on different parts of the body will not be decisive for the development of allergy. The hands and the face are the body areas that most frequently are exposed through cosmetic products, while the body is less exposed.

6.2.1.2 Calculation of three-year-old children's exposure through cosmetic products

Based on models and parameters that were selected and explained in previous chapters, exposure to MI through cosmetic products is calculated for a three-year-old. The results appear from Table 21.

Product	Weight fraction of MI (analysis data) [ppm] <sample no.>	Dermal load [ng/(cm² x day)] Based on analysis data	Dermal load [ng/(cm² x day)] Based on maximum permitted contents (100 ppm)	Dermal load [ng/(cm² x day)] Based on recommended maximum content (15 ppm) (SCCS, 2013)
Rinse-off:				
Liquid hand soap	4.8 <20>	3.3	68.3	10.2
Shower gel	71 <4>	1.1	0.2	0.2
Shampoo	55 <17>	11.5	20.9	3.1
Conditioner	59 <19>	4.6	7.8	1.2
Leave-on:				
Wet wipes	77 <23>	135	176	0
Moisturiser	41 <18>	126	308	0
Body lotion	51 <21>	35.6	69.8	0
Sunscreen	100[a]	400	400	0

a) No analysis data, so the maximum permitted content was used.

TABLE 21
CONTRIBUTION OF COSMETIC PRODUCTS TO THREE-YEAR-OLD CHILDREN´S EXPOSURE TO MI.

The same considerations as for an adult woman manifest themselves in the exposure of a three-year-old, where the largest dermal loads were obtained with leave-on products. The largest contribution comes from the theoretical calculation for sunscreen partly due to the anticipated concentration of 100 ppm and partly due to the large amount that is used. The recommended maximum limits from SCCS are expected to substantially reduce the exposure of children to MI in cosmetics, and especially in relation to using leave-on products.

Sensitization is a local effect and therefore the sum of exposure on different parts of the body will not be decisive for the development of allergy. The hands and the face are the body areas that most frequently are exposed through cosmetic products, while the body is less exposed.

6.2.2 Calculation of exposure through detergents and household cleaning products

The calculated exposure level to MI when washing-up by hand using the content of MI from the analysis of the purchased washing-up liquid is stated in Table 22. No consideration is taken for exposure when handling the container during dilution before use (”mixing and loading”), as the contribution is considered to be small. Non-intentional use, such as use for other types of cleaning, washing hands in the washing-up liquid or using a sponge and concentrated washing-up liquid to wash-up are not taken into account.

Product	Weight fraction of MI (analysis data) [ppm] <sample no.>	Dermal load [ng/(cm² x day)]
Hand washing-up liquid	40 <11>	0.655

TABEL 22
CONTRIBUTION OF DETERGENTS AND HOUSEHOLD CLEANING PRODUCTS TO ADULT WOMEN´S EXPOSURE TO MI.

Calculation example – hand washing-up liquid:

C(der) = (7 g x 10^9 ng/g x 40 x 10^{-6} x 1.17 day^{-1})/5000 cm^3 = 65.5 ng/(cm^3 x day)
L(der) = 65.5 ng/(cm^3 x day) x 0.01 cm = 0.66 ng/(cm^2 x day)

The calculated dermal load is low compared with the cosmetic products, which reflects the considerable degree the product is diluted before exposure and use of the product by the consumer. An anticipated dilution factor of 5000 will give a use concentration of MI of 0.008 ppm. In addition, the product is marked with the text ”Keep out of reach of children. Rinse thoroughly with water, if the product gets into contact with the eyes”. It can be expected that some consumers who frequently wash up by hand to a certain degree take preventive steps by using gloves when a lot of dishes have to be cleaned. Contrary, a smaller dilution than the recommended probably also takes place in practice, which will result in a higher dermal load. In general, the total contribution from hand washing-up liquid is expected to be low compared with cosmetic products. Broadly speaking, the application frequency for detergents and household cleaning products is also expected to be lower, and therefore the frequency of exposure to MI through this product type is limited.

6.2.3 Calculation of exposure through paint, varnish and adhesives

The calculated exposure levels of MI through Do-It-Yourself products such as wall paint, ceiling primer and paperhanging by using water-based wallpaper adhesive appear from Table 23.

Product	Weight fraction of MI (analysis data) [ppm] <sample no.>	Dermal load [ng/(cm² x day)]
Wall paint	135 <12>	237
Wall/ ceiling primer	21 <13>	148
Wallpaper adhesive	13 <14>	114

TABEL 23
CONTRIBUTION OF THE PRODUCT CATEGORIES PAINT, VARNISH AND ADHESIVES TO ADULT WOMEN'S EXPOSURE TO MI.

