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Consumer risk assessment for nanoproducts on the Danish market

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Consumer risk assessment for nanoproducts on the Danish market

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Preface

Nanomaterials (NM) are applied in a wide range of consumer products and the commercial use of NM in both amount and diversity is anticipated to increase rapidly in the near future. It is increasingly recognised that NM may have unique properties as compared to larger particles sizes of the same substances, favouring the use of NM in products, articles and technologies. At the same time, concerns in relation to possible health and environmental properties and impacts of NM have surfaced.

Based on this background, the Danish government and the Red-Green Alliance (in Danish, Enhedslisten) have signed an agreement for four years (2012-2015) that focuses on the use of nanomaterials in products on the Danish market and their consequences to consumers and the environment. The Danish Environmental Protection Agency (EPA) has initiated a series of projects with the aim of further clarifying possible risks to consumers and the environment.

The current project addresses consumer exposure and risk assessment of nanomaterials in products on the Danish market. It runs from the third quarter of 2013 through the second quarter of 2015.

The project is foreseen to result in four reports:

- Occurrence and exposure assessment of nanomaterials in consumer products and review of available risk assessment tools (Danish EPA, 2015a)
- Hazard assessment of nanomaterials in consumer products (Danish EPA, 2015b)
- Human exposure to nanomaterials in the environment – as a reference to nanomaterials exposure from consumer products (Danish EPA, 2015c)
- Consumer risk assessment and overall conclusions (the current report).

The project has been implemented with support from a reference group:

- Susan Dekkers, National Institute for Public Health and the Environment (RIVM), The Netherlands
- Andrea Haase, Bundesinstitut für Risikobewertung (BfR), Germany
- Gregory Moore, Swedish Chemicals Agency (KEMI), Sweden
- Derk Brouwer, Netherlands Organisation for Applied Scientific Research (TNO), The Netherlands
- Lena Høglund (Danish EPA)
- Katrine Bom (Danish EPA)
- Anne Mette Boisen (Danish EPA)
- Kim Petersen (Danish EPA).

The reference group has assisted with comments and ideas, but is not responsible for the content of the project reports.

Summary and conclusions

It should be stressed that the results presented in this project are based on initial and often worst case risks assessments based on current knowledge. The results and conclusions are therefore associated with uncertainties. Arriving at firmer conclusions would require data generation, as well as further detailed information on use and possible nanomaterial content of consumer products.

The results should therefore not be cited or used without also citing associated assumptions and uncertainties.

Background and purpose
Under the Agreement "Better Control of Nanomaterials" (“Bedre styr på nanomaterialer”), the Danish EPA has commissioned a number of projects aiming to investigate and generate new knowledge on the presence of nanomaterials in products on the Danish market and assess the possible associated risks to consumers and the environment.

Nanomaterials are increasingly applied in consumer products. The current project has addressed how consumers might be exposed to nanomaterials as contained in or released from consumer products, and assessed whether the exposure could be considered to constitute a consumer risk. This report is the final report from this project.

Approach
Based on a review of existing information and in dialogue with an international expert reference group, 20 consumer products were selected for risk assessment. The products were chosen as being representative of some typical consumer products from different product types/categories and covering various exposure routes, exposure levels and nanomaterials (7 different nanomaterials were addressed).

Thus, although care should be taken not to over-generalise from assessment of "only" 20 products, it is believed that the findings of the project provide valid examples illustrating consumer exposure and risk based on the current state of knowledge.

Still, the conclusions reached should be interpreted with care given the range of uncertainties associated with available exposure and hazard data, as well as methodologies for assessing these data in a consumer risk context.

Given these uncertainties and the scope of the project, the risk assessments performed in the current report have generally used worst case assumptions. Thus, the following should be seen merely as indications of "probably high" and "probably low" rather than as conclusive risk assessments.

As noted in the preface and further discussed in Chapter 2, earlier reports from the project have in more detail addressed: nanomaterials in consumer products, the choice of the 20 exposure scenarios, as well as exposure and hazard assessment of these scenarios. Furthermore, a report addressing population exposures to environmental sources of nanomaterials (as e.g. from ambient air and indoor air) has been published.

The current report aims at:

- Assessing consumer risks associated with 20 selected consumer exposure/use scenarios
- Integrating the learnings from these assessments with findings from previous activities of the project
- Discussing and putting into perspective what we know about the overall exposure and risks for Danish consumers, also considering other sources of nanomaterials exposure
- Identifying main gaps in knowledge and methodologies for assessing consumer exposure.

Results

Embedded nanomaterials. In many products, such as composite materials, sports equipment and plastic products, the incorporated nanomaterials are embedded in a solid matrix or bound on a surface. As long as the nanomaterials remain there, they will not lead to consumer exposure and risks. During the consumer use phase, such nanomaterials might however be released as a result of breakage, wear or mechanical impact such as cutting, sanding or drilling. In general, data on such releases are limited and further data are warranted; however, a number of careful conclusions can be reached. In general, it is assessed that general wear does not lead to significant exposures and thereby risks, whereas knowledge associated with releases following mechanical impact appears to point in different directions, depending on the energy put into the process and how the nanomaterial is bound in or on the article, as well as how it is possibly released. Sanding dust from surfaces treated with paint/lacquer in which the nanomaterials are bound in an acrylic/epoxy matrix does not appear to be more toxic than sanding dust from surfaces painted with non-nanomaterials containing paint, as the nanomaterials are largely released as embedded in this acrylic/epoxy matrix. On the other hand, a water-based primer where the nanomaterial (e.g. nano-TiO_2) is assumed to be more freely bound to the surface might lead to an inhalation risk following sanding, as assessed in this project. Similarly, even though releases are likely quantitatively rather low, release of carbon nanotubes from cutting/sanding composite materials or sports equipment may not be ruled out, and given the high hazard associated with some types of carbon nanotubes, even small exposure levels could potentially be associated with risk.

Inhalation. The inhalation route is generally considered the most critical exposure route following nanomaterial exposure. In line with this consideration, the current project has also identified risks or possible risks following inhalation of nanomaterials in powder products (such as nano-silica containing face powder and nano-TiO_2-containing cement), or following spraying. In particular, consumer spraying with a spray gun should be avoided (or at least conducted with appropriate use of personal protective equipment, which might not be available/properly used by the consumer); as well, use of propellant sprays (e.g. with nano-Ag, nano-silica, nano-TiO_2 or nano-ZnO) may be associated with risks. Based on the available knowledge, it is qualitatively assessed that the use of pump sprays will likely not lead to significant exposures and thereby risks, but further data on this assessment and on exposure following propellant spraying are necessary for more robust conclusions.

Oral exposure. More surprisingly, the risk assessments performed in the current study indicate possible/uncertain risks associated with oral intakes of food additives (nano-TiO_2 fraction in E171 and nano-silica fraction in E551) and nano-TiO_2/nano-ZnO in sunscreens following ingesting of sunscreen applied to the lips. An additional oral intake following children licking fingers might take place. Regarding food additives, new hazard data - published after the current scientific opinions were prepared by EFSA (The European Food and Safety Authority) – should likely be taken into account in the current EFSA re-evaluation of these opinions. In relation to sunscreen wherein the use of nano-TiO_2 and nano-ZnO has been assessed by SCCS (Scientific Committee on Consumer Safety), it might be warranted to conduct more quantitative estimations of the possible oral intake. Specifically for nano-TiO_2, it is important to examine whether recent data on oral toxicity would be relevant for the type of nano-TiO_2 used in sunscreens. Based on these assessments, more quantitative risk assessments might be performed. The authors of the current report are aware that

the worst case assessments performed in this project overestimate possible risks and, given the protection against UV-light (and possible skin disorders) provided by sunscreens, it is not currently recommended to discontinue their use. However, it is recommended to reduce oral intake of the sunscreens if possible. Other types of oral consumer exposures are assumed to be negligible or very low and are not assessed as leading to possible risks.

Dermal exposure. In general, consumer dermal exposure to nanomaterials may be significant (e.g. from sunscreens, other cosmetics, paints and spray deposition). However, the available data indicate that most nanomaterials are not likely to lead to local dermal effects, or to become systemically available as absorption is negligible through the skin. Exceptions are some carbon-based materials (e.g. some types of carbon nanotubes), which might lead to skin irritation effects, as well as nano-Ag and nano-ZnO, which are known to lead to low level dermal absorption following dermal exposure (possibly of the dissolved silver and zinc ions). Dermal exposure levels to these compounds are, however, not assessed to lead to consumer risks. Therefore, based on current evidence, dermal exposure to nanomaterials in consumer products is not likely to lead to any significant risk.

Perspective

In an attempt to put the obtained results/conclusions into perspective, we have compared the consumer risk assessment findings with typical exposure situations in the working environment, as well as indoor and outdoor exposure to ultrafine particles from other sources in the indoor and outdoor environment.

Generally, occupational dermal and inhalation exposure levels are higher and the exposure is of longer duration as compared to consumer exposures, because of handling of larger quantities/more product for longer periods (full working days) and because workers handle free nanomaterials in powder form to a larger extent than consumers do. On the other hand, workers are assumed to work in ventilated areas and to use high-quality personal protective equipment to a much larger extent than consumers do. Direct oral exposure is not frequent in the workplace, but it should be acknowledged that a significant fraction of inhaled particles may be cleared from the respiratory tract by the mucous layer and swallowed. Inadvertent oral exposure is therefore a potential route for significant oral exposure to some nanomaterials.

The general public might be exposed to rather high levels of particulate matter/ultrafine particles in ambient air (e.g. from traffic), in the indoor environment (e.g. following use of candles), and after cooking or in association with use of electrical/heating equipment. Available data indicate that, in particular, indoor exposures as measured in particle numbers reach very high levels. Based on available data, these exposures are at a significantly higher level and the exposure is of longer duration than exposure following use of consumer products. However, in three consumer exposure scenarios considered in this project (spray painting, sanding of dried paint and handling of cement), the estimated consumer exposure exceeded the indoor and outdoor exposure to ultrafine particles from other sources (when the concentration of the nanomaterials is quantified by the total mass of the particles). Although this quantification provides some indication of the magnitude of the various types of exposure, it may be questioned whether direct comparison of exposure levels without considering the different sources and the different characterization of the particles with respect to chemistry, size distributions etc. is valid. It has to be noted that limited physicochemical characterisation of particles is available, in particular for those particles generated in the indoor environment.

Trends

The use of nanomaterials and nanotechnology in general, and specifically in relation to consumer products, is predicted to increase in years to come. This increase pertains to amounts, diversity and market value of nanomaterials and nano-enabled products.

More sophisticated next-generation nanomaterials and nanotechnology solutions, such as self-assembly systems, may appear and need a different approach for assessing consumer health risks and possibly also other societal and ethical risks.

Uncertainties/data gaps

The following main uncertainties/data gaps have been identified in the current project:

- Many current inventories/databases list consumer products as possibly containing nanomaterials based on claims. "Nano" may sometimes be used as a sales parameter and evidence is not always available that such products actually contain nanomaterials. On the other hand, products containing nanomaterials but not claimed to be containing "nano" are not captured in these inventories/databases. This discrepancy is the main uncertainty associated with the exercise performed in the current project.
- If a nanoproduct is known to contain nanomaterial(s), there is generally limited information available on the chemical *identity* and/or characterisation of nanomaterials applied in consumer products (e.g. *surface modifications, particle size distributions*, etc.). This lack of information makes it difficult to match estimated exposures with appropriate hazard information in order to estimate the risk.
- Lack of a clear description of the physical *state of the nanomaterial* that the consumer is exposed to as released from the product (*free, agglomerated/aggregated, bound to a matrix, potential for migration/liberation, etc.*) leads to uncertainty. The nanoparticles to which the consumer will be exposed will in many cases be bound in a matrix or on a surface, where the potential release from the matrix (e.g. release from highly viscous droplets) or a surface layer (e.g. release of sanding fragment) is difficult to quantify as compared to exposure from soluble chemicals. Thus, the extent to which the nanomaterial can be released/migrate from the product matrix may be uncertain, and this very much influences the actual oral, dermal or pulmonary exposure and associated risk.
- Related to this, few hazard data in matrices on nanomaterials to which the consumer is exposed exist. Generally, hazard data for pristine nanomaterials have been conservatively applied in the current project, in absence of hazard data for the nanomaterials in matrices.
- Further, as detailed characteristics of the nanomaterials are often not available, the information used for evaluation of nanomaterials today may be based on data generated for different forms of the particles with varying surface area, coating or size distribution. There is little data on how these physico-chemical parameters influence toxicity. The quality of data varies significantly and test results with insufficient characterisation of the nano form may be included in the evaluations leading to uncertainty.
- On top of this, it is still challenging to recommend scientifically based assessment factors for nanomaterials for derivation of Derived No-Effect Levels (DNELs).
- Whereas semi-quantitative *oral and dermal exposure* assessment may be addressed in a rather simplistic and transparent way using few assumptions concerning e.g. the amount ingested or the amount applied on skin, it may be more difficult or complex to obtain semi-quantitative/quantitative estimates on *inhalational exposure*. This difficulty occurs because multiple factors in addition to the volume used may affect exposure. A key parameter is the concentration in the air in a subject's breathing zone, which depends on various factors such as emission rate of droplets/solid particles into air from the product, the air exchange rate in the room, particle size distribution, agglomeration and deposition rate of the different particle sizes in the airways, the subject's distance to the emission source (e.g. spray), and the breathing rate and breathing volume of the subject.

- Linked to this, and particularly relevant for inhalation exposure, exposure estimation data (based on measurements or models) and hazard data are often based on the mass of the nanomaterials (e.g. mg/m^3) rather than in metrics generally considered more relevant for nanomaterials, such as the concentration of particles or the surface area of the particles.
- Exposure estimation for chemicals in general is often performed using exposure estimation tools. Many of these tools have limitations in relation to assessing nanomaterials exposure (especially inhalation exposure). Potential tools for exposure, hazard and risk assessment of nanomaterials are not yet fully developed/validated and/or have limited scopes limiting their use in risk assessment.

Sammenfatning og konklusion

Resultaterne i dette projekt er baseret på indledende og ofte temmeligt konservative/worst case risikovurderinger baseret på aktuel viden. Resultater og konklusioner er derfor forbundet med usikkerhed. Mere sikre konklusioner ville kræve generering af nye data, samt mere detaljerede oplysninger om anvendelse af og muligt indhold af nanomaterialer i forbrugerprodukter.

Resultaterne bør derfor ikke citeres eller anvendes uden at også tilhørende forudsætninger og usikkerheder citeres.

Baggrund og formål
Under overskriften "Bedre styr på nanomaterialer" har den danske Miljøstyrelse iværksat en række projekter, der sigter på at undersøge og generere ny viden om forekomsten af nanomaterialer i produkter på det danske marked og vurdere potentielle risici for forbrugerne og miljøet.

Nanomaterialer anvendes i stigende grad i forbrugerprodukter, og nærværende projekt har undersøgt, hvorledes forbrugerne kan blive udsat for nanomaterialer, der er indeholdt i eller frigives fra forbrugerprodukter, samt vurderet, om eksponeringen kan anses for at udgøre en forbrugerrisiko. Dette er den afsluttende rapport for dette projekt.

Metodisk tilgang
Baseret på en gennemgang af eksisterende viden og i dialog med en international referencegruppe, er 20 forbrugerprodukter blevet udvalgt til risikovurdering. Produkterne blev udvalgt som repræsentative for forbrugerprodukter dækkende forskellige produkttyper og -kategorier, og for at repræsentere forskellige eksponeringsveje, eksponeringsniveauer og nanomaterialer (omfatter i alt 7 forskellige nanomaterialer).

Selvom der bør tages forbehold i forhold til at generalisere fra en vurdering af "kun" 20 produkter, vurderes det, at resultaterne af projektet repræsenterer pålidelige eksempler vedrørende forbrugereksponering og -risiko baseret på den aktuelle viden.

Dog bør konklusionerne fortolkes med stor forsigtighed, da der er en række usikkerheder forbundet med de eksisterende data om eksponering og de iboende egenskaber af nanomaterialerne, samt usikkerheder forbundet at benytte de nuværende metoder til vurdering af risici forbundet med forbrugernes anvendelse/håndtering af nanoprodukter.

Givet disse usikkerheder og omfanget af projektet, bygger risikovurderingerne i nærværende rapport generelt på konservative/worst case antagelser. Konklusionerne vedr. risici bør derfor fortolkes som "sandsynligvis høj" og "sandsynligvis lav" snarere end som absolutte vurderinger af risici.

Som nævnt i forordet (Preface) og yderligere diskuteret i kapitel 2, har tidligere projektrapporter mere detaljeret omtalt viden vedr. forekomsten af nanomaterialer i forbrugerprodukter, baggrunden for valg af de 20 eksponeringsscenarier, samt eksponering og farevurdering i henhold til disse scenarier. En anden tidligere publiceret rapport har undersøgt befolkningens eksponering for miljømæssige kilder til nanomaterialer, især mht. eksponeringen fra luften i ude- og inde-miljøet.

Den aktuelle rapport har til formål at:

- Vurdere forbrugerrisici forbundet med 20 udvalgte eksponerings/anvendelsesscenarier
- Integrere viden fra disse vurderinger med resultaterne fra tidligere aktiviteter i projektet
- Diskutere og perspektivere hvad vi ved om den samlede eksponering og risici for de danske forbrugere, herunder i forhold til eksponering af nanomaterialer fra andre kilder
- Identificere datamangler i viden og metoder til vurdering af forbrugernes eksponering

Resultater

Indlejrede nanomaterialer. I mange produkter, såsom kompositmaterialer, sportsudstyr og plastprodukter, er indholdet af nanomaterialer indlejret i en fast matrice eller bundet på en overflade. Så længe nanomaterialerne bliver der, vil de ikke føre til forbrugereksponering og -risici. Under anvendelse af artiklerne kan nanomaterialerne evt. frigives som følge af brud, slid eller mekanisk påvirkning, såsom skæring, slibning eller boring. Data vedr. frigivelse fra sådanne processer er begrænsede, og det er relevant at genere yderligere viden. Dog kan der gives et par forsigtige konklusioner på basis af nuværende viden. Generelt vurderes det, at almindelig slitage ikke vil føre til væsentlige eksponeringer og dermed risici, hvorimod viden om frigivelse i forbindelse med mekanisk påvirkning synes at pege i forskellige retninger afhængig af den energi som tilføres processen, hvordan nanomaterialet er bundet i eller på artiklen, samt hvordan det eventuelt frigives. Slibestøv fra overflader behandlet med maling/lak, hvor nanomaterialer er hårdt bundet i en akryl/epoxy matrice, synes ikke at være mere toksiske end slibestøv fra overflader som ikke indeholder nanomaterialer. Dette skyldes, at de indeholdte nanomaterialer stort set frigives i en form, hvor de er indlejret i denne akryl/epoxy matrice. På den anden side, som vurderet i dette projekt, kan en vandbaseret primer, hvor nanomaterialer (f.eks. nano-titaniumdioxid) antages at være mere frit bundet til overfladen, muligvis medføre indåndingsrisiko ved slibning. Selvom frigivelsesraten formentlig er ret lav, kan frigivelse af kulstof-nanorør ved skæring/slibning af kompositmaterialer eller sportsudstyr, muligvis medføre risici, da nogle typer kulstof-nanorør er meget giftige.

Indånding. Indånding betragtes generelt som den mest kritiske eksponeringsvej for nanomaterialer. På linje med dette, har også nærværende projekt identificeret risici eller mulige risici forbundet med indånding af nanomaterialer i pulverformige produkter (såsom nano-silica i ansigtspulver og nano-titaniumdioxid i cement), eller som følge af spray applikationer. Specielt sprøjtning med sprøjtepistol bør undgås, medmindre sprøjtning gennemføres med passende brug af personlige værnemidler. Dog er passende værnemidler muligvis ikke til rådighed for forbrugeren, som ydermere sandsynligvis ikke er uddannet i korrekt brug af disse værnemidler. Også anvendelse af sprays med drivmidler (f.eks. med nano-sølv, nano-silica, e.g. nano-titaniumdioxid eller nano-zinkoxid) kan være forbundet med risici. På basis af den tilgængelige viden vurderes det kvalitativt, at anvendelse af pumpesprays næppe vil føre til væsentlige eksponeringer og dermed risici, men yderligere data/viden om eksponering forbundet med anvendelse af alle typer sprays er nødvendig for at kunne foretage en mere sikker vurdering.

Oral eksponering. Mere overraskende indikerer risikovurderingerne i dette projekt mulige risici forbundet med oralt indtag af tilsætningsstoffer (f.eks. nano-titaniumdioxid fraktionen i fødevaretilsætningsstoffet E171 og nano-silica fraktionen i E551), samt nano-titaniumdioxid og nano-zinkoxid i solcremer efter indtagelse af solcreme/solpomade anvendt på læberne. Yderligere oral indtagelse som følge af at små børn slikker på fingrene vil kunne forekomme. I forhold til tilsætningsstoffer er der efter udarbejdelse af de nuværende videnskabelige udtalelser fra EFSA (Den Europæiske Fødevaresikkerhedsautoritet) fremkommet ny viden om nanomaterialernes farlighed. Det antages, at denne nye viden tages i betragtning i EFSAs igangværende revurdering af udtalelserne for E171 og E551. I relation til solcreme, hvor brugen af nano-titaniumdioxid og nano-zincoxid er blevet vurderet af SCCS (Den Videnskabelige Komité for Forbrugersikkerhed), synes det berettiget at foretage mere kvantitative vurderinger af det mulige orale indtag. For nano-

titaniumdioxid vil det endvidere være berettiget at vurdere, om de nye faredata vedr. oral indtag af en bestemt type nano-titaniumdioxid er relevante for den type nano-titaniumdioxid, som anvendes i solcreme. På basis af sådanne vurderinger kan der udføres opdaterede, kvantitative risikovurderinger. Forfatterne af denne rapport er opmærksomme på, at de worst case vurderinger, som er foretaget i dette projekt, overvurderer mulige risici. Givet solcremers beskyttelse mod UV-lys (og eventuelle hudlidelser), anbefales det ikke på nuværende tidspunkt at undlade at anvende solcremer. Det anbefales dog, så vidt muligt at reducere det orale indtag af solcremer. Oralt indtag af nanomaterialer fra andre typer af produkter, antages at være ubetydeligt eller meget lavt, og vurderes derfor til ikke at føre til mulige forbrugerrisici.

Dermal eksponering. Forbrugere kan udsættes for betydelige hudeksponeringer for nanomaterialer (f.eks. fra solcremer, anden kosmetik, maling og fra anvendelse af sprays). Dog tyder de foreliggende data på, at de fleste nanomaterialer sandsynligvis ikke vil medføre lokale effekter på huden, og at de ikke i væsentligt omfang bliver systemisk tilgængelige som følge af absorption gennem huden. Undtagelser er nogle kulstof-baserede materialer (f.eks. nogle typer af kulstof-nanorør med urenheder), som kan medføre irritation, samt nano-sølv og nano-zinkoxid, som er kendt for at medføre begrænset dermal absorption som følge af dermal eksponering (sandsynligvis er det dog de opløste sølv- og zinc-ioner brugeren som optages). Dermale eksponeringsniveauer for disse nanomaterialer skønnes dog ikke at medføre forbrugerrisici. Alt i alt indikerer den nuværende viden, at det ikke kan forventes, at dermal eksponering for nanomaterialer i forbrugerprodukter medfører væsentlige forbrugerrisici.

Perspektivering

I et forsøg på at perspektivere de opnåede resultater/konklusioner, har vi sammenlignet resultaterne fra forbrugerrisikovurderingerne med typiske eksponeringer i arbejdsmiljøet, såvel som med typisk eksponering for ultrafine partikler fra andre indendørs og udendørs kilder end forbrugerprodukter.

Generelt er er den erhvervsmæssige eksponering via hud og indånding på et højere niveau og af længere varighed end forbrugernes eksponering, da der håndteres større mængder/flere produkter i løbet af en hel arbejdsdag, og da arbejdere håndterer frie nanomaterialer i pulverform i større udstrækning end forbrugerne. På den anden side, antages arbejdere at arbejde i ventilerede områder og at anvende personlige værnemidler i langt højere udstrækning (og af bedre kvalitet) end forbrugerne. Direkte oral eksponering er mindre væsentlig i forbindelse med arbejdsmæssig håndtering, men det kan nævnes, at en betydelig del af de inhalerede partikler kan fjernes via slimlaget i luftvejene, som efter transport op i svælget sluges og derved give anledning til oralt indtag. Utilsigtet oral eksponering er derfor en potentiel betydelig oral eksponeringsvej for nogle nanomaterialer.

Den almindelige befolkning kan blive udsat for temmeligt høje niveauer af partikler/ultrafine partikler i luften (f.eks. fra trafik), i indeklimaet (f.eks. efter anvendelse af stearinlys) samt ved tilberedning af mad eller i forbindelse med anvendelse af elektriske apparater og varmeanlæg. Den tilgængelige viden tyder på, at især indendørs eksponeringer målt i partikelantal når meget høje niveauer. Baseret på tilgængelige data synes disse eksponeringer at være på et betydeligt højere niveau og af længere varighed end den eksponering, der kan forekomme ved anvendelse af forbrugerprodukter. I tre forbruger-eksponeringsscenarier, der er undersøgt i dette projekt (spraymaling, slibning af tørret primer og håndtering af cement), anslås det dog, at eksponeringen overstiger indendørs og udendørs eksponering for ultrafine partikler fra andre kilder (når koncentrationen af nanopartikler angives som den samlede masse af partiklerne). Selvom sammenligning af miljømæssig eksponering og forbrugereksponering kan give en ide mht. omfanget af eksponering for nanopartikler, skal man være meget varsom med at sammenligne disse eksponeringer uden at tage hensyn til at partiklerne kommer fra forskellige kilder, og at partiklerne er forskellige mht. kemisk sammensætning, partikelstørrelsesfordelinger mv. I den forbindelse skal

det nævnes, at der er meget begrænset viden særligt om sammensætningen af ultrafine partikler i indeluften.

Trends

Anvendelsen af nanomaterialer og nanoteknologi forventes at stige, og det gælder også anvendelsen i forbrugerprodukter. Såvel mængder som mangfoldighed af nanomaterialer forventes at stige i de kommende år, og dette gælder også for markedsværdien af nanomaterialer og produkter med nanomaterialer.

Sofistikerede "næste-generations" nanomaterialer og nanoteknologi-løsninger, såsom selvsamlende systemer, vil muligvis fremkomme og de vil muligvis kræve en anden tilgang til vurdering af sundhedsrisici for forbrugere og muligvis kræve, at også andre samfundsmæssige og etiske risici adresseres.

Usikkerheder / manglende data

Følgende overordnede usikkerheder/datamangler er blevet identificeret i nærværende projekt:

- Viden om nanomaterialer i produkter findes i stor udstrækning i en række opgørelser/databaser, som oplister forbrugerprodukter som sandsynligvis indeholder nanomaterialer. Disse lister er dog baseret på leverandørernes anprisninger. "Nano" som anprisning anvendes undertiden som en salgsparameter, og der er derfor ikke altid dokumentation for, at sådanne produkter rent faktisk indeholder nanomaterialer. På den anden side vil produkter som indeholder nanomaterialer, men som ikke anprises, ikke optræde i disse opgørelser/databaser. Dette er den væsentligste usikkerhed forbundet med det aktuelle projekt.
- Når det vides at et produkt indeholder nanomaterialer, er der typisk begrænset viden om den kemiske identitet og/eller karakterisering af det eller de nanomaterialer, som produktet indeholder (f.eks. overflademodifikationer, partikelstørrelsesfordelinger, osv. af de indeholdte nanomaterialer). Dette gør det vanskeligt at sammenholde estimerede eksponeringer med passende oplysninger om nanomaterialets toksicitet og derved at kunne vurdere risikoen.
- Mangel på entydig viden om den fysiske tilstand af det nanomateriale, som forbrugers eksponeres for (frit, agglomereret/aggregeret, bundet i en matrice, potentiale for migration/frigivelse, etc.), fører til usikkerhed. I mange tilfælde vil nanopartiklerne som forbrugeren kan eksponeres for være bundet i en matrice eller hæftet til en overflade, hvor den potentielle frigivelse fra matricen (f.eks. frigivelse fra højviskøse dråber) eller overfladen (f.eks. frigivelse af slibefragmenter) er vanskelig at kvantificere. Dette adskiller sig fra gængs eksponeringsvurdering for opløselige kemikalier. Således kan det være meget usikkert, i hvilket omfang nanomaterialet kan frigives/migrere fra den matrice det er bundet i, og dette kan i høj grad påvirke den faktiske eksponering via hud, indtag og/eller indånding, og derved den mulige risiko.
- Relateret til dette, er der meget få data om de iboende egenskaber af nanomaterialer, som er bundet i de matricer, som forbrugeren udsættes for. I mangel af faredata for nanomaterialer som del af disse matricer, har nærværende projekt generelt konservativt anvendt faredata for de frie nanomaterialer.
- Endvidere er der ofte ikke detaljerede karakteristika af de nanomaterialer, der anvendes til tests af iboende egenskaber. Derfor vil evaluering af nanomaterialer i dag være baseret på data, der er generet for nanomaterialer med varierende overfladeareal, overflademodificering eller størrelsesfordeling. Der er begrænset viden om, hvordan disse fysisk-kemiske karakteristika influerer på toksiciteten. Kvaliteten af rapporterede toksicitetsdata varierer derfor betydeligt og testresultater med utilstrækkelig karakterisering af den testede nano form kan indgå i evalueringerne, hvilket leder til usikkerhed.

- I tillæg til dette, er det stadig en udfordring at anbefale videnskabeligt baserede vurderingsfaktorer for nanomaterialer til bestemmelse af afledede nuleffektniveauer (Derived No-effect Levels - DNELs).
- Semikvantitative vurderinger af orale og dermale eksponeringer kan typisk gennemføres relativt enkelt og gennemskuelig på basis af et begrænset antal antagelser, såsom den mængde som indtages, eller den mængde som påføres huden. Det kan være mere vanskeligt eller kompliceret at opnå semikvantitative/kvantitative skøn for eksponering via inhalation. Dette skyldes, at flere faktorer ud over den anvendte mængde påvirker eksponeringen. En vigtig parameter er koncentrationen i luften i en persons vejrtrækningszone, der afhænger af forskellige faktorer såsom emission af dråber/faste partikler til luften fra produktet, luftskiftet i rummet, partikelstørrelsesfordeling, agglomerering og deponering/sedimentering af forskellige partikelstørrelser, personens afstand til emissionskilden (f.eks. spray), samt frekvens og volumen af personens vejrtrækning.
- I tilknytning hertil, og især relevant for eksponering ved indånding, er eksponeringsniveauer (baseret på målinger eller modeller) og faredata ofte baseret på massen af nanomaterialer (f.eks. i mg/m³), snarere end på enheder som generelt anses for at være mere relevante for nanomaterialer såsom koncentrationen af partikler eller overfladearealet af partiklerne.
- Vurdering af kemikalieeksponering udføres ofte ved hjælp af eksponeringsmodeller/-værktøjer. Mange af disse værktøjer har begrænsninger i forhold til at vurdere eksponering for nanomaterialer (især eksponering ved indånding). Generelt er de tilgængelige værktøjer til eksponerings-, fare- og risikovurdering af nanomaterialer således ikke fuldt udviklede/validerede og/eller har meget begrænsede anvendelsesområder, hvilket begrænser deres anvendelse for nanomaterialer.

1. Introduction

1.1 Background

Nanomaterials are found in a wide range of consumer products and the commercial use of nanomaterials is anticipated to increase rapidly in the future, both in quantity and diversity. It is increasingly recognised that materials in the nano form may have unique properties as compared to the microforms and macroforms of the same material. These properties favour the use of nanomaterials in products, articles and technologies. At the same time, concerns in relation to the possible health and environmental properties and impacts of nanomaterials have surfaced.

The current project aims at assessing whether nanoproducts (i.e. products containing nanomaterials) might constitute a risk for Danish consumers and what the main knowledge gaps would be in relation to assessing such risks.

The project has been divided into five work packages and been followed by a steering group and an international reference group.
Figure 1 provides an overview of the project, including how WP1-4 (the results of the WPs are published in three reports from the Danish EPA (2015 a,b,c)) are feeding into the final assessments and conclusions (WP5) presented in the current report.

Chapter 2 will address in further detail how the results of these previous activities have been used to feed into the risk assessments and overall conclusions presented in the current report.

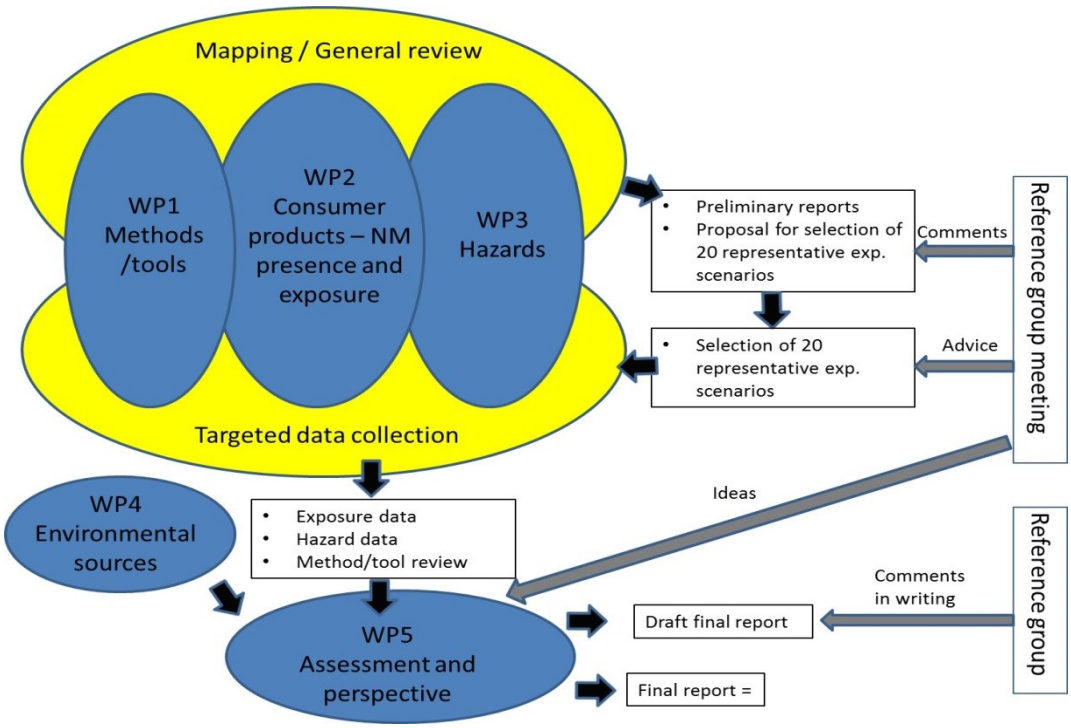

FIGURE 1
OVERVIEW OF PROJECT ACTIVITIES – THE CURRENT REPORT ADDRESSES WP5

1.2 Objectives

The objectives of the current report are to:

- Assess consumer risks associated with 20 selected consumer exposure/use scenarios
- Integrate the learnings from these assessments with findings from previous activities of the project
- Discuss and put into perspective what we know about the overall exposures and risks for Danish consumers, also considering other sources of nanomaterials exposure
- Identify main gaps in knowledge and methodologies for assessing consumer exposure.

1.3 Scope and delimitations

Some product groups/categories are outside the scope of this project, such as pharmaceuticals and tattoo colours, whereas medical devices (those related most closely to consumer use), food and food contact materials are within the scope. Also, the consumer life cycle steps after the initial consumer use of the product are included (e.g. wear of a product or sanding of a painted surface).

It should be noted that the project addresses *consumer* exposure to the nanomaterial in or released from a nanomaterial-containing product and possibly associated risks. Therefore, the project does not assess possible environmental impacts nor impacts in other life cycle stages (such as manufacturing/production and the waste stages). However, a general comparison/perspective is made in relation to how consumers might be exposed to nanomaterials and ultrafine particles from other sources (e.g. heating and combustion sources) and/or as a worker.

As is further detailed in Chapter 2, the product-specific assessments made in this report are generally based on likely worst case/highly conservative assumptions. On the other hand, deliberate or extreme misuses of consumer products will not be considered.

It should also be noted that the report addresses nanomaterials, products and articles assessed to be (or likely be) on the market today - often referred to as “first-generation” nanomaterials.

1.4 Consistency

New knowledge and information related to content and assessment of nanomaterials are continuously becoming available even during this project. Furthermore, the risk assessments performed in the current project report have provided new insights not realised in the previous reports of the project. Therefore, although we believe that the overall line of arguments and conclusions is consistent among the project reports, details may differ.

1.5 Terminology

Having a strict definition of "nanomaterial" in a project like this is difficult, as "nanomaterial" is used broadly by different authors without defining their understanding of the term. However, as a general rule of thumb, the current report refers to the European Commission's recommendation for definition of nanomaterials (European Commission, 2011). It should be noted that there are also other definitions, e.g. ISO/TS 80004-4, defining nanomaterials as having internal structures or surface structures in the nanoscale, thus including nano-objects and nanostructured materials.

Nano-scale or *nano-size* generally refers to sizes below 100 nm.

In this report, the term "nanoproduct" designates mixtures and articles containing nanomaterials. The term is used for a product containing (or claimed to contain) manufactured nanomaterials, and may cover products with even small amounts/contents of nanomaterials.

Product categories are defined by the purpose of the products e.g. food, cosmetics, or cleaning agents. However, there may be some overlap between the categories, e.g. paint could be placed in the "coating and impregnation" category as well as in the category for "construction materials". In addition, some cleaning agents could be placed in the category for "coating/impregnation" as well.

Product types reflect a subdivision of the product category, i.e. cosmetics contain product types such as shampoo, body lotion, and mascara.

The *Formulation* of a product describes whether the product is in a spray can, whether it is a liquid or solid. Thus, a formulation may be determined by the chemical content and matrix of a product in combination with the design, volume and packaging/container of the products.

Matrix is the physical entity in which the nanomaterial is contained. The nature of the matrix may be important as it determines the extent to which there is potential for liberation of the nanomaterial, e.g. whether the nanomaterial is tightly bound in a solid matrix or more freely available in a liquid matrix.

*Exposur*e estimates (as derived in WP2) refer as a starting point to the *external exposure* of the human body to nanomaterial; thus, the external exposure takes into account the extent to which the nanomaterial is liberated from the matrix.

An *exposure scenario* for a nanoproduct is understood as a qualitative and quantitative description for a given use of a product, which may lead to exposure to the nanomaterial with respect to dermal, oral, eye or inhalational exposure during product use by the consumer[1].

[1] This definition of exposure scenario is similar to "exposure scenario" as defined under REACH (the European Chemicals legislation) in terms of focusing on a given use/application. However, it should be noted that under REACH, an exposure scenarios should also outline the risk management measures necessary for safe use.

2. Approach and methodology

This chapter sets out the approach and methodology used in the current project, including how the results of the previous work packages (WP1-WP4) are used/incorporated into the activities presented in this final report.

2.1 Selection of scenarios

The activities in WP2 were the starting point of the project. Available databases, inventories, reports and other literature were reviewed leading to an overview of typical nanomaterials used in typical consumer products. Based on this research and in dialogue with the reference group and the Danish EPA, 20 consumer products were selected as representative of a range from low to high consumer exposure.

It should be noted that during discussions about the list of products to be assessed, the reference group stressed that such a selection of "only" 20 products/scenarios should not be over-interpreted in terms of being representative for the presence or absence of risks for consumer exposure to nanoproducts in general. The reason for this emphasis is that nanomaterials are potentially used in a wide range of products and that for a range of these, we do not know the identity of the contained nanomaterials. However, as noted, the reference group found the scenarios to be representative of typical consumer exposure scenarios.

It relation to this it should be realised, that the 20 products/scenarios addressed in more detail in this project were deliberately selected for products/product types where the type of contained nanomaterials was known. This was done in order to be able to perform a true assessment and not merely conclude "unknown". Another related inherent uncertainty, which will also be further discussed, is that for many nanoproducts (e.g. those listed in inventories/databases), "nano" is claimed on the packaging/in the product description, however, this does not guarantee that the products actually do contain nanomaterials.

2.2 Exposure assessment of the 20 selected scenarios

For each of the 20 selected consumer exposure scenarios, it was initially assessed, based on expert judgement, which exposure routes were relevant. Subsequently, consumer exposure associated with these routes (oral, dermal, inhalation and/or eye as relevant), were estimated based on identified information regarding the product, including possible measurement data. In estimating consumer exposure, generally the principles as set out in the REACH Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2012, R.15) were applied. The details of these assessments can be found in Part 8 of the appendix report to the combined WP1/WP2 report (Danish EPA, 2015a).

2.3 Hazard assessment

The 20 selected products/exposure scenarios altogether addressed 7 types of nanomaterials; nano-Ag, nano-ZnO, nano-TiO_2, nano-silica, carbon black, carbon nanotubes and nano-ZrO_2. WP3 reviewed the information available concerning the hazards of these nanomaterials. Assessing the hazards of these nanomaterials as part of the matrix in which they are present in consumer

products (solid, liquid, aerosol or dust matrix) was the initial aim, but very limited information was available in the literature. Thus, hazard information available for the pristine/free nanomaterials was reviewed and used and this was generally considered to constitute worst case hazard assessments. However, as will be elaborated later, nanomaterials may occur in many different forms (size, surface area, coating, etc.). Available hazard data do not reflect all these forms and information about which nano form is actually incorporated in a given consumer product is generally not available. This factor poses a challenge to hazard and risk assessment of nanomaterials in consumer products. This work is summarized in Appendix 1 of the current report, which also specifies in more detail how the hazard information can be used to estimate DNELs (Derived No-Effect Levels) for the relevant exposure routes where possible/relevant. In relation to DNEL derivation, the principles in the REACH guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2012, R.8) were used when possible.

2.4 Risk assessment of the 20 selected scenarios

WP1 examined the possibility of using or adapting one of the existing exposure/risk tools to assess consumer exposures and risks associated with nanoproducts. The analysis showed that no single tool (or set of tools) was capable (or could reasonably be adapted) to address the variety of product types and exposure routes of interest. Thus, the original idea set out in the tender specification of the project, of using one single qualitative/semi-quantitative tool to assess consumer exposure and risk for the selected exposure scenarios appeared unfeasible. Following dialogue with the reference group and the Danish EPA, it was decided instead to aim at carrying out case-by-case assessments. One advantage of this more flexible approach is that all relevant evidence/information identified for each of the individual exposure scenarios in the project could be considered in the assessment, and consequently, it could be judged how solid the information is in relation to performing qualitative, semi-quantitative and/or fully quantitative assessments. A limitation with this approach has been both a strict time and human resource constraint regarding performing 20 individual risk assessments – often for several exposure routes - within the scope of the project. Consequently, it has not always been possible to go to a level of detail which could further address borderline cases, and therefore, some of the assessments presented may appear as worst case scenarios or over-conservative. In any case, the results are thought to give a good indication of which types of nanomaterials and products may warrant further consideration. These risk assessments will be presented in Chapter 3.

2.5 Discussion, perspective, uncertainties, gaps and conclusions

Chapter 4 provides a cross-cutting evaluation of the risk assessments performed in Chapter 3 and discusses the results in relation to other exposures, such as exposure to (ultrafine) particles from the working environment as well as general indoor and outdoor sources and other human exposure via the environment as investigated in the WP4 report (Danish EPA, 2015c). Exposure levels will also briefly be discussed in relation to exposure to nanomaterials in occupational settings.

