Office for Product Safety & Standards

The Use of Metal and Non-metal Nanomaterials in Consumer Products and Associated Safety Issues

Final Report

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Abstract

Nanomaterials are being used in an increasing number of different products on both the global and UK markets, including consumer products, which is increasing the chances of consumers being exposed to nanomaterials. Nanomaterials are a wide class of materials that can be defined as having at least one external dimension within the range of 1-100 nanometres (nm). This report looks at consumer products that contain nanomaterials in the areas of cosmetics, toys, textiles (furniture and nightwear), and Personal Protection Equipment (PPE). Specifically, the research questions being addressed are as follows:

1. What is the prevalence of metal and non-metal nanomaterials in consumer products on the UK market?
2. What are the potential physical and chemical safety issues relating to the use of metal and non-metal nanomaterials in consumer products on/to be placed on the UK market and the associated risks?
3. What are manufacturers' responsibilities and relied upon industrial standards when characterising and performing toxicological assessment of metal and non-metal nanomaterials for use in consumer products on the UK market?

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Acronyms

The following acronyms are used in the report. Acronyms are defined on first use in each chapter and then the acronym is used.

Acronym	Meaning
AAS	Atomic absorption spectrometry
AOP(s)	Adverse Outcome Pathway(s)
ASTM	American Society for Testing and Materials
AWI	Approved Work Item (see also ISO)
BALF	Broncho alveolar lavage fluid
BBP	Benzyl butyl phthalate
BET	Brunauer-Emmett-Teller
BS	British Standard
BSI	British Standards Institute
CA Regulations	The Control of Asbestos Regulations 2012
CAS (number)	Chemical Abstract Service (number)
CB	Carbon black
Cd	Cadmium
CE (marking)	European Conformity (marking)
CEMFAW Regulations	The Control of Electromagnetic Fields at Work Regulations 2016
CEN	European Committee for Standardization
CEN/TC	CEN Technical Committee
CLAW Regulations	The Control of Lead at Work Regulations 2002
CLP Regulation	Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures
CLP Regulation (GB)	Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, as it has effect in Great Britain
CNT(s)	Carbon nanotube(s)
COSHH Regulations	The Control of Substances Hazardous to Health Regulations 2002

	Regulation (EC) No 1223/2009 on cosmetic products
Cosmetics Regulation	
Cosmetics Regulation (GB)	Regulation (EC) No 1223/2009 on cosmetic products, as it has effect in Great Britain
CPI	Nanotechnology Consumer Product Index
CP Regulations	The Cosmetic Products Enforcement Regulations 2013
Cr VI	Hexavalent chromium
Cu	Copper
DBP	Dibutyl phthalate
DEHP	Bis(2-ethylhexyl) phthalate
DIBP	Diisobutyl phthalate
DLS	Dynamic Light Scattering
DMA	Dynamic Mechanical Analyser
DNA	Deoxyribonucleic acid
DSEA Regulations	Dangerous Substances and Explosive Atmospheres Regulations 2002
DTR	Draft Technical Report (see also *ISO*)
DTS	Draft Technical Specification (see also *ISO*)
DTU	Technical University of Denmark
EC	European Commission
ECHA	European Chemicals Agency
EEE	Electrical and electronic equipment
EFSA	European Food Safety Authority
EPA	See *USEPA*
ES	Exposure Scenarios
EU	European Union
EUON	European Observatory for Nanomaterials
EUWA	European Union (Withdrawal) Act 2018
FFF	Field-flow fractionation
GC/LC-MS	Liquid chromatography–tandem mass spectrometry
GE	Gel Electrophoresis