Calculation example – painting of wall with water-based paint (roll or brush):
L(der) = 30 mg/min x 1000 µg/mg x 120 min/day x 135 x 10^{-6} x 0.4/820 cm² = 0.24 µg/(cm² x day)

The dermal load calculated on the basis of the chemical analyses on paint products, Table 23, is comparable with the values found for cosmetic leave-on products. The frequency of exposure to this type of product is expected to be much lower than for cosmetic products. In addition, the suppliers of the products within this type of product recommend using personal protective measures such as gloves to avoid the transfer of paint to hands. The right choice of gloves with regard to durability against chemicals and penetration time will depend on the product and application, but in general it is recommended to use gloves with a break-through time of more than eight hours, e.g., nitrile or butyl gloves.
In the exposure calculations it is assumed that the exposure concerns the entire palm of the hand, since RIVM's fact sheet gives no information on actual exposed area when painting. The distribution of the product to the skin can therefore not be expected to be the same on the whole area but should be delimited to a smaller area. The calculation will result in an overestimation of the local exposure. Furthermore, exposure calculation for these products was performed using 40% and 80%, respectively of the total product amount used for hand exposure, as recommended by RIVM. This quantity is evaluated to be worst-case exposure in this case (it is not specified on what part of the body, the remaining quantity ends).

6.3 Summary of exposure to methylisothiazolinone through consumer products

In Table 28 the calculated exposures are shown as the dermal load for a woman and a three-year-old child, respectively. Contributions from the individual products show that the greatest exposure is seen from cosmetic products when leave-on products are used. In general, the dermal load is a bit higher for a three-year-old than for a woman under the applied conditions, but is not regarded as significantly higher. For the woman, the highest individual contribution comes from cosmetics when deodorant is used (750 ng/cm²/day), and for the three-year-old the highest contribution comes from sunscreen (400 ng/cm²/day, calculated on a theoretical maximum content of MI of 100 ppm).

The cosmetic products are assumed to be the products that are used most frequently, and that is regarded to be essential for the development of contact allergy. Together with the presence of MI in the rather high concentrations determined through chemical analysis that makes the broad application of MI within this product category problematic in relation to frequent consumer exposure and subsequent development of contact allergy.

The contribution from paint, varnish and adhesives as well as cosmetics is comparable with the calculated dermal load, while hand washing-up liquid only gives a minor contribution to exposure under the applied conditions. In general, it is recommended to take protective measures against exposure (e.g. by using gloves) when using paint,

varnish or adhesives. Minimizing exposure in that way can be compared to a rather low frequency in the application of this product category among the average consumers.

The dermal dose from hobby products was not calculated, since product specific guidance for estimating exposure for these types of products was not available at the present time. Hobby products are not expected to be used every day, but in a much lower frequency than e.g. cosmetic products. Furthermore direct skin contact is not expected to be intentional. But given that the packaging and labelling of the hobby products indicate that they are intended for children who are more than three years old, and therefore they can be expected to be used by children down to the age of three. Therefore, a high MI content in these products is regarded as problematic in relation to developing contact allergy if the product gets in a prolonged and frequently contact with the skin.

Product	Women Dermal load [ng/(cm² x day)]	Three-year-old Dermal load [ng/(cm² x day)]
Rinse-off cosmetics:		
Liquid hand soap	1.2	3.3
Shower gel	0.8	1.1
Shampoo	4.2	11.5
Conditioner	1.7	4.6
Leave-on cosmetics:		
Cleansing tissue	144	-
Face serum	73.5	-
Wet wipe		135
Moisturiser	114	126
Hand cream	60.6	-
Body lotion	25.7	35.6
Sunscreen	217a)	400a)
Deodorant (roll-on)	750	-
Hair wax	47.3	-
Detergents and household cleaning products		
Hand washing-up liquid	0.655	-
Paint, varnish and adhesives		
Wall paint	237	-
Wall and ceiling primer	148	-
Wall paper adhesive	114	-

TABLE 26
OUTLINE OF DERMAL LOAD CALCULATED IN EXPOSURE SCENARIOS FOR AN ADULT WOMAN AND A THREE-YEAR-OLD.

On the basis of the 31 analysed products and their calculated exposure from cosmetic products, detergents and household cleaning products and paint, varnish and adhesives it cannot be expected that all sources of exposure to MI have been included in this evaluation. For instance, the exposure calculations that comprise wet wipes for facial cleansing and for babies do not include wet wipes for other purposes such as cleaning or intimate hygiene. In general, detergents and household cleaning products received low priority when purchasing products for analysis as they are normally used in a diluted form. Besides, few analysis data exist in the literature on that type of products. It is possible that this product category might give a higher contribution to the total exposure than

what this survey indicates, but exposure is expected to be low due to the very low use-concentration (corresponding to 0.008 ppm MI in the analysed product after dilution).

Some consumer products will also contain other isothiazolinones, e.g., the very potent contact allergen MCI (e.g., liquid hand soap, wallpaper adhesive, wall primer and several hobby products). The trend is that patients who are sensitized in relation to MCI/MI also react to MI, which seems to indicate that the two related compounds MI and MCI both can trigger the allergic reaction (SCCS, 2013). Finally, occupational exposure has not been included in the calculations.

In addition, the project has focused on dermal exposure to MI through direct contact with products that the consumer might be exposed to. A consumer can also be subject to MI through airborne exposure from, e.g., paint or household cleaning sprays.