Uncertainties and gaps pertaining to assessing nanomaterials were identified and described as part of the reporting of the previous activities in the project. This knowledge is integrated with the findings from the risk assessments presented in this report and an overall discussion of uncertainties, data availability and knowledge gaps is presented in Chapter 5, along with a discussion about what has been generally learnt in the project. Chapter 5 will also briefly address the possible future trends in amounts and variety of nanomaterials applied in consumer products.

3. Risk assessment of 20 consumer product scenarios

This chapter will assess the risks associated with the selected 20 exposure scenarios. The description and exposure estimation for these scenarios were addressed in the "exposure" report of this project (Danish EPA, 2015a) and the associated hazards of the nanomaterials covered by the scenarios were addressed in the corresponding "hazard" report (Danish EPA, 2015b). Rather than referencing these reports in the remaining part of this chapter, the reports will simply be referred to as the "exposure report" and "hazard report", respectively.

The detailed description of the exposure scenarios and exposure estimations for the 20 selected scenarios are given in Part 8 of the Appendix report to the exposure report. This information will briefly be summarised under the individual scenarios in the current chapter and the reader is referred to the exposure report for the details.

The hazard report reviewed the toxicological information relevant for the nanomaterials encountered in the 20 selected exposure scenarios. In Appendix 1 of the current report, the most relevant hazard information for the 20 selected scenarios is summarised and it has been specified in more detail how the hazard information was applied in relation to assessing the risks for the relevant exposure routes, including where possible/relevant estimation of DNELs (Derived No-Effect Levels).

As already noted in Chapter 2, we have generally attempted to apply the risk assessment principles outlined in the REACH guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2012). This guidance, inter alia, recommends that risk characterisation of nanomaterials should apply another metric (based on particle number or surface area) in addition to the mass metric. The appropriateness of performing risk assessment of nanomaterials with another metric than mass, in particular for inhalation, was also addressed in the hazard and exposure reports. However, given the data available, the risk assessments presented in this chapter are generally performed using the mass metric. This issue will be an inherent uncertainty in the assessment of all of the scenarios and will therefore not be repeated for each scenario.

Similarly, it is not entirely clear (at least in relation to the products investigated and thus the exposure assessment performed) what the characteristics of a given nanomaterial in a given product type are (e.g. coating, shape and exact size). Thus, in general, it is difficult to derive DNELs specific to the actual form of nanomaterials applied in a given product. As this uncertainty is considered very significant by the authors of this report and by the international reference group, it has been decided to highlight this issue in the following risk assessments where it is considered to be of relevance. It is realised that this approach leads to repetition.

It should be noted that, although often not part of general regulatory practice/guidance, we have, where relevant, addressed possible indirect oral intake, which might follow clearance from the airways via the mucociliary escalator.

Finally, despite the wealth of information presented in the exposure and hazard reports indicating that exposure and hazard knowledge regarding nanomaterials is substantial and increasing, data gaps still exist for many issues - not the least on useful emission rates or measurements specific for the cases studied.

Due to the above data gaps, further uncertainties discussed in the exposure and hazard reports, and the scope of the project (see Section 2.4), a conservative/worst case approach is generally applied in the risk assessments. The results are thus considered relatively robust, although they should be seen as "what is high" and "what is low" rather than the final truth. Related to this, we have deliberately chosen not to calculate risk characterisation ratios, but rather to compare quantitative exposure estimates and DNELs in a qualitative discussion. All assessments will be followed by a discussion of uncertainties, especially those uncertainties which might influence the conclusions drawn. Therefore, uncertainty discussions will be more thorough for borderline cases.

3.1 Scenario 1 – Chewing gum with nano-TiO_2

3.1.1 Exposure scenario

This scenario addresses chewing gum with TiO_2 in the form of E171 (food additive index number).

The European Food Safety Authority (EFSA) has approved the use of E171 as a food supplement.

Various authors have assessed the content on nano-TiO_2 in food grade TiO_2 and it appears that up to 20-40% of the number of particles are below 100 nm. Food grade E171 is thus not formally a nanomaterial in itself in relation to the recommended EU nanodefinition (requiring >50% of the particles to be below 100 nm), but the scenario is included in any case as nanoparticles are present and consumed. Further, it is noted that it has been reported that more than 93% of the particles are below 200 nm.

The only relevant exposure route considered for this scenario is the oral route. Adults and children, except babies and very young children, are assumed to potentially chew chewing gum. Children's exposure has been estimated for children with an age of 3-6 years, although the assumed worst case intake of nano-TiO_2 from 20 pieces gums per day would be more relevant for older children. The choice made will however provide a worst case intake as expressed in mg/kg bw/day.

The exposure scenario was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
1.	Chewing Gum	TiO_2 (Food grade E171 and estimated nano-part of E171)	Chewing Up to 20 pieces of chewing gum per day Each gum contain about 1.7 – 3.9 mg E171 per gram or 2.4 – 7.5 mg per gum	Children Adults	30 mg nano-TiO_2/day (150 mg E171) 1.62 mg nano-TiO_2/kg/day 30 mg nano-TiO_2/day 0.50 mg nano-TiO_2/kg/day	NCR	NCR	NCR

* NCR: Not considered a relevant exposure route

3.1.2 Risk assessment of chewing gum with food grade nano-TiO_2 (E171) containing nano-TiO_2 particles

3.1.2.1 Oral

Worst case oral intakes of 0.5 and 1.62 mg nano-TiO_2/kg bw/day for adults and children, respectively, have been used for the estimates.

As discussed in the hazard appendix (Appendix 1), EFSA has noted in their assessment that E171 would not pose any concern, and no restrictions for its use have been set. In their most recent assessment, EFSA assessed that there was no accumulation of titanium in the tissues following dietary administration of 200 mg food-grade TiO_2/kg. Thus, as food-grade nano-TiO_2 is a highly insoluble substance, it would hardly be absorbed, and therefore the establishment of an acceptable daily intake for humans was not considered necessary (EFSA, 2004).

The recent assessment of nano-TiO_2 by SCCS (SCCS, 2014a) refers to a study with a LOAEL of 5 mg nano-anatase TiO_2/kg bw/day from an oral study in mice where neurobehavioral effects were observed. It has been outside the scope of the current study to clarify in detail whether the type of TiO_2 used for establishing that lowest-observed-adverse-effect level (LOAEL) would be relevant for the TiO_2 nanoparticles found in E171. However, as EFSA itself has assessed that there is no notable difference between the oral toxicity of rutile and anatase TiO_2, it cannot be ruled out that this LOAEL would be relevant to consider. If assessment factors were applied to this LOAEL, it would be considerably below the estimated intake amounts of nano-TiO_2 and thus indicate a possible risk.

Uncertainties

The estimated intakes are worst case in terms of number of chewing gum pieces assumed to be consumed in one day (20 pieces), but are not considered completely unrealistic.

A very conservative assumption has been made in relation to the conversion of the number-based fraction of nano-TiO_2 in E171 (18-44%) to a mass-based fraction (assuming 20% by weight). Therefore, the real intake is probably considerably lower.

Furthermore, the upper end of the measured amount of E171 in one chewing gum was applied. This is worst case but not unrealistic.

The exposure estimates for intake of chewing gum also seem reasonable/reasonably conservative as they are in line with what Weir et al. (2012) estimated as realistic average oral exposure to E171 from all sources for the UK population: 2-3 mg TiO_2/kg bw/day for children under the age of 10 years, whereas exposure for higher age groups were estimated to about 1 mg TiO_2/kg bw day. It was noted that 36% of this exposure may occur as nano-TiO_2.

For the current case, a more average intake of e.g. five pieces of chewing gum per day would lead to a lower intake of nano-TiO_2/kg bw/day via chewing gum: about 0.4 mg nano-TiO_2/kg bw/day for children and about 0.12 mg nano-TiO_2/kg bw/day for adults.

As set out above and in Appendix 1, a LOAEL of 5 mg nano-TiO_2/kg bw/day following oral intake has been identified. It has been outside the scope of this project to judge whether this LOAEL is applicable for nano-TiO_2 in E171. However, under the assumption that it is applicable, it would have to be corrected to a NOAEL, normally by dividing by a factor of 3, and it would have to be corrected for intra- and inter-species variation, normally by dividing by a factor of about 100. Thus, the possible DNEL would be in the 0.01-0.02 mg nano-TiO_2 kg bw/day range.

Thus, if this LOAEL is applicable for nano-TiO_2 E171, even the exposure estimates corrected to intake of five pieces of chewing gum appears to be of an order of magnitude above the resulting DNEL, indicating a possible risk.

Furthermore, on top of the intake via chewing gum would come nano-TiO_2 from other sources as indicated by Weir et al. (2012).

All in all, the main uncertainty in this assessment is associated with the possible derivation of a DNEL based on the 5 mg nano-TiO_2/kg bw/day LOAEL.

As pointed out in Chapter 2 and in the introduction to this chapter, key uncertainties related to assessing nanomaterials in consumer products are: i) the general lack of knowledge as to which a specific nano form (size, shape, coating etc.) is present in a given product, and ii) the fact that toxicity has not been tested for all possible nano forms of a given nanomaterial chemistry. Therefore, the hazard assessment, including possible DNELs derived, may differ from the nano form in the consumer product, which again leads to uncertainties in the assessment of risks. This uncertainty is also relevant for the present scenario, although the general worst case approach applied should largely circumvent this uncertainty.

3.1.3 Conclusion

Based on the current estimation of oral intake of nano-TiO_2 in E171 in chewing gum and considering the LOAEL reported in a recent oral gavage study in mice, there may be a risk associated with high consumption of chewing gum containing E171. However, this is uncertain and it is recommended to:

- Consider the relevance of the referred LOAEL *vis-à-vis* the nanoparticles in E171.
- Consider new evidence on oral absorption and accumulation.

This statement is in line with a recommendation given by Jancovic (2014); we assume that EFSA is considering all available exposure and hazard evidence in its current re-evaluation E171[2].

Once a new DNEL/ADI is established, performing more realistic estimations of the oral intake of E171 via chewing gum could be considered.

3.1.4 Perspective

[2] Mandate M-2011-0160, which can be found by searching for "E171" at the following web-site: http://registerofquestions.efsa.europa.eu/roqFrontend/login. However, there is no public access to the details.

Generalisation to other product types
Similar considerations as those provided for E171 in chewing gum applies to other applications of E171.

Cumulative exposure/risks
As discussed in the exposure report, intake of E171 occurs via a range of food products (see also Weir et al. (2012) and a rough estimate of the possible intake via sweets with hard chocolate shells was shown to possibly lead to even higher intakes than from chewing gum.

Overall, this would support the above suggested action, in particular in considering whether a "DNEL", i.e. as we deal with food additives an acceptable daily intake (ADI) should be considered for E171, taking into account the possible effects of the nano-fraction of nano-TiO_2.

3.2 Scenario 2 – Silica (SAS) in various food items

3.2.1 Exposure scenario

The conventional form of synthetic amorphous silica (SAS) is known as the food additive E551. Specifications of commercially available quantities on the market indicate that the food additive contains nanoparticles. From analysis of two grades (Aerosil 200F and Aerosil 380F), specific surface areas of 199 m^2/g and 388 m^2/g were determined (BET nitrogen adsorption method). Primary particle size diameters of 12 nm and 7 nm were determined using transmission electron microscopy; however, most of the primary particles formed larger aggregates and agglomerates.

E551 is used in a wide range of food products e.g. sauce, soup, coffee cream, pancake mix, and seasoning products.

Dekkers et al. (2011) determined the nano-fractions of silica of E551 in various food items and, based on these data, made estimates of the daily oral intake of nano-silica from 14 food products containing E551. A total daily consumption of 124 mg nano-silica per day (corresponding to 1.8 mg/kg bw/day) was estimated from intake from the total of the 14 different food products (estimate made for adults only).

The exposure scenario for various food items with silica (SAS) was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
2.	Various food items	Silica (nano-fraction of E551)	Cumulative ingestion from use of E171 in various food items	Adults	124 mg/day 1.8 mg nano-silica/kg/day	NCR	NCR	NCR

*NCR: not considered a relevant exposure route

The exposure to total silica (i.e. both nano form and bulk form) was estimated at 9.4 mg silica/kg bw/day.

Only the oral exposure route is considered relevant when assessing nano-silica as a food additive.

3.2.2 Risk assessment of various food items containing silica (SAS)

3.2.2.1 Oral

In 2009, EFSA concluded that the use of food grade silica (silicon dioxide) up to 1,500 mg silica/day (corresponding to 21 mg/kg bw/day for a 70 kg person) was of no safety concern (EFSA Panel on Food Additives and Nutrient Sources added to food (ANS), 2009). For silicic acid gel (silica gel) a daily dose of 200 mg/day (or 3 mg/kg bw/day) was considered of no safety concern (silica acid gel in colloidal dispersion contains particle sizes of 5 nm to approximately 1000 μm) (EFSA, 2009). Both silicon dioxide and silicic acid gel comply with the specifications for the food additive E 551.

In connection with this project study, an alternative DNEL of 1.67 mg nano-silica/kg bw/day has been derived based on a LOAEL of 1,000 mg/kg bw/day in relation to liver fibrosis. An overall assessment factor of 600 was applied to the LOAEL to obtain the DNEL value (see Appendix 1). However, this DNEL may be uncertain due to a decrease in absorption at higher dose levels (van der Zande et al., 2014). Furthermore, it should be noted that some accumulation may occur.

This LOAEL was derived by van der Zande et al. (2014) after oral dosing of rats to nano-silica (10-25 nm particle size range) for 84 days up to a dose level of 2,500 mg/kg bw/day.

In relation to the EFSA (2009) level of no concern for silicon dioxide of 21 mg silicon dioxide/kg bw/day, the exposure estimate of 1.8 mg nano-silica/kg bw/day made by Dekkers et al. (2011) is smaller by a factor of 10. As well, in relation to the dose level of no concern for acidic acid gel (silica gel) of 3 mg/kg bw/day, the current exposure to nano-silica is below this level. However, when considering the total silica exposure estimate of 9.4 mg silica/mg bw/day derived by Dekkers et al. (2011), this level exceeds the level of no concern of 3 mg/kg bw/day for silica gel.

As well, the exposure estimate of 1.8 mg nano-silica/kg bw/day exceeds the DNEL value of 1.67 mg nano-silica/kg bw/day derived in the study of van der Zande et al. (2014).

However, a recent risk assessment by van Kesteren et al. (2014) elaborated further on the data from the study of van der Zande et al. (2014), using kinetic modelling in order to estimate human silica levels in the liver. After kinetic modelling the liver silica concentration in humans at the current human exposure level of 9.4 mg total silica/kg bw/day was found to be comparable to the measured liver silica concentration in the LOAEL dose level in rats exposed to SAS (10-23 nm nanoparticles). However, van Kesteren et al. (2014) noted that due to several uncertainties and assumptions in their risk assessment, it was difficult to draw further conclusions and it was stated that additional data were needed regarding absorption and effects of different forms of SAS at realistic exposure levels.

Uncertainties

Exposure estimations:

The exposure estimate as given by Dekkers et al. (2011) can be considered as a realistic average estimate as it was based on determination of the content of nano-silica in several food items containing silica (E551) and on average consumption figures for the various food items. Worst case exposure levels would therefore be higher.

As discussed in the exposure report, it appears that the main intake of nano-silica originates from products such as powder cream for coffee, exotic spice mixtures, powder soups and powder sauces. Some of these products are not normally eaten by children. This might therefore be an indication that child intake is lower than adult intake. However, data identified in this project does not allow for a more exact exposure estimate for child intake of nano-silica from E551.

Hazards:
Furthermore, it may be debated as to how to apply the levels of no concern as expressed by EFSA (2009) in relation to specific content of nano-particles, as this was not a specific parameter in the EFSA assessment that instead distinguished silica in either silicon dioxide and/or silica gel.

Risk assessment of SAS is complicated by the existence of different forms and types of SAS (van Kesteren et al., 2014). Different SAS forms (pyrogenic silica, precipitated silica and silica gel and colloid silica) are formed by different production processes (van Kesteren et al., 2014). Each of these SAS forms differs further by particle size, specific surface area, surface coating etc. We agree with the conclusion by van Kesteren et al.: "*These differences between forms and types of SAS may affect the kinetics and toxic potential of SAS. Currently, insufficient information is available on the effect of the different physicochemical characteristics on the behaviour (kinetics and toxicity) of SAS, which challenges a generalised risk assessment*" (van Kesteren et al., 2014).

The study by van der Zande et al. investigates two types of SAS nanomaterials (both pyrogenic but with different sizes, specific surface area etc.) and only one of them induces liver fibrosis (A NOAEL for fibrosis was considered 1000 mg/kg bw/day). In addition it is important - as stressed by the authors - that the relevance of comparing external dose level is dubious because a decrease in absorption has been detected at higher oral dose levels. Based on the study by van der Zande, liver absorption was calculated to decrease from 0.2% absorption at the low dose level to 0.01 to 0.02% at the high dose level. A risk assessment based on internal concentrations has therefore been suggested as an alternative by van Kesteren et al. (2014).

By the end of 2014 - after finalizing our literature search - two new OECD guideline studies on SAS were published: One study investigated toxicity in rats of negatively charged colloidal silica particles of different sizes (20 nm and 80 nm) following chronic administration once daily for 90 days (500, 1,000 and 2,000 mg/kg) (Kim et al., 2014). No toxic effects, clinical changes or histopathological findings were observed for any of tested silica particles. The authors conclude that the results indicate a NOAEL for both tested silica particles at 2,000 mg/kg bw/day. In another study, four different SAS with or without surface functionalization were tested in rats in a 28-day oral exposure study (Buesen et al., 2014). No effects were detected.

Based on the study that was the basis for the calculation of the DNEL of pyrogenic SAS in this report (LOAEL, 1,000 mg/kg bw/day) (van der Zande et al., 2014) and the recently published papers described above on colloid SAS (NOAEL, 2,000 mg/kg bw/day) (Kim et al., 2014) and SAS with different surface modifications (NOAEL = 1,000 mg/kg bw/day) (Buesen et al., 2014), it is obvious that differences between types of SAS are of key relevance when doing a detailed risk assessment.

3.2.3 Conclusion

Considering the EFSA (2009) evaluation regarding food-grade silica, the average exposure level to total silica of 9.8 mg silica/kg bw/day estimated in this study is below 21 mg silica/kg bw/day, which is considered as a no concern level. However, the exposure estimate is above the safe level of 3 mg/kg bw/day for silica gels derived by EFSA (2009).

For nano-silica specifically, the exposure estimate of 1.8 mg nano-silica/kg bw/day is just above the DNEL of 1.67 mg nano-silica/kg bw/day derived from the study of van der Zande et al. (2014).

However, due to the uncertainties described above, especially in relation to use of the most relevant acceptable exposure value (or DNEL value), it is premature to draw any firm conclusion from this scenario.

All in all, considering recent information regarding nano-silica in food in the current EFSA re-evaluation of E551[3] is warranted.

3.2.4 Perspective

Generalisation to other product types

This case on use of silica indicates that it may be difficult to determine the extent to which a certain content of silica in a product also represents a certain content of nano-silica, as this very much depends on the specific type of silica used.

Thus, for risk assessment purpose, it is very important that the hazard data on which the risk assessment relies pertains to the same form of silica in the exposure scenario to be assessed.

Cumulative exposure/risks

The dominant source for *oral* exposure to nano-silica is concluded to be from the use of silica as a food additive. Compared to this relatively high exposure, it is difficult to imagine significant oral contributions from other uses of SAS in consumer products.

3.3 Scenario 3 – Silver (Ag) in food supplements

3.3.1 Exposure scenario

Several nanosilver (nano-Ag) food supplement products can been found on the web-market, although the marketing of nanosilver in food supplement is illegal in the EU as nanosilver has not been approved either as a food additive or as a nutrient. The particle size typically varies within the range of 1-100 nm. In the present scenario, the particle size is specified to be 0.65 nm. The particles are suspended in a liquid matrix and sold in packages of 15-500 mL in concentrations of 10-500 mg/L. The supplements are targeted for daily oral intake by adults in volumes from 1.25 to 60 mL in a not specified period of time.

To obtain a worst case scenario and a conservative risk assessment, for this specific scenario a food supplement product containing 0.5 mg nano-Ag/mL was evaluated and the daily intake was set to be twice the recommended dose of 1.25 mL.

The exposure scenario for nano-Ag containing food supplements was elaborated in the exposure report, where it was summarized as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
3.	Food supple-ment, liquid	Ag	Ingestion of colloid Ag from food supplement product 2.5 mL liquid containing 0.5 mg Ag/mL	Adults	1.2 mg/day 0.021 mg/kg/day	NCR	NCR	NCR

*NCR: not considered a relevant exposure route

[3] Mandate M-2011-0160, which can be found by searching for "E551" at the following web-site: http://registerofquestions.efsa.europa.eu/roqFrontend/login. However, there is no public access to the details.

Therefore, only the oral exposure route is considered to be relevant for this scenario.

3.3.2 Risk assessment of food supplements containing silver (Ag)

3.3.2.1 Oral exposure

WHO (2003) considered argyria (greyish-blue discolouration of the skin caused by exposure to silver) in humans as the most critical effect after systemic uptake of Ag and based on an oral NOAEL of 10 g Ag as a lifetime dose level, a daily oral NOAEL of 0.005 mg/kg bw/day (5 µg/kg/day) can be calculated (assuming a person of 70 kg lives for 75 years). Therefore, an oral DNEL can be set to 0.005 mg Ag/kg/day. This DNEL can be used for nano-Ag including all soluble Ag species. See Appendix 1 for further hazard information.

The oral dose of Ag for intake of nano-Ag containing food supplements from an unspecified treatment period is estimated to be 21 µg Ag/kg/day. This represents a worst case scenario and is about four-fold higher than the long-life NOAEL as set by WHO (2003).

Consequently, life-long intake of the food supplement would indicate a risk for development of argyria.

As WHO (2003) estimated the life-long TDI levels on cases of argyria, which typically occur after short-term exposure to excessive levels of silver, a four-fold increase (i.e. a rather moderate increased level above the TDI) in daily exposure during shorter treatment periods is considered very unlikely to be of concern with respect to development of argyria.

Uncertainties

Exposure estimations: The exposure estimate is based on specific and reliable information on concentrations of nano-Ag content in the food supplement and the recommended doses for the specific product. Therefore, there is no great uncertainty regarding exposure for this specific scenario, although a reasonable worst case assumption is made regarding the intake (twice the recommended dose). However, it cannot be excluded that other food supplement products with higher nanosilver contents are available or that some consumers may use much higher doses than recommended.

Hazards: Due to its bacteriostatic effect, nano-Ag can induce changes in the composition of the bacterial flora and there is an ongoing debate about the possible development of resistance induced by silver, including nano-Ag. However, in the opinion presented by Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) it is concluded that no consistent documentation is available at this moment (SCENIHR, 2014). Thus, this risk assessment does not cover the aspect concerning the potential for indirect human effects in relation to resistance of microorganisms to silver. It should be noted that this discussion pertains to silver as such and not only nano-Ag.

Uncertainties also pertain to the DNEL value as human exposure leading to argyria is often poorly and imprecisely reported. Nevertheless, this figure for safe level of oral exposure is based on human data and is used by WHO for risk assessment of silver in drinking water and has also recently been used by EFSA (2011).

3.3.3 Conclusion

No risk is expected from intended use of the above specified nano-Ag-containing food supplements for shorter periods of treatments (the scenario above is considered as a worst case).

However, exposure during longer periods (several years) of life or excessive intake may lead to risk for the development of argyria.

3.3.4 Perspective

Generalisation to other product types

This assessment may cover similar food supplements using identical recommended daily doses. For products with higher recommended Ag doses there may be increased risk for the development of argyria.

The data and results from this scenario might be applied in relation to other applications of nano-Ag containing products that result in oral intake e.g. use in food, food contact materials, household appliances (freezers, refrigerators), food industrial production machinery, and carry-over in meat from animals fed nano-Ag containing feed. However, although nano-Ag may be used in many different consumer products, the exposure in relation to food supplement preparations seems to constitute by far the highest oral exposure.

Cumulative exposure/risks

As noted above, additional exposure from other applications (i.e. dermal exposure by use of cosmetics and wound dressings; inhalation exposure from spray applications, and exposure from use of biocides and medical devices) may add to the systemic nano-Ag exposure. The contributions from these sources have not been assessed in detail in this study, but are generally considered to contribute to systemic exposure to a lesser, but unknown extent. An exception is wound dressing, addressed in scenario 18.

3.4 Scenario 4 – Silica (SAS) in food container

3.4.1 Exposure scenario

The substance silicon dioxide, silanated, FCM (food contact material) substance 87 is authorised for use as an additive in all types of plastics without restrictions (EFSA, 2014). The substance has always been produced on the basis of synthetic amorphous silica (SAS) in nano form. Both the basic (unmodified) silica and the silanated silica have a primary particle size of less than 100 nm in the commercial products. In the powder, the primary particles are aggregated and agglomerated (EFSA, 2014).

The nano-silica as a FCM substance is embedded in a polymer matrix and, as indicated, there is no restriction on the concentration added to FCM (EFSA, 2014); however, a typical concentration could be 3% w/w.

Oral exposure from material migrated to the food would be the principal exposure route. All age groups could potentially be exposed to nano-silica migrated to the food item.

Based on migration testing and according to EFSA (2013) and EFSA (2014), no migration of nano-silica to the food items is expected from food contact materials containing nano-silica.

Based on this, the exposure scenario for food containers with silica was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
4.	Food container	Silica	Ingestion via food due to migration from container	All	≈ 0	≈ 0	≈ 0	≈ 0

3.4.2 Risk assessment of food containers containing silica (SAS)

3.4.2.1 Oral exposure

Based on the current information, migration appears to be very low or non-existent and thus oral exposure is considered negligible.

In the recent EFSA (2014) opinion, it is concluded that there was no detectable migration of silicon dioxide from the polyethylene film in which the particles are incorporated into appropriate food simulants. Therefore at the particle sizes reported, the substance silicon dioxide, silanated, does not raise a safety concern for the consumer in the currently authorised conditions of use.

Uncertainties

If also considering the relatively low oral toxicity of food-grade nano-silica as described in Scenario 2 for nano-silica as a food additive, it appears that nano-silica in FCM still is safe. Therefore, a slight release/migration would not change the conclusion of this risk assessment.

3.4.3 Conclusion

The use of nano-silica in food contact material is considered safe based on existing evidence as no significant consumer exposure is anticipated.

3.4.4 Perspective

Generalisation to other product types

The data on food contact materials could indicate that the potential for migration of nano-silica imbedded in polymers (also for other polymer product types) may be low/negligible. However, this supposition should be considered case-by-case.

Cumulative exposure/risks

As discussed in Scenario 2, oral intake of nano-silica is probably driven by silica added directly to the food as food additive E551.

3.5 Scenario 5 – Sunscreen lotion with nano-TiO_2

3.5.1 Exposure scenario

This exposure scenario considers sunscreen lotion with nano-TiO_2 as UV-filter.

It is assumed that such lotion would be used by children as well as adults and possibly lead to dermal exposure as well as oral intake.

For application of lotion to the lips (or concurrent application of sunscreen lipstick), the additional oral and dermal exposure estimates have been taken from Scenario 8.

The exposure scenario was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
5.	Sun screen Lotion	TiO_2	Dermal: 36 g/day for Denmark and 72 g/day South of Denmark Lips: 2 to 6 applications per day 25% nano-TiO_2	Adults Children (4.5 years)	2 and 6 lip applications: 0.24 mg/kg/day and 0.72 mg/kg/day Licking on fingers: 2.9 mg/kg bw/day 2 and 6 lip applications: 0.88 mg/kg/day and 2.6 mg/kg/day Total: up to 5.5 mg/kg/day	DK: 0.26 mg/cm² 150 mg/kg/day South of DK: 0.51 mg/cm² 300 mg/kg/day DK: 0.26 mg/cm² 223 mg/kg/day South of DK: 0.51 mg/cm² 447 mg/kg/day	NCR	Possible but less relevant and no data

NRC: Not considered a relevant exposure route

3.5.2 Risk assessment of sunscreen lotion containing nano-TiO_2

3.5.2.1 Oral

The worst case children's oral exposure estimate (assuming simultaneous applications of a nano-TiO_2 containing lipstick (amounts taken from Scenario 8) and children licking on fingers to which nano-TiO_2 containing sunscreen has been applied) gives an oral exposure of up to 5.5 mg nano-TiO_2/kg bw/day (2.9 mg from licking on fingers and 2.6 mg from lipstick). For adults (not assumed to be licking on fingers), the worst case estimated exposure is 0.72 mg nano-TiO_2/kg bw/day.

As elaborated in the hazard appendix (Appendix 1), SCCS (2014a) has assessed that as "*... oral intake is not likely to be the major route of exposure to TiO_2 nanomaterials from dermal application of formulations, the acute oral toxicity of TiO_2 is unlikely to be of a concern*." Still SCCS refers to an oral gavage study in mice in which a LOAEL of 5 mg anatase TiO_2/kg bw/day is given. Considering that the anatase and rutile forms are not assumed to deviate significantly in terms of oral toxicity, this LOAEL might be relevant for oral exposure to nano-TiO_2 used in sunscreens. If this is the case and if assessment factors are applied to this LOAEL, the estimated oral intakes would be significantly higher than the DNEL indicating a possible risk.

Uncertainties

Overall, the estimated oral intakes are considered highly conservative (25% nano-TiO_2 in product, 6 lip applications per day), not the least of which is the assumption that 100% of the amount on the lips and 50% of the amounts on the fingers are ingested. These are probably unrealistic worst case

scenarios. Some might argue that hand-to-mouth behaviour would not occur and thus, should not be considered.

The amount per lip application is taken from the SCCS cosmetics guidance and is therefore considered a realistic value.

If oral intake from hand-to-mouth behaviour of children is not considered and if only 2 lipstick applications are considered per day, this would give an oral intake of 0.24 mg nano-TiO_2/kg bw/day for adults and 0.88 nano-TiO_2/kg bw/day for children.

As set out above and in Appendix 1, a LOAEL of 5 mg nano-TiO_2/kg bw/day following oral intake has been identified. It has been outside the scope of this project to judge whether this LOAEL is applicable for nano-TiO_2 in sunscreens. However, under the assumption that it is applicable, it would have to be corrected to a NOAEL, normally by dividing by a factor of 3, and it would have to be corrected for intra- and inter-species variation, normally by dividing by a factor of about 100. Thus, the possible DNEL would be in the 0.01-0.02 mg nano-TiO_2/kg bw/day range.

Thus, if this LOAEL is applicable for nano-TiO_2 in sunscreens, even the exposure estimates not considering licking fingers and only two lipstick applications per day result in exposure estimates one to two orders of magnitude above the resulting DNEL, indicating a possible risk.

All in all, the main uncertainty in this assessment is associated with the possible derivation of a DNEL based on the 5 mg nano-TiO_2/kg bw/day LOAEL.

3.5.2.2 Dermal

Local effects

There are no indications that nano-TiO_2 would lead to local effects in either healthy or damaged skin.

Systemic effects

Worst case external dermal exposures are estimated at 223 mg nano-TiO_2/kg bw/day (for Denmark) and 447 nano-TiO_2 mg/kg bw/day (for more sunny regions South of Denmark).

A number of studies have shown that nano-sized TiO_2 particles can penetrate into the outer layers of the stratum corneum, and enter hair follicles and sweat glands, which could possibly generate reactive oxygen species (ROS) following UV-radiation (SCCS, 2014a). One study referred to in the hazard report found very low TiO_2 concentrations in viable dermis, but noted that this finding might be due to cross-contamination. All in all, there is no evidence at present to indicate that this pathway offers a viable mechanism of entry into systemic circulation. Therefore, also in line with the SCCS assessment of nano-TiO_2 in sunscreen, risks of systemic effects following dermal exposure to nano-TiO_2 are unlikely. See Appendix 1 for further hazard information.

Uncertainties

Overall, the estimated exposure levels are considered reasonable worst case scenarios. However, the exposure level does not really influence the assessment as long as the potential for local dermal effects or absorption are considered unlikely.

It should be noted that SCCS has recently lowered the recommended content of anatase nano-TiO_2 from 15% to 5% of the contained nano-TiO_2 (recommended to be 25% maximum) (SCCS, 2014a).

The anatase content might be an issue in relation to local dermal effects as some studies indicate that the nanoparticles may reach the hair follicles and it is speculated that such anatase TiO_2 could lead to generation of reactive oxygen species (ROS) on exposure to UV light.

Further, there is no conclusive evidence regarding the fate of TiO_2 nanoparticles which enter hair follicles and sweat glands. However, as noted above, there is currently no data indicating that this pathway offers a viable mechanism of entry into systemic circulation.

All in all, dermal exposure to sunscreen lotion with nano-TiO_2 is not considered to be associated with any risk based on the current knowledge.

3.5.3 Conclusion

Based on this study and the current knowledge regarding nano-TiO_2 as used in sunscreen lotions, the following is concluded:

- Risk following oral intake of sunscreens (from lipstick alone) might warrant further investigation as the worst case oral exposure estimates in this study indicate that this exposure route might not be insignificant as concluded by SCCS (2014a), considering recent knowledge related to oral toxicity of nano-TiO_2. Therefore, it may be warranted to look into establishing a DNEL for oral intake and to conduct more exact estimations of oral intake (in particular to determine what percentage of applied sunscreen lipstick might be swallowed and whether a contribution from children licking fingers could be expected and quantified).
- Risks of local and systemic effects following dermal application are considered unlikely considering current knowledge.

3.5.4 Perspective

Generalisation to other product types

Some of the exposure considerations applied in this scenario might be used when assessing other nanomaterials in sunscreens or other lotions (as is done in e.g. Scenario 6 addressing ZnO in sunscreens). Risks might however differ greatly for different types of nanomaterials.

Cumulative exposure/risks

This scenario integrates applications of sunscreens to the skin and lips. Application of paints and cements with nano-TiO_2 might also considerably add to the dermal exposure (see Scenario 10a and Scenario 17). Furthermore, oral exposure to food-grade TiO_2 used as food-additive in various food types (without upper concentration limits) may contribute to the oral nano-TiO_2 exposure.

3.6 Scenario 6 – Pump spray sun screen with nano-ZnO

3.6.1 Exposure scenario

This scenario addresses nano-zinc oxide (nano-ZnO) used as a UV-filter in sunscreen pump sprays.

The SCCS states that their opinion on nano-ZnO in sunscreens (SCCS, 2012b) does not cover spray applications. In a recent clarification of the opinion, SCCS indicates that “spray applications” both reflect propellant spray as well as pump sprays that generates a spray stream or mist of the content (SCCS 2014c).

Therefore, the SCCS (2012b) opinion does not cover possible inhalation exposure from pump sprays.

However, it is assumed that the nano-ZnO contained in pump sprays possesses characteristics similar to the nano-ZnO in lotions addressed in the SCCS opinion.

It is assumed that all age groups might be exposed to sunscreens via intended dermal application, but also via unintended oral intake and possibly inhalation.

Dermal exposure has been estimated using worst case assumptions based on values in authoritative literature and based on expert judgement. The exposure scenario was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
6.	Sun screen – pump spray	ZnO	Same amount as in Scenario 5 25% nano-ZnO	Adults: Children (4.5 years)	2 and 6 lip applications: 0.24 mg/kg/day and 0.72 mg/kg/day Licking on fingers: 2.9 mg/kg bw/day 2 and 6 lip applications: 0.88 mg/kg/day and 2.6 mg/kg/day Total: up to 5.5 mg/kg/day	DK: 0.26 mg/cm² 223mg/kg/day South of DK: 0.51 mg/cm² 447 mg/kg/day DK: 0.26 mg/cm² 150 mg/kg/day South of DK: 0.51 mg/cm² 300 mg/kg/day	No data, but qualitatively assessed that exposure is likely low. However, more information needed.	Possible but less relevant and no data

3.6.2 Risk assessment of pump sprays containing nano-ZnO

3.6.2.1 Oral

The worst case children's oral exposure estimate (assuming simultaneous applications of a nano-ZnO containing lipstick (amounts taken from Scenario 8) and children licking nano-ZnO sunscreen applied to the fingers) gives an oral exposure of up to 5.5 mg nano-ZnO/kg bw/day (2.9 mg from licking on fingers and 2.6 mg from lipstick). For adults (not assumed to be licking on fingers), the worst case estimated exposure is 0.72 mg nano-ZnO/kg bw/day.

An oral DNEL of 1.0 mg nano-ZnO/kg/day has been estimated (see Appendix 1) based on an oral 90-days study with soluble Zn ions referred to in the EU risk assessment report (EU, 2004) and the SCCS opinion assessing nano-ZnO in sunscreens (SCCS, 2012b).

These values indicate that there may be a risk as worst case oral exposure estimates for children appear to be about 5 times higher than the estimated no effect level.

For adults, the worst case oral intake appears to cause no risks.

Uncertainties
The assumed amount of nano-ZnO (25%) in the sunscreen must be considered absolutely worst case.

As further outlined in the exposure report, the intake assumption, especially the 50% intake following children's hand-to-mouth exposure and 100% intake of the amount applied to the lips is also considered absolutely worst case. Some might argue that hand-to-mouth behaviour would not occur and thus, should not be considered.

As ZnO is rather soluble in acidic media (and therefore in the stomach), it appears that the DNEL estimated based on soluble Zn ions is reasonable.

If the contribution from children licking fingers is not considered, the worst case lip applications (6 times) of 2.9 mg nano-TiO_2/kg bw/day would be above the DNEL and for two applications it would be 0.88 mg nano-TiO_2/kg bw/day, in the same range as the DNEL.

All in all, it appears that accounting for the uncertainties related to the exposure estimates would most likely lead to a no risk conclusion for adults and a borderline risk situation for children (especially for cases with maximum level of nano-ZnO content (25%) in the sunscreen).

However, to substantiate this conclusion, more exact oral exposure estimates are needed.

3.6.2.2 Dermal

The background for hazard statements in the following can be found in Appendix 1.

Local effects
According to SCCS (2012b), nano-ZnO does not appear to be irritating to the skin. Thus, no local effects on the skin are expected following dermal exposure.

Systemic effects
Worst case external dermal exposures are estimated at 223 mg/kg bw/day (for Denmark) and 447 mg/kg bw/day (for more sunny regions south of Denmark).

Against this, an external dermal DNEL of 667 mg nano-ZnO/kg/day has been estimated based on route-to-route extrapolation from the oral DNEL.

Thus, even considering the worst case estimates, it appears unlikely that dermal exposure will lead to a risk.

Uncertainties
As exposure estimates are based on worst case calculations and as the dermal DNEL seems reliable due to a very low potential for dermal absorption, it appears that there is little likelihood of risks following dermal exposure.

3.6.2.3 Inhalation

No data on nano-ZnO exposure during sun screen pump spray application have been identified and no model suitable of estimating pump spray exposure has been identified. As set out in the exposure report, SCCS (2012b) notes that pump spraying generally produce larger particles and SCCS (2012b) state that in general no more than 1 wt% of the product is aerosolized with sizes below 10 µm. Therefore, the respirable fraction is relatively low, whereas most of the particles can still be

inhalable. Considering that cosmetic formulations are relatively highly viscous, it is expected that the fraction of inhalable and respirable aerosols would be lower than the observations reported for the water and alcohol-based formulations studied by Nørgaard et al. (2009) and Hagendorfer et al. (2010). The data for propellant spray discussed in SCCS (2012b) indicates that even propellant spraying with cosmetic products might produce relatively large droplets. On the other hand, possible addition of surface active additives might influence the behaviour of cosmetic formulations.

Overall, based on the currently available knowledge, it is difficult to estimate the inhalation exposure. Based on inhalation data from other pump spray applications and assuming that viscous formulations possibly produce even less exposure, it is likely that inhalation exposure is low/very limited.

Against these exposure considerations, a rather low inhalation DNEL of 0.0011 mg nano-ZnO/m^3 (1.1 µg/m^3) has been derived (see Appendix 1). Whether there might be a risk is thus difficult to judge based on the available information. As this DNEL value pertains to an average daily exposure level, i.e. the exposure level for the total volume of inhaled air during a day (10 m^3 air for children), this DNEL is equivalent to a daily inhaled dose of 11 µg nano-ZnO. During 6 minutes of spraying per day with a 6-minutes breathing rate of 0.04 m^3 (10 m^3 x 0.1 h/24 h) this would equal a concentration of 11 µg nano-ZnO/0.04 m^3 = 275 µg nano-ZnO/m^3 ≈ 0.3 mg nano-ZnO/m^3 during the spraying event.

Uncertainties
As noted, no exact exposure data or modelling has been performed and is assumed to be low/very limited based on expert judgement.

As the estimated inhalation DNEL is also very low, even a relatively low inhalation exposure level might cause a risk. On other hand, it should be noted that the DNEL is estimated based on continuous exposure, whereas sunscreen exposure is an intermittent exposure occurring a couple of times a day in relatively short periods.

Qualitatively, risk might be assessed as being low, but a more thorough understanding of possible inhalation exposure is needed to arrive at a stronger conclusion. As a rough initial approach, this approach could consider whether a concentration of 0.3 mg ZnO/m^3 in the breathing zone of a child is a realistic concentration. Furthermore, this would be comparable to a concentration of 1.2 mg aerosol/m^3, where 100% of this aerosol should be within the respirable range, i.e. below about 5 µm in diameter.

3.6.3 Conclusion

Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- Possible oral exposure (children) following exposure to nano-ZnO containing sunscreens appears to be associated with a possible/potential low risk, but the assessment is borderline. Therefore, it may be warranted to conduct more exact estimations of oral intake (in particular to determine which percentage of applied sunscreen lipstick might be swallowed and whether a contribution from children licking fingers could be expected and quantified).
- Dermal application of nano-ZnO containing sunscreens does not appear to cause a risk.
- Inhalation exposure appears, based on expert judgement and data from other pump spray applications, to be very low. However, as no exposure data are available and as the estimated inhalation DNEL is also very low, a risk cannot be excluded and generation of further pump spray exposure data might be warranted. Therefore the risk of inhalation exposure in this scenario is uncertain.

3.6.4 Perspective

Generalisation to other product types

As can be seen for other scenarios, some of the considerations for oral and dermal applications can be applied for sunscreens with other nanomaterials. One should be careful in using this assessment for other pump sprays containing nanomaterials.

Cumulative exposure/risks

To the knowledge of the authors, no other nano-ZnO consumer products would lead to similar exposure levels as when applying sunscreens. However, cumulative exposures might occur in relation to consumer contact with other nano-ZnO containing consumer products such as additives in paints, coatings and other cosmetic products. In particular, ointment for babies might lead to cumulative dermal exposure. The possible use of nano-ZnO as a UV-filter in hair-spray would lead to inhalation exposure, possibly higher than what is assessed in this scenario.

3.7 Scenario 7 – Mascara containing carbon black

3.7.1 Exposure scenario

This scenario addresses brush applied mascara paste known to contain carbon black (CB). It is assumed that all population groups might apply mascara as an ordinary cosmetic (teenagers and adults) or as carnival colour (also children).

Cosmetics grade carbon black has been assessed by SCCS (2014d) and the median size (D_{50}) was indicated to be in the 59 – 76 nm range; however, the particles are slightly aggregated when applied in commercial solution.

Main exposure routes are considered to be dermal and eye exposure.