GLP	Good Laboratory Practice(s)
GPS Regulations	General Product Safety Regulations 2005
HDC	Hydrodynamic chromatography
HPLC	High-performance liquid chromatography
Hg	Mercury
ICP-MS	Inductively coupled plasma mass spectrometry
IgM	Immunoglobulin M (antibodies)
INCI	International Nomenclature Cosmetic Ingredient
IR Regulations	Ionising Radiations Regulations 2017
ISO	International Organization for Standardization
ISO/TS	ISO Technical Standard
JRC	Joint Research Centre
LDE	Laser Doppler electrophoresis
LMP	Lysosomal membrane permeabilisation
MAD	Mutual Acceptance of Data
mg/kg bw/d	mg per kg body weight
MoS	Margin of Safety
MS	Mass Spectrometry
MS	(EU) Member State
MSExcel®	Microsoft Excel®
NanoSIMS	Nanoscale Secondary Ion Mass Spectrometry
NIP	Northern Ireland Protocol
Nm	Nanometre
NM(s)	Nanomaterial(s)
NMR	Nuclear Magnetic Resonance
NOAA	Nano-objects and their aggregates and agglomerates
NP (exposure)	Nanoparticle (exposure)
NSC	NanoSafety Cluster
NTP	National Toxicology Program

OECD	Organisation for Economic Co-operation and Development
OECD GD(s)	OECD Guidance Document(s)
OECD TG(s)	OECD Test Guideline(s)
OPSS	Office of Product Safety and Standards
Pb	Lead
PBB	Polybrominated biphenyls
PBT	Persistent, Bioaccumulative and Toxic
PBDE	Polybrominated diphenyl ethers
PEN	Project on Emerging Nanotechnology
pH	See the *Glossary of common terms*
PK	Pharmacokinetics
PNA/NTA	Particle Tracking Analysis/Nanoparticle Tracking Analysis
PPE	Personal Protective Equipment
PPE Regulation	Personal Protective Equipment Regulation (EU) 2016/425
PPE Regulation (GB)	Personal Protective Equipment Regulation (EU) 2016/425, as it applies in Great Britain
prCEN/TS	Proposed CEN Technical Specification
PWI	Preliminary Work Item
R&D	Research and Development
REACH Regulation	The Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation (EC) No 1907/2006
REACH Regulation (GB)	The Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation (EC) No 1907/2006, as it has effect in Great Britain
RIVM	National Institute for Public Health and the Environment (The Netherlands)
RoHS	The Restriction of the Use of Certain Hazardous Substances in Electrical and Electronic Equipment Regulations 2012
RS	Raman Spectroscopy (see also *SERS*)
SCCS	Scientific Committee on Consumer Safety
SEM	Scanning electron microscopy
SERS	Surface Enhanced Raman Spectroscopy (see also *RS*)

SI(s)	Statutory Instrument(s)
SiO_2	Silicon dioxide
SPM	Scanning Probe Microscopy
SVHC	Substances of Very High Concern
t/y	Ton per year
TC	Technical Committee (see also *CEN/TC*)
TEM	Transmission electron microscopy
TiO_2	Titanium dioxide
TK	Toxicokinetics
TS	Technical Specification
UK	United Kingdom
UKCA (marking)	UK Conformity Assessed (marking)
USEPA	United States Environmental Protection Agency
UV(A), UV(B)	Ultra-violet (of type A), (of type B)
UV vis	Ultraviolet–visible spectroscopy
VSSA	Volume specific surface area
WD	Working Draft (see also *ISO*)
WEEE Regulations	The Waste Electrical and Electronic Equipment Regulations 2013
WI	Work Item
WNT	Working Group of National Co-ordinators of the OECD Test Guidelines programme
WOS	Web of Science
WPMN	Working Party on Manufactured Nanomaterials
XPS	X-Ray Photoelectron Spectroscopy
XRD	X-ray crystallography
Zn2+	Zinc ion
ZnO	Zinc oxide
µm	Micrometre

Glossary of common terms

The glossary below provides short descriptions of some commonly used scientific terms that are used throughout the report.