As stated above, a consumer is exposed to MI through many sources. Based on the available clinical knowledge it is according to SCCS not possible to determine a safe threshold value for the use of MI in leave-on cosmetics neither with respect to sensitization nor elicitation of contact allergy. For rinse-off cosmetics, SCCS considers 15 ppm to be a safe concentration of MI with regard to sensitization. From the results of this project, cosmetics are considered to be a major source of exposure to MI as the application frequency is high and MI is currently used in many different cosmetic products. The results also show that MI currently is used in cosmetics in concentrations close to the current limit value of 100 ppm. In relation to the new recommendation from the SCCS, these products may constitute a risk. The use of other products such as paint, varnish, adhesives and cleaning products is also expected to contribute to the exposure of the consumer and the risk of developing contact allergy. Concentrations of approximately 100 ppm MI have been analysed, but the application frequency is often lower in these products. All things considered, consumers are exposed to a wide range of products containing MI in concentrations that according to experts in the field are expected to be problematic in relation to the development of contact allergy.

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Appendix 1: Example of questionnaire sent to companies

Questionnaire – Toys and hobby products

This questionnaire concerns the preservative methylisothiazolinone (MI) in toys and hobby products that are accessible to Danish consumers
In cooperation with the Danish Environmental Protection Agency, Danish Technological Institute is currently surveying the use of the preservative methylisothiazolinone (CAS no. 2682-20-4). In that connection we would like to know if your company sells, makes or imports products into the Danish market that contain methylisothiazolinone. For the sake of good order, we would like to stress that Danish Technological Institute is under a duty of silence regarding company specific information and if your company regards some of the information to be confidential, then we will of course respect that. The objective of the survey is to outline the use and consumer exposure of the substances, but company name, trademark etc. can be treated confidentially.

Methylisothiazolinone – possible applications:
Methylisothiazolinone is a preservative and a biocide that is used in products where there is a risk of microbial growth. It exists in various consumer products such as cosmetics, cleaning agents, paint, glue, printing ink and toys.

In connection with hobby articles and toys, the product groups hobby paint, finger paint, window and glass paint, glue, soap bubbles, play dough and slime are especially expected to contain the substance.

We would be very grateful for your quick response and preferably on XX.XX 2013 at the latest.

If you have any questions to the above, then please do not hesitate to contact us.

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Please state company name and address below:

Questionnaire

	Yes	No
Does your company sell, make or import toys or hobby products?		

What type of products do you sell/make?

Paint	[ ]	Hobby articles	[ ]
Varnish	[ ]	Toys	[ ]
Adhesives	[ ]	Cosmetics	[ ]
Printing ink	[ ]	Cleaning agents / detergents	[ ]

Others:

	Yes	No	Don't know
Do you sell/make products that contain methylisothiazolinone?			

If yes, then please state which products with information about the product name, manufacturer and the concentration of methylisothiazolinone, if possible (please add as many new entries as necessary):

Product name:
Manufacturer:
Concentration of methylisothiazolinone: _____ mg/kg or _____% or_____
Is methylisothiazolinone the only preservative in the product (yes/no)?

Product name:
Manufacturer:
Concentration of methylisothiazolinone: _____ mg/kg or _____% or_____
Is methylisothiazolinone the only preservative in the product (yes/no)?

Product name:
Manufacturer:
Concentration of methylisothiazolinone: _____ mg/kg or _____% or_____
Is methylisothiazolinone the only preservative in the product (Yes/no)?

…please copy the above lines, if more entries are necessary in order to introduce all products.

	Yes	No	Don't know
Is methylisothiazolinone the only preservative in your products?			

If no, which other preservatives are typically used in combination with methylisothiazolinone?
We have identified the use of methylisothiazolinone in paint, adhesives, soap bubbles and slime. Can you point at other product categories in your trade where you have experienced that MI is used?
If you can't share information on specific products, would it instead be possible for you to tell us within which product category and in which concentration methylisothiazolinone typically is used in your business area?

	Yes	No	Don't know
Does it appear from the labelling of your products, if the product contains methylisothiazolinone and is it communicated to the consumer in an obvious way?			

	Yes	No
May we contact you if more questions arise when the results of this questionnaire are processed?		

If yes, then please state your name, e-mail address and/or telephone number:

Survey and Exposure Assessment of Methylisothiazolinone in Consumer Products

Methylisothiazolinone (MI) is a preservative and is found in a wide range of consumer products. Recently, there has been a rapid global increase in incidence of allergies to MI. 31 products within the following four product categories: cosmetics and personal care, detergents and household cleaning products, paints, varnishes and adhesives and toys and hobby products were selected for chemical analysis.

The products contained 1.8-135 ppm MI. Comparison with the existing legislation for cosmetic products including a limit of MI at 100 ppm and with the recent recommendation from SCCS that a content of more than 15 ppm is not safe when used in rinse-off cosmetics products was performed. The report concludes that consumers are exposed to a wide range of products containing MI in concentrations exceeding 15 ppm, while only a few products contained more than 100 ppm.

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