The exposure scenario was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
7.	Mascara	Carbon Black	2 applications per day 12.5 mg/application 10% Carbon Black (worst case)	Children	NCR	0.8 mg/cm² 0.13 mg/kg/day	NCR	0.5 mg/day
				Teenagers		0.8 mg/cm² 0.044 mg/kg/day		0.5 mg/day
				Adults		0.8 mg/cm² 0.042 mg/kg/day		0.5 mg/day

* NCR: Not considered a relevant exposure route.

3.7.2 Risk assessment of mascara with carbon black

3.7.2.1 Dermal

The background for hazard statements in the following can be found in Appendix 1.

Local effects
Based on available knowledge, carbon black is not considered to cause any topical effects.

Systemic effects
According to SCCS (2014d) "*…the available data show that there is no indication of CB particles (>20 nm) being absorbed through the intact skin*".

Thus overall, based on currently available information, carbon black in mascara does not seem to possess any risk following dermal exposure.

Uncertainties
The dermal exposure estimates might be relatively conservative; however, this does not affect the conclusion that as long as carbon black is neither causing topical effects nor dermal absorption it would not constitute a risk.

The SCCS evaluation pertains to products with up to 10% carbon black (which is considered a worst case for mascara) and to carbon black above 20 nm, which also seems to be the case for cosmetic grade carbon black.

Some shortcomings are however noted by SCCS in relation to the studies addressing possible dermal absorption, including the fact that the characterisation of the carbon black samples for purity was absent in the relevant studies. Thus, a high level of impurities might give other results. Cosmetic grade carbon black is noted to be >97% carbon (SCCS, 2014d).

Overall, risks following dermal exposure are not expected.

As pointed out in Chapter 2 and in the introduction to this chapter, key uncertainties related to assessing nanomaterials in consumer products are: i) the general lack of knowledge as to which a specific nano form (size, shape, coating etc.) is present in a given product, and ii) the fact that toxicity has not been tested for all possible nano forms of a given nanomaterial chemistry. Therefore, the hazard assessment, including possible DNELs derived, may differ from the nano form in the consumer product, which again leads to uncertainties in the assessment of risks. This uncertainty is also relevant for the present scenario, although the general worst case approach applied should largely circumvent this uncertainty.

3.7.2.2 Eye

The limited evidence available indicates that carbon black is not an eye irritant. See further details in Appendix 1.

Uncertainties
As only limited information is available (only one study cited by SCCS, 2014d), it is difficult to draw firm conclusions as to the possible risk following eye exposure to carbon black in mascara. However, it should be acknowledged that carbon black is chemically rather inert, indicting low potential for local irritation.

3.7.3 Conclusion

Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- Risk following dermal exposure appears to be absent given no/low topical toxicity and likely absence of dermal absorption.
- Eye exposure is assessed to cause no risk. This assessment is, however, based on limited data.

These conclusions may not hold if carbon black with a high level of impurities is applied, which, however, is not assumed to be the case for cosmetics.

3.7.4 Perspective

Generalisation to other product types

The results of this scenario might be considered relevant to other types of cosmetics containing carbon black, but not to other types of products containing nanomaterials, as such products are typically not applied in the eye region.

Cumulative exposure/risks

Consumers might be exposed to carbon black from other consumer products (e.g. inks), but as dermal and eye contact does not appear to be associated with any significant hazards, such accumulated exposures would not be assumed to lead to risks following dermal and eye exposure. Please note that this conclusion does not necessarily pertain to oral and inhalation exposure, which were not considered relevant for this scenario and therefore not assessed.

3.8 Scenario 8 – Lipstick sunscreen with nano-TiO_2

3.8.1 Exposure scenario

This exposure scenario considers sunscreen lipstick with nano-TiO_2 as a UV-filter.

It is assessed that sunscreen lipstick with nano-TiO_2 is available to consumers. It is assumed that such lipstick could be used by children as well as adults and possibly lead to dermal exposure as well as oral intake.

The exposure scenario was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
8.	Lipstick sun screen	TiO_2	2-6 applications per day 28.5 mg/application 25% nanoTiO_2	Children	2 and 6 lip applications: 0.88 mg/kg/day and 2.6 mg/kg/day	1.48 mg/cm² 2 appl.: 3.5 mg/kg/day 6 appl.: 10.5 mg/kg/day	NCR	NCR
				Adults	2 and 6 lip applications: 0.24 mg/kg/day and 0.72 mg/kg/day	1.48 mg/cm² 2 appl.: 0.9 mg/kg/day 6 appl.: 2.7 mg/kg/day		

NRC: Not considered a relevant exposure route

3.8.2 Risk assessment of lipstick containing nano-TiO_2

3.8.2.1 Oral

Oral exposure was estimated for adults and children at 0.72 and 2.6 mg nano-TiO_2/kg bw/day, respectively, assuming a worst case use of 6 applications per day.

As elaborated in the hazard appendix (Appendix 1), SCCS (2014a) has assessed that as "*... oral intake is not likely to be the major route of exposure to TiO_2 nanomaterials from dermal application of formulations, the acute oral toxicity of TiO_2 is unlikely to be a concern.*" Still SCCS refers to an oral gavage study in mice in which a LOAEL of 5 mg anatase TiO_2/kg bw/day is given. Considering that the anatase and rutile forms are not assumed to deviate significantly in terms of oral toxicity, this LOAEL might be relevant for oral exposure to nano-TiO_2 used in sunscreens. If this is the case, and if assessment factors are applied to this LOAEL, the estimated oral intakes will be significantly higher than the DNEL. The estimate under these assumptions indicates a possible risk.

Uncertainties

Overall, the estimated oral intakes are considered rather conservative (25% nano-TiO_2 in product, six applications per day), and in particular the assumption that 100% is ingested is probably an unrealistic worst case scenario.

The amount per application is taken from the SCCS cosmetics guidance and therefore considered a realistic value.

If only two lip applications per day are considered, oral intakes of 0.24 mg nano-TiO_2/kg bw/day for adults and 0.88 nano-TiO_2/kg bw/day for children are estimated.

As set out above and in Appendix 1, a LOAEL of 5 mg nano-TiO_2/kg bw/day following oral intake has been identified. It has been outside the scope of this project to judge whether this LOAEL is applicable for nano-TiO_2 in sunscreens. However, under the assumption that it is applicable, it would have to be corrected to a NOAEL, normally by dividing by a factor of 3, and it would have to

be corrected for intra- and inter-species variation, normally by dividing by a factor of about 100. Thus, the possible DNEL would be in the 0.01-0.02 mg nano-TiO_2/kg bw/day range.

Therefore, if this LOAEL is applicable for nano-TiO_2 in sunscreens, even the exposure estimates not considering licking fingers and only two lipstick applications per day result in exposure estimates one to two orders of magnitude above the resulting DNEL, indicating a possible risk.

All in all, the main uncertainty in this assessment is associated with the possible derivation of a DNEL based on the 5 mg nano-TiO_2/kg bw/day LOAEL.

3.8.2.2 Dermal

A dermal load of 1.46 mg/cm^2 and external dermal doses for adults and children of 2.7 and 10.5 mg nano-TiO_2/kg bw/day, respectively, have been estimated for six lip applications per day.

The background for hazard statements in the following can be found in Appendix 1.

Local effects

There are no indications that nano-TiO_2 would lead to local effects in either healthy or damaged skin as also indicated by SCCS.

Systemic effects

A number of studies have shown that nano-sized TiO_2 particles can penetrate into the outer layers of the stratum corneum, and enter hair follicles and sweat glands, which could possibly generate reactive oxygen species (ROS) following UV-radiation (SCCS, 2014a). One study referred to in the hazard report found very low TiO_2 concentrations in viable dermis, but noted that this might be due to cross-contamination. All in all, there is no evidence at present to indicate that this pathway offers a viable mechanism of entry into systemic circulation. Thus, also in line with the SCCS assessment of nano-TiO_2 in sunscreen, risks of systemic effects following dermal exposure to nano-TiO_2 are unlikely. See Appendix 1 for further hazard information.

Uncertainties

Overall, the estimated exposure levels are considered reasonable worst case. However, the exposure level does not really influence the assessment as long as the potential for local dermal effects or absorption are considered unlikely.

It should be noted that SCCS has recently lowered the recommended content of anatase nano-TiO_2 from 15% to 5% of the contained nano-TiO_2 (recommended to be 25% of the maximum) (SCCS, 2014a).

The anatase content might be an issue in relation to local dermal effects as some studies indicate that the nanoparticles may reach the hair follicles and it is speculated that such anatase TiO_2 could lead to generation of reactive oxygen species (ROS) on exposure to UV light.

Further, there is no conclusive evidence regarding the fate of TiO_2 nanoparticles which enter hair follicles and sweat glands. However, as noted above, there is at present no data indicating that this pathway offers a viable mechanism of entry into systemic circulation.

Finally, it should be noted that studies on dermal penetration of nano-TiO_2 have not been conducted on lips/lip skin, which are covered by a much thinner layer of stratum corneum than skin on other parts of the body. Stratum corneum acts as a barrier against exposures and lips may therefore be more prone to absorption. Furthermore, lips do not have sebaceous glands and sweat glands and easily become dry and chapped which may potentially facilitate penetration. See Appendix 1 and the hazard report for further details.

All in all, however, dermal exposure to sunscreen lipstick with nano-TiO_2 is not considered to be associated with any risk based on the current knowledge, although further information on absorption through the lips might warrant further research.

3.8.3 Conclusion

Based on this study and the current knowledge regarding nano-TiO_2 as used in sunscreens lotions, the following is concluded:

- Risk following oral intake of sunscreens (lipstick) might warrant further investigation as the worst case oral exposure estimates in this study indicate that this exposure route might not be insignificant, as otherwise concluded by SCCS (2014a), considering recent knowledge related to oral toxicity of nano-TiO_2. Thus, it might be warranted to look into establishing a DNEL for oral intake and to conduct more exact estimations of oral intake (in particular to determine which percentage of applied sunscreen lipstick might be swallowed).
- Risks for local and systemic effects following dermal application are considered unlikely considering current knowledge.

3.8.4 Perspective

Generalisation to other product types

Some of the exposure considerations applied in this scenario might be used when assessing other nanomaterials in lipsticks. Risks may, however, differ greatly for different types of nanomaterials.

Cumulative exposure/risks

Consumers might be exposed to nano-TiO_2 applied on the skin (see Scenario 5) and application of paints and cement with nano-TiO_2 might also considerably add to the dermal exposure (see scenario 10a and Scenario 17). Furthermore, oral exposure to food-grade TiO_2 used as a food additive in various food types (without upper concentration limits) may contribute to the oral nano-TiO_2 exposure.

3.9 Scenario 9 – Silica (SAS) in face powder

3.9.1 Exposure scenario

Silica (synthetic amorphous silica, SAS) can be used in face powder make-up for brush application. A particle size of 10 nm has been reported (Eshiko, 2014) in concentrations in the range of 1-10%. Dermal exposure is the principal exposure route, but oral, inhalation, and eye exposure may be relevant as well. The estimated applied amount is 0.51 g and the exposed area 565 cm^2 (50% of the area of the female head) (SCCS, 2012a). Duration of application and thus the potential for inhalation is expected to be less than 15 minutes. This time period covers the application time as well as the time following, in which the nano-silica in the powder may still lead to inhalation exposure. Dermal exposure is for several hours and the frequency of exposure is daily (SCCS, 2012a). The particle number concentration is estimated based on measured data from test chamber experiments where face powder containing nano-silica was applied (by brush) to a mannequin head (Nazarenko et al. 2012).

The exposure scenario for face powder with silica was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
9.	Face powder	Silica	Application in face using brush 0.51 g powder containing 100 mg nano-silica/g (10%)	Teenagers	0.43 mg/day 0.008 mg/kg/day	0.09 mg/cm^2 51 mg/day 0.90 mg/kg/day	0.26 mg/m^3 0.051 mg/day 0.0009 mg/kg/day 10,000 particles (20 nm)/cm^3 2 x 10^9 particles (20 nm)/day	0.00009 mg/cm^2 0.006 mg/day 0.00001 mg/kg/day

3.9.2 Risk assessment of face powder containing silica (SAS)

3.9.2.1 Oral

As specified in Appendix 1, rats were orally dosed to nano-silica (10-25 nm) for 84 days in an experimental study. In this study a LOAEL of 1000 mg nano-silica/kg bw/day was found as liver fibrosis was observed at this dose level. From this study a DNEL of 1.67 mg/kg bw/day was established from the LOAEL when using an overall assessment factor of 600.

This DNEL value may be compared with the oral exposure to nano-silica in face powder of 0.008 mg nano-silica/kg/day (from licking skin surface in the mouth region). It can easily be seen that the oral exposure from face powder is far below the derived DNEL values, indicating the absence of any risk associated with oral exposure.

Also when considering the exposure from inhalation of 0.0009 mg/kg bw/day (which may end up in the gastrointestinal tract by swallowing), this dose does not lead to concern either.

Uncertainties

Although uncertainties pertain to the estimated exposure level and also to the DNEL calculation, these uncertainties are not considered to hamper the conclusion of the risk assessment to a significant degree as the estimated consumer oral exposure is several orders of magnitude below the estimated DNEL level.

As pointed out in Chapter 2 and in the introduction to this chapter, key uncertainties related to assessing nanomaterials in consumer products are: i) the general lack of knowledge as to which a specific nano form (size, shape, coating etc.) is present in a given product, and ii) the fact that toxicity has not been tested for all possible nano forms of a given nanomaterial chemistry. Therefore, the hazard assessment, including possible DNELs derived, may differ from the nano form in the consumer product, which again leads to uncertainties in the assessment of risks. This uncertainty is also relevant for the present scenario, although the general worst case approach applied should largely circumvent this uncertainty.

3.9.2.2 Dermal

Due to lack of data indicating adverse effects from dermal exposure to nano-silica (local effects as well as possible absorption and related systemic effects), it has not been possible to derive any meaningful DNEL value for dermal exposure (Appendix 1). However, based on expert judgement, low toxicity is anticipated in relation to dermal exposure to nano-silica.

Uncertainties

Data is lacking about the ID/characterisation of nano-SiO_2 used in cosmetics. Therefore, as described above, uncertainty applies when using the toxicity data and DNEL value for a specific quality in the risk assessment for an unknown quality used in cosmetics.

Furthermore, based on the information identified in this study, it might appear uncertain whether a fraction of the nano-silica could be dermally absorbed. If absorbed, the fraction absorbed would probably be rather low and, taken along with the anticipated relatively low systemic toxicity (as e.g. expressed by the relatively high oral DNEL), risks would still be considered negligible.

3.9.2.3 Inhalation

A chronic inhalation DNEL for synthetic amorphous silica of 0.0017 mg nano-silica/m^3 has been estimated from a NOAEL of 1 mg/m^3 (in relation to lung inflammation) from inhalation data where rats were exposed 6 hours per day over 5 days. The NOAEL value was averaged over a 24 hour exposure period and an overall assessment factor of 160 was used for estimating the chronic DNEL value. See Appendix 1 for further details.

The data do not allow a derivation of a DNEL value expressed in particle number/m^3, so the risk assessment has to rely on the DNEL value expressed as a mass concentration.

A daily exposure level of 0.26 mg/m^3 was estimated for a period of 15 minutes during and immediately after the application of the face powder. In relation to the critical effect - lung inflammation - it is assumed that this effect is related to the daily deposited dose of silica in the lung. Therefore, in order to compare the 15 minute exposure to the 24 hour chronic DNEL value, the 15 minute exposure would be averaged over 24 hours:

The daily 15 minutes (0.25 h) dose corresponds to a 24 hour average dose level of 0.26 mg silica/m^3 x 0.25 h/24 h = 0.003 mg silica/m^3.

Thus the estimated exposure exceeds the DNEL value with about a factor of 2, indicating a potential risk for this inhalation scenario.

Uncertainties

As the outcome of the risk assessment indicates a borderline risk, it is important to take uncertainties of the exposure estimations as well as the DNEL estimations into account.

Exposure estimation: Although uncertainty pertains to characterisation of the nano-silica and the quantitative content of nano-silica in face powder, a content of 10% may not be unrealistic. The amount applied may represent a conservative but not unrealistic scenario. The exposure duration for inhalation has been set to 15 minutes which may be seen as a conservative assumption for application of face powder. However, considering that the nano-silica in the face powder might be airborne after the actual application, 15 minutes is not considered an unrealistic upper level regarding the exposure period.

In the exposure calculation, it is assumed that a fraction of 1% of the used face powder is released into the air as respirable particles and it is assumed that 10% of the airborne dust is inhaled, i.e. a total of 1% of the volume of face powder (containing 10% of silica) is considered to be inhaled.

Whether this estimate is realistic will depend on the dustiness of the face powder which may vary from brand to brand, so a certain degree of uncertainty applies to the exposure estimate. Overall, the applied values are assumed to be rather conservative.

Hazards: With respect to the DNEL value, this is based on data on synthetic amorphous silica and a 5 day inhalation study, which is highly uncertain for estimating a chronic DNEL value. Uncertainty also pertains to whether the quality of nano-SiO_2 used for the toxicity testing actually matches the quality of nano-SiO_2 used in cosmetics.

Therefore, taking these uncertainties into account, this non-conclusive risk assessment indicates that further data are warranted in order to be able to make a more valid risk assessment of the inhalation scenario.

3.9.2.4 Eye

Due to lack of data indicating adverse effects from eye exposure to nano-silica (see Appendix 1), it has not been possible to assess possible risk associated with eye exposure. However, based on expert judgement, low toxicity is anticipated in relation to eye exposure to nano-silica.

3.9.3 Conclusion

In relation to nano-silica in face-powder there appears to be no concern for dermal, oral and eye exposure. For inhalation exposure, this initial risk assessment indicates some concern, but more precise knowledge as to the inhalation exposure and the inhalation DNEL value seems warranted in order to perform a more conclusive risk assessment.

To this end, it can be noted that the Scientific Committee for Consumer Safety (SCCS) has been asked to prepare an opinion about the use of silica in cosmetics (European Commission, 2014).

3.9.4 Perspective

Generalisation to other product types

The uncertainty regarding inhalation exposure may be relevant for other face powders containing other types of nano- particles. Especially the potential for inhalation exposure to nano-silica should be considered when evaluating other types of consumer products containing nano-silica, as the potential for oral and dermal toxicity is considered low.

Cumulative exposure/risks

There may be a potential for aggregate exposure in relation to consumer use of products containing nano-silica where especially the additional exposure via inhalation should be considered e.g. from products in powder or spray formulations.

3.10 Scenario 10a – Paint with nano-TiO_2 (roller application)

3.10.1 Exposure scenario

This exposure scenario considers paint with nano-TiO_2 applied to walls/surfaces by rolling.

It is assumed that painting of walls/installations in consumer homes would generally be performed by adults or possibly teenagers and the main exposure routes would be dermal and eye contact.

The exposure scenario was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
10a	Paint	TiO_2 (anatase)	Roller application Paint with 25% nano-TiO_2 5 litres applied per day	Teenagers Adults	NCR	1.34 mg/cm² 4.3 mg/kg/day 0.98 mg/cm² 3.1 mg/kg/day	NCR	Possible/ likely, but no data

NRC: Not considered a relevant exposure route

3.10.2 Risk assessment of paint containing nano-TiO_2 applied by rolling

3.10.2.1 Dermal

The highest exposures were estimated for teenagers and conservatively estimated to be a dermal load of 1.34 mg/cm² and an external dermal dose of 4.3 mg/kg bw/day.

The background for hazard statements in the following can be found in Appendix 1.

Local effects

There are no indications that nano-TiO_2 would lead to local effects in either healthy or damaged skin.

Systemic effects

A number of studies have shown that nano-sized TiO_2 particles can penetrate into the outer layers of the stratum corneum, and enter hair follicles and sweat glands, which could possibly generate reactive oxygen species (ROS) following UV-radiation (SCCS, 2014a). One study referred to in the hazard report found very low TiO_2 concentrations in viable dermis, but noted that this might be due to cross-contamination. All in all, there is no evidence at present to indicate that this pathway offers a viable mechanism of entry into systemic circulation. Therefore, also in line with the SCCS assessment of nano-TiO_2 in sunscreen, risks of systemic effects following dermal exposure to nano-TiO_2 are unlikely. See Appendix 1 for further hazard information.

Uncertainties

It is assessed that paint with nano-TiO_2 is available to consumers, although it is thought that the consumer market penetration of this type of paint is not widespread (Danish EPA, 2015d).

The assumed concentration of 25% anatase TiO_2 in the paint is considered a worst case scenario both in terms of percentage and in terms of form of nano-TiO_2 (which is often added to products in a grade with mixed rutile and anatase forms).

The dermal exposure estimates might be conservative, but the assumptions do not influence the assessment as long as the potential for local dermal effects or absorption are considered unlikely.

However, it should be noted that the assumed concentration of anatase TiO_2 in the paint (25%) is higher than the maximum concentration recommended in the recent SCCS opinion on nano-TiO_2 in sunscreen (5% anatase TiO_2 of 25% nano-TiO_2= 1.25%).

The anatase content might be an issue in relation to local dermal effects as some studies indicate that the nanoparticles may reach the hair follicles and it is speculated that such anatase TiO_2 could lead to generation of reactive oxygen species (ROS) on exposure to UV light.

Furthermore, there is no conclusive evidence regarding the fate of TiO_2 nanoparticles which enter hair follicles and sweat glands. However, as noted above, there is at present no data indicating that this pathway offers a viable mechanism of entry into systemic circulation.

All in all, dermal exposure to paint with nano-TiO_2 is considered to be associated with low risks, although paints with very high concentrations of anatase nano-TiO_2 might need to be used with care and/or assessed in further detail.

3.10.2.2 Eye

Exposure has not been estimated quantitatively, but it is assessed that exposure to paint droplets is likely, e.g. when paint rolling a high strictures/ceilings. This situation may lead to nuisance, but based on available data, the potential for eye effects caused by nano-TiO_2 is assessed to be low.

Uncertainties

SCCS in its assessment of nano-TiO_2 in sunscreens notes that limited data in relation to eye exposure for the nano form of TiO_2 is available. See Appendix 1.

3.10.3 Conclusion

Based on this assessment, it is concluded that for nano-TiO_2 containing paint applied via rolling:

- Dermal expose is not likely to lead to any risks; however, further assessment of paints with high concentration of anatase nano-TiO_2 might be warranted.
- Based on current knowledge, eye exposure is not assessed to lead to irritation caused by the content of nano-TiO_2.

3.10.4 Perspective

Generalisation to other product types

Some of the exposure considerations applied in this case might be relevant for nanomaterials in other paints or liquid nanoproducts which come into contact with the skin. The considerations regarding possible absence of dermal penetration are similar to those related to many other nanomaterials.

Cumulative exposure/risks

In relation to cumulative dermal exposure to nano-TiO_2, it is assessed that the main other product type which could lead to dermal exposure is sunscreens, addressed in several other scenarios in this study. However, application of cement (see Scenario 17) might also lead to dermal exposure. Cumulative risks would be relevant to consider if new knowledge regarding dermal penetration of nano-TiO_2 becomes available.

3.11 Scenario 10b – Sanding surface with UV-protective primer consisting of nano-TiO_2

3.11.1 Exposure scenario

This scenario addresses sanding of a UV-protective primer coating consisting of < 3 nm-size nano-TiO_2 dispersed in water. The product can be used either as a primer before painting or as a stand-alone UV-protective coating.

In the exposure scenario, it is assumed that a person is sanding wooden planks treated with the product as a UV-protective coating alone using an electrical sanding machine. Consequently, the surface coating principally consists of a layer of UV-reactive nano-TiO_2 (assumed to be the anatase form). The exposure dose was assessed for adults and young teenagers (11-16 years), which both could be considered consumers to conduct sanding. It is assumed that the sanding operation is repeated once every year.

The primary exposure pathway in the sanding process is inhalation of sanding dust particles liberated from the nano-TiO_2 surface during sanding, as well as direct dermal contact exposure to residual surface treatments while touching the sanded surfaces.

The inhalation exposure dose has been estimated based on knowledge from laboratory studies on emissions generated during sanding and Tier 1 REACH modelling of exposure levels assuming one event per year. Dermal exposure was also assessed from Tier 1 REACH modelling. In the inhalation exposure assessment, it is assumed that 100% and 20% of the nano-TiO_2 is liberated, respectively, in a worst case and more realistic scenario, from a 1 m^2 layer with an area concentration of 0.70 g nano-TiO_2/m^2. Sanding was assumed to take 30 minutes and results in a release rate of 1.39 and 0.28 g/hour, at 100 and 20% release, respectively. Work was conducted in a 20 m^3 unventilated room as a worst-case scenario (standard according to ECHA, 2012, R.15) and leaving the room immediately after sanding.

The dermal load and dermal contact exposure was estimated using ECETOC TRA Equation R.15-5, 15-6 and 15.7 (ECHA, 2012, R.15). In the scenario, the consumer is touching a sanded surface fully covered by a 0.1 mm layer of nano-TiO_2 with the palms of the hands after which 100% is transferred to the skin.

The consumer was assumed not to use respiratory protection or gloves in any of the assessments.

The results of the exposure assessments are listed in the table below. Further details and background information can be found in the exposure report.

No.	Product	NM	Exp. scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
10b	Nano-TiO_2 primer paint	TiO_2	Sanding nano-TiO_2-based UV-protective UV-primer treated wooden planks in a 20m³ room using an electrical sanding machine for 30 min once every year. Sanding hardened primer 1 m2 with 0.70 g nano-TiO2/m2	Adults Teenagers	Negligible	Palm of hands: 29.81 (male) 28.93 (female) mg/kg Palm of hands: 24.78 mg/kg	Sanding (100%): 18 mg/m³ 0.216 (male) 0.247 (female) mg/kg/day Sanding (100%): 18 mg/m³ 0.238 mg/kg/day	Negligible

3.11.2 Risk assessment of sanding surface with UV-protective primer consisting of nano-TiO_2

3.11.2.1 Oral exposure

Direct oral exposure was assumed negligible. Oral uptake would come from Nano-TiO_2 deposited in the nose and mouth as well as brought up along the mucociliary escalator from the respiratory tract (which is implicitly covered by the inhaled dose). Some nano-TiO_2 may also enter the gastro-intestinal tract from lips and inadvertent hand-to-mouth dust transfer.

It is not considered that the indirect oral exposure from inhalation is of any concern, as the total inhaled dose of 0.25 mg nano-TiO_2/kg bw/day as a once-in-a-year exposure is far below acute toxicity levels. Acute oral exposure to 5,000 mg nano-TiO_2/kg in rats hardly resulted in any signs of toxicity (ECHA, not dated).

Uncertainties

Only a fraction of the exposure of 0.25 mg/kg bw/days would potentially be ingested, and furthermore, the exposure event would only take place once a year.

All in all, a possible oral risk associated with this scenario is considered unlikely.

3.11.2.2 Dermal exposure

The dermal load was estimated to be 3.9 mg nano-TiO_2/cm² corresponding to a dermal exposure dose of 24.8 and 29.8 mg nano-TiO_2/kg/day (event) for a teenager and an adult male, respectively, for a single day per year.

The background for hazard statements in the following can be found in Appendix 1.

Local effects

No evidence of local effects of nano-TiO_2 has been mentioned by the SCCS evaluation (SCCS, 2014a). Therefore, no risk of local effects is expected.

Systemic

A number of studies have shown that nano-sized TiO_2 particles can penetrate into the outer layers of the stratum corneum, and enter hair follicles and sweat glands, which could possibly generate reactive oxygen species (ROS) following UV-radiation (SCCS, 2014a). One study referred to in the

hazard report found very low TiO_2 concentrations in viable dermis, but noted that this might be due to cross-contamination. All in all, there is no evidence at present to indicate that this pathway offers a viable mechanism of entry into systemic circulation. Therefore, also in line with the SCCS assessment of nano-TiO_2 in sunscreen, risks of systemic effects following dermal exposure to nano-TiO_2 are unlikely. See Appendix 1 for further hazard information.

Uncertainties
Exposure estimation: The dermal exposure was assessed for palms touching the sanded surface with 100% loose nano-TiO_2, as detached by sanding, resulting in a 0.001 cm layer transferred onto the skin. Dermal exposure from aerosol deposition, changing sanding paper and cleaning the sanded surface, etc. was not considered. Even though the dermal deposition may be higher, it is assumed that at least the maximum possible palm concentration was close to being reached in the given calculations. Additional dermal exposure will occur on other skin surfaces accessible for dust. However, the assumption of the 100% efficient transfer from the sanded surface to inner hand is a highly conservative assumption. The exact transfer and possible load of nano-TiO_2 and sanding dust as well as the deposition efficiency of airborne dust onto accessible skin is not known at this point.

Hazards:
The dermal exposure estimates might be conservative, but the assumptions do not influence the assessment as long as the potential for local dermal effects or absorption are considered unlikely.

However, it should be noted that the assumed concentration of anatase TiO_2 in the paint (25%) is higher than the maximum concentration recommended in the recent SCCS opinion on nano-TiO_2 in sunscreen (5% anatase TiO_2 of 25% nano-TiO_2= 1.25%).

The anatase content might be an issue in relation to local dermal effects as some studies indicate that the nanoparticles may reach the hair follicles and it is speculated that this anatase TiO_2 could lead to generation of reactive oxygen species (ROS) on exposure to UV light.

Furthermore, there is no conclusive evidence regarding the fate of TiO_2 nanoparticles which enter hair follicles and sweat glands. However, as noted above, there is at present no data indicating that this pathway offers a viable mechanism of entry into systemic circulation.

All in all, dermal exposure to a sanded surface with UV-protective nano-TiO_2 primer is not considered to be associated with any risk based on current knowledge.

3.11.2.3 Inhalation

The derived exposure estimates for inhaled nano-TiO_2 are high in this assessment. At 100% release of nano-TiO_2 from the sanded UV-protective primer-treated surface, the average 30 min airborne dust concentrations reach 18 mg/m³. The peak value reaches 34.75 mg/m³. Assuming only 20% release of TiO_2 from the surface results in 3.6 mg/m³ (peak 7.0 mg/m³).

Based on 30 minutes of exposure of 18 mg nanoTiO_2/m³, the average daily concentration is calculated below:

Average daily concentration $= \frac{18\ mg/m3}{2*24\ \text{h/day}}$ = 0.375 mg/m³/day

Comparing the average daily concentration with an estimated inhalation DNEL for pulmonary inflammation of 0.007 mg/m³ = 0.7 µg/m³ (see Appendix 1), the average daily exposure exceeds the DNEL by a factor of approximately 535. Compared to OELs (Occupational Exposure Limits), the worst case exposure level is borderline to exceed the existing Danish OEL for acute TiO_2 exposure (2 x 10 mg/m³), but the average daily exposure levels for both the worst case and 20% release case clearly exceed the daily Recommended Exposure Level (REL) of 0.004 mg/m³ ultrafine TiO_2 for

pulmonary inflammation recently proposed by NIOSH (U.S. National Institute for Occupational Safety and Health) (NIOSH, 2011).

It should be considered that this scenario is a single annual event, but at the same time that TiO_2 is a biopersistent material. All in all, the exposure indicates that pulmonary exposure is likely to cause risk and more frequent exposures of this type are assessed to be of concern.

Uncertainties
Exposure estimation: Based on literature data on emission characteristics of sanding dust (e.g. Hsu and Chein, 2007; Göhler et al., 2010; Gomez et al., 2014), it is assumed that all emitted particles are in the respirable fraction and dominated by particles between 10 and 200 nm. In addition, the airborne exposure concentrations are set very conservatively by assuming that the surface layer consists of 100% nano-TiO_2 and dispersing the sanding emission into 20 m^3 volume of the standard small room recommended in R.15 without ventilation. Normally, sanding is expected to occur under better indoor ventilated conditions or outdoors with high rate of ventilation and dilution and in both cases during use of personal respiratory protection. In small rooms, it can be assumed that the ratio between near-field source exposure concentrations and the average room concentrations of respirable particles approach unity.

If this type of process is conducted for extended durations of time or with higher frequency, the potential exposure increases dramatically. However, due to modifying factors not considered in this assessment, measurements or more advanced modelling are required to assess the potential exposure levels and doses in such cases.

Hazards: The DNEL is set based on the recommended exposure limit for inflammation proposed by NIOSH (NIOSH, 2011). This exposure limit is a limit for ultrafine and nanosized TiO_2.

Overall, it is concluded that sanding of a nano-TiO_2 primer is likely to cause a risk to consumers (not assumed to wear personal protective equipment) by inhalation in the present scenario.

As pointed out in Chapter 2 and in the introduction to this chapter, key uncertainties related to assessing nanomaterials in consumer products are: i) the general lack of knowledge as to which a specific nano form (size, shape, coating etc.) is present in a given product, and ii) the fact that toxicity has not been tested for all possible nano forms of a given nanomaterial chemistry. Therefore, the hazard assessment, including possible DNELs derived, may differ from the nano form in the consumer product, which again leads to uncertainties in the assessment of risks. This uncertainty is also relevant for the present scenario, although the general worst case approach applied should largely circumvent this uncertainty.

3.11.3 Conclusion
Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- Dermal and oral exposure of nano-TiO_2 is not expected to cause a risk.
- Inhalation exposure is likely to cause a risk in this scenario.

Overall, the assessment of daily dose should be used with caution as the results rely mostly on model and worst case exposure considerations. It is, however, evident that this type of process is associated with very high peak exposure concentrations to both airways and skin.

3.11.4 Perspective
Generalisation to other product types
The product assessed was relatively well-described regarding nanomaterial contents and recommended use. The specific type of TiO_2 was not specified, but anatase is assumed considering

the stated photocatalytic properties. The amount present in the UV-protective surface coating is an estimate based on the reported application per m^2.

The calculated scenario is relevant for a sanding of a specific group of surface coatings including primer paints, particle-based or solid nanoscale surface coatings, as well as paints with very high loads of specific nanomaterials. The calculations are assumed to consider typical worst case scenarios. However, quantitative measurements are still needed in order to build up the knowledge base and perform more accurate exposure assessments. Such data generation should address a number of issues, including the extent to which free nanoparticles are released.

Cumulative exposure/risks
Consumers may also be exposed to nano-TiO_2 from other sources such as cosmetics and textiles where TiO_2 is added as a UV-filter, and from other coatings and inks, as well as from cement. Furthermore nano-TiO_2 may be released from different articles/matrices.

3.12 Scenario 11 – Spray painting with a nano-Ag paint

3.12.1 Exposure scenario

The exposure scenario in this case considers spray painting with an acrylic paint containing nano-Ag using a spray gun. It is assumed that the paint contains 1 wt% nano-Ag and suppliers' information recommends use of 0.35 mL/m^2. The durability of the paint is relatively high and it is assumed that repainting is done every fifth year, which is assumed to be a worst case assumption.

In the use scenario the paint is applied using a spray gun that can apply 50 mL paint/min. At this rate, 0.417 m^2 wall area is covered per minute with the nano-Ag containing paint. Dermal exposure is also assessed from aerosol overspray to head and hands region and direct dermal contact exposure to the paint by the palms of the hands.

In the inhalation exposure scenario, spray painting is conducted in a small 20 m^3 standard room with no ventilation. All walls (8.7 m^2 assuming standard 2.3 m room height) are painted in 30 min, including refilling the paint gun and time to leave the room after painting has been finished. At the specified spray gun use rate, the effective spray duration is 20.86 min and refilling of a 600 mL tank is assumed to take place between 16 and 22 min after start of painting. The inhalation exposure is estimated based on Tier-1 calculation of inhaled doses following the recommendations in the guidance ECHA R.15 (2012).

Dermal exposure was assessed using two methods: 1) an overspray model by Brouwer et al. (2009) for assessment of the airborne concentration following calculation of the dermal exposure dose using a modified ECETOC TRA procedure considering facial (60% of head) and upper hand (50% of hand area) exposure (ECHA, 2012, R.15) and 2) dermal contact exposure following ECETOC TRA equations R.15-5-R.15-7 considering the palms of the hands (50% of hand area) (ECHA, 2012, R.15).

The consumer was assumed as not using respiratory or eye protection or gloves in any of the assessments.

The results of the exposure assessments are listed in the table below. Further details and background information can be obtained in the exposure report.

No.	Product	NM	Exp. scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
11	Acrylic paint with nano-Ag	Ag	Painting walls with acrylic paint with nano-Ag using a spray gun. Assumed frequency is once every five year. 1.3 L paint 1 wt% nano-Ag is assumed in wet paint Paint thickness is assumed 1 mm	Adults Teenagers and young adults (16-21 years)	Negligible	Palm of hands: 0.918 (male) 0.869 (female) mg/kg Dermal overspray 0.0236 (male) 0.0257 (female) mg/kg Palm of Hands: 0.665 mg/kg Dermal overspray 0.0167 mg/kg	Spray paint 109.48 mg/m³ 1.314 (male) 1.533 (female) mg/kg Spray paint (100%): 109.48 mg/m³ 1.193 mg/kg	Negligible

3.12.2 Risk assessment of spray painting with a nano-Ag containing paint

3.12.2.1 Oral exposure

Direct oral ingestion is assumed negligible; however, some nano-Ag may enter the gastro-intestinal tract from lips and inadvertent hand-to-mouth dust transfer.

Furthermore, indirect oral and gastrointestinal exposure may occur from nano-Ag deposited in the nose and mouth as well as brought up along the mucociliary escalator from the respiratory tract and afterwards swallowed. Thus, the systemic exposure from the inhaled dose of 1.193 mg Ag/kg bw may be considered further at a second tier level of the risk assessment, if the inhalation exposure as such is considered of no concern, see below.

All in all, risk is considered unlikely for the direct oral exposure.

3.12.2.2 Dermal exposure

The dermal exposure is assessed considering accidental touching of a newly painted surface with bare hands (50% of the total hand area) and overspray deposition in faces (60% of the head area) and hands (50% of the total hand area). The contact exposure resulted by far in the highest dermal exposure dose (male: 0.92 mg nano-Ag/kg bw; female: 0.87 mg nano-Ag/kg bw; teenager: 0.67 mg nano-Ag/kg bw). The corresponding dermal load was 0.12 mg nano-Ag/cm². Overspray resulted in dermal dose of ca. 0.02 mg nano-Ag/kg bw.

The background for hazard statements in the following can be found in Appendix 1.

Local effects

Data do not indicate any local effects except for discoloration of the skin at the contact site (localised argyria). The risk of discoloration at the contact site is considered much less important than pulmonary effects and is not considered further in this risk assessment.

Systemic effects
Comparing the combined contact and overspray dermal exposure dose of 0.94 mg (male) nano-Ag/kg bw (in a scenario that only occurs once in five years) to a dermal DNEL for generalised argyria of 2.5 mg/kg bw/day (for every day exposure during lifetime) (Appendix 1). Considering agyria as the critical systemic effect after dermal exposure to nano-Ag paint does not appear to pose a health risk in this paint scenario.

Uncertainties
The dermal contact exposure was assessed for overspray as well as palms of the hands touching a newly painted surface with 100% transfer from the exposed area to the hand. The overspray exposure was assessed from a conceptual model and produces uncertain and probably overestimated exposure levels. In all cases it was assumed that all nano-Ag would be accessible to the skin even though the exposure occurs from paint droplets. This assumption appears to be a worst case estimate and therefore further supports the above no/low risk conclusion.

3.12.2.3 Inhalation
The estimated average 30 min paint dust exposure levels reached 10,948 mg total paint dust/m^3 (peak value = 19,665 mg/m^3) and resulted in an estimated nano-Ag concentration of 109 mg Ag/m^3 (peak value = 197 mg Ag/m^3). The fraction of respirable paint dust is not known and, combined with the fact that respiratory protection equipment was not used in the assessment, the exposure levels are considered as being absolute worst case.

These concentration values are extremely high as they by far exceed the occupational exposure limit values for workers by several orders of magnitude (for dust: OEL = 5 mg dust/m^3 and for Ag: OEL = 0.01 mg/m^3) (see Appendix 1). Therefore, the estimated exposure can be concluded to be associated with high risk.

This high risk is put into perspective below:

Based on 30 minutes of exposure of 109 mg nano-Ag/m^3, the single-day average concentration is calculated below:

Average daily concentration $= \frac{109\ mg/m3}{2*24\ \text{h/d}} = 2.3$ mg/m^3/day

This value is still 228 times higher than the OEL for Ag. Therefore, considering these exceedances of the OEL for Ag and that the inhalation DNEL for consumer exposure to nano-Ag is much lower (0.06 μg/m^3), any use of a spray gun for painting without respiratory protection is associated with a high risk.

Uncertainties
Product: It is not verified whether this product contains nano-Ag or ionic silver and the concentration is not specified. In the assessment, it is assumed that the product contains 1 wt% nano-Ag. Generally, the amounts of Ag in paints are not thought to exceed 1 wt%. The amounts and physical form of the Ag needs to be better clarified for this type of product and silver-based products in general.

Exposure estimation: The exposure estimate is deemed to represent worst case scenarios for the paint area covered. The exposure was assessed as a spray case (airless), the ventilation was set to zero and the 20 m^3 volume of the standard room in the model used (REACH guidance R.15) is small. Moreover, the consumer exposure was assessed without taking into consideration that the user should wear gloves, mask/respirator and eye protection in addition to a full-body suit during spray painting. We also assume a 100% air-way deposition efficiency. These precautionary assumptions are made because we were not able to identify suitable exposure measurement data for

application of paints with Ag using a spray gun. In addition, no data appears to be available showing the entire size distribution during spraying this type of paint in different scenarios. In addition to better product information, measurement data are needed to improve exposure assessment and allow for more advanced modelling.

Hazards: Comparison to the derived DNEL value for chronic and continuous exposure is not relevant as the exposure levels exceed the OELs for dust and silver by a factor of 2,000-10,000 times, indicating high risk for even acute effects.

Given the high exceedance of the OEL and DNEL shows that painting with a nano-Ag paint by consumers using a spray gun without use of respiratory protection equipment would pose risks, even for less conservative exposure estimates.

3.12.3 Conclusion

Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- For oral exposure risk is considered unlikely.
- Dermal exposure does not appear to constitute a risk.
- Inhalation exposure is very likely to cause an acute respiratory risk.

All in all, consumer gun spray painting with nano-Ag containing paint appears to pose risks.

It has to be noted that only the direct toxicity of nano-Ag in relation to human health is covered in this evaluation. Therefore, indirect impact on human health e.g. aspects concerning any potential for development of resistance of microorganisms towards silver and antibiotics are not covered.

3.12.4 Perspective

Generalisation to other product types

This scenario illustrates the difficulties in assessing overspray and inhalation exposure to nanomaterials in spray processes. Several factors influence the actual aerosol release and resulting overspray and inhalation exposure, which could not be considered in this assessment. The lack of measurement data limits the ability to assess the relevance of the estimated concentrations.

The given Tier 1 exposure estimates should be used with appropriate care in relation to other spray-paint scenarios. It is, however, evident that painting using a spray gun is likely to lead to very high exposure levels of paint dust (even if nanomaterials are not involved), requiring the use of personal protective equipment (including full high-efficiency respiratory protection). It might therefore be considered whether such consumer scenarios should be avoided without proper instruction or avoided for precautionary reasons.

Cumulative exposure/risks

Consumers may also be exposed to nano-Ag from other sources such as jewellery, cosmetics, textiles, and from other coatings and food supplements. However, the inhalation exposure levels from other sources appear to be minor compared to the levels estimated in this scenario.