Term	Definition
Active ingredient	The part of a substance or compound that produces its chemical or biological effect
Agglomerate	A group of large particles joined or bound together, and whose original identity can still be visible in the final agglomerate form
Aggregate	A group of atoms or molecules that are held together by strong chemical bonds
Atomic Force Microscopy (AFM)	AFM is a high-resolution microscope that uses a probe to touch or feel a surface to gather information; its resolution can be in the order of fractions of a nanometre
Benthic	Pertaining to or occurring at the bottom of a body of water, especially referring to the ocean depths
Biopersistent	Which tends to remain inside a biological organism rather than being expelled or broken down
Boolean	A logical combinatorial system that represents symbolic relationships between entities
Bulk form	The form of a particle whose size is above 100 nm in all its dimensions
Carcinogen category 2	A substance which should be regarded as suspectedly carcinogenic to humans
Chemical property	A characteristic or behaviour of a substance that may be observed when it undergoes a chemical change or reaction
Complex matrices	See *Matrix*
Downstream user	The user of chemicals who uses a substance, either on its own or in a mixture, in industrial or professional activities
Endpoint	The conclusion of a chemical reaction or an adverse effect of a contaminant on a biological system
Exposure	The amount of, and the frequency with which, a chemical substance makes contact with an organism or environment (See also *Hazard*, *Risk*)

Exposure concentration	The amount of a substance making contact with the outer boundary of an organism or the concentration of a contaminant in the medium in which an organism is exposed to
Formulation	A mixture of chemicals that do not chemically react but have desirable properties as a mixture
Grey literature	Research produced by organisations outside the traditional commercial or academic publishing and distribution channels
Hazard	The inherent properties of a chemical substance that make it capable of causing harm to people or the environment (see also *Exposure*, *Risk*)
Impurities	The chemical substances inside a confined amount of material or compound which differ from the intended chemical composition of that material or compound
Insoluble	The properties of a chemical or material which indicate it cannot be dissolved in a defined solvent and physical conditions (typically water in environmental risk assessment.
Intentionally manufactured	The property of a material which indicates it is produced in the nano size range in order to achieve unique or novel size-related properties
Ionic form	The form of a particle which has gained or lost electrons, becoming electrically charged
Matrix	The component of a chemical sample other than the substance of interest for the purpose of analysis
Medium	See *Vehicle*
Mesocosm (study)	Any experimental system more complex than standardised test systems that examines the natural environment under controlled conditions
Nano-enabled	A product or material whose action or functioning depends on the properties of the nano element
Number size distribution	When looking at a group of particles, the proportion of particles counted of each size
One-generation reproductive toxicity	In an animal study, adverse effects of the substance investigated found in the animals tested, with no effects investigated or found in their offspring
Particle	A small localised object to which physical or chemical properties can be ascribed
pH	Historically “potential of hydrogen”, the scale used to measure the acidity or basicity of an aqueous solution

Phys-chem properties	See *Physical property*, *Chemical property*
Physical property	A characteristic of matter that can be observed and measured without changing the chemical identity of the sample
Purity	The measurement of the amount of intended constituents found in a sample (see also *Impurities*)
Pyrophorous	A substance that ignites spontaneously on exposure to air
Read-across	The approach where information on the physicochemical properties, toxicity, environmental fate and ecotoxicity of a chemical is used to predict the same properties for another, similar chemical
Reasonably foreseeable use	The conditions of use of a product that can be anticipated as likely to occur because of its function and physical form
Risk	The possibility of harm arising from a particular exposure to a chemical substance under specific conditions (See also *Exposure*, *Hazard*)
Safety profile	A compilation of the properties and potential effects of a chemical substance
Solvent	A substance that allows (an)other chemical(s) to dissolve and combine in a solution
Solute	A substance that can be dissolved in a solution
Solution	A mixture of solvent and solute
Surface area	The total area that the surface of a solid object occupies
Surface charge	A two-dimensional surface with non-zero electric charge
Vehicle	A substance used to facilitate the administration of another substance
Wide-dispersive use	The widespread use of a chemical substance by individual consumers and industrial users, resulting in its direct release into the environment

1. Introduction to nanomaterials in consumer products

This introduction presents a general overview of nanomaterials and introduces the research that has been undertaken. Specifically, this section will provide some background information around why nanomaterials are used in consumer products, a short presentation of the science behind nanomaterials, and detail regarding the research questions to be answered in this study. The reader will also be pointed to further sources that can be used to find out more about nanomaterials and their use in products. The following chapter will introduce the study and provide background to the research.