3.13 Scenario 12 – Use of a nano-silica pump spray for surface impregnation

3.13.1 Exposure scenario

This scenario addresses the use of a pump spray for application of a nano-silica-based surface impregnation product. There is limited information available on the product and its ingredients, but it is assumed that the product contains nano-silica as claimed. The assessed product may in fact

contain silane or siloxane as the active ingredient. There is no specific information on the concentration in the product or amount of product required to treat a surface area. Literature information indicates that the amount of product required for treatment is highly variable and ranges from 0.5 to 50 mL/m^2. Here it is assumed that 0.5 mL/m^2 is applied, which was the value for the most similar products in Michel et al. (2013). The concentration of nano-silica in the product is assumed to be 1 wt%.

In the scenario, a consumer is treating a 5 m^2 kitchen countertop. The treatment is done twice the first time applied, and then maintained with an annual treatment. The calculated exposure doses given here are hence both daily doses.

Inhalation exposure was assessed based on a traditional Tier 1 estimation of inhaled dose in R.15 (ECHA, 2012, R.15) and compared to scaling of release and exposure information in two relevant scientific studies (Nørgaard et al., 2009 and Michel et al., 2013). As a worst case in the Tier 1 scenario, it is assumed that the 2.5 mL product (1 wt% nano-silica) is sprayed directly onto the countertop or onto a sponge with the same distance between the nozzle and the sponge in a 20 m^3 room with no ventilation.

The aerosol release rate for exposure was assumed to be 0.01 wt% of the sprayed product based on data for a TiO_2 spray in Nørgaard et al. (2009). Consequently, the airborne nano-silica release rate was 0.0025 mg/min (2.5 µg/min) (this is a correction to the release rate given in the exposure report). The duration of pump application was set to 10 min based on the pump spray efficiency. The entire exposure duration for each treatment was 30 min including the time for wiping the countertop, after which the consumer was assumed to leave the room.

Dermal load and dose was assessed for wiping and direct contact following the procedure by ECETOC TRA Equation R.15-5, 15-6 and 15.7 (ECHA, 2012, R.15). It was assumed that the consumer polished and touched the newly treated wet countertop resulting in transfer of 0.1 mm product to the palms of the hands. Overspray exposure was not assessed.

Oral and eye exposure are possible in this scenario, but are assumed to be negligible and thus not assessed quantitatively.

The target groups comprise adults and older teenagers.

The results of the R.15 Tier 1 exposure assessments are listed in the table below. Further details and background information can be obtained in the exposure report.

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
12	Pump spray for impregnation	Nano-silica	A 5 m^2 kitchen countertop was treated with a 1 wt% nano-silica spray by direct spraying or spray onto sponge in a 20 m^3 room with no ventilation. The duration of application was 10 min. The entire exposure duration was 30 min including time for wiping the countertop. Dermal exposure was only assessed for direct contact exposure. All calculations are for one treatment. The treatment requires 2.5 mL product for 5 m^2. The surface layer taken up by dermal contact exposure is 0.1 mm. The product nano-silica concentration was assumed to be 1 wt%.	Adult Teenagers and young adults (16 -21 years)	Negligible	Palm of hands 0.076 (male) 0.080 (female) mg/kg/day 0.056 mg/kg	Spray* 0.00266 mg/m^3 (2.66€ µg/m^3) 0.0000032€ mg/kg/day (0.032 µg/kg/day) (male) 0.0000037€ mg/kg/day (0.037 µg/kg/day) (female) 0.0000029€ mg/kg/day (0.029 µg/kg/day) (teenager)	Negligible

€ Values are corrected as compared to calculations in the exposure assessment report.

* Note that a 1 mg/m^3 exposure concentrations was estimated by scaling of exposure estimates for use of a comparable silane-siloxane product (Norgaard et al., 2009), while direct scaling of data from another study assessing a nano-silica window-cleaner spray suggests air concentrations of at least 0.06 mg/m^3 (Michel et al., 2013). Scaling of the data in the study by Michel et al. (2013) results in at least 22 times higher exposure levels as assessed from this Tier 1 assessment.

3.13.2 Risk assessment of a nano-silica pump spray for surface impregnation

3.13.2.1 Oral exposure

Direct oral exposure was considered negligible and not assessed quantitatively. Oral uptake would come from nanomaterial deposited in the nose and mouth as well as brought up along the mucociliary escalator from the respiratory tract and, finally, by accidental uptake via inadvertent hand-to-mouth transfer. Worst case potential for oral exposure by inhalation can be assumed if 100% of the inhalational dose (expressed in µg/kg bw/day) is swallowed. Still, if inadvertent exposure from dermal-to-oral transfer, the oral dose may be greater than the inhaled dose as the dermal dose to palm of the hand is about 2,850 times higher than the inhaled dose in the Tier 1 assessment.

The DNEL for oral exposure has been calculated (see Appendix 1) to be 1.67 mg nano-silica/kg/day. This corresponds to a daily dose of 117 mg nano-silica/day for a person weighing 70 kg.

However, in contrast to the Tier 1 estimate giving an exposure level of 0.00266 mg/m^3 (2.66 µg/m^3) based on the fraction of product nanomaterial aerosolised found in Nørgaard et al. (2009), scaling directly from estimated exposure levels in another study resulted in an airborne concentration of 0.06 mg/m^3 (Michel et al., 2013). Direct scaling of a study spraying with a silane/siloxane product gives a concentration of around 1 mg/m^3. Therefore, exposure concentrations between at least 0.00266 and 1 mg/m^3 should be considered possible. The different calculated levels may be linked to both type of pump spray, formulation, differences in the specific scenarios and different procedures for calculations.

Below we have calculated the daily oral dose for the worst case scenario of oral exposure by inhalation of 1 mg/m^3 where it is assumed that 100% of the inhalational dose is swallowed:

> 1 mg/m^3 * 40.32 m^3/d*0.5 h/(24h) = 0.84 mg (assuming the same inhalation rate of 40.32 m^3/day during the 0.5 h exposure as applied in the inhalation exposure assessment)

This corresponds to $\frac{0.84\ mg}{70\ kg}$= 0.012 mg/kg per application. This result is much lower than the DNEL and therefore no risk is expected from the oral exposure.

Uncertainties

The large margin of exposure between the estimated exposure and the DNEL makes further discussion regarding uncertainties superfluous.

3.13.2.2 Dermal exposure

The dermal contact exposure was assessed for palms of the hands touching a newly treated surface (0.1 mm) with 100% transfer from the exposed area to the hand. The exposure doses range between 0.076 and 0.080 mg/kg bw/day for adults for one treatment. For first treatment, the value could double. This assumption is a worst case estimate.

The background for hazard statements in the following can be found in Appendix 1.

Local effects

ECETOC concludes that synthetic amorphous silica is neither a skin irritant nor a sensitizer. Assuming that there is no difference in the toxicity of synthetic amorphous silica and nano-silica, the results suggests that there is no risk of topical dermal effects following dermal contact (ECETOC, 2006).

Systemic
ECETOC did not report any studies on dermal absorption of synthetic amorphous silica (ECETOC, 2006). However, the external dermal exposure of 0.08 nano-silica mg/kg bw/day per application is far below the DNEL for oral exposure of 1.67 mg nano-silica/kg/day, indicating no concern for the dermal exposure in this scenario, as dermal absorption can generally be assumed to be (much) lower than possible oral absorption.

Uncertainties
The Tier 1 dermal exposure assessment was completed without taking into consideration that the user should wear gloves during application of the surface treatment. The thickness of the dermal load is a (qualified) guess and is associated with great uncertainty. It is, however, assumed that the exposure assessment is for the worst case scenario.

3.13.2.3 Inhalation
The Tier 1 assessment suggested a 30 min average exposure level of 0.00266 mg/m^3 (2.66 µg/m^3) and inhaled exposure doses of 0.0000032 mg/kg bw (0.0032 µg/kg bw) (male), 0.0000037 mg/kg bw (0.0037 µg/kg bw) (female), and 0.0000029 mg/kg bw (0.0029 µg/kg bw) (teenager) for one treatment. However, the first treatment with this product requires application in two rounds and this doubles the worst case exposure doses. Therefore, for the first application, the inhalation doses would be on the order of 0.0000058 to 0.0000074 mg/kg bw (0.058 to 0.0074 µg/kg bw).

The exposure concentrations estimated here are 22 to 376 times lower than exposure estimates calculated from direct scaling of measured data during use of two different analogous products (experimental data on nano-TiO_2 pump spray and simple small room dispersion model: Nørgaard et al., 2009; experimental data and ConsExpo modelling of nano-silica pump spray: Michel et al., 2013), which showed that that inhalable airborne concentrations could reach 1 and 0.06 mg silica/m^3, respectively. The assessment is therefore associated with great uncertainty and it is possible that the exposure could be considerably higher than that given by the Tier 1 estimate. Therefore exposure concentrations between at least 0.00266 and 1 mg/m^3 should be considered possible. For comparison with our derived DNEL, these values result in a daily inhaled quantity of:

1) Exposure of 0.00266 mg/m^3 (2.66 µg/m^3)

Based on 30 minutes of exposure of 0.00266 mg nano-silica/m^3 (2.66 µg/m^3) once every year, the average daily exposure is:

Average daily concentration = $\frac{0.00266\frac{mg}{m^3} x\ 0.5\ h}{24\ \mathrm{h/d}}$ = 0.0000055 mg/m^3/day (0.055 µg/m^3; 0.111 for the first time applied)

2) Exposure of 1 mg/m^3 (1000 µg/m^3)

Based on 30 minutes of exposure of 1 mg nano-silica/m^3 (1000 µg/m^3) once every year, the average daily concentration is:

Average daily concentration = $\frac{1\frac{mg}{m^3} x\ 0.5\ h}{24\ \mathrm{h/d}}$ = 0.021 mg/m^3/day (21 µg/m^3; 42 for the first time applied)

Comparing the average daily concentrations for the two extremes (0.00266 and 1 mg/m^3) with the estimated inhalation DNEL of 0.0017 mg/m^3 (= 1.7 µg/m^3) (see Appendix 1) for long-term continuous exposure indicates at first glance that there may be a risk associated with this pump spray scenario.

However, all in all the risk may be borderline, as the spraying with the specific product is done twice during the first application and then annually, so in fact the pulmonary load of silica on the day of spraying is outweighed by long periods with no pulmonary load of nano-silica particles. In conclusion, it is likely that more frequent use may lead to a possible risk in association with this type of consumer scenario if the highest exposure scenario is considered and when comparing the exposure levels with the DNEL for repeated/chronic exposure.

Uncertainties

Product: The details available for this product are limited. It is questionable for this product and several similar products identified in the nanoproduct databases (see exposure report) whether they do contain silica in suspension at all. However, literature data does report silica in relevant products on the European market (Michel et al., 2013). There are likely two groups of products, of which one may contain silica and the other only silanes or siloxanes. The product concentrations of the nanomaterials and the amount required for treatment are also uncertain. Literature information indicates that the amount of product required for treatment is highly variable and ranging from 0.5 to 50 mL/m^2.

Exposure estimation: This exposure assessment is highly uncertain and values range from 0.06 to 1 mg/m^3 using read across from a silica nanospray (Michel et al., 2013) and a nano-TiO_2 spray (Nørgaard et al., 2009), respectively to 0.00266 mg/m^3 in a case-specific scenario and release fractions from data published Nørgaard et al. (2009). Some of these variations might result from the above described uncertainties on the formulation and concentration in the product, the relevant scenario on product group level, the amount of product required to treat the surface and the release characteristics.

In the case presented here, we assume 0.5 mL/m^2 as this was the value for the most similar product in Michel et al. (2013). However, the emission and exposure characteristics determined for this product may not fully reflect reality as contrasts exist between the data for a silica pump spray in Michel et al. (2013) and the nano-TiO_2 pump spray in Nørgaard et al. (2009). Nørgaard found that all airborne particles were respirable and below 4 μm in size with peaks in the nano-size range as they measured the airborne particles behind the spray nozzle. However, the amount of nano-TiO_2 was not quantified. Michel et al. (2013) found that all airborne particles were inhalable (primarily above 10 μm in size) as they measured the emission from the spray nozzle. Many differences may be ascribed to different test methods and differences in the spray configurations. The differences call for the need to have specific emission characteristics and source strengths from specific products.

Overall, our assumptions are considered to range between two types of realistic data sets on potential exposure.

To consider the relevant worst case, the exposure assessment was completed without taking into consideration that the user should wear respiratory protection masks and work in a ventilated area. In the exposure assessment, we assume no mask is used by the consumer and 100% airway deposition efficiency, because the published data suggest that the entire airborne fraction is respirable. As discussed above, high uncertainty still exists on the relevant size distribution.

All in all, the exposure assessment is considered potentially worst case, but the estimated exposure levels are associated with great uncertainty.

Hazards: The derived DNEL seems robust because it is generated based on a study of four different types of synthetic amorphous silica (including synthetic amorphous silica with surface modifications). However, no information on the size distribution was given (Appendix 1).

Overall, it is concluded that the risk of using a nano-silica pump spray for surface impregnation in this scenario ranges from unlikely to possible and that the exposure is associated with considerable uncertainty.

As pointed out in Chapter 2 and in the introduction to this chapter, key uncertainties related to assessing nanomaterials in consumer products are: i) the general lack of knowledge as to which a specific nano form (size, shape, coating etc.) is present in a given product, and ii) the fact that toxicity has not been tested for all possible nano forms of a given nanomaterial chemistry. Therefore, the hazard assessment, including possible DNELs derived, may differ from the nano form in the consumer product, which again leads to uncertainties in the assessment of risks. This uncertainty is also relevant for the present scenario, although the general worst case approach applied should largely circumvent this uncertainty.

3.13.3 Conclusion

Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- No risk is expected for oral exposure.
- No risk is expected for dermal exposure.
- Regarding inhalation, it is concluded that there might be a possible risk in this specific scenario due to the considerable uncertainty associated with the exposure assessment. Certainly, more frequent use and higher content of nano-silica in the spray product could lead to an unacceptable inhalation risk.

3.13.4 Perspective

Generalisation to other product types

The assessment of this spray product has demonstrated that highly different exposure and final risk assessment results may arise depending on the release data and case studies used. Differences arise due to different concentrations in the products, the formulations, and different ways of measuring release rates, calculation principles and construction of the scenarios. It must be concluded that read across on release data and previously calculated scenarios is currently associated with a high degree of uncertainty.

Cumulative exposure/risks

Consumers may also be exposed to silica from many other types of products such as food and beverages, dental care products and natural sources.

3.14 Scenario 13 – Silver (Ag) in nano-air purifier

3.14.1 Exposure scenario

Nano-Ag can be used in air filtering devices working as air conditioners in indoor rooms. Nano-Ag is bound to the filter surface and the air is circulated continuously. Dermal exposure is theoretically possible when changing filters or during repair work. Oral, inhalation and air exposure appear to be negligible.

The exposure scenario for nano-air purifier with nano-Ag was elaborated in the exposure report where it was summarised as follows:

Air cleaners								
No.	Product	NM	Exp.scenario (application/use)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
13	Nano-air purifier	Ag	Filtering of air in a room	All	≈ 0	≈ 0	≈ 0	≈ 0

3.14.2 Risk assessment of nano-air purifier containing nano-Ag

3.14.2.1 Dermal exposure

It has not been possible to derive a quantitative exposure estimate for dermal exposure which is seen as a probable exposure route during the occasional maintenance of the purifier. However, the exposure based on the existing information may be considered as very low to negligible.

Thus, risk following this exposure route is assessed to be unlikely.

Uncertainties
It is assessed that the above qualitative assessment is robust.

3.14.2.2 Inhalation exposure

It has not been possible to derive a quantitative exposure estimate for inhalation exposure that may constitute a probable exposure route; however, the exposure based on the existing information may be considered as very low to negligible.

Uncertainties
No great uncertainties exist that may compromise the assessment of zero to negligible exposure to nano-Ag; as the nano-Ag is bound to a filter matrix in the air-purifier, very low to zero emission into the air is considered.

On the other hand the inhalation DNEL levels are also very low (see Appendix 1). However, the calculated DNEL values are considered conservative based on one experimental animal study indicating mild effects on lung function at a low exposure (0.6×10^6 particles or 0.049 mg nano-Ag/m^3).

All in all, risks following inhalation are assessed to be unlikely.

3.14.3 Conclusion

Due to the above considerations, no concern in relation to adverse effects is considered likely in relation to consumer use of air purifiers containing nano-Ag fixed in a filter matrix.

It has to be noted that only the direct toxicity of nano-Ag in relation to human health is covered in this evaluation. Therefore, indirect impact on human health, e.g. aspects concerning any potential for development of resistance of microorganisms towards silver and antibiotics, are not covered.

3.14.4 Perspective

Generalisation to other product types
No generalisation to other product types appears relevant.

Cumulative exposure/risks
The low to negligible exposure level is of no concern in relation to the cumulative nano-Ag exposure that may occur from other types of consumer products containing nano-Ag.

3.15 Scenario 14 – Spraying an article or surface with a pump spray containing nano-Ag

3.15.1 Exposure scenario

This scenario addresses use of a disinfectant pump spray containing nano-Ag. There was no information on particle size or concentrations of nano-Ag for this specific product. Based on literature data, the nano-Ag concentration was assumed to be 1 wt% (Hagendorfer et al., 2010), which is the highest nano-Ag concentration reported in spray products so far. There is no immediate information on the volume required to treat a product. It is assumed that the amount of product required to treat and disinfect an article is 10-25 mL/m^2, which is the amount required for preparing surface coating using comparable, not silver-based, products (http://www.nanocover.dk). The product is applied weekly.

Inhalation and dermal exposure are considered to be the key exposure routes. Both inhalation and dermal exposure are considered in this case as a result of direct aerosolization and due to overspray during use. Additional dermal exposure could arise from direct spraying on hands while holding an object to be treated, as well as from dermal contact with freshly treated objects. General dermal exposure due to overspray and aerosolized product is possible, but not considered further.

The spray scenario includes administration of the spray onto a 4 m^2 article followed by wiping for 6 minutes. The total inhalation exposure duration was therefore set to 10 minutes. The 4 minutes spray rate was assumed to be 25 mL/min and the product was assumed to contain 1 wt% nano-Ag. The aerosol release rate for exposure was assumed to be 0.01 wt% of the sprayed product based on data for TiO_2 and silane and siloxane spray products in Nørgaard et al. (2009). Consequently, the airborne nano-Ag release rate was 0.025 mg/min (25 µg/min). Work was assumed to take place in a 20 m^3 unventilated room. The mass based inhalation exposure is assessed using the traditional Tier 1 estimation of inhaled dose in REACH Guidance (ECHA, 2012, R.15) as well as data on release rates and size-distribution data from experimental studies on comparable, not silver-based, pump spray products.

Dermal exposure to hands was considered during wiping and direct contact exposure. In the exposure estimation it is assumed that a 0.1 mm surface layer with 1 wt% nano-Ag is transferred to the palms of the hands. Calculations were made using the ECETOC TRA equations R.15-5-R.15-7 considering the palms (50% of hand area) of the hands (ECHA, 2012, R.15).

Inadvertent ingestion and oral exposure may occur, but were not assessed specifically.

The results of the R.15 Tier 1 exposure assessments are listed in the table below. Further details and background information can be obtained in the exposure report.

No.	Product	NM	Exp. scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
14			Pump spraying 4 m2 product for 4 minutes followed by 6 minutes of wiping. Volume used 100 mL (25 mL/m2) The surface layer taken up by dermal contact exposure is 0.1 mm. Concentration of nano-Ag assumed to be 1 wt% The exposure is repeated weekly and the annual dose is therefore 52 times higher.	Adult Teenagers and young adults (16-21 years)	Very Low	Palm of hands: 0.189 mg/kg/day (male) 0.200 mg/kg/day (female) 0.145 mg/kg/day teenager)	Spray: 0.00425 mg/m3 (4.25 µg/m³) 0.0000017 mg/kg (0.0170 µg/kg) (male) 0.00000198 mg/kg (0.0198 µg/kg) (female) 0.00000154 mg/kg (0.0154 µg/kg) (teenager)	Negligible

3.15.2 Risk assessment of spraying an article or surface with a pump spray containing nano-Ag

3.15.2.1 Oral exposure

Oral exposure was not assessed directly, but the inhaled exposure dose (up to 0.00000198 mg/kg (0.00198 µg/kg) per spray event; females) is an order of magnitude lower than the oral DNEL value of 0.005 mg/kg bw/day (Appendix 1). Therefore, the oral dose is considered negligible despite weekly use of the spray.

Uncertainties

Not relevant to discuss further given the gap between exposure and DNEL values.

3.15.2.2 Dermal exposure

It is considered that the consumer may be subject to dermal exposure. In this case, it is assumed that the consumer touches a newly treated surface with the palms of the hands and a 0.1 mm layer is transferred from the surface to the hands. The corresponding estimated dermal contact exposure amounts to between 0.145 and 0.2 mg/kg bw/event day for a teenager (16 to ≤21 years) and an adult female, respectively based on a dermal load of 25 µg/cm² for coverage of the inner palms during direct contact. It should be noted that these values originate from short-term exposure, which may be minutes. A scenario could involve 5 minutes' exposure before the product is washed off the hands.

The background for hazard statements in the following can be found in Appendix 1.

Local effects

Nano-Ag at this very low concentration (1%) and the resulting dermal load is not considered to cause any local effects.

Data do not indicate any local effects except for discoloration of the skin at the contact site (localised argyria). The risk of discoloration at the contact site is considered much less important than pulmonary effects and is not considered further in this risk assessment.

Systemic
Comparing the average daily event dermal dose of up to 0.2 mg nano-Ag/kg bw/day with the derived DNEL for argyria of 2.5 mg/kg bw/day indicates that the average daily dermal dose on the day of spraying is sufficiently below the DNEL. The weekly dose would be 0.029 mg nano-Ag/kg bw/week. Therefore, we do not foresee any risk following dermal exposure in this scenario.

Uncertainties
The dermal contact exposure was assessed for a case where the palm of the hands touched a treated surface (0.1 mm) with 100% transfer from the exposed area to the hand. This assumption appears to be a worst-case estimate. In addition to direct contact, dermal exposure may also arise from overspray. The level of overspray was not assessed, as no model is yet appropriate for assessment of this type of product.

All in all, it is still considered that dermal exposure is unlikely to lead to any risks.

3.15.2.3 Inhalation
Using the above-mentioned estimated release rate of 0.001 mg/mL and a total exposure time of 10 min (effective spraying for 4 minutes in a 20 m^3 unventilated room (according to R.15 version 2.1; 2012)) adding 6 minutes for wiping, the exposure level would reach 0.00425 mg Ag/m^3 (peak value = 0.005 mg/m^3 from 4 to 10 min). The corresponding average daily event exposure doses were estimated to be rather low: 0.00000170 (male), 0.00000198 (female), and 0.00000154 (teenager) mg/kg bw/day. Based on experimental data using pump sprays, these emissions are clearly respirable with size distributions ranging from 10 nm to ca. 4 µm size-ranges for different silane, siloxane and TiO_2 pump sprays (Norgaard et al., 2009), whereas no nano-size particles were detected using a nano-Ag pump spray in Hagendorfer et al. (2010; particles larger than 500 nm were not documented).

Based on 10 minutes of exposure to 0.00425 mg nano-Ag/m^3 (4.25 µg/m^3), the average daily concentration is calculated below:

$$\text{Average daily concentration} = \frac{0.00425\frac{mg}{m^3} x\ 0.17\ h\ (10\ \text{min}\quad)}{24\frac{\text{h}}{\text{d}}\text{x}} = 0.00003\ \text{mg/m}^3\text{/day}\ (0.03\ \mu\text{g/m}^3\text{/day})$$

Comparing the average daily concentration with an estimated inhalation DNEL of 0.00006 mg/m^3 = 0.06 µg/m^3 (see Appendix 1) indicates that pulmonary exposure does not cause risk of reduced lung function (the average daily concentration is half the chronic DNEL, but only on exposure event days). However, given the uncertainties in the available exposure evidence, risk is considered uncertain.

Uncertainties
Product: Little information is available on the type of Ag actually used in these types of products. However, it is known that nano-Ag is used in some of the products and it might be emitted during spraying. No data are available on the characteristics of the nano-Ag in the specific case and limited high-quality information exists on the exposure characteristics and source strengths from consumer products. In this case, we assume a content of 1 wt% nano-Ag in the pump spray, which is considered as a reasonable maximum concentration in this type of product.

Exposure estimation: The assessment of inhalation exposure levels should be considered with some care as it arises from read-across from different pump spray products. There is a profound need to

establish data on products with specific relevance for this product group. In the inhalation scenarios, the airborne exposure concentrations are set based on assumptions about use, concentrations in the product and information from published experimental results on typical nano-Ag concentrations, relevant and partially analogous emissions and exposure data. Overall, the assumptions on the product alongside exposure characteristics are assumed to be reasonable worst case scenarios.

Real exposure measurement data on this product group do not exist at this point in time. In the exposure assessment, we assume that there was no ventilation in the room, that the consumer did not use a mask and gloves and that the exposure had 100% airway deposition efficiency, because the published data suggest that the entire airborne fraction is respirable.

Hazards: The used DNEL for silver is very low and can be considered as highly conservative.

Overall, it is concluded that spraying an article with a pump spray containing nano-Ag is not expected to cause risk based on available information, but regarded as uncertain due to uncertainties in available exposure data.

3.15.3 Conclusion

Based on the Tier 1 estimates above, the following conclusions can be reached for this scenario:

- No risk expected from oral exposure due to the low frequency of use.
- We do not foresee any risk following dermal exposure in this scenario.
- Inhalation exposure is not expected to cause risk based on available information, but regarded as uncertain due to uncertainties in available exposure data.

It has to be noted that only the direct toxicity of nano-Ag in relation to human health is covered in this evaluation. Therefore, indirect impact on human health e.g. aspects concerning any potential for development of resistance of microorganisms towards silver and antibiotics are not covered.

3.15.4 Perspective

Generalisation to other product types

All assessments were made following Tier 1 exposure assessments and no measurement data appears to be available. As mentioned above under scenario 12, exposure assessments of spray products are highly uncertain. Read across on release data and previously calculated scenarios is currently associated with a high degree of uncertainty.

Cumulative exposure/risks

Consumers may also be exposed to nano-Ag from other sources such as jewellery, cosmetics, textiles, wound dressings, and from other coatings and food supplements.

3.16 Scenario 15 – Use of disinfectant propellant spray with nano-Ag

3.16.1 Exposure scenario

This scenario addresses application of a water-based nano-Ag-based disinfectant propellant spray (pressurized spray can). There was no information about particle sizes and nano-Ag concentrations in the spray product. Scientific literature suggests disinfectant pump sprays may have nano-Ag concentrations between 12.5 ppm and 1 wt% Ag (Quadros and Marr, 2011; Hagendorfer et al., 2010). Consequently, a product concentration of 1 wt% was chosen to consider a reasonable worst case situation. There was no immediate information about the volume required to treat a product. It is assumed that 25 mL/m² is required for treatment, which is an upper typical area-dose for comparable non-silver-based products (http://www.nanocover.dk). It is also assumed that the

spray delivers the product four times faster as compared to pump sprays, resulting in a total dispensing time of 1 minute (see scenario 14). Hence, the spray can delivers 100 mL/min (equal to 100 g/min). Assuming that the solvent is water and the nano-Ag content is 1 wt%, the total use rate of nano-Ag is then 1 g/min. The product type is reported to be reasonably resistant to wash out. Therefore annual re-application of the spray is considered as a worst case scenario.

In this scenario the consumer is spraying a 4 m^2 textile using a pressurized spray with nano-Ag in a concentration of 1 wt%. The work is conducted in a 20 m^3 room with no ventilation, but inhalation exposure could not be assessed quantitatively due to high uncertainty in the emission characteristics. The aerosol release rate from using a spray can is specific to the product and varies with the type of propellant, nozzle configuration, pressure in the spray can, presence of condensable matter etc. Therefore, it was considered too uncertain to extrapolate from estimated aerosol release rates from use of pump spray products.

The external dermal load and dose at direct contact was assessed following the procedure by ECETOC TRA Equation R.15-5, 15-6 and 15.7 (ECHA, 2012, R.15). For this model, a layer of 0.1 mm liquid product was assumed to be transferred to the palms of the hands.

Oral and eye exposures are considered possible, but were not assessed specifically. The inhaled exposure dose is the upper limit for gastro-intestinal exposure dose.

The results of the R.15 Tier 1 exposure assessments are listed in the table below. Further details and background information can be obtained in the exposure report.

No.	Product	NM	Exp. scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
15	Propellant spray	Nano-Ag	A 4 m² textile is sprayed with a nano-Ag product using a pressurized spray can in 20 m³ room with no ventilation. The duration is 4 min. The total product volume used is estimated to be 100 mL (25 mL/m²) Dermal exposure was set to 0.1 mm layer is transferred to the palms of the hands Nano-Ag concentration in product is assumed 1 wt%	Adults Teenager (16 to ≤21 years)	Negligible	Palms of hands: 0.025 mg/cm² 0.200 (male) 0.189 (female) mg/kg/day 0.145 mg/kg/day	Spraying: Yes with relatively highly acute exposure as compared to the one expected from pump sprays.	Negligible

3.16.2 Risk assessment of use of disinfectant propellant spray with nano-Ag

3.16.2.1 Oral exposure

Oral exposure was assumed negligible. Oral uptake would come from nanomaterial deposited in the nose and mouth as well as brought up along the mucociliary escalator from the respiratory tract and finally by accidental uptake via inadvertent hand-to-mouth transfer.

Uncertainties

Not relevant to discuss further given the gap between exposure and DNEL values (oral DNEL value of 0.005 mg/kg bw/day; i.e. 5 µg/kg/day, see Appendix 1).

3.16.2.2 Dermal exposure

The dermal load to the palms was estimated to be 0.025 mg/cm² after contact with the treated surface and transfer of a 0.1 mm layer to the skin, resulting in a dermal exposure.

The background for hazard statements in the following can be found in Appendix 1.

Local effects

Nano-Ag at this very low product concentration (1%) and the resulting dermal load of 0.025 mg/cm² is not considered to cause any local effects. Data do not indicate any local effects except for discoloration of the skin at the contact site (localised argyria). The risk of discoloration at the contact site is considered much less important than pulmonary effects and is not considered further in this risk assessment.

Systemic
Comparing the average daily dermal dose of up to 0.200 mg/kg bw/day with the derived DNEL for argyria of 2.5 mg/kg bw/day indicates that the daily dermal dose is one order of magnitude below the DNEL. Therefore, we do not foresee any risk following dermal exposure in this scenario.

Uncertainties
The dermal exposure was assessed without taking into consideration that the user should wear gloves. The dermal contact exposure was assessed for a case where the palms of the hands touched a newly treated surface (0.1 mm) with 100% transfer from the exposed area to the hand. This assumption appears to be a worst case estimate. Again, overspray exposure is possible, but it is not possible to assess the dose due to this effect without a proper model or data. It appears unlikely that overspray exposure would cause exceedance of the DNEL for chronic exposure.

All in all, dermal exposure is unlikely to lead to risks.

3.16.2.3 Inhalation
No reliable inhalation exposure estimations have been made due to high uncertainty in the emission characteristics and aerosol emission rates. The emission rate from using a spray is very specific to the product and varies with the type of propellant, nozzle configuration, pressure in the spray can, presence of condensable matter etc. It can, however, be assumed that the exposure concentrations per mL used product normally would be significantly higher than for pump spray products. If we conservatively assume that 10% of the aerosolized spray (a total of 100 g spray containing 1 g of nano-Ag) is released and immediately mixed into the air in a 20 m^3 room, this would result in 1000 mg nano-Ag x 10%/20m^3 = 5 mg nano-Ag/m^3 air. Based on experimental data, the size distributions of aerosols generated during use of propellant sprays would be clearly respirable with dominant particle sizes in the 10 to 300 nm range (Norgaard et al., 2009; Hagendorfer et al., 2010).

Based on 4 minutes of exposure, the average daily concentration is calculated below:

$$\text{Average daily concentration} = \frac{5\frac{mg}{m^3} \times 0.07h}{24\ \text{h/day}} = 0.015\ \text{mg/m}^3\text{/event d (15 µg/m}^3\text{/day)}$$

Comparing the once-in-a-year daily exposure of 0.015 mg/m^3 with the chronic inhalation DNEL of 0.00006 mg/m^3 = 0.06 µg/m^3 (see Appendix 1), this exposure is 250 times the DNEL for chronic exposure. Therefore, this rough exposure estimate indicates that an exposure level of concern may be related to this user scenario.

Uncertainties
Product: The characteristics are poorly specified for the product assessed. There is no information on the size distribution of the nano-Ag and Ag concentrations in the product. However, it is known that nano-Ag is used in some of the products and it might even be generated during spraying if present as ionic Ag. No data are available on the characteristics of the nano-Ag in the specific case and limited high-quality information exists on the exposure characteristics and source strengths from consumer products.

Exposure estimation: A rough exposure estimate was made for the nano-Ag spray to understand the potential scale of exposure during use of this pressurized spray can. A proper Tier-1 estimate could not be made due to lack of appropriate data. There are some indications from previous studies, but the variability between emissions from pump sprays to pressurized spray cans are great and it is also expected that there would be variations between different types of pressurized spray cans. Based on pump-spray data and experience from other types of spray cans, nano-size particles will be released or formed during use of a pressurised spray can and result in relatively high exposure levels. However, the fraction and behaviour of the nano-Ag or ionic Ag during spraying is not described and the emission rate from the product is not known. This is considered a significant

information gap in relation to a potentially high consumer exposure situation. There is a profound need to establish data on products with specific relevance for this product group.

Hazards: The used DNEL for silver is very low and can be considered as highly conservative.

Overall, it is concluded that a possible risk has been identified in relation to inhalation exposure. A more precise risk assessment will be needed in order to make a more definitive conclusion, and especially more accurate knowledge is needed about realistic exposure levels in association with use of propellant aerosols containing nano-Ag.

3.16.3 Conclusion

Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- Oral exposure is considered negligible.
- Dermal exposure is unlikely to lead to any risks.
- The inhalation exposure indicates a possible risk in relation to reduced lung function.

It has to be noted that only the direct toxicity of nano-Ag in relation to human health is covered in this evaluation. Therefore, indirect impact on human health e.g. aspects concerning any potential for development of resistance of microorganisms towards silver and antibiotics are not covered.

3.16.4 Perspective

Generalisation to other product types

All assessments were made quantitatively except for the dermal exposure assessment which was made following Tier 1 exposure assessments and no measurement data appears to be available. As mentioned above under scenario 12, exposure assessment of spray products, and in particular spray cans, is highly uncertain. Read across on release data and previously calculated scenarios are currently not possible.

Cumulative exposure/risks

Consumers may also be exposed to (nano-)Ag from other sources such as jewellery, cosmetics, textiles, and from other coatings and food supplements.

3.17 Scenario 16 – Silver (Ag) in T-shirt

3.17.1 Exposure scenario

Silver (Ag) as nanoparticles are used as antimicrobials in textiles. Most often, and in the case as described here, no specific information about characteristics, including size distribution of Ag in the textile, is given (Goetz et al., 2013). Therefore, textiles that are claimed to contain nano-Ag may often not contain nanoparticles.

Contained nano-Ag, metallic nano-Ag or nano-Ag-salts may be embedded in the textile fibres or in a surface coating of the fibres (Danish EPA, 2012). There may be migration of nano-Ag or formation of nanoparticles from precipitation of soluble Ag^+ into sweat when wearing the textile. Goetz et al. (2013) reported that about 50% of the migrated Ag particles into artificial sweat had a diameter <450 nm and were mainly in the form AgCl.

Adults as well as children may wear clothes containing nano-Ag. The principal exposure route is dermal exposure, but mouthing of part of the T-shirt by children cannot be excluded (a surface area of 100 cm^2 is assumed). Inhalation exposure from wearing the textile is judged to be negligible (Danish EPA, 2012). Using the data from Goetz et al. (2013), the nano-Ag concentration in the T-

shirt is assumed to be 0.18 mg Ag/g and the weights of the T-shirt for females and males are assumed to be 64 and 89 g, respectively, implying an exposed area of 6,900 cm² and 9,800 cm², respectively. Migration into artificial sweat has been measured to be 43 µg dissolved Ag/g textile/L liquid, and 31 µg particulate Ag/g textile/L for particles <450 nm (Goetz et al., 2013). The maximum migration is considered to come from a sweat soaked T-shirt that is worn for 1 hour during intense activity (Goetz et al., 2013). The T-shirt may be used on a daily basis for 1 hour/day. Migration may be lowered after initial use because of wash out of Ag.

The exposure scenario for T-shirt with nano-Ag was elaborated in the exposure report where it was summarised as follows:

Textiles								
No.	**Product**	**NM**	**Exp.scenario (application/use) (product volume used) (NM concentration in product)**	**Target group**	**Nanomaterial Exposure**			
					Oral	**Dermal**	**Inhalation**	**Eye**
16	T-shirt	Ag	Exposure due to migration of Ag from textile into sweat. 1 hour soaked T-Shirt. 64-89 g T-shirt 183 µg Ag/g textile	Adult (female)	NCR	0.036 µg/cm² 0.25 mg/day 0.004 mg/kg/day	NCR	NCR
				Adult (male)	NCR	0.071 µg/cm² 0.70 mg/day 0.009 mg/kg/day	NCR	NCR
			Sucking 100 cm² T-shirt	Children	0.0083 mg/day 0.00045 mg/kg/day	MD Considered below adult values**	NCR	NCR

*NCR: not considered as a relevant exposure route
**: due to significant lower sweat production by children
MD: missing data for estimation

3.17.2 Risk assessment of T-shirt containing nano-Ag

3.17.2.1 Oral exposure

WHO (2003) considered argyria in humans as the most critical effect after systemic uptake of Ag and based on an oral NOAEL of 10 g Ag as a lifetime dose level, a daily oral NOAEL of 0.005 mg/kg bw/day (5 µg/kg/day) can be calculated (assuming a person on 70 kg lives for 75 years). Therefore, an oral DNEL can be set to 0.005 mg Ag/kg/day. This DNEL can be used for nano-Ag including all soluble Ag species.

This DNEL value may be compared to the estimated oral exposure of children of 0.00045 mg/kg bw/day which is an order of magnitude below the DNEL level and thus considered of no concern. See Appendix 1 for further details.

Uncertainties

Little uncertainty pertains to the content of Ag in the T-shirt as this content was measured. However, it was not specifically addressed whether the silver content was in the form of nano-Ag particles. This might, however, be less relevant as the silver ion is considered the toxic moiety for oral intake.

The maximum migration takes place from a soaked T-shirt; migration will most likely decrease after the initial use because of washing out of Ag, so that the maximum exposure may only occur during the first day or days of use. The calculations are based on total silver and overestimate exposure to nano-Ag as liberated from the fabric, representing a conservative estimate both in relation to dermal and oral exposure.

Furthermore, it cannot be considered realistic that a child would suck on a nano-Ag impregnated T-shirt every day.

Uncertainties also pertain to the DNEL value as human exposures leading to argyria are often poorly and imprecisely reported. Nevertheless, this figure for safe level of oral exposure is based on human data and is used by WHO for risk assessment of silver in drinking water and has also recently been used by EFSA (2011).

All in all, the uncertainties indicate a lower daily exposure than used in the scenario which should be considered highly conservative. Also, the DNEL for shorter duration of exposure may be considerably higher than a DNEL value in relation to chronic long tern exposure.

Therefore, the no concern conclusion reached is considered to be robust.

3.17.2.2 Dermal exposure

The background for hazard statements in the following can be found in Appendix 1.

Local effects

No dermal DNEL for local effects on the skin has been derived and the relevance of a dermal DNEL is questionable. No irritation is expected from nano-Ag in a textile, also consistent with the use of nano-Ag in wound dressings on very susceptible skin areas.

Therefore, no local dermal risk is expected.

Systemic effects

After systemic absorption, Ag may accumulate and be deposited in the skin and eyes where it causes discoloration (argyri/argyrosis). A dermal DNEL of 2.5 mg nano-Ag/kg bw/day has been derived

for these effects by route-to-route extrapolation of the oral DNEL, taking into account the poor dermal absorption of Ag.

This DNEL for dermal exposure can be compared to the dermal Ag exposure from a T-shirt of 0.009 mg/kg bw/day (highest for males due to the higher sweat rate of males).

It can be noted that the dermal exposure from the T-shirt is far below the dermal DNEL level by several orders of magnitude.

Therefore, the dermal exposure to nano-Ag from the T-shirt does not indicate any risks.

Uncertainties

Exposure estimation: Little uncertainty pertains to the content of Ag in the T-shirt as this content was measured. However, it was not specifically addressed whether the silver content was in the form of nano-Ag particles.

The maximum migration takes place from a soaked T-shirt; migration may be decreased after initial use because of washing out of Ag. The calculations are based on total silver and overestimate exposure to nano-Ag as liberated from the fabric, representing a conservative estimate both in relation to dermal and oral exposure.

Hazards: The DNEL levels pertain to all forms of Ag, including nano-Ag. When transforming the oral DNEL to a dermal DNEL (route-to-route extrapolation), uncertainties also pertain to the absorption rates used. As a dermal absorption of 0.1% from damaged skin is used, a DNEL for intact skin may be considerably higher than the one calculated.

All in all, a low degree of uncertainty pertains to the conclusion of negligible risk for dermal exposure.

3.17.2.3 Inhalation

No further risk assessment is made as exposure by inhalation of textile fibres containing nano-Ag is considered negligible/not relevant.

3.17.2.4 Eye exposure

No further risk assessment is made as eye exposure is considered negligible/not relevant.

3.17.3 Conclusion

Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- No risk following oral exposure (children sucking on textiles/t-shirts) is expected.
- No risk following dermal exposure is expected.

It has to be noted that only the direct toxicity of nano-Ag in relation to human health is covered in this evaluation. Therefore, indirect impact on human health, e.g. aspects concerning any potential for development of resistance of microorganisms towards silver and antibiotics, are not covered.

3.17.4 Perspective

Generalisation to other textiles and product types

Due to challenges regarding the sensitivity of analytical methods, there is great uncertainty as to whether textiles claimed to contain nano-Ag actually contains Ag in nano form. Additionally, it is important for the extent of migration as to whether silver is embedded in the fibres or coated on their surface. The speciation of silver is also important for migration, but speciation is often not specified.

As the oral and dermal DNEL value is valid for all forms of Ag (including nano-Ag) and due to the wide gap between the estimated exposure and the DNEL value, it may be concluded that no risk is to be expected from nano-Ag treated textiles unless rather extreme Ag migration from the textiles occurs.

For other product types it is also relevant to address the total Ag exposure (to all forms of Ag, not only nano-Ag exposure) when making risk assessments for dermal and oral exposure as systemic absorption of silver may be higher for dissolved Ag as compared to nano-Ag.

The exposure considerations/estimations for this scenario are not considered representative for less soluble nanomaterials forming part of textiles (as e.g. textiles treated with carbon nanotubes, CNTs).

Cumulative exposure/risks
Unless high migration of silver from nano-treated textile occurs, there would generally be low systemic contributions to Ag from textiles. Therefore, other product types may be more important in relation to nano-Ag exposure, e.g. food supplements, cosmetics, or sprays for cleaning/surface treatment. See also scenarios 3, 11, 14, 15 and 18.

3.18 Scenario 17 – Cement with nano-TiO_2

3.18.1 Exposure scenario

This scenario addresses the possible consumer use of cement containing nano-TiO_2. Given the information identified in the current study, it is still uncertain to what extent such products have penetrated the market, especially in relation to consumers. It has been estimated that such cement could typically contain 5% nano-TiO_2.

Adults renovating (or perhaps even building) their own house/driveway might use cement products over longer periods. Inhalation, dermal and eye contact are considered the most relevant exposure routes. Exposure during handling/mixing and possible exposure during grinding of concrete surfaces have been addressed.

Inhalation exposure has been estimated based on measurements in occupational settings, dermal exposure by modelling and eye exposure has been addressed qualitatively.

The exposure scenario for cement with nano-TiO_2 was elaborated in the exposure report where it was summarised as follows:

No.	Product	NM	Exp. Scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure*			
					Oral	Dermal	Inhalation	Eye
17	Cement	TiO_2	Repairing own house/driveway > 10 kg/day 5% nanoTiO_2	Adults	NCR	Arms/hands: 36.6 mg/kg/day Whole body: 179 mg/kg/day	Handling: 0.25 mg/m³ 0.042 mg/kg/day Grinding: 0.75 mg/m³ 0.13 mg/kg/day	Possible but no data to quantify

NCR: Not considered a relevant exposure route

3.18.2 Risk assessment of cement containing nano-TiO_2

3.18.2.1 Dermal exposure

The background for hazard statements in the following can be found in Appendix 1.

Local effects
The hazard report found that nano-TiO_2 appears to possess a low irritation potential. Thus, possible eye irritation/corrosion would be driven by cement as such, known to be irritating/corrosive, and not by the contained nano-TiO_2.

Systemic
The exposure report estimated the dermal exposure conservatively using the ECETOC TRA model. However, the hazard report found that dermal absorption is highly unlikely, not the least based on a thorough review performed by SCCS (EU Scientific Committee for Consumer Safety) in relation dermal exposure following application of nano-TiO_2 as UV-filter in sunscreens.

Cement is, however, different from sunscreens and is known to cause irritation/corrosion, possibly damaging the skin, and it may be speculated whether this could lead to increased uptake of e.g. nano-TiO_2. Whether this is the case is uncertain. As described in the hazard report, experiments with nano-TiO_2 on sunburnt and psoriasis-affected skin has not found TiO_2 in viable cells of the epidermis.

A number of studies have shown that nano-sized TiO_2 particles can penetrate into the outer layers of the stratum corneum, and enter hair follicles and sweat glands, which could possibly generate reactive oxygen species (ROS) following UV-radiation (SCCS, 2014a). One study referred to in the hazard report found very low TiO_2 concentrations in viable dermis, but noted that this might be due to cross-contamination. All in all, there is no evidence at present to indicate that this pathway offers a viable mechanism of entry into systemic circulation. Therefore, also in line with the SCCS assessment of nano-TiO_2 in sunscreen, risks of systemic effects following dermal exposure to nano-TiO_2 are unlikely. See Appendix 1 for further hazard information.

Uncertainties
Product: As already noted, the market penetration of cement with nano-TiO_2 is uncertain, and may in particular be limited for consumers. It is uncertain whether consumers are exposed at all.

The 5% nano-TiO_2 content in this type of cement is uncertain. It is believed to be representative of a reasonable worst case scenario, but it cannot be excluded that products with higher nano-TiO_2 content will surface, which could lead to higher exposures.

Hazards:
The main uncertainty associated with dermal exposure is whether nano-TiO_2 can penetrate skin which has been damaged by the irritating/corrosive action of the cement. Available evidence however suggests that this situation is not very likely.

Overall, the estimated exposure levels are considered as reasonable worst case scenarios. However, the exposure level does not really influence the assessment as long as the potential for local dermal effects or absorption are considered unlikely.

It should also be noted that that SCCS has recently lowered the recommended content of anatase nano-TiO_2 from 15% to 5% of the contained nano-TiO_2 in sunscreens (recommended to be 25% maximum) (SCCS, 2014a).

The anatase content might be an issue in relation to local dermal effects, as some studies indicate that the nanoparticles may reach the hair follicles and it is speculated that such anatase TiO_2 could lead to generation of reactive oxygen species (ROS) on exposure to UV light.

Overall, it is assessed that dermal exposure to nano-TiO_2-containing cement is unlikely to lead to significant systemic exposure, although slight dermal absorption cannot be excluded and some uncertainty exists as to whether skin damaged by cement might lead to uptake.

3.18.2.2 Inhalation

The derived exposure estimates for inhalation (0.25 for mg nano-TiO_2/m^3 for handling cement and 0.75 mg nano-TiO_2/m^3 for grinding cured concrete) are based on measured reasonable worst case concentrations for workers. The scenario assumes that nano-TiO_2 constitutes 5% of cement (and of concrete, although this is additionally conservative as cement is mixed with other materials) and the inhalation estimate is based on the assumption that nano-TiO_2 would constitute 5% of the measured inhalation concentration of cement dust. Therefore, the actual measured cement exposures are 20-fold higher than those indicated in the above table.

The background for hazard statements in the following can be found in Appendix 1.

The US National Institute for Occupational Safety and Health (NIOSH) has suggested Recommended Exposure Levels (REL) of 0.3 mg ultrafine TiO_2/m^3 (based on reduction of the risk for lung tumours to 1/1000 lifetime risk) and 0.004 mg ultrafine TiO_2/m^3 based on prevention of pulmonary inflammation. These values represent time-weighted averages over a work day (10 hours corresponding to a 40 hour workweek for up to 10 hours per day.

It can be seen that the estimated nano-TiO_2 exposure levels are about two orders of magnitude above the level considered to protect against pulmonary inflammation.

In most situations, consumers would probably not handle (mix) cement powder or grind concrete surfaces for long periods. However, if it is assumed that such an operation would last one hour, the average inhalation concentration over 10 hours would be 0.025 and 0.075 mg nano-TiO_2/m^3. These values are still about an order of magnitude higher than the lower REL value of 0.004 TiO_2/m^3.

In line with normal practice, consumer protection levels should generally be higher than worker protection levels. In line with this, and considering the principles in the REACH guidance, consumer DNELs of 0.05 mg ultrafine TiO_2/m^3 and 0.0014 mg ultrafine TiO_2/m^3 respectively were

derived based on the two recommended exposure limits (RELs) suggested by NIOSH, see Appendix 1.

It can be seen that when comparing with these levels, the estimated consumer exposures averaged over 10 hours are about two orders of magnitude or more above the value established to prevent inflammation.

Uncertainties
Product: As already noted, the market penetration of cement with nano-TiO_2 is uncertain, and might in particular be limited for consumers. It is uncertain whether consumers are exposed at all.

The 5% nano-TiO_2 content in this type of cement is uncertain. It is believed to be representative of a reasonable worst case scenario, but it cannot be excluded that products with higher nano-TiO_2 content will surface, which could lead to higher exposures.

Exposure estimation: The exposure estimate is based on the assumption that nano-TiO_2 would constitute the same share of the inhaled concentration as its share of the cement product mass. It is uncertain whether this makes the assessment more or less conservative. For concrete it is probably rather conservative as the cement in this case would be mixed with other materials "diluting" the nano-TiO_2 content.

The exposure estimates are based on measurements in occupational settings and it must be assumed that consumers are generally applying lower volumes of the product, and with less intensity, during a working day. Consumers would also generally apply cement for a shorter period. Therefore, consumers are generally less likely to be at risk following application of cement as compared to workers. However, extreme consumer segments (e.g. those building their own house), possibly without use of personal protective equipment, might be exposed to high concentrations.

Regarding exposure following grinding, it is doubtful whether consumers are actually exposed to nano-TiO_2 or to larger particles. In this case, the 0.75 mg/m³ estimate might relate to coarser grinding particles and not to nano-TiO_2.

Hazards: As cement is also irritating/corrosive in itself, it may be that this effect alone causes the consumer to avoid inhalation either by changing operation or by applying personal protective equipment. If this is the case, exposure and thereby risks would be considerably lower than what is estimated above.

Furthermore, it should be noted that the RELs and DNELs discussed above are based on data from animal experiments with rats. It is known that rats are more sensitive than humans in relation to lung overload and some of the effects, e.g. the generation of tumours seen at high exposure concentrations in rats, may only happen at even higher exposure levels in humans. Therefore, the RELs/DNELs may reflect a highly conservative approach.

Overall, it is concluded that if cement with nano-TiO_2 is available on the market, it could constitute a consumer inhalation risk, in particular if consumers are handling large quantities of dry, dusty cement over longer periods without use of inhalation protective equipment. In addition to this, risks may be potentiated by the irritation effects of other cement components.

As pointed out in Chapter 2 and in the introduction to this chapter, key uncertainties related to assessing nanomaterials in consumer products are: i) the general lack of knowledge as to which a specific nano form (size, shape, coating etc.) is present in a given product, and ii) the fact that toxicity has not been tested for all possible nano forms of a given nanomaterial chemistry. Therefore, the hazard assessment, including possible DNELs derived, may differ from the nano

form in the consumer product, which again leads to uncertainties in the assessment of risks. This uncertainty is also relevant for the present scenario, although the general worst case approach applied should largely circumvent this uncertainty.

3.18.2.3 Eye exposure

The hazard report found that nano-TiO_2 seems to possess a low irritation potential (Appendix 1). Thus, possible eye irritation/corrosion would be driven by the cement itself, a material known to be irritating/corrosive.

Therefore, eye contact with cement should be avoided, because of cement components other than nano-TiO_2.

3.18.3 Conclusion

Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- Nano-TiO_2 in cement is not expected to lead to dermal irritation/sensitisation (although cement itself may cause such effects).
- Nano-TiO_2 containing cement is unlikely to lead to significant systemic exposure following skin contact, although minor dermal absorption cannot be excluded. However, further investigation as to whether skin damaged by cement might lead to increased absorption may be warranted.
- Nano-TiO_2 containing cement may constitute an inhalation risk to consumers not using personal protective equipment during dusty operations.
- Nano-TiO_2 is not expected to lead to eye irritation (although cement itself may cause irritation).

It should be noted that market penetration of nano-TiO_2-containing cement is uncertain. Possible further investigations might aim at surveying the extent to which this type of product will be on the consumer market in years to come, and if so, the percentage nano-TiO_2 in the cement. Furthermore, more accurate estimations of consumer inhalation exposure may be warranted as well as establishing realistic inhalation no-effect levels for consumers.

3.18.4 Perspective

Generalisation to other product types

The results of this scenario may be considered in relation to other possible applications of nano-TiO_2 products, such as plaster/gypsum and powder paints.

Cumulative exposure/risks

Accumulated inhalation exposure could be considered if a consumer is renovating his own house and working with large amounts of cement and spray painting of the house with nano-TiO_2 containing paint. Scenario 10 and 11 address possible nanomaterial inhalation exposure during painting. Dermal exposure to nano-TiO_2 might be further elevated if sunscreen is applied as addressed in scenario 5 and 6.

3.19 Scenario 18 – Silver (Ag) in wound dressing

3.19.1 Exposure scenario

Nano-Ag is used in wound dressings. Particle size has been measured in the range of 200-450 nm (using scanning electron microscopy); a load of nano-Ag on the dressing of 1.64 mg/cm^2 has been reported (Rigo et al., 2012; Roman et al., 2013). The exposure can occur daily for an assumed treatment period of a maximum of 21 days. Dermal exposure is the only relevant route of exposure. In general, use of dressings for larger wounds is related to professional/medical treatment.

Therefore, the scenario considers possible private treatment at home of smaller wounds (patch sizes of 120 cm^2 with a nano-Ag load of 1.64 mg nano-Ag/cm^2 and a release factor of 0.6) and a maximum of 21 days' treatment of a child, as this is considered as a worst case scenario for systemic exposure due to the smaller body weight of children (here 13 kg bw).

The exposure scenario for wound dressing with nano-Ag was elaborated in the exposure report where it was summarised as follows:

Medical devices								
No.	**Product**	**NM**	**Exp. scenario (application/use) (product volume used) (NM concentration in product)**	**Target group**	**Nanomaterial Exposure**			
					Oral	**Dermal**	**Inhalation**	**Eye**
18	Wound dressing	Ag	Dermal application of wound dressing Migration from dressing	Children	NCR	0.98 mg/cm^2 118 mg/day 9.08 mg/kg/day	NCR	NCR

*NCR: not considered as a relevant exposure route

3.19.2 Risk assessment of wound dressing containing nano-Ag

3.19.2.1 Dermal exposure

The background for hazard statements in the following can be found in Appendix 1.

Local effects
No dermal DNEL for local effects (irritation) on the skin has been derived; the relevance of such a dermal DNEL is questionable, as no irritation has generally been recognised in wound treatment with nano-Ag.

Local discoloration at the wound site may, however, occur due to precipitation of poorly soluble silver species.

Systemic effects
After systemic absorption, Ag may accumulate and be deposited in the skin and eyes where it causes discoloration (argyri/argyrosis). A dermal DNEL of 2.5 mg nano-Ag/kg bw/day has been derived based on a worst case absorption of 0.1% from wounded areas (i.e. damage skin).

This DNEL for dermal exposure can be compared to the dermal Ag exposure from the wound dressing of 9.08 mg/kg bw/day, i.e. the exposure exceeds this DNEL value by a factor of 3-4.

When translating this into evaluation of the risk for discoloration, it has to be recognized that the DNEL is based on the accumulation of Ag over a lifetime in relation to daily exposure (i.e. to the total amount of silver over a lifetime). Therefore, 21 days of exposure to 3-4 times the DNEL value would not appear to contribute to any significant increase of exposure to the total amount of silver and therefore is not considered to constitute a risk for the development of argyria.

Uncertainties
Little uncertainty pertains to the content of Ag in the wound dressing and the release factor in this specific scenario, as these are specific and measured data reported from literature, thus indicating realistic product characteristics.

The treated area is considered relevant for consumer use. Argyria following professional treatment of larger skin areas has been reported, so the conclusion reached should not be generalized to larger skin areas.

The DNEL level pertains to all forms of Ag, including nano-Ag. When transforming the oral DNEL to a dermal DNEL (route-to-route extrapolation) in Appendix 1, uncertainties also pertain to the absorption rates used. As, however, a maximal dermal absorption of 0.1% from damaged skin is used in connection with use of wound dressings, this figure specifically addresses the exposure scenario given here.

Furthermore, it is conservative to consider the same absorption from the fraction of intact skin that would also be covered by the patch.

All in all, the conclusion reached regarding possible risk following consumer application of smaller skin areas is considered robust. However, it does not apply to professional treatment of larger skin areas.

3.19.3 Conclusion
Treatment of smaller wounds with nano-Ag wound dressings is not considered to pose any risk with regard to development of argyria.

It has to be noted that only the direct toxicity of nano-Ag in relation to human health is covered in this evaluation. Therefore, indirect impact on human health e.g. aspects concerning any potential for development of resistance of microorganisms towards silver and antibiotics, are not covered.

3.19.4 Perspective
Generalisation to other product types
As this is a rather special consumer scenario (treatment of a wound), it is difficult to generalise to other consumer products containing nano-Ag or other nanomaterials. However, it should be noted that even if the DNEL for systemic exposure (either following dermal or oral exposure) is exceeded for a shorter period of time, this does not necessarily indicate a concern for the development of argyria.

Cumulative exposure/risks
It should be recognised that the systemic exposure to Ag from the use of wound dressings should be seen in connection with other sources for Ag exposure to consumers, especially food supplements containing nano-Ag, and also other possible contributions from consumer products e.g. cosmetics, textiles and disinfection sprays. See also scenarios 3, 11, 14, 15 and 16.

3.20 Scenario 19 – Mechanical finishing of ceramic dental tooth (nano-ZrO_2 and nano-silica)

3.20.1 Exposure scenario
This scenario addresses the mechanical fitting and finishing of a nano-ceramic dental tooth. A scientific paper describes this product as containing 20 nm nano-silica and 5-20 nm nano-zirconia (nano-ZrO_2) (Van Landyot et al., 2012) and a Material Safety Data Sheet in one case states that the silica is a silane-treated silica with a concentration of 5-10% and that the material consists of 65-75% silane-treated ceramics (assumed to be ZrO_2). In the scenario, a consumer undergoes dental

surgery with placement of a ceramic tooth. The tooth is cast and fitted *in situ* in the oral cavity using electrical fitting tools.

The primary routes of exposure of concern are inhalation during installation of the tooth and re-shaping (fitting) as well as oral exposure during installation of the tooth and re-shaping (fitting) as well as long-term use. It is assumed that the fitting takes 30 min and leads to both inhalation and oral exposure. The tooth is assumed to have a lifetime of 10 years during which the consumer is exposed to slow release of wear debris of the composite.

The inhalation exposure is estimated based on measured worker exposure during dental surgery of a similar tooth material (Van Landyot et al., 2012). In this study, average concentrations of particulate matter smaller than 10 μm in size (PM_{10}) exceeded 0.060 mg/m^3 during processing in a workplace measurement in a dental clinic. The total suspended dust concentrations reached 10 mg/m^3 (Van Landyot et al., 2012). Since respirable dust includes particles up to 4 μm size (PM_4) and at least the final shaping is conducted in the client's mouth, it is assumed that the average respirable dust concentration would be in the order of 1 mg/m^3 during the 30 min of processing the tooth. The exact composition of the dust was not characterized, so it is conservatively assumed that all dust occurred because of the nanocomposite debris. The inhaled exposure dose was estimated using the traditional Tier 1 estimation of inhaled dose in R.15 (ECHA, 2012, R.15).

Oral exposure during use was considered likely during surgery and during long-term use. The product has been shown to be highly durable. Wear tests reveal that approximately 5 μm were worn off after 200,000 standard test cycles. Assuming a 0.75 cm^2 chewing area encompassing a tooth repair and the wear test data corresponds to the wear during 1 year of use, this gives an annual release of 0.75 cm^2 x 0.0005 cm= 3.75x10^{-4} mg (assuming a density of 1 g/cm^3) over 10 years. The value is, however, highly speculative, and can only be used for general range-setting the oral exposure.

Consumers ranging from children with permanent teeth to aged adults could be subject to this exposure scenario. Given the uncertainties associated with this scenario, only adults have been considered, although the conclusions would also be relevant for children.

The results of the R.15 Tier 1 and read-across exposure assessments are listed in the table below. Further details and background information can be obtained in the exposure report.

No.	Product	NM	Exp. scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
19	Nano-ceramic dental tooth	5-10 wt% nano-silica and 65-75 wt% nano-ZrO_2	A ceramic tooth is fitted by abrasion and polishing techniques for 30 min leading inhalation and oral exposure. Oral long-term exposure occurs for 10 years followed by new dental replacement tooth. One tooth is assumed to weigh 1 g A tooth consists of up to 85 wt% nano-silica and nano-ZrO_2	Adults	Acute during surgery and likely to wear during 10-year use	NCR	Finishing: 1 mg/m³ 0.014 (male) 0.012 (female) mg/kg*	NCR

NCR: Not considered relevant exposure route

* This is the acute dose on the day of tooth replacement and equals the annual dose, and a 0.1 factor for the 10-year average annual exposure dose.

3.20.2 Risk assessment of mechanical finishing of ceramic dental tooth (nano-ZrO_2 and nano-silica)

3.20.2.1 Oral exposure

There is a high likelihood of oral exposure.

During treatment

The daily oral dose can be calculated for the worst case scenario for oral exposure by inhalation of 1 mg nanocomposites debris per m³ where it is assumed that 100% of the inhalational dose is swallowed:

$\frac{0.5\ h * 1\ mg/m3}{24\ \text{h/day}}$ * 20 m³/day *1.0 = 0.42 mg (assuming that a consumer inhales 20 m³/day)

This corresponds to $\frac{0.42\ mg}{70\ kg}$= 0.006 mg/kg. This is more than 250 times lower than the DNEL for daily intake of nanosilica (1.67 mg nano-silica/kg bw/day) (Appendix 1). No data are available on oral toxicity of ZrO_2, but it was qualitatively assessed to be of low toxicity following oral intake (see Appendix 1). It should be noted that the nanocomposites contain 5-10 wt% nano-silica and 65-75 wt% nano-ZrO_2. Based on these data, risk is considered unlikely for this exposure scenario.

Uncertainties

Product: The product assessed was relatively well-described and from this point of view the scenario has low uncertainty.

Exposure estimation: Gastric exposure (oral cavity) was not assessed specifically due to insufficient material detail or exposure data. Oral uptake would also come from the inhalation dose where transport from nose and mouth as well as the mucociliary escalator from the respiratory tract contribute to the oral exposure. So the inhaled dose is also the worst case oral dose. Considering the

theoretical oral exposure based on wear test data, an annual wear of one tooth would result in 0.0000375 mg (0.0375 µg) release from the tooth every year. Using the body weight of a small child (18.6 kg), this amounts to 0.0000202 mg/kg bw/year (0.0202 µg/kg bw/year) (child). This is approximately 461 times less than the inhalation exposure assessed for the clinical exposure.

Hazard: No data are available on oral toxicity of ZrO_2, which, however, was qualitatively assessed to be of low toxicity following oral intake (Appendix 1).

All in all, based on available data, oral exposure is not considered to constitute any significant risk.

3.20.2.2 Inhalation

Assuming 1 mg/m³ of airborne nanocomposite debris in the consumer's inhalation zone, the traditional Tier 1 estimation in R.15 (ECHA, 2012, R.15) reached 0.012 and 0.014 mg nanocomposites debris/kg bw on the day of dental replacement for a female and a male, respectively.

Based on 30 minutes of exposure to 1 mg nanocomposite/m³, the average daily concentration in the inhalation zone is calculated below on the day of treatment:

$$\text{Average daily concentration} = \frac{0.5\ h/d * 1\ mg/m3}{24\ \text{h/day}} = 0.021\ \text{mg/m}^3\ (21\ \mu\text{g/m}^3)$$

Comparing the average daily concentration with an estimated inhalation DNEL of 0.0017 mg/m³ (1.7 µg/m³) for nano-silica and DNEL of 0.016 mg/m³ (16 µg/m³) for nano-ZrO_2 (see Appendix 1) indicates that pulmonary exposure may pose a risk (the average daily concentration is about 12 times (nano-silica) and 1.3 times (nanoZrO_2) higher than the estimated no effect level, respectively). The debris is a mixture of nano-silica and nano-ZrO_2 (the ceramic composition was 5-10 wt% nano-silica and 65-75 wt% nano-ZrO_2). A real health risk might be considered unlikely in the given scenario, because dental surgery is a relatively rare event that more properly should be compared to an acute DNEL value with a significantly higher value than the DNEL for chronic exposure. However, this should still be said with caution as the exposure assessment is highly uncertain because of lack of data for the consumer exposure in this scenario. Overall, it is therefore concluded that inhalation risks are uncertain.

Uncertainties

Product: The product assessed was relatively well-described and from this point of view the scenario has low uncertainty.

Exposure estimation: In the inhalation scenario, the airborne consumer exposure during treatment is estimated based on measured room concentration values found in a dental office as reported in a scientific publication. It was observed that the concentrations of particulate matter (PM_{10}) exceeded 0.06 mg/m³ in a dental clinic and the total suspended dust concentrations reached 10 mg/m³ (Van Landyot et al., 2012). It was assumed that the average concentration of respirable dust (PM_4; particles up to 4 µm size) at the consumer was 1 mg/m³ and therefore higher than the room concentration of PM_{10} (particles up to 10 µm in size). This is a highly uncertain estimate, but assuming that the entire estimated respirable dust consisted of nanomaterial and that the duration of the treatment was 30 min, the scenario is considered to be reasonably precautionary. However, experimental evidence is certainly warranted to clarify this type of exposure, including whether released particles contain free nanoparticles.

Hazards: Risk has been estimated based on DNEL of nano-silica and nano-ZrO_2 but it is likely that the sanding dust particles will consist of matrix embedded particles as has been previously observed for nanoparticle-containing paints (Saber et al., 2012a; Saber et al., 2012b). The hazard of matrix

embedded nano-silica and nano-ZrO_2 particles is unknown and may well be lower than the hazard of the pristine particles as has been observed for paint dust (Saber et al., 2012a; Saber et al., 2012b).

As pointed out in Chapter 2 and in the introduction to this chapter, key uncertainties related to assessing nanomaterials in consumer products are: i) the general lack of knowledge as to which a specific nano form (size, shape, coating etc.) is present in a given product, and ii) the fact that toxicity has not been tested for all possible nano forms of a given nanomaterial chemistry. Therefore, the hazard assessment, including possible DNELs derived, may differ from the nano form in the consumer product, which again leads to uncertainties in the assessment of risks. This uncertainty is also relevant for the present scenario, although the general worst case approach applied should largely circumvent this uncertainty.

3.20.3 Conclusion

Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- No risk is expected from the oral exposure.
- Overall the inhalation risks could be considered unlikely in the scenario because it is assumed to be a rare event. However, the exposure assessment is highly uncertain because of lack of data. Overall, inhalation risk is therefore considered to be uncertain.

3.20.4 Perspective

Generalisation to other product types

The specific ceramic dental product was relatively well described regarding the composition of the nano-composite and information on particle sizes for development of this scenario. However, the composition of different ceramic tooth repair materials and replacements can vary considerably. In this assessment, the material had a relatively high total concentration of nanomaterials in the nanoceramics. Other products may have different compositions, and from the reported standardized wear-data a higher potential release rate, during both finishing and use, may lead to higher acute and long-term (chronic) exposure. On a relative scale, the assessment is possibly not representative of a worst case scenario, considering the whole product group. This scenario and its considerations are relevant to other nanomaterial containing products used for dental fittings.

Cumulative exposure/risks

There are rarely other sources for nano-zirconia inhalation and oral exposure, whereas exposure to nanosilica can arise from different sources such as food and beverages, toothpaste, and cosmetics.

3.21 Scenario 20 – Sanding end of CNT-reinforced shaft of a golf club

3.21.1 Exposure scenario

This scenario addresses a situation where a consumer, a golfer, sands the carbon nanotube (CNT) reinforced shaft of a golf club for fitting and otherwise may be exposed to CNT from wear and tear during use. There is no detailed information available on the concentrations and location of CNT in golf clubs. Many different types of CNTs may be used, including single-walled, multi-walled and cup-stack CNT, but the specific CNT qualities are not revealed.

In the exposure scenario assessed, a consumer fits the length of the CNT reinforced golf shaft using a cutter and sanding paper and uses the club for golfing up to 1½ hour per week. The consumer fits or breaks a golf club two times every year, which may lead to exposure. Release is especially possible if the product is aged or breaks after extensive use and through UV-degradation of the matrix (see review by Danish EPA, 2015e). The consumer may be subject to both inhalation and dermal exposure, which also could lead to inadvertent oral exposure.

It has been demonstrated that CNT may be partially liberated from layer composites and also matrix nanocomposites, especially if the product is aged by UV-degradation.

All exposure routes are assessed qualitatively due to lack of input parameters for modelling and relevant exposure measurement data.

The results of the R.15 Tier 1 and read-across exposure assessments are listed in the Table below. Further details and background information can be obtained in the exposure report.

No.	Product	NM	Exp. scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
					Oral	Dermal	Inhalation	Eye
20			Cutting and sanding a CNT-reinforced golf shaft/breaking a golf club with exposure durations of 30 min. Dermal exposure during intended use for 1½ hour. Product volume and CNT concentrations are not known.	Adults	Inadvertent oral exposure is possible in both exposure situations, but the exposure dose is considered very low.	Possible in both exposure situations, but concentrations assumed very low	Likely during sanding and breaking a CNT reinforced golf shaft. The annual exposure levels are considered very low.	Possible, but considered negligible

3.21.2 Risk assessment of sanding end of CNT-reinforced golf rod

3.21.2.1 Oral exposure

Inadvertent oral exposure is possible, but the possible dose for consumer use is considered low. Regarding oral uptake of CNT, the Danish EPA report concludes: "*For assessment of oral uptake, there is very little literature, but no ingested CNT has been detected beyond the GI tract. Thus, there is no evidence to suggest that CNT are taken up from the GI tract*"(Danish EPA, 2015e).

Uncertainties

Absolute exposure estimates could not be established due to lack of relevant emission and exposure data.

Overall, possible risk associated with oral exposure is considered very low.

3.21.2.2 Dermal exposure

There are no data available on the dermal exposure during use of golf clubs with CNT. The dermal consumer exposure risk and exposure levels are generally evaluated to range from negligible to very low for the product types currently identified on the market. However, there is potential for exposure during use of UV-degraded products, especially layer nano-composites, and products with mechanical failure and their mechanical reworking (Danish EPA, 2015e).

The background for hazard statements in the following can be found in Appendix 1.

Local effects
Based on a dermal exposure study, a NOAEL for inflammation of 0.04 mg (40 µg) of free CNT/mouse and a LOAEL of 0.08 mg (80 µg) free CNT/mouse for 5 days was identified (Murray *et al.* 2009 as cited by Ascherger *et al.*, 2010). The study was not a guideline study but was used by Aschberger *et al.* due to the lack of better studies. This limitation was accounted for by applying an extra assessment factor. The following DNELs were calculated for the acute and chronic situation, respectively (details on calculations are specified in Appendix 1):

$DNEL_{Acute}$ = 2.3 mg/person

$DNEL_{Chronic}$ =0.4 mg/person

These values are difficult to use further in the risk assessment as the values do not represent a dermal load in mass per cm^2.

Systemic
We did not identify any studies on dermal absorption of CNTs. In general, the uptake of insoluble nanomaterials appears negligible and the same is expected to be true for CNT.

Uncertainties
Absolute exposure estimates could not be established due to lack of relevant emission and exposure data. DNELs were derived for a study of unpurified CNTs with a high amount of metals, which are suspected to contribute significantly to the observed toxicity. Other types of CNTs with a higher degree of purity might be less toxic. More studies are needed to get information on local and systemic effects of dermal exposure to CNTs. It should be stressed that the DNELs are derived for free CNTs and not for CNTs as part of a matrix. The toxicity of dusts obtained by sanding other matrices (cement and thermoplastic) containing CNTs was not increased compared to sanding dusts from the conventional product without CNTs following pulmonary exposure in rats (Wohlleben et al., 2011).

Overall, risk following dermal exposure to CNT during golf club fitting is considered to be low/non-existent concerning local effects and possible uptake and subsequent systemic effects.

3.21.2.3 Inhalation
There are no directly applicable data or modelling opportunities for assessment of the inhalation exposure risk to CNT released from abrasion or breaking golf rods. Therefore, no quantitative exposure estimates are given. However, exposure to free CNT is possible. This is especially true during shaft fitting and if the product has been subjected to wear and tear.

Products based on epoxy resins are hard and brittle, the matrix degrades by UV-irradiation (CNT can stabilize this), they are susceptible to oxidation and hydrolysis, but have overall low rate of mechanical degradation resulting in a low release potential. Sanding newly made CNT-reinforced epoxy composites does not cause release of free CNT, but fragments with protruding CNT were observed (Gomez et al., 2014). However, others have observed release of free CNT during abrasion of another epoxy nanocomposite at 0.1 and 1 wt% CNT (Schlagenhauf et al., 2012).

In the exposure report it is stated that especially CNT-layer nano-composites have the potential to result in exposure during use of UV-degraded products, and products with mechanical failure and their mechanical reworking. However, at the percentages normally used in consumer products, it appears unlikely that critical exposure levels would be reached during normal consumer use.

Based on the OECD guideline subchronic (90 days) inhalation studies, a NOAEL (Pauluhn, 2010) and a Lowest Observed Adverse Effect Level (LOAEL) (Ma-Hock et al., 2009) of 0.1 mg/m^3

Multiwalled CNT (MWCNT) were identified for pulmonary inflammation. Based on these studies, Aschberger et al. (2010) propose 0.00025 mg/m^3 (0.25 µg/m^3) as a chronic human DNEL for inhalation by the general public using overall assessment factors of 100. See Appendix 1 for further information on CNT hazards.

As described above, exposure is assessed qualitatively due to lack of input parameters for modelling and relevant exposure measurement data. Therefore no quantitative risk assessment can be performed.

However, as a very rough worst-case scenario the pulmonary deposition of CNT during lifetime exposure at the DNEL of 0.00025 mg/m^3 can be estimated to 306 mg CNT (70 years * 365 days/year * 24 hr/day * 20 m^3/hr * 0.00025 mg/m^3 * 0.1). It is assumed that 20 m^3 air is inhaled per hour and that the pulmonary deposition is 10%. A lifetime exposure of 306 mg is considered a very low dose. Therefore, a lifetime exposure exceeding this value is not considered unlikely and therefore the uncertainty of the exposure assessment will influence the actual risk.

Overall, the risk associated with cutting and sanding a CNT-reinforced golf shaft/breaking a golf club with exposure durations of 30 min is uncertain. We do not know the exposure level (probably the exposure is low) but the hazard is high.

Uncertainties
Product: There is great uncertainty as to which amounts CNT is used in golf clubs and at what structural location. Relevant data for this product group is needed. Further, many different types of CNTs might be used.

Exposure estimation: Absolute exposure estimates could not be completed due to lack of relevant emission and exposure data. Although considered relatively low based on expert judgement, this is therefore a significant source of uncertainty.

Hazards: As concluded by Aschberger et al: “For the general public, only the higher assessment factor and the resulting lower DNEL from the LOAEC of 0.1 mg/m^3 is suggested as environmental exposure is expected not be restricted to one CNT type and therefore the more conservative approach is applied” (Aschberger et al., 2010). It should be stressed that the DNELs are derived for free CNTs and not for CNTs as part of a matrix. The toxicity of dusts obtained by sanding other matrices (cement and thermoplastic) containing CNTs was not increased compared to sanding dusts from the conventional product without CNTs following pulmonary exposure in rats (Wohlleben et al., 2011).

As pointed out in Chapter 2 and in the introduction to this chapter, key uncertainties related to assessing nanomaterials in consumer products are: i) the general lack of knowledge as to which a specific nano form (size, shape, coating etc.) is present in a given product, and ii) the fact that toxicity has not been tested for all possible nano forms of a given nanomaterial chemistry. Therefore, the hazard assessment, including possible DNELs derived, may differ from the nano form in the consumer product, which again leads to uncertainties in the assessment of risks. This uncertainty is also relevant for the present scenario, although the general worst case approach applied should largely circumvent this uncertainty.

3.21.3 Conclusion
Based on the evidence identified in this study, the following conclusions can be reached for this scenario:

- There is a very limited literature on oral uptake of CNT. No ingested CNT has been detected beyond the gastrointestinal (GI) tract. Therefore, there is no evidence to suggest that CNT are taken up from the GI tract and the risk is considered low.

- We did not identify any studies on dermal absorption of CNTs. In general, the uptake of insoluble nanomaterials is negligible and the same is expected to be true for CNT. Therefore, dermal exposure to very low levels of CNT from the golf club is not considered to cause any effects following dermal exposure.
- It is not possible to conclude on the risk associated with pulmonary exposure by cutting and sanding a CNT-reinforced golf shaft/breaking a golf club with exposure durations of 30 min. The exposure level during sanding is unknown (probably low). However, the hazards in relation to inhalation of CNTs are severe, even at low doses.

3.21.4 Perspective

Generalisation to other product types

This scenario is assessed to be generally relevant for CNT in sports equipment such as rackets, skis and other equipment where the products has a relatively low concentration, but potentially accessible CNT.

Cumulative exposure/risks

Consumers might be exposed to CNT from other sources such as possible release from other sports equipment, mechanical treatment or wear of other composite materials ranging from vehicle components to antistatic plastics and coatings, technical textiles, sensors etc.

4. Discussion of risk assessment cases and comparison with other sources of exposure

This chapter aims at discussing the findings and conclusions in the 20 risk assessment cases and to compare the results with exposure and risk levels resulting from other sources where the consumer could be exposed, i.e.: i) from other sources as addressed in WP4 of this project (Danish EPA, 2015c) and ii) in occupational settings. Chapter 5 will discuss the findings in a broader perspective.

As already noted several times, it has not been within the scope of this project to perform final and highly detailed assessments, as further iterations and data generation would be required for several of the scenarios (especially inhalation scenarios). Therefore, the results obtained in this project should be seen as indications rather than final conclusions. The following summary provides an overview of the current knowledge level regarding risks associated with consumer exposure to nano products.

4.1 Cross-cutting evaluation of performed RA and result

Given the variation in the exposure scenarios assessed in Chapter 3 it is not straightforward to summarise the findings. However, based on the "conclusion" section from each of the scenarios/cases, we have summarised the findings in Table 1 using the following legends:

- Risk likely: In the sense that the assessment indicates that there is a risk.
- Risk possible: Borderline case indicating a possible risk (would need further investigation).
- Risk unlikely: Current evidence rather clearly suggests that risks are unlikely/not present.
- Risk uncertain: Data are too uncertain to arrive at any of the above conclusions.
- Not relevant/not assessed (exposure routes which were already deselected as relevant in previous project activities are marked in grey).

TABLE 1
SUMMARY TABLE FOR THE RISK ASSESSMENT OF THE 20 SELECTED EXPOSURE SCENARIOS

Scenario	Oral	Dermal	Inhalation	Eye
1 Chewing gum (nano-TiO_2 in E171)	Risk uncertain			
2 Food item (nano-silica in E551)	Risk uncertain			

Scenario	Oral	Dermal	Inhalation	Eye
3 Food supplement (nano-Ag)	Risk unlikely			
4 Food container (nano-silica in food contact material)	Risk unlikely			
5 Sunscreen lotion (nano-TiO_2)	Risk possible	Risk unlikely		
6 Sunscreen pump spray (nano-ZnO)	Risk possible (children)	Risk unlikely	Risk uncertain	
7 Mascara (carbon black)		Risk unlikely		Risk unlikely
8 Sunscreen lipstick (nano-TiO_2)	Risk possible	Risk unlikely		
9 Face powder (nano-silica)	Risk unlikely	Risk unlikely	Risk possible	Risk unlikely
10a Paint, rolling (nano-TiO_2)		Risk unlikely		Risk unlikely
10b Sanding painted surface (nano-TiO_2 in a primer)	Risk unlikely	Risk unlikely	Risk likely	
11 Paint, spray gun (nano-Ag)		Risk unlikely	Risk likely	Risk unlikely
12 Easy to clean surface impregnation, pump spray (nano-silica)	Risk unlikely	Risk unlikely	Risk possible	Risk unlikely
13 Air-cleaner/nano-filtering (nano-Ag)			Risk unlikely	
14 Disinfectant pump spray (nano-Ag)	Risk unlikely	Risk unlikely	Risk uncertain	
15 Disinfectant propellant spray (nano-Ag)	Risk unlikely	Risk unlikely	Risk possible	
16 Textile (nano-Ag)	Risk unlikely	Risk unlikely	Risk unlikely	
17 Cement (nano-TiO_2)		Risk unlikely	Risk possible	Risk unlikely
18 Wound dressing (nano-Ag)		Risk unlikely		
19 Dental fillings (nano-silica and nano-ZrO_2)	Risk unlikely	Risk unlikely	Risk uncertain	

Scenario	Oral	Dermal	Inhalation	Eye
20 Golf club fitting (carbon nanotubes)	Risk unlikely	Risk unlikely	Risk uncertain	

The table clearly shows that among the 20 selected scenarios which have been assessed, consumer risks might be present in relation to the inhalation route and to some extent via the oral route when significant amounts of nanomaterials are ingested. Risks in relation to dermal and eye exposure seem in general to be unlikely.

It should be noted that the above table does not take into account possible effects from other components in the products. As an example, the other components in cement might e.g. cause dermal, inhalation and eye effects.

4.1.1 Inhalation

Inhalation risks have been assessed to be likely in the scenarios addressing spray gun painting (Scenario 11) with nano-Ag containing paint and following sanding of a surface painted with a water-based primer with anatase nano-TiO_2 (Scenario 10b). It should be noted that in the latter scenario, nano-TiO_2 on the surface is not assumed to the embedded in a matrix (no binders in the assessed primer) and therefore the release of very fine particles, including individual nano-particles, cannot be excluded. In both situations, exposure (and thereby risks) can be reduced significantly if proper personal protective equipment is applied. This, however, cannot generally be assumed to be the case for consumers.

Inhalation risks have been assessed to be possible for the two scenarios addressing powder products (Scenario 9 nano-silica in face powder and Scenario 17 nano-TiO_2 in cement) and for the disinfectant propellant spray containing nano-Ag (Scenario 15), as well as for the nano-silica pump spray impregnation scenario (Scenario 12). For the powder scenarios addressed, risk would likely mainly be possible given relatively frequent use of the products, which seems likely for face powder. Frequent use may also be likely for some consumers (at least for periods of time) using nano-TiO_2-containing cement, e.g. consumers building or renovating their own house, driveways or similar. In the cement scenario, the above mentioned exposure/risks might be reduced following use of personal protective equipment, which is considered less likely for the nano-Ag containing disinfectant spray. Some consumers, but not all, might use filter masks when handling cement. For these scenarios, more detailed assessment of exposure levels and duration could provide input for drawing more firm conclusions. Specifically for the cement scenario it is not known to what extent nano-TiO_2 containing cement is actually available to consumers.

Inhalation risk has been assessed to be uncertain for two pump spray scenarios (Scenario 6 sunscreen with nano-ZnO and Scenario 14 disinfectant with nano-Ag) and for the two scenarios addressing mechanical impact on nanocomposites (Scenario 19, sanding a dental filling assumed to contain nano-ZrO_2 and nano-silica and Scenario 20, fitting a carbon nanotube-containing golf club by cutting and sanding).

In general, for the pump spray scenarios, considerations regarding exposure levels have been extrapolated from other types of products, indicating that pump spray particles have a wide size distribution from small-size nano-range to more than 100 µm. Water and alcohol-based pump sprays have been shown to generate fine respirable airborne particles with peak sizes in the sub-µm- and µm-size-ranges. Other studies only report the droplets' size at the spray nozzle and these droplets are normally reported to be larger than 100 µm. This is especially relevant for highly viscous sprays. Use of spray cans and spray guns is expected to result in finer aerosols than pump sprays. Based on these considerations, all sprays should in principle be assumed to produce

particles in the respirable range, and therefore assumed to contain particles that can penetrate deep into the lung. Thus, the exposure to spray products must be assumed to always involve exposure of the lower parts of the airways. In addition, when toxicologically potent nanomaterials are applied, even relatively low exposure levels might lead to concern. All in all, it may be warranted to further investigate exposure related to these types of scenarios. A key point to consider/address is the role of the solvent used, as volatile solvents can significantly increase the generation/release of respirable aerosols/particles.

For the dental filling scenario, uncertainty is concluded, because relatively high room concentration levels have been reported based on actual measurements, levels which might be even higher in the breathing zone of the patient. On the other hand, this type of treatment is not frequent and water spray applied during treatment will reduce the extent to which the nanomaterials become airborne in the breathing zone of the person being treated. Further exposure characterisation for this scenario may be warranted.

The reason for the uncertain conclusion related to fitting a CNT containing golf club is that the exposure is uncertain, while carbon nanotubes are considered very hazardous. Therefore, small differences in exposure have significant impact on the risk estimates. Whereas release by mechanically fitting the golf club might be rather limited, it is also known that inhalation of very low levels of certain carbon nanotubes may lead to severe effects comparable to effects from exposure to asbestos. Therefore, further investigation of the type of carbon nanotube contained, possible releases during fitting (quantity as well as whether release happens as free carbon nanotubes) and better understanding of the long-term effects of even short-term carbon nanotube exposure are warranted.

For the remaining cases/scenarios addressed, it is assessed that the nanomaterials are embedded in the matrix and will not be released under the conditions assumed in the scenarios; therefore, risks associated with these scenarios are assessed to be unlikely.

4.1.2 Oral

Risks following oral exposures have been assessed to be negligible in most of the scenarios and are therefore not assessed or the risk is considered unlikely based on a qualitative or quantitative assessment.

However, some conclusions have been reached for situations where oral intake might possibly be high.

It is assessed that nano-TiO_2 and nano-ZnO (for children only) in sunscreens constitute a possible risk following oral exposure (Scenarios 5, 6 and 8). These conclusions differ from the opinions of the SCCS for these nanomaterials as used in sunscreens. The current study applied very conservative estimates as a starting point for the oral intake (including ingestion of 100% of sunscreen applied to the lips and that children lick the fingers and thereby ingest 50% of the sunscreen applied to the fingers). However, even if no intake from licking fingers and only moderate lipstick application is assumed, there might still be a risk. More detailed exposure assessments are, however, needed. For nano-TiO_2 as applied in sunscreen, the main uncertainty is related to whether the LOAEL of 5 mg/kg bw/day as mentioned by SCCS is relevant for nano-TiO_2 in sunscreen. If this is the case and if assessment factors are applied to this LOAEL value, a low no-effect level for oral intake would be derived.

Finally, risk following oral exposure has been assessed to be uncertain for intake of food grade TiO_2 (E171) and silica (E551) (Scenario 1 and 2), both containing fractions of nanoparticles. Especially for nano-TiO_2, the estimated intakes via chewing gum (as well as other sources including possible intake via sweets with hard core chocolate shells) are high. However, even when modifying the

intake by e.g. considering intake of five pieces of chewing gum (rather than the initially assumed 20 pieces), the results of the assessment do not change. As for sunscreens with nano-TiO_2, the main uncertainty is related to whether the LOAEL of 5 mg/kg bw/day would be relevant for nano-TiO2 in E171. For nano-silica in E551 as well, it may be warranted to take into account new knowledge regarding the hazards associated with oral intake of nano-silica. EFSA is currently re-evaluating E171 and E551 and it is assumed that all new knowledge regarding nano-silica and nano-TiO_2 would be taken into account.

4.1.3 Dermal

Chapter 3 addressed nanomaterials in a range of spray, liquid and powder products, which might lead to considerable dermal exposure as shown in these cases.

However, in general, the available data indicate that most nanomaterials are not likely to lead to local dermal effects nor to becoming systemically available given no/negligible absorption (at least not to any detectable degree) through the skin. Exceptions are some carbon based materials (e.g. some types of carbon nanotubes), which might lead to irritation effects and nano-Ag and nano-ZnO, which are known to lead to low level dermal absorption following dermal exposure (possibly of the dissolved silver and zinc ions). Dermal exposure levels to these compounds are, however, not estimated to lead to any risks. Therefore, based on current evidence, dermal exposure to nanomaterials in consumer products is not likely to lead to any significant risk.

A minor question mark is flagged for nano-TiO_2 in the anatase form (Scenario 5, 8, 10 and 17) as some studies indicate that the nanoparticles may reach the hair follicles and it is speculated that this could lead to generation of reactive oxygen species (ROS) on exposure to UV light, possibly leading to local effects in the skin. This is the main concern raised by SCCS, which resulted in a restriction on the amount of the photocatalytic anatase form to be used in cosmetics to 5% of the 25% nano-TiO_2 allowed as UV-filter in cosmetics. It is also speculated whether this might lead to (minor) absorption, but this supposition is not supported by evidence.

4.1.4 Eye

Eye exposure associated with the addressed scenarios has initially been assessed to be negligible or, when specifically addressed in the cases, risks have been assessed to be unlikely. Although data are scarce, the limited dermal irritation/corrosion potential of nanomaterials might support the conclusions that risks associated with eye exposure is low/unlikely.

4.2 Comparison with other sources

The purpose of this section is to discuss the findings of the consumer exposure and risk assessment in perspective with other exposures to nanomaterials/nanoparticles/ultrafine particles as encountered in occupational settings or indoor and outdoor air.

4.2.1 vis-a-vis Environmental sources

Human exposure to nanomaterials from the environment (generally referred to as nanoparticles or ultrafine particles) has been assessed in another report of this project: "Exposure to nanomaterials from the Danish Environment" (Danish EPA, 2015c).

The purpose of this section is to discuss the findings in that report with the findings regarding consumer exposure presented in Chapter 3 in terms of levels of exposure, hazards and risks levels. Given the uncertainties associated with the results presented in Danish EPA (2015c) and in Chapter 3, such as chemical composition and other characterisation of ultrafine particles, the following should be taken as indications rather than comprehensive quantitative comparisons.

The Danish EPA (2015c) report showed that a large amount of data have been identified on nanoparticles/ultrafine particles characteristics and concentrations in ambient and indoor air. The data on ambient air especially provide a reliable indication concerning exposure levels and the associated human risks. Indoor-outdoor studies of air pollution have shown that outdoor air pollution does enter indoor environments, but many different indoor sources play a major role when analysed by particle number concentrations.

In contrast to the situation for air pollution, only limited amounts of data are available regarding measured levels of nanoparticles/nanomaterials in the environmental matrices (soil and surface water/ground water/drinking water). This lack of data is partly due to the general lack of suitable analytical methods (including sample preparation techniques) that are sensitive and selective enough to identify and quantify nanoparticles in the different complex environmental matrices. In addition, the nanoparticles in the environment may undergo many transformations due to aggregation, phase transformation, dissolution and re-precipitation with or without interaction with biological systems. Additionally, since current manufactured nanomaterials are often chemically and mineralogically comparable to nanoparticles and minerals found and formed in the environment, sophisticated techniques are required to potentially distinguish between nanoparticles of anthropogenic origin ("engineered" nanoparticles) and nanoparticles of natural origin.

The available data covering modelled predictions were considered too uncertain to use for exposure estimations from these matrices as these data varied by several orders of magnitude for a specific nanomaterial.

As a consequence, this section will only address inhalation exposure and risks.

4.2.1.1 Exposure to ultrafine particles in ambient air

The fraction of ultrafine particles in urban and rural air is highly dominated by combustion-generated particles from e.g. traffic exhaust and wood burning. The concentrations of ultrafine (<100-nm-size) particles have high spatial variations as the levels of these particles drop rapidly according to the distance from the emission sources due to dilution, deposition, agglomeration/aggregation and other transformation processes affecting the particle sizes. Measured particle number concentrations in ambient air are highly dominated by particles of the ultrafine fractions. However, when exposed to typical ambient particulate air pollution (often referred to as PM2.5 levels, i.e. mass based levels consisting of particles and agglomerated/aggregated particles with a particle size up to 2.5 μm), this fraction contains, apart from free ultrafine particles (which only contribute to a lesser extent in this mass based metric), a significant proportion of agglomerated/aggregated ultrafine particles.

The general variations and concentrations of free ultrafine particles in ambient air may best be illustrated by Figure 2 below, which shows an example of the diurnal variation of ultrafine particle levels in high-traffic street (HCAB), urban (HCOE) and rural background (LVBY). It is seen that the ultrafine particles reached up to 36,000-37,000 particles/cm^3 at a busy road in Copenhagen (HCAB) while the number at the same time reached 8000 particles/cm^3 in the urban background (HCOE), and reached about 5,000 particles/cm^3 in the rural background (LVBY) (NERI, 2011).

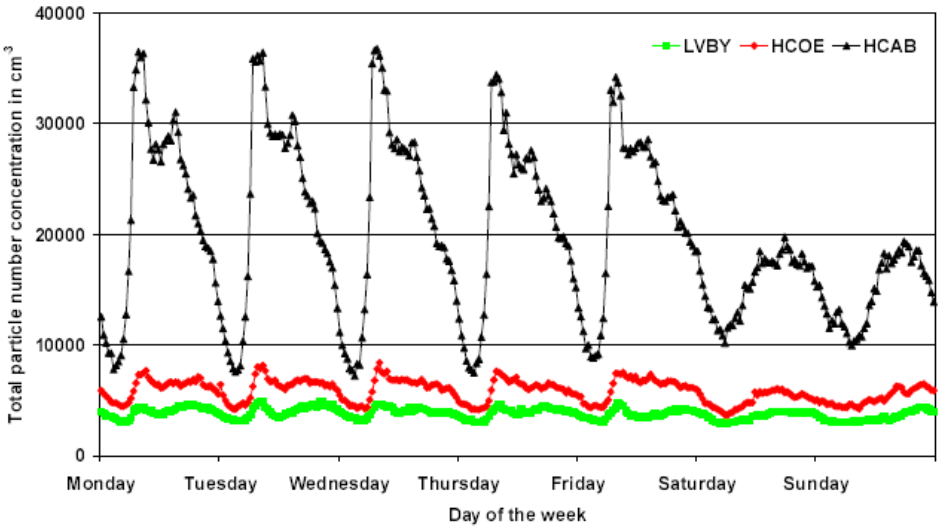

FIGURE 2.
DIURNAL VARIATION OF TOTAL PARTICLE NUMBER CONCENTRATIONS OF PARTICLES. BLACK CURVE: BUSY STREET. RED CURVE: URBAN BACKGROUND. GREEN CURVE: RURAL BACKGROUND, 2008-2010 DATA. (NERI 2011)

In 2011, the *annual average rural background* levels were around 4,000 ultrafine particles per cm^3. The air in a busy street in Copenhagen contained ca. 11,000-14,000 more particles per cm^3 than the rural background, whereas urban background contained only about 2,000 particles per cm^3 more than in rural background.

In 2011, the average level of PM2.5 in Copenhagen (at a busy road) was about 20 $\mu g/m^3$ and the average number concentration was about 15,000 particles/cm^3 whereas, in the rural background, the figures were about 15 $\mu g/m^3$ and 4,000 particles/cm^3 (DCE, 2012).

The ultrafine particles from combustion are mainly composed of elemental and organic carbonaceous particulate matter associated with various fractions of nano-size and sub-µm-size inorganic compounds, sulphates and nitrates etc. depending on the quality and types of the fuels and lubrication oils. Organic carbon particles may be generated as *secondary organic aerosols,* which are particles generated from gases from volatile organic carbons (biogenic or anthropogenic) which have reacted with atmospheric oxidants such as O_3, NO_3 or OH to form low-volatility products (particles) (NERI, 2011). The levels of these combustion fractions may be reflected in measurements of particle number (measurement of free ultrafine particles) or in mass based metrics such as black smoke, soot, elemental carbon or organic carbon, which all are fractions dominated by ultrafine particles (either as free or agglomerated particles).

According to Figure 3 below, the combustion fractions (i.e. the levels of organic matter (OM) and elemental carbon (EC) that, to a great extent, contain ultrafine particles free and agglomerated/aggregated) - as a rough estimate - contribute 25-33% of the PM2.5 content in ambient air for background levels and for urban street stations.

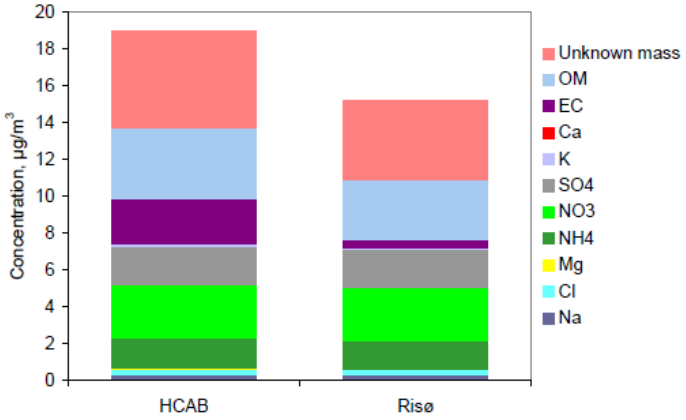

FIGURE 3
ANNUAL AVERAGE CONTRIBUTIONS TO THE CHEMICAL COMPOSITION OF PM2.5 AT A BUSY STREET IN COPENHAGEN (HCAB) AND AT RURAL BACKGROUND IN RISØ (DCE 2012). OM = ORGANIC MATTER; EC = ELEMENTAL CARBON.

BASED ON THESE DATA, HUMAN EXPOSURE TO ULTRAFINE PARTICLES FROM AMBIENT AIR WAS DANISH EPA (2015C), SEE

Table 2.

4.2.1.2 Exposure to ultrafine particles from indoor air

Several studies have used different types of mobile devices for measuring ultrafine particles and particle numbers in the indoor environment. In these studies, the levels are measured in different locations in different situations and during different indoor activities.

In a study in 56 Danish homes, Bekö et al. (2013) reported a geometric mean of 22,300 particles/cm^3 during the period when the occupants were awake. During sleep and when the homes were vacant, the mean levels were below 6,100 particles/cm^3.

A very high variation in the 24-hour average levels was found among the 56 homes, ranging from about 1,500 particles/cm^3 to 250,000 particles/cm^3 for the geometric means. At the high exposure levels, 97% of the particles originated from the use of candle lights.

The overall average mean for the integrated 24-hour exposure was calculated as 334,000 particles (hour/cm^3 day). The average particle diameter was found to be 76 nm with only 5% of the measured particles above 120 nm.

BASED ON THESE DATA, EXPOSURE ESTIMATES FOR ULTRAFINE PARTICLES FROM INDOOR AIR HAVE SHOWN IN

Table 2.

4.2.1.3 Comparison of inhalation exposure to ultrafine particles from various sources

A DIRECT COMPARISON BETWEEN ULTRAFINE PARTICLE EXPOSURE FROM ENVIRONMENTAL
OF CONSUMER PRODUCTS IN CHAPTER 3 MAY BE DIFFICULT, BECAUSE THE EXPOSURES ORIGINATE
SOURCES AND THEREBY CONSIST OF DIFFERENT COMPOUNDS. IN ADDITION, POSSIBLE DIFFERENCES
METHODS AND MEASUREMENT CONDITIONS MAKE DIRECT COMPARISONS DIFFICULT. HOWEVER, A
COMPARISON OF THE MEASURED VALUES CAN GIVE SOME INDICATION OF THE APPARENT RELATIVE
THE DIFFERENT SOURCES AS REGARDS INHALATION EXPOSURE (

Table 2).

TABLE 2.
ESTIMATED AND MEASURED EXPOSURE LEVELS TO ULTRAFINE PARTICLES/NANOMATERIALS FROM AMBIENT AIR, INDOOR AIR AND CONSUMER PRODUCTS (SEE DANISH EPA, 2015C FOR DETAILS)

Exposure levels of ultrafine particles			
	Particle no/cm^3	**mg/m^3**	**µg/kg/day**
Environmental 24-hours exposure levels			
Ambient air, annual average	(4 – 15) x 10^3	0.005 - 0.006	1.4 - 1.7
Indoor air Range 24-hours Average 24-hours	 (1.5 – 250) x 10^3 14 x 10^3	 0.007 - 0.010	 2 - 3
Person borne measurement (integrated exposure) average 24-hours for non-smokers	 (9.2-29) x 10^3	 -	 -
Use of products -estimated exposure levels			
Face powder 15 min	>10 x 10^3	0.26	0.9
Paint sanding 30 min	-	18	220
Paint spraying 30 min	-	109	1 300
Surface coating 30 min	-	0.0021	0.02
Pump spray 10 min	(3.4 – 6) x 10^3	0.0043	0.017
Cement Handling 8 hours Grinding 8 hours	 - -	 0.25 0.75	 42 130
Indoor sources - measured exposure levels			
Frying meat	151 x 10^3	-	-
Electric stove	112 x 10^3	-	-
Gas stove	80 x 10^3	-	-
Radiator	218 x 10^3		
Vacuum cleaning	(21-38) x 10^3	-	-
Candle burning	(70 – 242) x 10^3	-	-
Cigarette	213 x 10^3	-	-

Particle number concentrations (particle no/cm^3)
In the table, only a selection of indoor sources is presented. However, the high number concentrations that have been measured for various indoor sources support the idea that the 24-hour measurements in the indoor environment are profoundly impacted by these sources. As well,

the person borne measurements indicate that the highest number-based exposure to ultrafine particles comes from the indoor environment and indoor sources, although the exposure levels from ambient air also contribute significantly.

Data on particle number concentrations from use of consumer nano products are sparse. The few available data (in relation to use of face powder and pump sprays) indicate, however, lower exposure levels compared to many other indoor sources. Furthermore, the duration of exposure to the particles from face powder is very short (assumed up to 15 minutes per day). Short exposure duration may also apply to application of other consumer products, e.g. sprays, that are often used only for a couple of minutes.

All in all, it appears that particle exposure from indoor sources, such as those generated from heating sources, results in considerably higher exposure levels for longer durations than does the use of consumer products.

Mass based concentrations (mg/m³ and µg/kg bodyweight/day)

Very few PM0.1 measurements on a particle mass basis are available for evaluating the mass-based exposure to free ultrafine particles in the air. Therefore, the mass-based concentrations estimated here, including the exposure estimate for both free and agglomerated ultrafine particles as about 1/3 of environmental PM2.5 levels, are considered to consist of free and agglomerated/aggregated ultrafine particles.

Estimates of exposure levels from the products have been made based on the fraction of nanomaterial used in the product; e.g. it may be uncertain whether exposure during paint spraying could actually be considered as exposure to a nanomaterial due to the inclusion of the nanomaterial into the paint matrix.

For other product scenarios, such as face powder and cement handling and grinding, considerably higher mass-based concentrations may be reached compared to ambient and indoor levels. It should be noted that the average daily exposure (expressed in µg/kg bw/day) for face powder is nearly at the same level as for environmental exposure, whereas the daily exposure from cement handling and grinding is considerably higher.

The estimated exposure level to nanomaterials of 0.004 mg/m³ from pump spray containing 1% of nanomaterial is not considered to exceed the environmental levels of ultrafine particles. Therefore, the daily exposure from a pump spray used over 10 minutes is, in this case, estimated to result in a daily exposure of 2 orders of magnitudes lower than the environmental exposures (expressed in µg/kg bw/day).

Based on available mass-based exposure levels, it can be seen that the mass-based exposure to nanomaterials from consumer products may vary by several orders of magnitude with exposure up to 130-1 300 µg/kg bw/d for grinding of cement and spray painting. Compared to this, the mass-based exposure estimated from the indoor and outdoor air would normally be within the order of 1-10 µg/kg bw/d. However, these figures should be interpreted with care, given the significant characterisation/measurement uncertainties indicated.

4.2.1.4 Comparison of risk

Ambient air

Adverse health effects have been attributed to the content of ultrafine particles (free plus agglomerated/aggregated particles) in the ambient air, especially in relation to long-term exposure where increased mortality is the most prominent finding. From the data on PM2.5 in ambient air, it may be assumed (if the fraction of ultrafine and agglomerated/aggregated ultrafine particles is as hazardous as the remaining fractions of PM2.5) that an annual exposure level of 1 μg/m^3 of ultrafine particles (free plus agglomerated particles) is associated with an increase in the annual mortality in the population of at least 0.6% (dose-response relationship as used by the WHO and EU for PM2.5).

This dose-response relationship can be put into perspective if the current annual levels of free plus agglomerated ultrafine particles in Denmark is assumed to contribute about 5-6 μg/m^3 of the current PM2.5 level (i.e. as a rough estimate this fraction may contribute to increased annual mortality by about 3%).

Indoor Air

Due to many indoor emission sources of ultrafine particles, the levels of free ultrafine particles as well as the levels of free plus agglomerated/aggregated ultrafine particles are considered higher than the ambient exposure.

However, few data on human health hazards in relation to indoor particle levels exist. At present, the same dose-response relationship as for the ambient air particles is often used. However, it should be emphasised that great uncertainty applies to this approach.

Consumer products

Even though data on ultrafine particles in ambient air call for concern in relation to exposure from manufactured nanomaterials/nanoparticles, extrapolation of risk from data on ambient air particles is not recommended, as the composition of the particles from nano-consumer products is quite different from the composition of ambient air particles. Therefore, read-across from environmental and indoor air pollution to assess the adverse health effects from exposure to consumer products would be based on guesswork rather than substantiated by sound scientific argumentation.

In conclusion, and in relation to risk assessment of nanomaterial exposure from consumer products, the most appropriate approach at the present time is a case-by-case approach where data on actual exposure levels and hazards regarding the specific nanomaterials are used. Through the use of this approach in 20 exposure scenarios in this report, a likely or possible risk in relation to inhalation exposure has been identified in a total of five cases. Here, however, the risk is expressed in purely qualitative terms as no dose-response relationship and human health impact assessment information can be provided for the ultrafine particles in ambient air.

4.2.1.5 Summary

A range of data is available regarding indoor and outdoor exposure levels to ultrafine particles, largely generated from combustion sources, whereas very limited data are available regarding nanomaterials in soil and water originating from natural and/or combustion sources.

Available data indicate that the use of typical consumer products lead to lower particle-number exposure (magnitude and duration) than the exposure to ultrafine particles from other indoor sources.

In any case, exposure to ultrafine particles from the outdoor air and from the indoor environment appears significant. Especially for the indoor environment, exposure may be reduced by simple measures such as regular ventilation, especially following the use of candles, after cooking and other sources as indicated in Table 2.

Although significant adverse health effects are associated with the outdoor air content of fine and ultrafine particles, the origin and composition of these ultrafine particles is quite different from the composition of nanoparticles from consumer products. Therefore, at present there appears to be no scientific justification to compare risks from exposure to ambient air ultrafine particle to the potential risk from nanomaterial exposure of consumers.

4.2.2 vis-à-vis occupational sources

To understand the scale of consumer exposure as compared to occupational exposure and exposure scenarios, we briefly summarize some of the important differences between the exposure situations.

First, in work places, the amount of nanomaterials used in each handling scenario is usually very large, ranging from kg to tonnes, even though small-scale uses also exist. Secondly, for processes with mechanical treatments such as grinding, cutting and sanding, the work is made using high energy machinery and large objects to treat, resulting in risk for high nanomaterial emissions levels as compared to the emission levels in consumer use scenarios. However, in occupational settings, the exposure is normally reduced by controlling the emissions for example by using screens, closures and designed ventilation systems equipped with high-efficiency particulate air filters. If the emissions cannot be well controlled, e.g. by cleaning of a reactor, workers use personal protective equipment. Such emission controls are not usually available in private homes where emission control relies mainly on improved cross ventilation e.g. by opening windows.

Furthermore, in occupational settings, nanomaterial exposures may be repeated on a daily basis, and the average daily, yearly and lifetime exposure levels are also expected to be much higher as compared to the consumer and general population exposure via the environment. The occupational exposure limits are higher than the environmental exposure limits, leading to higher exposures in the working environment. However, in many of the assessed consumer exposure scenarios, the exposures were very high on a short-term basis; for example, during use of nanomaterial-containing spray products. Even though the exposure duration for consumers is shorter, the potentially high concentrations assessed may be of particular concern because consumers rarely use the proper personal protection equipment.

A key difference between consumer and occupational exposure scenarios is that workers to a much higher extent handle free nanomaterials in powder form, e.g. during production of composite materials or during powder coating operations. Thus, in the occupational settings it is expected that the general primary exposure will be to dust from powder nanomaterials. However, exposure to abrasion fragments from nanomaterial containing composites may also occur, and as noted above, the amounts and energy involved might be higher than for consumer exposure situations.

In contrast, exposure to nanomaterials in consumer and environmental settings would primarily be to nanomaterials already incorporated into products or to nanomaterials released from the products during the lifecycle (weathering and disposal).

In the occupational setting, inhalation is the route for nanomaterial uptake of current greatest concern, even though dermal and (inadvertent) oral exposures may occur as well. Because nanomaterials are used in various different consumer products (composite materials, coatings, food, sprays and cosmetics); the major exposure route will depend strongly on the product. Cosmetics are e.g. applied directly onto skin and food additives are swallowed intentionally, whereas many other products might incidentally lead to oral exposure due to lower hygiene levels than in occupational settings. Therefore, in relation to consumer exposure, all exposure pathways, namely the lungs, gastrointestinal tract, skin and eyes were considered equally as starting points in this project. The highest dermal exposure pertains to cosmetic leave-on products such as body lotion and sunscreen where dermal exposure to nanomaterials for small children may exceed 100 mg/kg bw/day) of nano-TiO_2. Gastro-intestinal consumer exposure can occur through intended or

inadvertent oral exposure as well as by transport of nanomaterials from the airways to the gastro-intestinal tract (secondary exposure). However, the contribution from secondary exposure routes to the gastrointestinal system is normally considered relatively low.

Quantitative comparison of occupational and consumer exposure levels is challenging mainly because there is a limited number of studies considering occupational exposure levels that can be linked with the consumer exposure scenarios as addressed in the current project. Very few results on consumer exposure to nanomaterials were available. Therefore, most of the assessments made in this project were made based on product information, products concentrations or release rates, and contextual information. Attempts were made to achieve read-across from workplace-relevant exposure measurements. However, this approach was generally challenging because occupational exposure studies focus mainly on inhalation exposures. There is limited information about dermal, gastrointestinal tract exposures or eye exposure levels. In some scenarios (e.g. for cement), consumer inhalation exposure levels were estimated based on occupational measurements, although differences exist in terms of amounts applied, duration and frequency of exposure, as well as expected application of personal protective equipment.

To enable comparison, relevant occupational exposure levels in comparable scenarios are listed in Table 3 along with the consumer exposure levels presented in the current project. As intended and expected, the modelled exposure levels from consumer assessments were generally overestimated because in the modelling, the following assumptions are made: 1) all (or an overestimated fraction) emissions from the process result in exposure, 2) the standard room size for consumer exposure assessment is rather small (e.g. 20 m^3), and 3) there is little or no ventilation in the model room. In many processes (e.g. grinding, sanding, pump sprays), mass concentrations are governed by large particles where most of the particles are lost rapidly and do not affect exposure levels. This contributes to a significant uncertainty in the mass-based modelling. Another major source of uncertainty is the amount of dilution air for particle dispersions in the air. In consumer exposure situations, many of the processes take place indoors with low volume for dilution, whereas outdoors the dilution is usually assumed to be ten times higher. This is why spraying onto objects is recommended to take place outdoors.

Finally, engineered and personal protection equipment are very often used in industrial exposure scenarios. This practice is likely not the case in many consumer exposure scenarios. Information about the use and effectiveness of personal protective equipment towards nanomaterials is scarce. Published studies mainly focus on potential exposure levels, which then can be used to estimate exposure when the protective equipment protection factor is known. However, information about both structural emission controls and personal protective equipment efficiencies towards nanomaterials in occupational settings are not well known, which is why the calculated exposure levels gives only the exposure magnitude. In the case that the consumer does use personal protection equipment, these devices are expected to be of lower quality with much lower performance than professional equipment because of low cost-efficiency. Also, guidance for selecting proper personal protective equipment is clearly better for occupational use because materials and processes are better known than for consumer use (see e.g. http://www.i-bar.dk).

Summary

Taken together, different conditions of exposure make direct comparison between worker and consumer exposure very difficult. It is clear, however, that short-term consumer exposure levels to nanomaterials from consumer products can be relatively high, whereas the average long-term (chronic) consumer exposure would be low in most comparable exposure scenarios due to the use rate.

It is also clear that consumers might be exposed orally to significant amounts of nanomaterials in scenarios not relevant for workers (e.g. via cosmetics and food additives), whereas workers might

potentially be exposed to nanomaterials via inhalation during exposure scenarios not relevant for consumers (e.g. production processes using nanomaterials in powder form).

It is also expected that consumers in general use personal protective equipment to a lesser extent and possibly of lower quality than workers.

TABLE 3
MODELLED/ESTIMATED CONSUMER EXPOSURE CONCENTRATIONS FROM THE PRESENT WORK COMPARED WITH OCCUPATIONAL/LABORATORY EXPOSURE MEASUREMENTS

Scenario	Remarks	Nanomaterial exposure consumer (model)/occupational		
		Inhalation, [mg/m³]	Dermal (males), [mg/kg bw/day]	Oral
Sanding of nano-TiO_2 coated wooden planks	Removal rate in occupational studies was ~90 g/hour and in this scenario it was 0.28 or 1.39 g/hour.	18/<0.42	30/-	VL[a]/-
Sanding of a CNT-reinforced golf rod	Jensen et al. (submitted) showed that sanding concentrations reach up to 0.42 mg/m³. Assuming CNT content of 1 wt% the CNT exposure is 4.2 µg/m³.	VL/(<0.042)[b]	VL/-	VL/-
Mechanical finishing of ceramic dental tooth	Occupational studies showed 0.060 mg PM_{10}/m³ in room air (Van Landuyt et al., 2012).	1/0.06	VL/-	-/-
Application of disinfectant propellant spray with nano-Ag	Occupational measurement: 5 wt.% TiO_2 solution, generation rate 59 g/min, Model: 1 wt.% nano-Ag solution, 50 g/min (inhalation Chen et al. 2010 and dermal Berger-Preiß et al. 2009)	>0.004/0.17	0.20/<0.05	VL/
Application of pump nano-spray product containing nano-Ag	Laboratory tests were not able to detect concentrations of below 500 nm particles. (Hagendorfer et al. 2010; Lorenz et al. 2011; Losert et al. 2014). Another study showed presence of particles in the size-range 10 nm to ca. 4 µm size-ranges for silane, siloxane and TiO_2 pump-sprays (Nørgaard et al., 2009),	0.004/-[b]	0.19/-	VL/-
Application of pump nano-spray product containing nano-silica		0.002/-	0.076/-	VL/-
Spray painting with nano-Ag paint	Occupational concentrations were measured in a paint booth during high ventilation rates (Tan et al. 2002)	109/<0.3	0.9/-	VL/-

[a]VL IS VERY LOW ; B ESTIMATED CONCENTRATION FROM GENERAL DUST CONCENTRATION

5. Perspective and uncertainties

This chapter will aim at discussing the overall issue of possible consumer risks taking into account the findings from the case studies (Chapters 3 and 4) and other knowledge obtained from the model, exposure and hazard activities of this project (Danish EPA 2015 a,b). This will include discussion of key uncertainties related to risk assessment of consumer exposure to nanoproducts and some considerations about possible future trends.

5.1 Extrapolation of case findings

As also mentioned earlier, a range of consumer products claiming to be "nanoproducts" can be found in shops and via the Internet, often without any clear indications of whether the product actually contains nanomaterials or what the identities of the possibly contained nanomaterials would be. Thus, specific types of nanomaterials not encountered in this project might exist and possibly constitute specific hazards and risks. The following considerations are therefore mainly based on knowledge about products known to contain specific types of nanomaterials, although some of the general conclusions for some of the product categories mentioned would be relevant for nanoproducts in general.

The general findings regarding exposure routes presented in Section 4.1 are also assessed to be relevant for nanomaterials in general; i.e. the main concern is associated with inhalation of aerosols and powders, whereas some concern might pertain to oral intake of large amounts of nanomaterials. In addition, inhalation exposure of particles deposited in the respiratory tract may lead to indirect oral exposure.

Unless more specific references are given, the below discussions are based on the findings in the exposure and hazard reports from this project (Danish EPA, 2015a, 2015b).

5.1.1 Inhalation

5.1.1.1 Spraying/spray products

Spray guns

The case assessments showed that spraying with spray guns can lead to very high exposure levels. Therefore, this type of applications might lead to risks - also for paints with other and less toxic types of nanomaterials than nano-Ag. Hence, considering that unexperienced consumers cannot be assumed to wear personal protective equipment, such scenarios would clearly indicate a risk. On the other hand, considering more experienced consumers, inhalation of spray mist could be avoided/reduced by wearing respiratory protection.

Propellant sprays

A range of propellant sprays possibly containing nanomaterials are or might be present on the market. This range includes disinfectant sprays with nano-Ag, impregnation sprays with nano-silica and sunscreen sprays with nano-TiO_2 and nano-ZnO. Exposure to nanomaterials from such sprays is highly dependent on e.g. nozzle size, duration of spraying and propellant gas and the solvent

applied, ventilation and room size. The propellant gas and solvent type will influence aerosol evaporation and thus how fast free nanoparticles become available for inhalation. In general, propellant sprays generate rather small aerosol particle sizes leading to significant exposure levels to respirable aerosols/free nanoparticles. Possible nanomaterials/propellant gas combination effects have also been reported and should be taken into account. Given the many parameters to consider, the current knowledge about possible exposure following propellant spraying is scattered and further assessment of exposure resulting from propellant spraying appears warranted. All in all, risks might be associated with most types of propellant sprays, in particular when used indoors without protection and appropriate ventilation.

Pump sprays
In general, pump sprays are assessed to lead to significantly lower pulmonary exposure compared to propellant sprays because generally larger droplets/aerosols are generated and less volatile solvents are used. However, pump spray exposure data are limited. Further data on exposure levels possible depending on solvent and possible emulsifiers (such as possibly used in sunscreens) may be warranted.

Powders products
As shown in the previous chapters, powder products such as cement with nano-TiO_2 and face powder with nano-silica might lead to possible consumer risks. It might be warranted to further asses/measure actual exposure levels associated with consumer use of powder products, such as plaster/gypsum, powder paints with nano-TiO_2 and cosmetics in powder form containing nanomaterials. It is known that SCCS is currently preparing an opinion on nano-silica in cosmetics. We have not identified other types of powder products, which could lead to significant consumer exposure in the current project, but the same considerations regarding avoiding/reducing consumer exposure might be warranted for such products.

Nanomaterials in solid matrices and on surfaces
Various types of nanomaterials are used in a range of products such as sports equipment and electronics, and for surface treatment of equipment and buildings. As long as the nanomaterial stays embedded in the solid matrix, the nanomaterials are assessed not to constitute any consumer exposure and thereby risk. As noted earlier, this conclusion might not hold for production, repair, and disposal of such products, which are, however, outside the scope of the current project.

Wear
Nanomaterials might wear off surfaces and products due to weathering e.g. from UV-light, wind and other environmental impacts. Current evidence, however, does not indicate that such wear would lead to significant releases, possibly constituting significant consumer risks.

Sanding/grinding and other mechanical fitting of solid nanoproducts
The three scenarios addressing sanding or other mechanical fitting of nanomaterial-containing products lead to risk conclusions ranging from uncertain to likely. Generally, it has been shown that when the nanomaterials are released as part of a matrix (e.g. from lacquers and paints with binders), the nanomaterials content would probably not lead to additional risks compared to products without nanomaterials. On the other hand, if the free nanomaterials can be released, there may be a risk associated with the release. Further investigations quantifying and characterising the exposure associated with sanding and mechanical impacts might be warranted, including possible release following fitting of carbon nanotube containing sports equipment and other composite materials.

5.1.2 Oral
It is the belief of the authors that the food additive and sunscreen scenarios addressed in Chapter 3 and 4 probably constitute situations where consumers might currently be most significantly

exposed to nanomaterials. As well, $CaCO_3$ used as food additive (E170), containing a nano-fraction, could lead to a high oral exposure. However, considering the generally low toxicity and the water-solubility of $CaCO_3$, risks are qualitatively assessed to be unlikely. As already concluded in Section 4.1.2, it might be warranted to revisit: i) the recent hazard information regarding nano-TiO_2 and nano-silica in the ongoing EFSA re-evaluations of TiO_2 and silica as food additives, and ii) the assessments of nano-TiO_2 and nano-ZnO as UV filters in sunscreen in order to more quantitatively assess the possible risk following oral exposure to the sunscreen.

It can be noted that adverse effects following oral intake of products with colloidal silver (which can be self-prescribed through the Internet, although not allowed on the EU market) have been reported (Chang et al., 2006). However, such cases do not seem to be widespread and specific misuse is difficult to control.

5.1.3 Dermal

The conclusions reached in Section 4.1.3 regarding unlikely local and systemic toxicity following dermal exposure are in line with the general understanding indicating low irritation potential and very low (if any) dermal penetration/absorption of nanomaterials.

It should be noted that the wound dressing scenario addressed in scenario 18 is related to small wound dressings like those which could be applied at home. Hospital treatment of burns of large areas of the body have been shown to lead to systemic toxicity such as argyria and elevated liver enzyme levels, see e.g. Trop et al. (2006) addressing a case where 30% of the body surface was treated. In those situations, risks may be acceptable considering the risk associated with non-treatment.

5.1.4 Eye

Given the current knowledge, it does not appear that eye exposure to nanomaterials would lead to any significant risks, although further information on eye toxicity might be warranted.

5.1.5 Children

Based on the findings in the current study, it appears that the main possible concerns in relation to children's exposure to nanomaterials are associated with oral intakes of food additives (E171 TiO_2 and E551 Silica) and sunscreens, i.e. intake of sunscreen lipstick and possibly from hand-to-mouth behaviour of fingers with sunscreen (nano-TiO_2 and nano-ZnO). As noted above (Section 5.1.2), it is suggested that EFSA and SCCS reassess these cases.

Children may also be exposed to high inhalation levels if they stay in rooms in which spraying takes place, e.g. with shoe impregnation product containing nanomaterials. However, children would generally not be expected to be close during spraying events.

5.2 Cumulative exposure

The purpose of this section is to reflect on where consumers might be exposed to the same nanomaterial from various sources/consumer products. As already noted previously, it is inherently difficult to use the term "same nanomaterial" considering that the same chemistry of the pristine nanomaterial may occur in many forms with different sizes, shapes, coatings, etc. In any case, the following should give an indication as to where cumulative exposures might occur.

It is considered outside the scope of the current project to quantitatively estimate accumulated exposures and risks. Therefore, the following will largely focus on qualitative considerations based on the findings in the current project.

It is also considered outside the scope to discuss possible synergistic effects or cumulative effects across nanomaterial chemistry.

The following sections will discuss the issue of cumulative exposure for the seven types of nanomaterial chemistry addressed in the 20 exposure scenarios of this project.

5.2.1 Nano-TiO_2

As already discussed in previous sections, the main oral intakes of nano-TiO_2 appear to stem from food additives (which might stem from several types of food) and sunscreens, two sources which were in themselves assessed to constitute a possible risk in Chapter 3. Thus, from a cumulative perspective, even higher oral nano-TiO_2 exposures might occur. Other oral sources appear to be insignificant.

Consumers may be dermally exposed to significant amounts of nano-TiO_2 from sources such as sunscreens, paints and cement. However, given the current state of knowledge regarding (lack of) local dermal effects and absorption, this can currently not be assumed to constitute a risk.

Cumulative inhalation exposures seem to be possible in particular in relation to building, maintenance and renovation activities. Thus, a consumer spray painting with a nano-TiO_2 containing paint and/or sanding a nano-TiO_2 treated surface and/or using nano-TiO_2 containing cement might be cumulatively exposed via inhalation to nano-TiO_2. Such potential cumulative exposure would lead to higher concern for risk.

5.2.2 Nano-silica

As discussed above, oral intake of nano-silica in food grade silica (E551) from various food products might possibly cause a risk. Other possible oral intakes of nano-silica are assessed to be comparably negligible.

Dermal exposure to nano-silica might occur from various sources (e.g. spray and cosmetics). However, given the current state of knowledge regarding (lack of) dermal absorption, this pathway is not currently assumed to constitute any risk.

Significant inhalation exposure might however arise from use of several consumer products, such as cosmetics (face powder), impregnation spraying (and possibly from dental implants fitting and repair). As risks cannot be excluded for these uses alone, the possible cumulative exposure might lead to a higher potential for risk.

5.2.3 Nano-Ag

Nano-Ag and Ag are known to be absorbed to various degrees via all exposure routes and it is known that silver can lead to systemic effects such as argyria.

Thus, oral, dermal and inhalation exposure associated with nano-Ag containing products such as food supplements, jewellery, textiles, medicine, wound dressings, paints and various cleaning/disinfectant products, can lead to cumulative systemic silver exposure. It has been outside the scope of the current project to estimate cumulative systemic exposure from all these exposure routes; however, oral exposure from food supplements and inhalation exposure when spray-painting may be significant sources.

Specifically in relation to inhalation exposure, nano-Ag can lead to local respiratory effects. Cumulative inhalation exposure to nano-Ag may arise for consumers using various disinfectant sprays and spraying with nano-Ag-containing paint. The use of spray painting on its own is known to lead to risks; thus, concurrent use of other spray products would result in a further potential for risk.

Another potential effect of silver being discussed among experts is the generation of bacterial resistance following use of silver, including nano-Ag. It has been outside the scope of this project to assess this issue.

5.2.4 Nano-ZnO

From a volume perspective, nano-ZnO is mainly found in cosmetic products, including sunscreens and possibly zinc lotions/ointments, e.g. for irritated baby skin, rashes and burns.

In relation to oral exposure, we have identified a possible risk associated with nano-ZnO in sunscreen (lipsticks and possibly from children licking fingers). We do not think that other applications would contribute significantly to accumulated exposure.

In relation to dermal contact, use of various types of cosmetic products with nano-ZnO (e.g. for children) would lead to cumulative exposure. Use of nano-ZnO in other products, such as paints, would also contribute to dermal exposure. We have not assessed the possible risk associated with such cumulative exposure, but given the low dermal absorption rate of zinc (the zinc ion being released from the nano-ZnO), we believe that the oral exposure is probably of more concern as compared to the dermal route.

The current project addressed nano-ZnO in sunscreen pump spraying. Possible exposure from propellant spray products with nano-ZnO as a UV filter (sunscreens or possibly hair sprays) would potentially lead to higher pulmonary exposure than from pump sprays, which were considered in the nano-ZnO pump spray scenario. Such exposure might be of concern considering that SCCS (2012b, 2014c) states the following: "*Upon inhalation of ZnO nanoparticles, serious local effects in the lung were observed. Even if this may be due to the solubilized Zn ions, the effects are a direct result of the exposure to the ZnO nanoparticles*".

5.2.5 Carbon black

Consumers might experience cumulative exposure to carbon black from various sources, including a range of cosmetic products (such as mascara and eye liner) and carbon black in printer cartridges.

It is not expected that these products would lead to significant oral exposures, but cumulative dermal (and eye) exposures are very likely. However, as assessed in scenario 7, eye and dermal exposures are not assumed to lead to adverse effects/risks based on the limited current knowledge.

Some of these products (cosmetics in dusty forms) and powder toner from laser printers might lead to cumulative inhalation exposures. The possible exposure and risks associated with inhalation of carbon black have not been assessed in the current project.

5.2.6 Nano-ZrO_2

In the current project, we have not identified any major sources that could lead to cumulative exposure to nano-ZrO_2 other than those addressed in scenario 19 (dental fillings).

5.2.7 Carbon nanotubes (CNT)

A range of consumer products contain carbon nanotubes (CNT), including various types of sports equipment, sensors, technical textiles and a range of composite materials, such as vehicle components, antistatic plastics and coatings.

In these consumer products, the CNT is bound in a matrix and will only be released in the case of accidents, wear or mechanical treatment of the articles/surfaces containing CNT.

As addressed in relation to scenario 20 (golf club), relatively limited information on such possible releases is available in order to perform a risk assessment with a satisfactory degree of certainty.

However, given the high inhalation toxicity of some types of CNTs, even a small amount of free CNT possibly released could be of concern. Several of the indicated CNT containing products could, in some cases, contribute to cumulative releases following wear and mechanical impact/treatment.

5.2.8 Cumulative exposure - summary

The considerations about possible cumulative exposure have largely confirmed the findings regarding potential risks as already concluded based on the assessments of the individual scenarios/cases performed in Chapter 3 and discussed in Section 4.1 and 5.1. This finding is not surprising given that some of the scenarios have deliberately been chosen to represent assumed high-level exposures and because the scenarios have generally been assessed considering worst case scenarios. Still, the considerations about cumulative exposure have led to some new conclusions.

Possibly higher risks than those identified based on assessing the individual scenarios have been identified for the following cumulative exposures:

- Oral intake of nano-TiO_2 from sunscreens and from various food sources with the food additive E171
- Inhalation of nano-silica from cosmetics in powder form (e.g. face powder), from impregnation spraying and from fitting of dental implants
- With high uncertainty, carbon nanotubes possibly released by wear or mechanical treatment/impact from various composite materials and, to a minor degree, sports equipment.

The consideration of cumulative exposure has highlighted the following additional areas of possible concern:

- Systemic exposure to silver following concurrent oral, dermal and inhalation exposure to various nano-Ag (and non-nano-Ag) containing products such as food supplements, jewellery, textiles, medicine, wound dressings, paints and various cleaning/disinfectant products
- Inhalation of carbon black from various sources such as cosmetics in powder form and powder from laser printer toners (it should be noted that the risk assessments performed in Chapter 3 do not address any carbon black inhalation exposures).

More quantitative assessment of the above cumulative scenarios may be warranted.

As noted in the introduction to this section, possible synergistic or cumulative exposures and risks following exposure to different types of nanomaterial chemistry have not been addressed in the current study.

Nevertheless, it should be noted that cumulative inhalation exposure to "particles" (defined as engineered nanomaterials or ultrafine particles from other sources), which might all lead to generation of Reactive Oxygen Species (ROS), inflammation and possibly cancer or cardio-vascular diseases, would lead to cumulative risks. We will not discuss this issue further in this section, but refer to the discussion presented in Section 4.2.1.

5.3 Uncertainties

This section of the report aims at summarising what can be considered the main uncertainties as regards the exposure and hazards conclusions (and thereby the derived risk conclusions) in the current project.

5.3.1 Exposure

Although efforts have been made to collect as much and as specific data as possible on the consumer products for the 20 scenarios covered by this report, uncertainties pertain to several key parameters important for the reliability of the exposure assessment. Uncertainties as discussed in

the single scenarios in Chapter 3 of this report have also been discussed on a more general level in the exposure report (Danish EPA, 2015a).

Overall uncertainties
The overall degree of uncertainty may be seen in the context of the uncertainty for each of the parameters that are important to address when establishing an exposure scenario. These are listed below (taken from Danish EPA, 2015a):

IMPORTANT QUALITATIVE AND QUANTITATIVE EXPOSURE PARAMETERS

Qualitative exposure parameters
• ID of nanomaterial • Product category • Type of product • Volume/package design of the product • Matrix for the nanomaterial (nanomaterial location in the product free/matrix bound) • Product use/handling of the product during use/application method or processes involved (various life-cycle steps may be covered by different exposure scenarios/assessments) • Considerations regarding foreseeable misuse • Site of body area exposed • Identification of specific exposure routes (primary and secondary exposure routes) • Direct/indirect use (intended for human exposure/or not intended but a follow by normal use) • Indoor/outdoor use (inhalation exposure) • Generation of nanomaterial during use (especially inhalation exposure) • Specific target groups (children, teenagers, adult men, adult women, etc.)
Quantitative exposure parameters
• Size distribution of particles and fraction in nano-size • Concentration of nanomaterial in the product • Volume used per use event • Retention rate of product (e.g. dermal exposure or fraction ingested) • Degree of liberation/migration of nanomaterial from a matrix (dermal exposure, oral exposure) • Body surface area exposed (dermal exposure) • Article surface area in contact (dermal exposure, oral exposure) • Volume released to air (inhalation) • Concentration in air (inhalation) • Duration of exposure • Frequency of exposure

When specific information is not available for a certain parameter, assumptions have to be made. This will automatically introduce further uncertainty into the exposure assessment. Particularly when a whole range of parameters have to be assumed, the exposure assessment becomes very uncertain.

"Nano-specific uncertainties"
Many of the parameters above are also relevant for articles and chemical products in general; however, at present an increased level of uncertainty pertains to exposure assessment of nanomaterials for consumer products. The following are assessed to currently represent the main drivers for uncertainties in relation to assessing consumer exposure from nano products:

- Many current inventories/databases list consumer products based on claims. "Nano" might sometimes be used as a sales parameter and there is therefore not always evidence that such products do contain nanomaterials. On the other hand, products containing nanomaterials, but not claimed to contain "nano", will not be captured in these inventories/databases. This is a main overall uncertainty associated with the exercise performed in the current project, which aims at answering at a general level whether consumers are at risk.
- If a nanoproduct is known to contain nanomaterial(s), there is generally limited information on the chemical *identity* and/or characterisation of nanomaterials applied in consumer products (e.g. *surface modifications, particle size distributions*, etc.).
- Lack of clear description of the physical *state of the nanomaterial* that the consumer is exposed to as released from the product (*free, agglomerated/aggregated, bound to a matrix, potential for migration/liberation, etc.*) leads to uncertainty. The nanoparticles to which the consumer will be exposed are in many cases bound in a matrix or on a surface, where the potential release from the matrix (e.g. release from highly viscous droplets) or a surface layer (e.g. release of sanding fragment) is difficult to quantify as compared to exposure from soluble chemicals. Therefore, it may be uncertain to which extent the nanomaterial can be released/migrate from the product matrix, and this factor influences the actual oral, dermal or pulmonary exposure and associated risk.
- Whereas semi-quantitative *oral and dermal exposure* assessment may be addressed in a simplistic and transparent way using relatively few assumptions concerning e.g. the amount ingested or the amount applied on skin, it may be more difficult or complex to obtain semi-quantitative/quantitative estimates on *inhalational exposure*. This problem occurs because multiple factors in addition to the volume used may affect the exposure. A key parameter is the concentration in the air in a person's breathing zone, which depends on various factors such as emission rate of droplets/solid particles into air from the product, the air exchange rate in the room, particle size distribution, agglomeration and deposition/sedimentation rate of the different particle sizes, the person's distance to the emission source (e.g. spray or air cleaner), and the breathing rate and breathing volume of the person.
- Linked to this, and particularly of relevance for inhalation exposure, exposure estimation data (based on measurements or models) are often based on the mass of the nanomaterials (e.g. mg/m^3) rather than in metrics generally considered more relevant for nanomaterials, such as the concentration of particles or the surface area of the particles.
- Exposure estimation for chemicals in general is often performed using exposure estimation tools. Many of these tools have limitations in relation to assessing nanomaterials exposure. This issue will be addressed in more detail in Section 0.

5.3.2 Hazards

This section will outline methodological considerations and uncertainties associated with hazard assessment of nanomaterials and bridging to risk assessment of products containing the nanomaterials. To address hazards related to consumer products, one first has to consider the exposure context in which hazards should be assessed.

Examples of the occurrence and exposure to nanomaterials in consumer products have been published in a separate project report (Danish EPA, 2015a). A number of these exposure scenarios were addressed in Chapter 3 of this report. In brief, consumer products may contain nanomaterials in liquid suspension (e.g. cosmetics and paints), in powder form (e.g. cosmetic powder and cement) or the nanomaterials may be incorporated in a solid matrix (e.g. cured paint and sports equipment).

In many cases, consumers are only exposed to free nanomaterials to a limited extent. However, free nanomaterials may be released from solid matrices containing nanomaterials during the use phase, e.g. when sanding a nanomaterial-containing product or by wear and tear of such products. Other direct exposure may occur from liquid and powder products. Especially for spray products, significant release and exposure to nanomaterials may occur (see also Section 4.1 and 5.1).

Hazard assessment for consumers when using nano products is published in the hazard report from this project (Danish EPA, 2015b). In brief, hazard assessment of nanomaterial containing consumer products is challenging because very little is known regarding adverse effects of nanomaterials when part of a matrix. A limited number of animal studies on how the toxicity is affected when nanomaterials are part of a matrix have been published. Most of these have focused on the effects following pulmonary exposure of nanomaterial-containing spray products or dusts obtained by sanding of nanomaterial-containing paints, cements or thermoplastics (see details in Danish EPA, 2015b). Other studies have focused on the uptake of ZnO from sunscreens. In some of the studies described in the hazard report, the toxicity of the nanomaterial-containing product was compared to the conventional product without nanomaterial. None of these studies involving nanomaterials such as Nano-TiO_2 or CNT showed increased toxicity of the nanomaterial-containing product compared to the conventional product. However, the studies only assessed acute toxicity up to 1 month after the last exposure. No DNELs or other no-effect levels for nanomaterials when part of matrix were identified in our literature search. This problem is, in principle, the same for the assessment of "traditional" chemicals in matrices. However, they may be more pronounced for nanomaterials where the physical entity and characteristics may be especially important and affect the properties of the material.

Due to lack of information on hazards of nanomaterials when part of a consumer product, the hazard data for the free/pristine nanomaterials were used to predict the hazard in a worst-case scenario where it is assumed that the pristine nanomaterial is released from the product or that the consumer is in direct contact with the nanomaterial in the product. DNELs for materials such as carbon black, TiO_2 and Ag, can be found on the ECHA dissemination site as extracted from REACH registrations by importers and manufacturers. However, these DNELs are usually representative of the macro-form of the material rather than for the nano form. Furthermore, it has to be noted that derivation of the DNEL-values is the responsibility of the registrants and is the outcome of the registrant's interpretation of the data and use of assessment factors. Therefore, these DNEL-values cannot be regarded as generally accepted values. For some of the materials, DNELs are given both for consumer and occupational exposure. In general, the assessment factors recommended by ECHA to be used for deriving consumer DNELs are larger than the assessment factors used for deriving occupational DNELs by a factor of 2. Thus, the consumer DNELs are generally lower than occupational DNELs (ECHA, 2012).

In the ECHA guidance on information requirements and chemical safety assessment and Appendix R8-15 on recommendations for nanomaterials, it is mentioned in relation to evaluation of the quality of the whole database used to calculate the DNEL that application of an extra assessment factor to account for deficiencies within the data set may be particularly relevant for nanomaterials. The current guidelines on risk assessment of nanomaterials reflect the fact that no other paradigm for assessing nanomaterials can currently be recommended compared to the existing paradigm for chemicals, as no scientifically based alternative is available.

Research has primarily focused on the challenges regarding worker safety. OELs are traditionally based on the toxicity of the macro-material. Therefore, concern has been raised as to whether the existing OELs are sufficient when it comes to the nano form. A recent workshop report summarises the challenges regarding setting OELs for engineered nanomaterials (Gordon et al., 2014). Although consumers are not assumed to be exposed to free nanomaterials to the same extent as workers, the requirements for sufficient hazard data are relevant in relation to setting DNELs for consumers as

well. The report lists the following conditions as important barriers for the establishment of health-based exposure limits for nanomaterials:

1. There is a lack of hazard data. This is particularly the case for long-term animal inhalation experiments and epidemiological studies. The continuous introduction of new nanomaterials (including variations of "first generation" nanomaterials such as TiO_2 and carbon black) with an enormous diversity of physico-chemical attributes makes it unlikely that appropriate hazard data can be generated for each compound.
2. There is a limited understanding of how the physico-chemical properties affect the toxicity of a nanomaterial and it is still not possible to predict the toxicity based on the physico-chemical properties alone.
3. There is an uncertainty regarding the most appropriate dose and exposure metric. Traditionally, existing OELs are mass-based (mg/m^3) with the exception of asbestos, which is given as the number of fibres in the air ($fibres/m^3$). Animal studies have shown correlations between hazard of nanomaterials and a number of different dose metrics (surface area, number, volume etc.). More research is required to clarify if dose-metrics other than mass should be considered when setting exposure limits.
4. There is still a lack of standardised and validated methods for measuring air concentrations of nanomaterials.

These issues have also been challenging in the current project, as will be discussed in the following.

Hazard assessment of nanomaterials should ideally be done for each form of a nanomaterial with specific characteristics separately, unless it is evidenced that different nanomaterials may be grouped. However, for both economical and time reasons, it is not possible to test all specific forms of nanomaterials before use. Therefore, much effort has been invested into intelligent testing strategies and grouping of nanomaterials in order to be able to predict the adverse effects based on the physico-chemical properties in the future (Stone et al., 2014; Finnish Institute of Occupational Health, 2013). One of the research strategies emphasised that knowledge of the biological mechanism of action would enable grouping and ranking of nanomaterials and allow design of high through-put testing and computer-based hazard testing of nanomaterials (Quantitative nanoStructure-Activity Relationship) (Stone et al., 2014). However, nano(Q)SAR is still in the early stages of development and its implementation is far from being realised (Tantra et al., 2014). Consequently, as also noted earlier in Chapter 3 in the current study, we have not been able to consider different forms of the same nanomaterial chemistry. This is inherently a great uncertainty associated with the risk assessment in the current project.

The hazard assessments performed are, to the extent possible, based on data for the nanomaterials, although information is limited for some of the substances. However, toxicity data for the non-nano form of the substances have been used for ZrO_2 because data for nano-ZrO_2 were not available. In this case, a new DNEL was derived based on data from the non-nano form by introducing an extra assessment factor as suggested in the ECHA guidance for nanomaterials. As a consequence of data limitations, DNELs for some endpoints relevant for the exposure scenarios were assessed based on other routes of exposure, as is normal practice for other chemicals where it is known that uncertainties in absorption rates via different routes impacts the precision of the DNELs established.

The quality of the available hazard data of the nanomaterials vary and often the tested materials are not sufficiently characterised to allow robust evaluation of the mode of action and comparison of the results for different materials. This issue is also linked to the need for further development of validated test systems and the fact that nanomaterials vary endlessly.

The above item 3 regarding choice of appropriate metric, in particular relevant for inhalation, has also been relevant in the current project where DNELs have generally been expressed in mass units

due to data availability, although surface area or particle number might have been more appropriate. This issue has introduced further uncertainties.

All in all, the current project has encountered many of the same uncertainties as highlighted by other authors/authorities attempting to derive no-effect levels and conduct risk assessment of nanomaterial containing products.

Based on the case studies in the current project, some further observations should be highlighted:

- In general, the DNELs for inhalation for the studied nanomaterial containing consumer products were very low. Therefore, the significant uncertainties regarding inhalation exposure are of extra concern since the combination of high hazard and highly uncertain exposure leads to very uncertain risk estimates for inhalation exposure.
- When making the risk assessments in the present project, DNELs were derived according to the REACH guidance (consumers) for continued exposure. These DNELs were compared to the average daily exposure level on the day of exposure, even for exposure scenarios occurring only few times during a year or even more seldom. This may lead to an overestimation of the actual risk. As a follow-up, it might be considered – in addition to a chronic DNEL – also to derive short-term/medium-term DNELs, including agreeing on methods on how to do this for nanomaterials.
- Finally, as noted in the beginning of this section, a main uncertainty associated with assessing nanomaterials in consumer products is the fact that hazard data for the nanomaterials as part of a matrix are not available.

Overall, the main uncertainties related to hazard assessment and derivation of DNELs for nanomaterials in consumer products for further risk assessment have turned out to be:

- Hazard data for pristine nanomaterials are applied in absence of hazard data for the nanomaterials in matrix.
- Results are not always available for the most relevant exposure routes to be addressed.
- As detailed characteristics of the nanomaterials are often not available, the information used for evaluation of nanomaterials today may be based on data generated for different forms of the particles with varying surface area, coating or size distribution. There is little data on how these physico-chemical parameters influence toxicity. The quality of data varies significantly and test results with insufficient characterisation of the nano form may be included in the evaluations but may be less useful.
- Hazard data are generally expressed in the mass metric, although in particular for inhalation it would be more appropriate if DNELs in relation to the particle number or the surface areas could be derived.
- It is still challenging to recommend scientifically based assessment factors for nanomaterials.

Altogether these uncertainties justify the conservative approach applied in the current project, as more appropriate data and methods might lead to other conclusions.

5.4 State of play regarding models for risk assessment

The current project has reviewed a number of risk assessment tools potentially relevant for assessing exposure, hazards and/or risks of consumer nano products. Based on this review, this section discusses the state-of-play regarding models for risk assessment of consumer products.

The reviewed models/tools were identified in cooperation with the Danish EPA. The tools were selected based on their specificity for assessing nanomaterials or for their general applicability for assessing conventional chemicals and possible relevance for assessment of nanomaterials. The reviewed tools comprised:

- NanoRiskCat (DTU and NRCWE)
- NanoSafer (NRCWE, DTI)
- Stoffenmanager Nano (TNO)
- Stoffenmanager (TNO)
- The ANSES tool
- Swiss Precautionary Matrix (Swiss consortium)
- ECETOC TRA
- ConsExpo (RIVM)
- DREAM (TNO and IOM)
- Margin of Exposure (MOE) concept (The US Soap and Detergent Industries).

These models and tools are intended for assessment of consumer and occupational exposure/risk assessment, as well as risk categorization and control-banding-types of model assessment.

Thus, all in all the selection covers the topic broadly.

The reviews of the tools were conducted following an assessment template with relevant questions in relation to the approach/performance of the models/tools. A completed assessment template for each tool can be found in Appendix 5 in the appendix report belonging to the "Exposure report" of this project (Danish EPA 2015a).

5.4.1 Exposure estimation

All the selected tools - both the nano-specific and the non-nano-specific tools - have methods or modules for exposure assessment. An initial evaluation of whether the evaluated tools (possibly) could be used to address the exposure scenarios associated with relevant consumer product categories was assessed in the exposure report (Danish EPA, 2015a).

From this initial assessment the results included:

- Most tools have limited coverage in terms of exposure routes. Inhalation exposure is the focus in most of the tools intended for exposure (control-banding-like) assessment of nanomaterials.
- Only some of the general tools (ECETOC TRA, ConsExpo and MoE) have relevant "built-in" consumer exposure scenarios. However, none of these scenarios and exposure profiles specifically consider exposure to nanomaterials and use of nano products. One exception may be ConsExpo, which has the possibility to include size-distribution information for the spray assessment. Certainly none of the tools are readily applicable to assess the consumer exposure to nano products considering the scenarios of using construction materials, medical devices, shoe polish and release from abrasion (matrix) nanocomposites.
- Common products such as cleaning agents, coatings/impregnation and maintenance products could potentially be addressed by several of the tools. Still, however, the tools make mass-metric based assessments and nanomaterial aspects are in principle not covered.
- Less detailed/generic tools such as the NanoRiskCat and the Swiss Precautionary Matrix could potentially be used for many/most types of exposure scenarios. One drawback with these risk categorization tools is that they might be too broad/conservative in their scaling to be applied

for risk assessment and that they do not e.g. specifically address the relevant exposure routes and levels of exposure.
- That combination of different modified and further developed tools may enable a framework for semi-quantitative risk assessment of several types of consumer products and exposure scenarios.

It should be noted that the conclusions from this assessment are based on theoretical assessment of the different tools considering their intended use and application domains and exposure routes. Practical tests coupled with actual exposure measurements are needed to ascertain whether apparently appropriate tools *de facto* would be applicable within their specific application areas. As stated in the exposure report "*Sometimes the devil is in the detail and only actual application of the tools on the exposure scenarios to be selected might reveal whether it actually makes sense to use a given tool.*"

All of the models use mass concentrations as the exposure metric and cannot directly use e.g. particle number concentrations and size-distributions for the assessment, except for the spray model in the ConsExpo tool. Several of the models and tools are developed to assess whether specific exposure levels are exceeded and do not make stand-alone exposure assessment. Therefore, direct application requires the existence of a limit value (e.g., NOEL or DNEL). Therefore, direct use of existing tools generally requires that a nanospecific hazard assessment has been made considering mass-concentrations as the exposure metric.

In general, modules estimating dermal exposure might be used with notation that nanomaterial properties could results in special needs in the assessment, whereas modules estimating inhalation exposure should be used with more caution as particle behaviour in air (e.g. deposition and agglomeration/de-agglomeration) is not well-addressed in estimation equations, which are often based on mass conservation.

5.4.2 Hazard

All nano-specific tools have hazard modules, whereas some of the selected non-nano-specific tools only address exposure.

The ANSES, NanoSafer, NanoRiskCat, and Stoffenmanager Nano tools - due to expected absence of nano-specific exposure limits - also apply hazard data for the nearest analogue macro/bulk compound. Although such macro/bulk data are applied in a way that the final hazard score of the nanomaterials is higher than for the macro/bulk form, it should be noted that nano forms might possess hazards which are not identified based on the hazard profile for the macro/bulk form and the physicochemical hazard indicators. Depending on the level of precautionary approach taken, these potential unknown hazards, e.g. carcinogenicity or mutagenicity, could have graver implications than estimated by the model procedures.

The general (non-nano) tools are generally exposure estimation/assessment tools, although three of the tools have a "hazard module". However, the hazard modules are not made for hazard specific estimation, but hazard scaling (from larger to smaller particles, e.g. based on size) using a precautionary approach. In the conventional tools, the hazard module does not exist and is merely a facility to enter a NOAEL/DNEL/reference value in order to be able to carry out a quantitative risk characterisation. Thus, in principle, from a hazard perspective, the conventional and some nanospecific risk assessment tools could be used if an appropriate reference value could be estimated (done outside of the tools). As further addressed in the hazard assessment report (Danish EPA, 2015b), this depends on the hazard data(base) available for individual nanomaterials, which at this point in time will be rather limited. In cases where toxicological data are completely missing, one may turn to the hazard prediction or scaling procedures embedded in several of the control banding tools. As hazard scaling is based on uncalibrated "bulk to nano" read-across and

physicochemical indicators, they are uncertain, but could still give valuable information for qualitative risk assessment. Finally, a major issue in the current state of hazard/risk assessment tools or procedures is the uncertainty in application of the conventional mass-based metrics. This uncertainty is problematic in assessment of nanomaterials, where particle size and surface area appear to play an important role, especially in inhalation exposure. It is not yet clear to what extent this size and surface area play a role in risk assessment of dermal and oral exposure.

5.4.3 Risk

The review of the 10 selected risk assessment tools vary considerably in terms of coverage, scope/approach, level of quantification, populations and exposure routes addressed etc. The nano-specific tools are generally rather qualitative, but also not specifically designed to assess whether there necessarily is a true risk, but rather to indicate where there could be a risk and how strong its indications, which could be subject to risk mitigation. Further, inhalation exposure risk is the key focus of the nanomaterial tools, although not quantitatively estimating inhalation exposure. None of the nanomaterial exposure assessment tools address eye, dermal and oral exposure specifically. In contrast, the general (non nano-specific) tools are more quantitative with a wider coverage, e.g. in terms of exposure routes addressed. Of note is that the exposure assessment algorithms in most of the non nano-specific tools are simpler and more conservative for inhalation than the algorithms in the most advanced nano-specific tools (Stoffenmanager Nano and NanoSafer).

All nano-specific tools have exposure as well as hazard modules, leading to “risk-based” approaches, where some of the reviewed non-nano-specific tools only address exposure. In relation to possible further application of these tools in this project, it was found that the tools are generally not designed to explicitly confirm “no risk”, but rather to prioritize areas for exposure/risk reduction. On the other hand, one might implicitly assume that “non-prioritization”/”low banding” could indicate low/no risk, also considering that the tools generally apply conservative approaches.

It was clear from the model assessments that no single tool would enable a harmonized proper exposure assessment for all nano-products. Significant work effort was assessed to be required to further develop the tools with modification for incorporating nano-specific properties and harmonizing the output, not mentioning its validation. The results showed that selection/adaptation of one tool (as speculated in the project specifications) would also be a major effort, which was out of the scope of the current project. Using this background, we chose an alternative approach by performing a case-by-case expert assessment of each of the selected scenarios, in some cases by applying (components of) of several tools as appropriate.

Several further developments are required to enable quantitative (consumer) risk assessment of nano-enabled products through modelling. A number of developments are needed for current model refinements and documentation:

- The models should be further developed to include quantitative exposure estimates in several metrics on all key exposure routes.
- Databases or libraries on emission rate data and exposure characteristics (e.g. aerosol size distributions) should be developed considering mass and number size distributions, at least, in the exposure metrics.
- Predictive hazard models should be further developed starting from simple hazard grouping and scaling based on physicochemical properties and knowledge of existing compatible compounds.
- All model segments (hazard, exposure, and integrated assessment) need to be documented by calibration and performance testing to determine the uncertainties associated with the assessment.

5.5 Future trends

The current section aims at providing an outlook in relation to possible future trends in the use of nanomaterials and nanotechnology in consumer products.

5.5.1 The nano-market in general

Various actors have quantified and predicted the increased market volume for nanomaterials and nano-enabled products. Bcc Reasearch (2014) has quantified the market for nanotechnology products to $22.9 billion in 2013 and estimated an increase to $64.2 billion by 2019. Therefore, an increase of about a factor of three over 6 years is predicted. Lux Research (2014) quantifies the revenue from nano-enabled products to $731 billion in 2012, increasing to an estimated $4.4 trillion ($4,400 billion) in 2018, equalling a six-fold increase over 6 years. The figures from these two sources (and from other similar sources) are difficult to compare as the scope of the assessments differ. Enormous differences in the estimations are observed when, for example, the value of the nanomaterials itself is applied in the calculations (e.g. the value of carbon nanotubes in car bumpers), compared to calculations based on the value of the nanoproduct part (e.g. the value of the car bumper), or the value of the nano-enabled assembled product (the entire car). Therefore, the exact figures of such estimations should be interpreted and compared with caution. However, there seems to be no doubt that the market for nanomaterials and nano-enabled products is growing very rapidly.

5.5.2 The market for consumer products

It has not been possible to acquire up-to-date market survey data for nano-enabled consumer products within this project. However, given the findings in the exposure report of this project (Danish EPA, 2015a), it appears that nanomaterials are increasingly used - also in consumer products. An older survey conducted by Bcc Research (2005) estimated that the nano-technology input to produce consumer products would increase by 9.1% annually from 2005 to 2010.

The Nanotechnology project/database (formerly Woodrow Wilson) mapping consumer nano-products based on internet searches found a 24% increase in the number of products in the database from 2010 to 2013[4] . As noted previously, this database is based on nano claims rather than definite knowledge about actual nanomaterials in the products. In any case, the trend seems clear. The Danish Nanodatabase[5] has revealed similar increases in the number of available consumer nano-products (Foss Hansen, personal communication, 2015). It should be noted that the increased number of products may also, to some extent, be a result of increased awareness of branding with "nano". On the other hand, the increased health and safety focus on nanomaterials may also have led to fewer products being claimed to contain nano.

The following sections aim at indicating trends within some of the consumer product categories where nanomaterials appear to be increasingly applied.

5.5.2.1 Cosmetics

Raj et al. (2012) outlines the opportunities for applying nanomaterials for improving cosmetic properties such as colour, transparency and solubility. Nanomaterials potentially applied include nanosomes, liposomes, fullerenes and solid lipid nanoparticles. Mihranyan et al. (2012) concluded, among others, that in relation to cosmetics, the main focus on nanomaterials is in terms of active substances, carriers and formulation aids, and states as part of the summary that "*Based on recent patents and the scientific literature on the use of nanotechnology in cosmetics, this review shows that this emerging technology is about to become a crucial tool, not only for scientific research on – but also for industrial development of – new cosmetic products. Whereas nanotechnology is presently being developed for both creating new packaging materials and manufacturing*

[4] http://www.nanotechproject.org/news/archive/9242/
[5] http://nanodb.dk/da/

equipment for cosmetics, it is within the area of cosmetic materials formulation that one currently finds the highest number of nanotechnology-related patents and scientific reports."

5.5.2.2 Food and feed

Jiang et al. (2014) and Reig et al. (2014) look into the opportunities for applying nanomaterials and nanotechnology with focus on food packaging and to some extent for treating the contained food. Possibilities for applying nanomaterials as oxygen scavengers, as antimicrobial agents and for nanobiosensors are discussed.

Based on an EFSA (European Food and Safety Authority) commissioned study, Peters et al. (2014) looked into nanomaterial applications in food and feed. Although mainly focusing on current applications - largely within the food sector - indications of possible future applications are also addressed including, within "Agriculture": i) Nanocapsules for more efficient delivery of pesticides, fertilizers and other agrochemicals, ii) nanomaterials for detection of animal and plant pathogens, and iii) nanomaterials for identity preservation, tracking and tracing, as well as within the feed sector such as for encapsulation of nutrients, increased absorption of minerals, as antibiotics, for absorbing bacteria and for improving digestibility.

5.5.2.3 Medicines and medical equipment

A report prepared by Allianz and the OECD (Lauterwasser, 2005) discusses, among others, the possible future application of nanomaterials and nanotechnology for medical purposes, such as for drug delivery, diagnostic purposes, for hearing and vision, and for repair and replacement of damaged tissues and organs.

5.5.3 Next generation nanomaterials

The development of nanomaterials and nanotechnology is often discussed in the context of "generations" of nanomaterials, not the least following a publication by Roco (2004), which outlined a four generation vision for such a development:

- First Generation of products (~2001-): passive nanostructures
- Second Generation of products (~2005-): active nanostructures
- Third Generation (~2010-): 3-D nanosystems and systems of nanosystems
- Fourth Generation (~2015-): heterogeneous molecular nanosystems

The interested reader can read more about the definitions of these generations in the Roco publication and assess the extent to which we are actually in the fourth generation as of today. Even though first and second generation nanomaterials, as defined in this publication, likely still account for the most widespread uses (examples of which have been assessed in this project), there is no doubt that nanotechnology and certain types of nano-enabled products are becoming more sophisticated, for example in relation to drug delivery.

Future outlook is also addressed in the report "Nanotechnology research directions for societal needs in 2020" issued by the World Technology Evaluation Center (WTEC) authored by Roco et al. (2010), outlining a more updated outlook. Among many others, the following nano-enabled products/technologies are foreseen to evolve:

- Multiscale self-assembly of materials form the molecular or nanostructure level upwards
- Complex behaviour of large nanosystems
- Creation of molecules, materials, and complex systems by design from the nanoscale
- Artificial organs, including the use of fluid networks and nanoscale architectures for tissue generation.

The report, for example, also states that *"New theories on nanoscale complexity, tools for direct measurements, simulations from basic principles, and system integration at the nanoscale will*

accelerate discovery". It is difficult to estimate when these types of technologies will become frequently available in consumer products.

It is likely that such "next generation" nano-enabled consumer products might present health risks that cannot be captured by current tools and methodologies, and potentially present other types of societal and ethical risks that need to be addressed in addition.

5.5.4 Summary - trends

The use of nanomaterials and nanotechnology in general, and specifically in relation to consumer products, is currently increasing and predicted to increase rapidly is years to come. This increase pertains to amounts, diversity and market value of nanomaterials and nano-enabled products.

More sophisticated next generation nanomaterials and nanotechnology solutions, such as self-assembly systems, may appear and might need a different approach for assessing consumer health risks and possibly also other societal and ethical risks.

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Abbreviations and acronyms

ADI	Acceptable Daily Intake
Ag	Silver
AgCl	Silver chloride
ANS	EFSA Panel on Food Additives and Nutrient Sources added to food
BfR	Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment)
bw	body weight
$CaCO_3$	Calcium Carbonate
CB	Carbon black
CNT	Carbon Nanotube
ConsExpo	Consumer Exposure assessment tool
D50	Median size (in a particle size distribution)
DK	Denmark
DNEL	Derived No Effect Level
EC	Elemental Carbon
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
EU	European Union
FCM	Food Contact Material
ISO	International Organization for Standardization
KemI	Kemikalieinspektionen (Swedish Chemicals Agency)
LOAEL	Lowest Observable Adverse Effect Level
MWCNT	Multiwalled Carbon Nanotube
NCR	Nor considered Relevant
NIOSH	National Institute for Occupational Safety and Health (US)
NM	Nanomaterial
NOAEL	No Observable Adverse Effect Level
OEL	Occupational Exposure Limit
OM	Organic Matter
PM4	Particulate Matter smaller than 4 µm
PM10	Particulate Matter smaller than 10 µm
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical substances (Regulation EC 1907/2006)
REL	Recommended Exposure Level
ROS	Reactive Oxygen Species
SAS	Synthetic Amorphous Silica
SCCS	Scientific Committee for Consumer Safety
SCENIHR	The Scientific Committee on Emerging and Newly Identified Health Risks
TDI	Tolerable Daily Intake
TEM	Transmission Electron Microscopy
TiO_2	Titanium dioxide
TNO	The Netherlands Organisation for Applied Scientific Research
TRA	Targeted Risk Assessment (ECETOC Targeted Risk Assessment tools)

TS	Technical Specification (ISO/TS)
UV	Ultra Violet
WHO	World Health Organisation
WP	Work Package
wt%	weight percent
ZnO	Zinc oxide
ZrO_2	Zirconium dioxide

Appendix 1: Hazard appendix

The following sub-appendices aim at summarising hazard information for the seven nanomaterials addressed in the 20 selected exposure scenarios. The focus will be on the exposure routes relevant for the 20 assessments and where relevant and possible, it will be attempted to establish Derived No-Effect Levels (DNELs). As discussed in the introductory remarks to Chapter 3, the DNELs have been estimated considering the relevant REACH guidance while acknowledging shortcomings in the data available, e.g. data in metrics other than the mass metric.

Appendix 1.1: Nano-TiO_2

The hazard assessment summary of nano-sized TiO_2 is intended to serve as background documentation for the risk assessment of TiO_2 used in chewing gum, sunscreen, sunscreen lipstick, paint, and cement and in relation to sanding of a surface painted with nano-TiO_2-containing paint. The different applications of TiO_2 involve exposure via the oral, dermal, eye and inhalation routes; the focus will therefore be on the hazards associated with these exposure routes.

The Scientific Committee on Consumer Safety (SCCS) updated its opinion on nano-TiO_2 used as a UV filter in cosmetics in April 2014 (SCCS, 2014a). The hazard assessment related to the oral and dermal route is primarily based on conclusions in that opinion and supplementary information from EFSA regarding use of food-grade TiO_2 in chewing gum. Hazards related to inhalation exposure are primarily based on information in the NIOSH Current Intelligence Bulletin disseminating new scientific information about occupational hazards related to titanium dioxide (NIOSH, 2011).

Since this evaluation by EFSA was made in 2004, the more recent evaluation by SCCS from 2014 indicating an effect from oral ingestion is also considered in the following.

Oral exposure

JECFA (1969) has approved food-grade TiO_2 in both anatase and rutile forms as food colouring with "no limit" and concluded that establishment of an acceptable daily intake was not necessary based on lack of significant absorption and tissue storage following oral ingestion.

Based on the JECFA assessment, the EU allows TiO_2 as food colouring in the anatase form without any restrictions as specified in the Directive 94/36/EEC (Annex I). EFSA (2004) has evaluated the rutile form as an alternative to anatase TiO_2, which is the form permitted in Directive 94/36/EC on colours for use in foodstuffs. EFSA concluded that food-grade nano-TiO_2 is a very insoluble compound and that absorption of small amounts of titanium ions did not result in toxic effects, and that establishment of an acceptable daily intake for humans is not considered necessary. Results also indicate that there is no accumulation of titanium in the tissues following dietary administration of 200 mg food-grade TiO_2/kg. No toxicological or carcinogenic effects were observed in a chronic dietary study with administration of up to 5% TiO_2 coated mica in rats for 130 weeks.

Weir et al. (2012) have found that that roughly 36% of food-grade TiO_2 (E171) consists of particles which are less than 100 nm in at least one dimension and that it readily disperses in water as fairly stable colloids.

The total estimated intakes of rutile TiO_2 for the proposed food and medicinal product uses in the EU is 1.3 mg rutile TiO_2/kg bw/day. This is considered to be a worst-case estimate by EFSA, and is likely a gross over-estimate of the potential total exposure.

EFSA (2004) made the following conclusions regarding rutile TiO_2 in food-grade TiO_2 (E171):

> The Panel concluded that the use of rutile titanium dioxide in the platelet or amorphous forms would not pose any safety concerns.

SCCS (2014a) has concluded as follows regarding safety related to oral exposure and dermal application:

> *"The studies provided on acute oral toxicity in the submission mainly relate to TiO_2 na nomaterials that are anatase/rutile mixtures, coated with trimethoxy-n-octyl-silane. From the limited relevant information provided, and considering that oral intake is not*

likely to be the major route of exposure to TiO_2 nanomaterials from dermal application of formulations, the acute oral toxicity of TiO_2 is unlikely to be of a concern. "

However, it should be noted that the SCCS referred to a study where a LOAEL of 5 mg nano anatase TiO_2 (5 nm)/kg bw/day was derived based on impaired neurofunction and behaviour after 60 days of oral exposure (gavage) in mice. (SCCS, 2014a).

In this project we will discuss this LOAEL in relation to estimated oral intake of nano-TiO_2. Given the scope of the present project, we have chosen not to derive a DNEL, but rather discuss our findings qualitatively vs. the EFSA and SCCS conclusions.

Uncertainties

Most studies regarding oral toxicity of TiO_2 have been performed at doses below the estimated human consumption and without performing relevant particle characterisation. Estimated human consumption of food-grade TiO_2 (E171) is 0.2 to 2 mg/kg bw/day (Weir et al., 2012) which is close to the estimated LOAEL value of 5 mg anatase TiO_2 (5 nm)/kg bw/day.

No ADI has been established for food grade TiO_2 (E171), although some of the evidence regarding lack of absorption and accumulation used for the initial approval has been challenged by newer results (Jankovic, 2014).

Dermal exposure

Local effects

Several studies based on a range of *in vitro* to *ex vivo* or *in vivo* experimental conditions and intact and UV damaged skin suggest that TiO_2 nanoparticles, when applied to skin in a sunscreen formulation, are likely to stay largely on the skin, with potential for a small proportion of the particles penetrating to the outer layers of stratum corneum (SCCS, 2014a).

Some studies indicate that the nanoparticles may reach the hair follicles and it is speculated that this could lead to generation of reactive oxygen species (ROS) on exposure to UV light. This is the main concern from SCCS, which resulted in a restriction on the amount of the photocatalytic anatase form to be used in cosmetics to 5% of the 25% nano-TiO_2 allowed as a UV-filter in cosmetics.

Systemic effects

There is no evidence of dermal penetration of nano-TiO_2 into the living epidermis (SCCS, 2014a). Exposure to cement could cause damage to the skin due to other corrosive components of the product. However, even in the case of psoriasis, comparable to skin conditions following strong irritation of the skin, no penetration into viable layers of epidermis has been demonstrated (SCCS, 2014a).

Uncertainties

There is no conclusive evidence regarding the fate of TiO_2 nanoparticles which enter hair follicles and sweat glands. However, at present there is no evidence to confirm that this pathway offers a viable mechanism of entry into systemic circulation (Choksi et al., 2010).

Inhalation

Local effects

1) NIOSH (2011) has recommended an exposure limit (REL) of 0.3 mg/m³ for ultrafine (including engineered nanoscale) TiO_2 , as time-weighted average (TWA) concentrations for up to 10 hours per day during a 40-hour work week based on pulmonary inflammation and reduction of the risk of lung tumours to a 1/1000 lifetime excess risk in workers.

Using this REL and adjusting for 24 hour respiratory volume for consumers (20 m^3 air/day) and worker exposure during a day of work (10 m^3 air/day) an adjusted REL can be calculated:

REL_{adj}: 0.3 mg ultrafine TiO_2/m^3 × 10 m^3/20 m^3 × 5d/7d = 0.1 mg TiO_2/m^3
Further, assessment factors are introduced to account for the uncertainty related to the difference between the intraspecies assessment factors for workers and the general population, and the general quality of the database regarding inhalation toxicity.

Assessment factors

AF1: 2 (difference between the intraspecies assessment factors for workers (5) and the gen. population (10); REACH Guidance R8)

$DNEL_{inh}$ = REL_{adj}/AF1
$DNEL_{inh}$ = 0.1 mg ultrafine TiO_2/m^3/2 = 0.05 mg ultrafine TiO_2/m^3 (50 µg ultrafine TiO_2/m^3)

Thus, 0.05 mg ultrafine TiO_2/m^3 can be considered as derived no effect level for lung tumours, as a threshold approach using assessment factors is considered the most appropriate approach for assessing the potential for tumorigenic effects from TiO_2 inhalation exposure..

2) NIOSH (2011) has recommended an exposure limit of 0.004 mg/m^3 for ultrafine (including engineered nanoscale) TiO_2 , as time-weighted average (TWA) concentrations for up to 10 hours per day during a 40-hour work week based on prevention of pulmonary inflammation.

Using this REL and adjusting for 24 hour daily exposure provides the following adjusted value:
REL_{adj}: 0.004 mg ultrafine TiO_2/m^3 × 10 m3/20m3 × 5d/7d = 1.4 $x10^{-3}$mg ultrafine TiO_2/m^3
An assessment factor is introduced to account for the uncertainty related to the difference between the intraspecies assessment factors for workers and the general population.

Assessment factors

AF1: 2 (difference between the intraspecies assessment factors for workers (5) and the gen. population (10); REACH Guidance R8)

$DNEL_{inh}$ = REL_{adj}/AF1
$DNEL_{inh}$ = 1.4$x10^{-3}$ mg ultrafine TiO_2/m^3/(2) = 0.7 $x10^{-3}$ mg ultrafine TiO_2/m^3

As the latter value, established to prevent pulmonary inflammation, is very conservative, both these values will be considered and discussed in the relevant risk assessment.

Uncertainties
The REL used to derive the DNEL is based on modelled data. The approach by NIOSH has been to estimate the pulmonary particle surface area dose associated with a 1/1000 increase in rat lung tumours and to extrapolate that dose to humans on the basis of particle surface area per unit of lung surface area. It is noted by NIOSH that the choice of model has a significant impact on the risk estimate. In addition, pulmonary inflammation is not a specific biomarker for lung cancer – and the precise level of sustained inflammation necessary to initiate a tumorigenic response is not yet known (NIOSH, 2011). It is also noted by NIOSH that extremely low-level exposures to (ultrafine) TiO_2 —i.e. at concentrations less than the pulmonary inflammation-based RELs—may pose no excess risk of lung tumours.

It is known that rats are more sensitive than humans in relation to lung overload and some of the effects, e.g. the generation of tumours seen at high exposure concentrations in rats, may only

happen at even higher exposure levels in humans. Thus, the RELs/DNELs may reflect a very conservative approach.

Eyes

The SCCS has concluded that eye irritation potential is low (SCCS, 2014a).

Uncertainties

Limited useful data are available for the nano form of TiO_2 as concluded by SCCS. Studies typically lack information on particle size distribution.

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Appendix 1.2: Nano-silica

The hazard assessment of synthetic amorphous silica (SAS) as part of a matrix is primarily based on recent reviews by Dekkers et al. (Dekkers et al., 2011; Dekkers et al., 2013), a review of the hazard of SAS by (Fruijtier-Pôlloth, 2012), and reports on SAS by the International Agency for Research on Cancer (IARC) (IARC Monographs on the evaluation of carcinogenic risks to humans, 1997) and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Joint Assessment of Commodity Chemicals (JACC) (European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2006). The purpose of a hazard assessment is to serve as an input for the hazard part of the risk assessment of SAS in 1) food items and food containers, 2) face powders, and 3) "easy to clean" impregnation. Thus, the focus is put on the potential hazards associated with exposure by the gastrointestinal route (relevant for the food items and food container scenarios) and exposure by the dermal and inhalation routes (relevant for the face powder and the "easy to clean" impregnation product). The critical effect following oral exposure is assessed as the hepatic effect. The No Observed Adverse Effect Level (NOAEL) has been suggested to be 1,500 mg/kg bw/day (Dekkers et al., 2011). The critical effect following pulmonary exposure is pulmonary inflammation. Based on the evaluation by ECETOC the Lowest Observed Adverse Effect Levels (LOAELs) and NOAELs were typically 1-50 mg/m^3 and 0.5-10 mg/m^3, respectively (European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2006). These differences were evaluated by ECETOC as particle size dependent: i.e. in general the NOAEL/LOAEL decreased by particle size. Our literature search identified several recent studies showing that the NOAEL/LOAEL was affected by size and surface modification, highlighting that the physico-chemical properties have to be taken into account. No studies were identified by ECETOC on the dermal or oral absorption of SAS (European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2006). For that reason, no NOAEL/LOAEL has been suggested. Thus, the overall conclusion by ECETOC is that "*SAS is essentially non-toxic in humans via the oral, dermal/ocular and inhalation routes of exposure and no data exist on systemic effects in humans*".

Oral exposure

In 2009, EFSA has concluded that the use of silica up to 1500 mg silica/day (corresponding to 21 mg/kg bw/day for a 70 kg person) added to food supplements is of no safety concern (EFSA Panel on Food Additives and Nutrient Sources added to food (ANS), 2009). This limit is a general limit for "traditional" SAS.

A later study by van der Zande et al. (2014) investigated the potential effect of two different types of SAS with primary particle sizes of 7 nm and 10-25 nm, respectively. Rats were orally exposed to two different types of silica for 28 days for the two lowest doses and 84 days for the highest dose. The doses were 100, 1000 or 2500 mg/kg bw/day for a commercially available food grade pyrogenic SAS (7 nm) and 100, 500 or 1000 mg/kg bw/day of commercially available pyrogenic NM-202 (10-25 nm). After 84 days of exposure, liver fibrosis was detected in rats exposed to 1000 mg/kg bw/day NM-202: this is considered the LOAEL (van der Zande et al., 2014). As stated by van Kesteren et al., a limitation for setting a NOAEL of this study is that only one dose was studied for 84 days and therefore this dose automatically becomes the LOAEL.

Assessment factors

AF1: The starting point of the calculation is a LOAEL and it is suggested to use an assessment factor between 3 (as minimum/majority of cases) and 10 (as maximum/exceptional cases) to extrapolate from LOAEL to NOAEL. We have chosen to use 3 as the assessment factor.
AF2: For interspecies variation: For rat to human and remaining differences, the factors 4 and 2.5 are applied, respectively. Together this gives 4* 2.5 = 10
AF3: For intraspecies variation the default factor 10 is applied (systemic effects)
AF4: For extrapolation from sub-chronic to chronic the default factor 2 is applied

DNEL

$$\text{DNEL}_{\text{Liver fibrosis}} = \frac{LOAEL}{AF1*AF2*AF3*AF4} = \frac{1000\frac{mg}{kg}bw/day}{3*10*10*2} = 1.67 \text{ mg/kg bw/day}$$

This DNEL deviates from the DNEL derived by EFSA. We have chosen to include the study because the sizes of the primary particles are known.

Uncertainties

Risk assessment of SAS is complicated by the existence of different forms and types of SAS (van Kesteren et al., 2014). Different SAS forms (pyrogenic silica, precipitated silica and silica gel and colloid silica) are formed by different production processes (van Kesteren et al., 2014). Each of these SAS forms differs further by particle size, specific surface area, surface coating etc. We agree with the conclusion by van Kesteren et al: "*These differences between forms and types of SAS may affect the kinetics and toxic potential of SAS. Currently, insufficient information is available on the effect of the different physicochemical characteristics on the behaviour (kinetics and toxicity) of SAS, which challenges a generalised risk assessment*"(van Kesteren et al., 2014).

The study by van der Zande et al. investigates two types of SAS nanomaterials (both pyrogenic but with different sizes, specific surface area etc.) and only one of them induces liver fibrosis (A NOAEL for fibrosis was considered 1000 mg/kg bw/day). In addition it is important - as it is stressed by the authors - that the relevance of comparing external dose level is dubious because a decrease in absorption has been detected at higher oral dose levels. Based on the study by van der Zande et al., the liver absorption was calculated to decrease from 0.2% absorption at the low dose level to 0.01 to 0.02% at the high dose level. A risk assessment based on internal concentrations has therefore been suggested as an alternative by van Kesteren et al. (2014).

By the end of 2014 - after finalizing our literature search - two new OECD guideline studies on SAS were published: One study investigated the toxicity in rats of negatively charged colloidal silica particles of different sizes (20 nm and 80 nm) following chronic administration once daily for 90 days (500, 1,000 and 2,000 mg/kg) (Kim et al., 2014). No toxic effects, clinical changes or histopathological findings were observed for any of tested silica particles. The authors conclude that the results indicate a NOAEL for both tested silica particles at 2,000 mg/kg bw/day. In another study four different SAS with or without surface functionalization were tested in rats in a 28-day oral exposure study (Buesen et al., 2014). No effects were detected.

Based on the study that was the basis for the calculation of the DNEL of pyrogenic SAS in this report (LOAEL, 1,000 mg/kg bw/day) (van der Zande et al., 2014) and the recently published papers described above on colloid SAS (NOAEL, 2,000 mg/kg bwday) (Kim et al., 2014) and SAS with different surface modifications (NOAEL = 1,000 mg/kg bw/day) (Buesen et al., 2014), it is clear that differences between types of SAS are of key relevance when doing a detailed risk assessment.

Dermal

Local effects

ECETOC concludes that SAS is neither a skin irritant nor a sensitizer (European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2006). Repeated skin exposure does not result in any significant toxicity. However, dryness and cracking may be the result of repeated skin exposure (European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2006). With this background it is not possible to derive a DNEL for local, dermal effects.

Systemic effects

ECETOC does not report any studies on dermal absorption of SAS (European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2006). A literature search of more recent

studies on the toxicity of nanoSAS following dermal application identified a single study (Nabeshi et al., 2011). The transdermal penetration and biodistribution was evaluated by TEM after application of 70 nm sized SAS particles on the skin on the inner side of both ears of mice. After 28 days, SAS particles were detected in the skin, regional lymph nodes, the liver, the cerebral cortex and the hippocampus but no level of translocation was given. The study suggests that SAS particles may translocate through the skin and be systemically distributed. However, the results from this study need to be confirmed by other studies before a final conclusion on skin uptake can be made. With this background, we have chosen not to calculate a DNEL.

Inhalation

For sub-acute inhalation exposure, a LOAC of 1 mg/m^3 based on the absence of inflammatory effects has been identified for three different types of SASs:
"In a sub-acute study, rats were exposed to three different types of SAS (precipitated, gel and pyrogenic) by inhalation for 6 hours a day on 5 consecutive days (1, 5 or 25 mg/m^3) and pulmonary effects were evaluated 1 day, 1 or 3 months after last exposure (Arts et al., 2007). The effects were compared with the effects in rats exposed to 25 mg/m^3 crystalline silica. Pulmonary inflammation (measured as influx of neutrophils) was induced both in rats exposed to SAS and crystalline silica. At day 1, the inflammatory response was greater in rats exposed to 25 mg/m^3 SAS than in rats exposed to crystalline silica. However, after 1 and 3 months the neutrophil influx of SAS was almost reversed while the neutrophil influx in rats exposed to crystalline silica was increased. For all types of SAS the NOAEL was evaluated as 1 mg/m^3. "

Conversion of an inhalation rat NOAEL into a corrected inhalation NOAEL for the general public:

Corrected NOAEL $= NOAELRat * \frac{6\ h/day}{24\ h/day}$

$= 1\ mg/m^3 * \frac{6\ h/day}{24\ h/day}$

$= 0.25\ mg/m^3$

Assessment factors

AF1: For interspecies variation the default factor 2.5 is applied (local effects)
AF2: For intraspecies variation the default factor 10 is applied (local effects)
AF3: For extrapolation from sub-acute to chronic the default factor 6 is applied

DNEL

$DNEL_{Chronic} = \frac{NOAL\ corrected}{AF1*AF2*AF3} = \frac{0.25\ mg/m3}{2.5*10*6} = 0.0017\ mg/m^3$

Uncertainties

The study by Arts et al. investigates three types of SAS (Arts et al., 2007). No information on primary size is given but SAS is a nanostructured material consisting of nanosized primary particles, of nano- or micrometre-sized aggregates and of agglomerates in the micrometre-size range (Fruitier-Pölloth, 2012). The agglomerate sizes of the SASs used in the study are stated to be 20-100 μm and the specific areas are stated to be 200-250 m^2/g. Regarding the assessment factor used for the extrapolation from sub-acute to chronic (AF3), it could be argued that a higher assessment factor should be considered because 5 days of exposure is closer to acute exposure than sub-acute exposure (28 days). However, due to lack of default values for acute exposure and because of the rather conservative approach, we have chosen not to do so.

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Appendix 1.3: Nano-Ag

The purpose of this hazard appendix on nano-Ag is to serve as a brief background input for the risk assessment of nano-Ag when used in food supplements, paints for spraying, nano-filtering, disinfectant pump and propellant sprays, textiles, and wound dressings. Therefore, oral, dermal, and inhalation exposures are relevant exposure routes for the chosen risk scenarios. The emphasis is put on studies underlying the assessment of DNEL values.

Silver has no known function in humans. Ionic silver has been used for centuries as an antimicrobial agent.

The daily human intake of silver (all types of silver) has been estimated to be 0.007-0.5 µg/kg/day (0.007-0.5 x 10^{-3} mg/kg bw/day as the sum from all sources of oral exposure. The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded that the toxicity of Ag, including nanoparticles of Ag, to humans is generally low (SCENIHR 2014). Further details on the toxicity can be found in the report "Hazard assessment of nanomaterials in consumer products" Chapter 6.6.

The hazard assessment is mainly based on recent reports on nano-Ag by Risks (SCENIHR, 2014) and the Danish EPA (2011). In addition, relevant publications from the open literature are included.

Nano-Ag dissolves in solution and gradually releases Ag^+ and there is substantial evidence suggesting that, in fact, it is the released Ag^+ ions that are responsible for toxicological effects after systemic absorption. When inhaled local effects in the lungs may be due to nano-Ag particles *per se*. Ag cannot be metabolized by endogenous enzymes.

No consistent information exists on the importance of form, shape, or surface chemistry for absorption and toxicity. However, endogenous binding to compounds with low solubility (e.g. chloride, selenide and sulfide), aggregation and especially agglomeration seems to reduce toxicity (SCENIHR, 2014).

In the available studies it is generally not clarified whether oral, inhalation, and dermal absorption and the following distribution occurred as nano-Ag, Ag ions, or a combination. If nano-Ag is absorbed, nanomaterial may continuously release Ag ions in the tissue and may therefore be more toxic than non-nano forms (Danish EPA, 2011).

Ag seems to be distributed to all of the organs investigated (Hadrup & Lam 2014). The main organs for distribution are spleen, liver, kidney, and sometimes the testes (SCENIHR 2014), whereas a lesser distribution is reported to other organs, including the brain and epidermis (Hadrup & Lam 2014; Danish EPA 2011). Ag-nanoparticles from 8 nm appear to be able to pass the placental barrier (Lee et al., 2012).

In order to describe the potential toxicity of nano-Ag it is considered relevant both to consider data on nano-Ag and conventional forms (metal, salts, colloids) of Ag.

It has to be noted that only the direct toxicity of nano-Ag in relation to human health is covered in this evaluation. Therefore, indirect impact on human health e.g. aspects concerning any potential for development of resistance to antibiotics in microorganisms are not covered.

Oral exposure

At present, *human* risk assessment of Ag is most often based on the human data showing development of argyria (bluish-grey discoloration of the skin) in humans WHO (2003). WHO (2003) considered argyria in humans as the most critical effect and, based on an oral NOAEL of 10g

Ag as a lifetime dose level, a daily oral NOAEL of 5 µg/kg/day (0.005 mg/kg bw/day) can be calculated (assuming a person on 70 kg lives 75 years).

Therefore, an oral DNEL is set to 0.005 mg Ag/kg/day for all species of Ag including nano-Ag. No further assessment factor to the NOAEL is applied as the NOAEL by WHO (2003) is a human NOAEL for the general population.

Uncertainties
Uncertainties pertain to this figure as human exposures leading to argyria are often badly and imprecisely reported.

Nevertheless, this figure for safe level of oral exposure is used by WHO (2003) for risk assessment of silver in drinking water and has also recently been used by EFSA (2011).

Dermal exposure

Local effects
Data do not indicate any local effects other than discoloration of the skin at the contact site, due to the precipitation of silver e.g. in connection with use in wound dressings. No irritation is expected which also is consistent with the use of nano-Ag in wound dressings i.e. on very susceptible skin areas. Also, SCENIHR (2014) found that the data on nano-Ag did not suggest any irritation or other local effects other than discoloration on the site of application (SCENIHR, 2014).

Therefore, we do not foresee local effects and thereby risks following dermal applications.

Systemic effects
Dermal absorption through damaged skin has been reported in humans treated with wound dressings containing nano-Ag. The primary adverse effect from several cases with severe wound burning and treatment of large body area was the development of argyria. Inaddition, cases on liver toxicity were observed; however, it may be difficult to attribute effects from e.g. the liver specifically to silver treatment in patients, as the patient most probably have been in treatment with other types of medicines (e.g. analgesics). Less than 0.1% of the topically applied dose of nano-Ag was estimated to be absorbed from the wound dressing during wound treatment (Moiemen et al., 2011; Danish EPA, 2011; Vlachou et al., 2007). The absorption through intact human skin - if any - is uncertain primarily due to strong binding of silver to cell surface structures (Walker and Parsons, 2014).

As starting point for the dermal DNEL, the oral DNEL as set by WHO (2003) may be used and differences in absorption rates (route-to-route extrapolation: oral versus dermal absorption) have to be considered in order to obtain a dermal DNEL:

DNEL, dermal = DNEL oral x oral abs. rate/dermal abs. rate

WHO (2003) referred to a maximum oral absorption by humans of 5% in connection to oral exposure to colloid silver, whereas studies assessing the dermal absorption from wound dressings indicate a maximum dermal absorption of 0.1% in damaged skin/wounds. Using these figures, a dermal DNEL value may be calculated by route-to-route extrapolation:

$DNEL_{dermal}$ = 0.005 mg Ag/kg/day x 0.05/0,0001 = 2.5 mg Ag/kg/day for all species of Ag including nano-Ag.

Uncertainties
Although the oral absorption may be below 5% (and therefore not a conservative choice of the absorption rate when calculating the dermal DNEL value), the use of 0.1% for dermal absorption is considered very conservative as this figure pertains to severely damaged skin and not intact skin

where absorption would be much lower. Therefore, overall, the dermal DNEL value is considered protective and conservative.

Inhalation exposure

A NOAEL of 1.4 x 10^6 particle/cm^3 (133 µg nano-Ag/m^3) with respect to lung inflammation has been found in a 13 weeks inhalation study in rats (exposed 5d/week for 6 h/day) using nano-Ag with an average particle diameter of 18-19 nm. However, in the same study a LOAEL of 0.6 x 10^6 particle/cm^3 (49 µg nano-Ag/m^3) was found for impaired lung function (Sung et al., 2008 & 2009; Christensen et al., 2010).

There is no consistent data describing the acute toxicity of nano-Ag, but decreases in lung function were also found after 21 days of exposure in the Sung *et al.* (2008) study.

DNEL (local effects), expressed in mass-based concentration

A LOAEL of 49 µg/m^3 (corresponding to 0.6 x 10^6 particle/cm^3) in relation to reduced lung function is used for our DNEL calculation.

In order to derive a chronic DNEL for consumers the following adjustments of the dose metric have to be made.
Dose level on a daily 24 hours basis:

LOAELadj = 0.049 mg Ag/m^3 x 6h/24h x 5/7 = 0.009 mg Ag/m^3

Assessment factors

AF(1): 2.5 (default assessment factor for inhalation. Interspecies extrapolation, REACH guidance R8)
AF (2):10 (default assessment factor for intraspecies variation, REACH guidance R8)
AF (3): 3 (assessment factor to consider a LOAEL instead of an NOAEL)
AF (4): 2 (duration extrapolation from 90 days to chronic exposure, REACH guidance R8)

DNEL = LOAEL/(AF(1) x AF(2) x AF(3) x …)
DNEL = 0.009 mg Ag/m^3/(2.5 x 10 x 3 x 2) = 0.00006 mg nano-Ag/m3 (0.06 µg nano-Ag/m^3)

DNEL (local effects), expressed in particle number concentration

In order to derive a chronic DNEL for consumers, the following adjustments of the dose metric have to be made.
Dose level on a daily 24 hour basis:

LOAELadj = 0.6 x 10^6 particles/cm^3 x 6h/24h x 5/7 = 1.1 x 10^5 particles/cm^3

Assessment factors

AF(1): 2.5 (default assessment factor for inhalation. Interspecies extrapolation, REACH guidance R8)
AF (2):10 (default assessment factor for intraspecies variation, REACH guidance R8)
AF (3): 3 (assessment factor to consider a LOAEL instead of an NOAEL)
AF (4): 2 (duration extrapolation from 90 days to chronic exposure, REACH guidance R8)

DNEL = LOAEL/(AF(1) x AF(2) x AF(3) x …)

DNEL = 1.1 x 10^5 particles/cm^3/(2.5 x 10 x 3 x 2) = 7.3 x 10^2 nano-Ag particles/cm^3

Uncertainties

The inhalational DNEL values (mass-based metric and particle number-based metric) for nano-Ag particles with a diameter of 18-19 nm have been calculated based on data from a study of high quality. However, the estimated DNEL may be considered rather conservative as the moderate (but significant) decrease in lung function (tidal volume) may be considered as a minor effect and was only found in male rats and not in both sexes.

Further, it should be noted that the DNEL value is expressed as an average 24-hour exposure level. Peak exposure during a day at higher concentration may not be in conflict with the average exposure value as long as the time weighted average exposure over a day does not exceed the average 24-hour exposure level.

Eyes

No consistent evidence is available indicating that nano-Ag is an eye irritant.

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Appendix 1.4: Nano-ZnO

The purpose of this hazard appendix on nano-ZnO is to serve as a brief background input for the risk assessment of sunscreen pump sprays containing nano-ZnO. Here, the most relevant exposure route is dermal exposure but oral and pulmonary exposure may also occur to a lesser extent. The emphasis is put on studies underlying the assessment of DNEL values. Further details on the toxicity can be found in the hazard Chapter 6.6.

The hazard assessment of nano-ZnO is primarily based on the SCCS opinion on ZnO (SCCS, 2012b) and two recent addenda related to this opinion (SCCS 2014b; SCCS 2014c), as these are considered highly relevant for the present purpose.

Nano-ZnO dissolves in biological fluids including artificial gastrointestinal fluid and lung fluid to form Zn^{2+} that seems to be distributed systematically to organs. Zinc absorption is slightly higher for the small particles compared to the larger ones, which could be due to a higher dissolution rate (The Danish Environmental Protection Agency 2013b). Zn cannot be metabolized by endogenous enzymes.

In order to describe the potential toxicity of nano-ZnO, both data on nano-ZnO and conventional forms (metal, salts, colloids) can be applied.

Oral exposure
Zinc is an essential trace element and part of human food at present and during evolution. Zinc is regarded to be of low oral toxicity to man. Furthermore, the amount of absorbed Zn on a daily basis is likely to be insignificant compared to the large amount of Zn already present in the body (SCCS 2012b).

In laboratory animals, toxic effects have been shown in liver of mice and pancreas of rats orally exposed to nano-ZnO. Generally, the oral toxicity is considered to be low in laboratory animals.

A number of studies have demonstrated that nano-ZnO releases Zn^{2+} in aqueous solution (SCCS, 2012b; Massalski, 1990) including artificial body fluids *in vitro* but the degree of solubilisation *in vivo* is not known. However, in order to describe the potential toxicity of nano-ZnO, data on both nano-ZnO and conventional forms (metal, salts and colloids) can be applied.

An oral NOAEL of 50 mg water soluble Zn/day corresponding to 0.83 mg Zn^{2+}/kg/day (for a 60 kg person) has been set from a 90-days study in humans exposed to an oral Zn-supplement (SCCS, 2012b). This value is reported in the EU Risk Assessment Report, 2004. The relevance and applicability of this NOAEL as an exact value can be questioned as the real no effect level may be considerably higher.

Although ZnO is only very slightly soluble in water at neutral pH values (up 47 mg/L for nano-ZnO), studies at low pH indicate a high degree of solubility (98.5% for ZnO particles even in bulk form) indicating that an oral DNEL for water soluble Zn may also apply to nano-Zn.

Assessment factors
As SCCS (2012b) does not address a further intraspecies factor in relation to the NOAEL of 0.83 mg Zn^{2+}/kg/day, this value is considered as a DNEL value as well.

However, this dose may be converted from Zn^{2+} to nano-ZnO by multiplying 0.83 mg Zn^{2+}/kg/day by a factor of 1.24, representing the ratio of the molecular weights for Zn and ZnO (81.4/65.4). Thus the DNAL value can be set to:

DNEL,oral: 1.0 mg nano-ZnO/kg/d

Uncertainties:
Even though nano-ZnO is only slightly soluble in water, the high solubility in acidic media (e.g. the stomach) justifies the use of an oral DNEL value on humans based on exposure to a water soluble Zn-species.

Dermal exposure

Local effects

Local dermal effects are not considered of concern by SCCS (2012b). With regard to local irritation, SCCS (2012b) referred to a skin irritation study performed in which guinea pigs were dosed with 20 nm nano-ZnO. In one of three animals dosed with 40% ZnO, slight erythema was observed on day 3 of administration; no effects were seen in applying 25% ZnO.

The lack of irritating potential is consistent with the use of ZnO in cosmetic preparations in the treatment of irritated skin e.g. nappy areas of infants.

Thus, local effects and thereby risks following dermal applications are not foreseen.

Systemic effects

The SCCS opinion concludes the following on dermal absorption: "From the available information, there is no indication for penetration of ZnO nanoparticles through the skin. In one study it was shown that Zn from ZnO nanoparticles in a tested sunscreen formulation made a minor contribution to the blood Zn pool of human volunteers. This shows that some Zn was absorbed from the sunscreen, although it was not known whether this was absorbed in nanoparticulate form or as solubilized Zn ions. Considering the dissolution of ZnO, it is most likely that the zinc was absorbed in ionic form. The overall weight of evidence therefore suggests that a very small proportion of Zn ions released from the ZnO nanoparticles may be available for systemic exposure when applied dermally." (SCCS 2012b).

As a starting point, SCCS (2012b) used the oral NOAEL value and considered the different absorption rates from oral and dermal exposure, when making risk assessment of the dermal exposure. When assessing nano-ZnO in sunscreen, an oral absorption factor of 20% was used in relation to the oral NOAEL and a dermal absorption of 0.03% in relation to nano-ZnO in the sunscreen.

Thus, for our project a DNEL value can be calculated by route- to-route extrapolation using these specific absorption factors:

DNEL, dermal (systemic effects) = DNEL oral systemic x oral abs. rate/dermal abs. rate

DNEL, dermal (systemic effects) = 1.0 mg nano-ZnO/kg/day x 0.2/0.0003 =667 mg nano-ZnO/kg/day

Uncertainties

The high dermal DNEL value seems to be consistent with the very low dermal absorption of nano-Zn and a rather low oral toxicity of Zn^{2+}. So, although the exact oral NOAEL has not been determined precisely (this was done using only one dose level in the study) the DNEL value calculated for dermal exposure is considered reliable to use for further risk assessment.

Inhalation exposure

A DNEL value of 2.5 mg ZnO/m^3 has been set for the general population in the REACH registration for ZnO (non-nano form) (European Chemicals Agency (ECHA) 2014). In Denmark an occupational exposure limit value of 4 mg ZnO/m^3 has been set (Danish Working Environment Authority, 2011).

SCCS concludes that *"Upon inhalation of ZnO nanoparticles, serious local effects in the lung were observed. Even if this may be due to the solubilized Zn ions, the effects are a direct result of the exposure to the ZnO nanoparticles."* (SCCS 2012b & 2014c)

The key study in relation to inhalation of nano-ZnO is a recent repeated-dose 90 days inhalation study in rats. Rats were nose-only exposed for 0, 0.3, 1.5 or 4.5 mg/m^3 6 hours/day, 5 days/week. The particle size was not specified. No persistent toxicity was found. Transient (recovered within the 28 day recovery period) local effects on the respiratory tract were only observed in the highest dose group. The authors concluded a NOAEL of 1.5 mg/m^3 based on observations in BAL and lung histopathology but in contrast the SCCS concluded a NOAEL of 0.3 mg/m^3 based on activation of lung macrophages and lung draining lymph nodes (SCCS 2014b).

Thus, a NOAEL of 0.3 mg nano-ZnO/m^3 is used for DNEL derivation for consumers.

In order to derive a chronic DNEL for consumers, the following adjustments of the dose metric have to be made.

Dose level on a daily 24 hour basis:

NOAELadj = 0.3 mg ZnO/m^3 x 6h/24h x 5d/7d= 0.054 mg/m^3

Assessment factors
AF(1): 2.5 (default assessment factor for inh. Interspecies extrapolation, REACH guidance R8)
AF (2):10 (default assessment factor for intraspecies variation, REACH guidance R8)
AF (3): 2 (duration extrapolation from 90 day to chronic exposure, REACH guidance R8)

DNEL = NOAEL/(AF(1) x AF (2) x AF (3) x …)
DNEL = 0.054 mg nano-ZnO/m^3/(2.5 x 10 x 2) = 0.0011 mg nano-ZnO/m^3

Uncertainties
The basis for the NOAEL value is an experimental animal study of high quality. However, it should be noted that the DNEL value is estimated for chronic 24-hour exposure and therefore applies to the total daily dose rather than a specific exposure concentration. Peak exposure during a day reaching higher concentration levels may therefore not be in conflict with 24-hour exposure value as long as the time weighted average exposure of the peaks over a day do not exceed the average 24-hour exposure level.

Eyes
No relevant study was identified to assess whether nano-ZnO is an eye irritant. From the REACH-registration of ZnO in bulk form, no irritation was observed in an OECD test for eye irritation.

References
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Appendix 1.5: Carbon Black (CB)

The hazard assessment of CB in a matrix is primarily based on the recent Scientific Committee on Consumer Safety (SCCS) opinion on CB (SCCS, 2014d). The aim of this SCCS opinion on CB was specifically to decide if CB is safe for use as a colorant with a concentration of up to 10% in cosmetic products, and is therefore considered highly relevant for the present purpose, namely to serve as an input for the hazard part of the risk assessment of CB in mascara. The focus in the present assessment was on hazard related to skin and eye exposure because these routes of exposure are considered to be the most relevant in relation to consumer use of mascara. Three studies on skin absorption of cosmetic formulations containing CB (all 20-30 nm in size) were evaluated by SCCS and did not indicate any skin absorption. As emphasized by SCCS, the conclusion as to no risk of adverse effects of up to 10% as CB as a colorant in cosmetic products is only valid when the skin is intact and the CB particles are 20 nm or larger. No studies on eye absorption of CB were evaluated by SCCS. Therefore, hazard associated with eye absorption cannot be evaluated even though it is highly relevant for the hazard assessment of consumer use of mascara containing CB. The risk of eye irritation from CB cannot be excluded (SCCS, 2014d). We agree with the final concluding remarks of the SCCS opinion stressing that the skin absorption studies have only been done for CB sizes above 20 nm and that it is therefore not possible to conclude about cosmetic products containing smaller sized CB.

Dermal exposure

Local

Application of CB on intact and abraded skin of rabbits under occlusion for up to 24 hours did not result in any cutaneous signs of oedema or erythema. The testing of up to 10% CB in sunflower oil also did not result in any irritation when tested on an *in vitro* model of reconstructed human epidermis (SCCS, 2014d). SCCS concludes that no carcinogenicity was observed following dermal exposure to CB (SCCS, 2014d).

Systemic

SCCS concludes that: "*…the available data show that there is no indication of CB particles (>20 nm) being absorbed through the intact skin*" (SCCS, 2014d). Not relevant to derive a DNEL due to lack of dermal absorption.

Uncertainties

As emphasized by SCCS, the conclusion as to no risk of adverse effects of up to 10% as CB as a colorant in cosmetic products is only valid when the skin is intact and the CB particles are 20 nm or larger.

SSCS notes that the available studies on skin absorption have several shortcomings, e.g. : 1) TEM imaging was not considered to be sufficiently quantitative, 2) The smallest particles tested were 20 nm and therefore the available data do not give any information regarding possible uptake of particles smaller than 20 nm, and 3) The CB samples are not characterized regarding purity and the amounts of aggregates in the formulation before and after exposure (SCCS, 2014d).

Eyes

SCCS did not report any studies on absorption of CB into the eyes (SCCS, 2014d).

SCCS refers a study on eye irritation: "*The acute ocular irritation potential of undiluted CB (furnace blacks Printex G: Degussa AG, 1977d; Spezialschwarz 4: Degussa AG, 1977e; Printex-140: Degussa AG, 1978c) was evaluated following a single instillation to rabbit eyes. No irritant effects were found in any of the animals at any observation time. The study authors concluded "that under the conditions used in those studies, CB was considered to be non-irritating to rabbit eyes*""(SCCS, 2014d).

Not possible to derive a DNEL for eye exposure.

Uncertainties

There are no studies on eye absorption and too few studies on eye exposure to draw general conclusions on local eye effects.

References

SCCS (2014d). Opinion on Carbon Black (nano form). SCCS/1515/13. 2014. European Union; Scientific Committee on Consumer Safety.

Appendix 1.6: Nano-ZrO_2

The purpose of this hazard appendix on nano-sized zirconium dioxide is to serve as background documentation for the risk assessment of ZrO_2 when used in dental fillings (implants). This particular use involves exposures of the consumer related to the application process (with spatula), to sanding and polishing, and to contact with the material migrating from the dental filling to the oral mucosa and saliva. The focus will be on the hazards associated with exposure by the inhalation route and exposure by the gastrointestinal route. In addition, exposure to the eye will be briefly addressed.

There is limited information available about the nano form of the substance and the hazard evaluation is therefore based on industry information submitted with the REACH registration available at the ECHA dissemination website (for the macro/bulk form) where no other information is available.

No ADME data are available for the nano form. Information from the ECHA dissemination tool suggests worst case absorption factors of 10% for all exposure routes.

Zirconium dioxide is generally described as a substance of low toxicity. There are, however, very few *in vivo* studies available investigating the toxicity of ZrO_2, particularly regarding the nano form. ZrO_2 has extremely low solubility in water and absorption is expected to be low from all exposure routes. When deposited in the alveolar region, particles are expected to be engulfed by alveolar macrophages with only a small amount ending up in the blood via the lymphatic system. No specific adverse effects have been identified for the substance in the more recent literature. In cytotoxicity studies the nano-ZrO_2 particles were less toxic than the micro-particles but more bioactive. In older literature, immunostimulating effects of ZrO_2 are reported following injections in the thorax cavity and the peritoneum of mice. In addition, an ability to cause axillary granulomas when applied in deodorants is described. The application in deodorants was ceased due to this effect.

The OEL (8-hour average) for macro Zirconium compounds (calculated as Zr) is 5 mg/m^3 in Denmark (Danish Working Environment Authority, 2011). OSHA in the US has applied the same value. No DNEL value is suggested in the ECHA dissemination tool for the non-nano form.

Oral exposure

No data on oral toxicity or systemic effects are available. No reports on zirconium poisoning in humans are reported (Inchem, 1998). With regard to the relevant consumer scenario and establishing a DNEL, acute toxicity is likely to be most relevant. Acute toxicity is considered low. Solubility of the nano form is reported in the range of 4-190 ppm.

All in all, ZrO_2 is considered low/not toxic following oral exposure.

Uncertainties

No data available for the nano form of ZrO_2.

Dermal exposure

Local effects

No irritation or other local dermal effects are identified for the nano form of the substance or in the ECHA dissemination tool for the non-nano form. Earlier reports suggest possible development of local granulomatosis following dermal application of Zr4+ in sensitized individuals. No information on elicitation levels is identified. Given the low solubility of ZrO_2, we consider no/low risk for local effects following dermal exposure.

Systemic effects
No data are available regarding dermal absorption of (nano-)ZrO_2; however, no systemic toxicity has been reported for the substance from any exposure route. In addition, considering the generally low absorption rate following dermal exposure to other no/low soluble nanomaterials, systemic toxicity following dermal exposure is considered unlikely.

Uncertainties
No data available for the nano form of ZrO_2.

Inhalation
No inhalation toxicity data are available for the nano form of the substance; information is therefore based on data for the non-nano form. No treatment related effects were observed in rats exposed head-nose to ZrO_2 dust aerosols for five days, six hours per day at a concentration up to 10 mg/m³. A NOAEC of 10 mg/m³ was established based on this study. Another report on humans exposed to ZrO_2 showed that even under long-term exposure conditions of up to 20 years and peak concentrations up to 30 mg/m³, zirconium exposure elicited neither abnormal chest radiographs, for example granuloma formation, nor did it impair lung function parameters such as Forced Expiratory Volume (FEV1)/Forced Vital Capacity (FVC) (Klein et al., 2012). Another report from 1981 states that 32 manual finishers of zirconium metal were exposed to 5.75–14.7 mg/m³ of dust (25% zirconium) without any effect on lung health. No systemic toxicity is reported.

It is therefore suggested to use the Danish OEL (8-hour average) for Zirconium compounds (calculated as Zr) of 5 mg/m³ (corresponding to 6.75 mg/m³ macro ZrO_2) as the starting point for the DNEL calculation.

Using this OEL and adjusting for 24 hour respiratory volume for consumers (20 m³ air/day) and worker exposure during a day of work (10 m³ air/day) an adjusted OEL can be calculated:

$$OEL_{adj}: 6.75 \text{ mg macro } ZrO_2/m^3 \times 10\ m^3/20\ m^3 \times 5d/7d = 2.4 \text{ mg macro } ZrO_2/m^3$$

Assessment factors are introduced to account for the uncertainty related to the effects of the nano form of ZrO_2, the difference between the intraspecies assessment factors for workers and the general population, and the general quality of the database.

Assessment factors
AF1: 10 (estimated extrapolation from macro to nano; Appendix on nanomaterials to REACH Guidance R8)
AF2: 2 (difference between the intraspecies assessment factors for workers (5) and the gen. population (10); REACH Guidance R8)
AF3: 5 (quality of database in general, considering that human data are available for the macro-form; REACH Guidance R8)

$$DNEL = OEL_{adj}/AF1 \times AF2 \times AF3$$
$$\mathbf{DNEL_{inh} = 1.6\ mg\ ZrO_2/m^3/(10 \times 2 \times 5) = 0.016\ mg\ ZrO_2/m^3\ (16.0\ \mu g\ ZrO_2/m^3)}$$

Uncertainties
The DNEL is based on data for macro ZrO_2 due to lack of data for the nano form. OEL for Zirconium compounds used to derive DNEL. This OEL is similar to the OSHA OEL. Available reference to this OEL primarily refers to pulmonary effects observed with other zirconium compounds like silicates, although some indication of zirconium-compound-induced pulmonary fibrosis exists (see e.g. CDC, 1978). Assessment factors are therefore introduced to account for the uncertainty regarding the effects of the nano form and limitations in the database for both nano and macro ZrO_2.

Eyes

No relevant studies are identified on irritating effects on the eyes, although industry-suggested classifications could indicate such an effect. Possible eye irritation will therefore be discussed qualitatively in the risk assessment.

Uncertainties

No data available for the nano form of ZrO_2.

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Appendix 1.7: Carbon nanotubes (CNT)

The hazard assessment of CNT will serve as background documentation for the risk assessment of use (wear and tear) and sanding of a golf club containing CNT. With regard to the intended use of a golf club, dermal exposure is considered to be the only relevant exposure route. No studies were identified on the dermal toxicity of CNT incorporated into a solid matrix. If the CNT containing golf club is sanded, sanding dust containing CNT and potentially free CNT may be liberated and exert toxicity primarily by the pulmonary and dermal routes. The hazard assessment of free CNT is based on a recently published report on risk assessment of CNT by the Danish EPA (Danish EPA, 2015e) . Animal studies have shown that pulmonary exposure to some specific types of CNT consistently give asbestos-like toxicological responses characterised by persistent inflammation, granulomas and fibrosis with low no-effect levels. Chronic human indicative no-effect levels (INELs) have been suggested to be 0.00025 mg CNT/m^3 (0.25 µg/m^3) (inhalation) for the general public and 0.78 mg/person (dermal) for workers (Aschberger et al., 2010). Two studies were identified on the toxicity of sanding dusts from different types of CNT composites (Wohlleben et al., 2011; Wohlleben et al., 2013). None of the studies showed increased toxicity of sanding dust from the CNT materials compared to the conventional products without CNT. However, it has not yet been tested if sanding dust from UV-exposed or otherwise weathered materials have a different toxicity profile due to a potentially increased liberation of free CNT.

Oral exposure

Regarding oral uptake of CNT the Danish EPA report concludes: "*For assessment of oral uptake, there is very little literature, but no ingested CNT has been detected beyond the GI tract. Thus, there is no evidence to suggest that CNT are taken up from the GI tract*"(Danish EPA, 2015e).

Dermal exposure

The calculations are made as described by Aschberger et al. (2010). However, regarding the assessment accounting for intraspecies differences, we have used the factor 10 for the general population instead of 5 which applies for workers.

Local effects

Based on a dermal exposure study, a NOAEL for inflammation of 0.04 mg CNT (40 µg) of free CNT/mouse and a LOAEL of 0.08 mg CNT (80 µg) free CNT/mouse for 5 days was identified (Murray et al. 2009 as cited by Aschberger et al., 2010). The study was not a guideline study but was used by Aschberger et al. due to the lack of better studies. This limitation was accounted for by applying an extra assessment factor.

The NOAEL of 0.04 mg CNT/mouse (40 µg/mouse) is converted to 2.5 mg/kg bw for a 16 g mouse. It would have been relevant to calculate the exposure as the dermal load (mg/cm^2). However, this is not possible because the surface area is not reported.

Acute and chronic DNEL

Assessment factors:
AF1: For interspecies variation the default factor 2.5 is applied (local effects)
AF2: For intraspecies variation the default factor 10 is applied (general population)
AF3: Additional assessment factor for a limited database: 3
AF4: For extrapolation from sub-chronic to chronic the default factor 6 is applied (only for the chronic DNEL)

DNEL

$DNEL_{Acute} = \frac{LOAEL}{AF1*AF2*AF3} = \frac{2.5\frac{mg}{kg\ bw}}{2.5*10*3}$=0.033 mg/kg bw =0.033 mg/kg bw *70 kg = 2.3 mg CNT/person

$DNEL_{Chronic} = \frac{LOAEL}{AF1*AF2*AF3*AF4} = \frac{2.5\frac{mg}{kg\ bw}}{2.5*10*3*6}$=0.0056 mg/kg bw =0.0056 mg/kg bw *70 kg = 0.4 mg CNT/person

Systemic effects

We did not identify any studies on dermal absorption of CNTs. In general, the uptake of insoluble nanomaterials is negligible and the same is expected to be true for CNT and will, thus, be assumed in the risk assessment in this project.

Uncertainties

DNELs were derived for a study of unpurified CNTs with a high content of metals which is suspected to contribute significantly to the observed toxicity. Other types of CNTs with a higher degree of purity might be less toxic. More studies are needed to get information on local and systemic effects of dermal exposure to CNTs. It should be stressed that the DNELs are derived for free CNTs and not for CNTs as part of a matrix. The toxicity of dusts obtained by sanding other matrices (cement and thermoplastic) containing CNTs was not increased compared to sanding dusts from the conventional product without CNTs following pulmonary exposure in rats (Wohlleben et al., 2011).

We did not identify any studies on dermal absorption of CNTs and the expert assumption about negligible uptake is therefore not backed by CNT data.

Inhalation

Based on the OECD guideline subchronic (90 days) inhalation studies, a NOAEL (Pauluhn, 2010) and a Lowest Observed Adverse Effect Level (LOAEL) (Ma-Hock et al., 2009) of 0.1 mg/m³ MWCNT were identified for pulmonary inflammation. Based on these studies, Aschberger et al. propose 0.00025 mg CNT/m³ (0.25 µg/m³) as a chronic human INEL for inhalation in the general public, using overall assessment factors of 100 (the calculations are inserted below and further details are specified in (Aschberger et al. (2010).

Conversion of an inhalation rat LOAEL into a corrected inhalation LOAEL for the general public[6]:

Corrected LOAEL = $LOAELRat * \frac{6\ h/day}{24\ h/day}$

= 0.1 mg/m³ * $\frac{6\ h/day}{24\ h/day}$

= 0.025 mg CNT/m³

Assessment factors

AF1: For the extrapolation from LOAEL to NOAEL the default factor Aschberger et al. suggest to apply 2.

AF2: For interspecies variation the default factor 2.5 is applied (local effects)

AF3: For intraspecies variation the default factor 10 is applied (local effects)

AF4: For extrapolation from sub-chronic to chronic the default factor 2 is applied

AF5:

DNEL

$DNEL_{Chronic} = \frac{LOAL\ corrected}{AF1*AF2*AF3*AF4} = \frac{0.025\ mg/m3}{2*2.5*10*2}$=0.00025 mg CNT/m³ (0.25 µg/m³)

Uncertainties

Aschberger et al. use the term INELs instead of DNELs because the authors do not want to give the impression that these values could be used for regulatory risk assessment: The INELs were derived from studies on certain types of CNT and the evaluated endpoints were inflammation and non-

long-term effects such as carcinogenicity (Aschberger et al., 2010). Furthermore, Aschberger et al. conclude: “For the general public, only the higher assessment factor and the resulting lower INEL from the LOAEC of 0.1 mg/m^3 is suggested as environmental exposure is expected not be restricted to one CNT type and therefore the more conservative approach is applied”(Aschberger et al., 2010). It should be stressed that the DNELs are derived for free CNTs and not for CNTs as part of a matrix. Regarding the conversion of the rat NOAEL to a NOAEL for the general public, we could have adjusted for a 5 week exposure study by multiplying by 5 days/7 days. However, we chose not to do so in order to follow the same approach as Aschberger et al. (2010). As noted by Aschberger et al., one study determined a NOAEC of 0.1 mg/m^3, which was a LOAEC in the other study. Therefore, we follow the suggestion by Aschberger et al. regarding using a reduced assessment factor of 2 (instead of default 3) for deriving a NOAC from the LOAEC (Aschberger et al., 2010).
The toxicity of dusts obtained by sanding other matrices (cement and thermoplastic) containing CNTs was not increased compared to sanding dusts from the conventional product without CNTs following pulmonary exposure in rats (Wohlleben et al., 2011).

Eye

Not relevant for the chosen scenario.

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Consumer Risk assessment for nanoproducts on the Danish market
Under the Agreement "Better Control of Nanomaterials" (“Bedre styr på nanomaterialer”), the Danish EPA has commissioned a number of projects aiming to investigate and generate new knowledge on the presence of nanomaterials in products on the Danish market and assess the possible associated risks to consumers and the environment.

This report is the final report from a project, which addresses consumer exposure and risk assessment of nanomaterials in products on the Danish market.

Risikovurdering af forbrugerprodukter med nanomaterialer på det danske marked
Under overskriften "Bedre styr på nanomaterialer" har den danske Miljøstyrelse iværksat en række projekter, der sigter på at undersøge og generere ny viden om forekomsten af nanomaterialer i produkter på det danske marked og vurdere potentielle risici for forbrugerne og miljøet.

Denne rapport er den afsluttende rapport for projektet, som omhandler forbrugereksponering og risikovurdering af nanomaterialer i produkter på det danske marked.

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