1.1 Nanotechnology

Nanotechnology is the understanding and control of matter at the nanometre scale (1-100 nanometres or nm). A nanometre in the International System of Units (Système international d'unités or SI) is one billionth of a metre, or 10^{-9} metres.[1] Internationally, there is no single agreed definition of a nanomaterial, but it is usually accepted that they are materials with at least one dimension in the range of 1-100 nm (Jeevanandam *et al*., 2018,19). The materials that are of interest to most scientists and companies are, however, not just small. Rather, they are manufactured for their functional properties conferred to them by their size. Nanomaterials can have enhanced properties that are very different from the properties of the same chemical composition at a larger scale, often referred to as the bulk material. Such properties have been explored in Table 1.

Table 1. Examples of enhanced properties of nanomaterials.

Enhanced properties	**Example**	**Example nanomaterial used in products**
Mechanical	Increased strength	Carbon nanotubes (CNT) used in tennis rackets (Jensen *et al*., 2015)
Chemical	Increased reactivity	Platinum nanoparticles used as a catalyst in fuel cells (Stephen *et al*., 2019)
Optical	Changing colour	Quantum dots used to enhance LED TV screens (Bang *et al*., 2021)
Electrical	Enhanced conductivity	Silver nanowires used in inks for printable electronics (Wu *et al*., 2020)
Thermal	Reduced melting point	Copper nanowires (Barako *et al*., 2018)

[1] See https://www.nano.gov/nanotech-101/what/nano-size

There are two main reasons for the differences in properties between a nanomaterial and the bulk material of the same chemical composition. Firstly, the increase in the ratio of surface area to volume of a nanomaterial. A 1 cm^3 block of material has 1 in 10,000,000 (or 1 in 10^7) of its atoms on its external surface. At 1 cubic micrometre (μm^3) the same block of material has 1 in 1,000 of its atoms on the surface. At 1 nm^3 the same block of material would have 80% of its atoms on the surface, which makes a nanomaterial more reactive than the same material at the bulk scale. Secondly, at the nanoscale, classical laws of physics give way to quantum effects. Nanomaterials, as opposed to bulk materials, have few atoms, forming discrete energy levels which leads to a wider band gap between the conduction band and the valence band, this in turn leads into a change between the magnetic, electrical, and optical behaviours of the material compared to the bulk material. One such example is graphite *vs* carbon nanotubes, while bulk graphite shows excellent conductivity properties (Cermak *et al*., 2020), carbon nanotubes represent a material with semi-conductor properties (Kolahdouz *et al*., 2022).

1.2 Nanoscale

Nanomaterials, for context, can be illustrated by comparing their dimension with the dimensions of everyday objects and particles that people are familiar with (Table 2).

Table 2 Size of nanoparticles compared to other particles.[2]

Particle	**Diameter**
Atoms and small molecules	0.1 nm
Nanoparticles	1-100 nm
Fine particles (also called particulate matter or $PM_{2.5}$)	100-2,500 nm
Coarse particles (PM_{10} or dust)	2,500-10,000 nm
Thickness of paper	100,000 nm

Understanding the nanoscale and being able to measure and manipulate matter at this scale has allowed manufacturers to make use of the properties that nanomaterials exhibit to create new and/or standard products with enhanced functionalities. It should be noted however that, even before the ability to detect matter at the nanoscale was possible, some of the properties of naturally occurring or incidental nanomaterials were already exploited. Naturally occurring nanomaterials are those that are made by nature through a process not connected with human activity, for instance the natural erosion of tree bark results in nanocellulose. Incidental nanomaterials are unintentionally produced nanomaterials as a result of direct or indirect human influence aimed at creating a different product (Hochella *et al*., 2019). One example of this is medieval stained-glass windows, where adding metals such as gold and silver into the glass resulted in different colours due to the creation of incidental nanoparticles.[3]

1.3 Nanomaterials in consumer products

Over the last two decades, nanomaterials have been included in both industrial and consumer goods to make use of a size-related functionalities. Usually, nanomaterials are

[2] From https://www.bbc.co.uk/bitesize/guides/z8m8pbk/revision/1
[3] https://www.sciencehistory.org/distillations/from-nanotech-to-nanoscience

used as part of an existing product and may provide some additional function that is useful for the user by way of an enhancement to the overall product. For example, silver nanoparticles may be used as part of a textile coating to provide anti-microbial protection. The functional effects of the nanomaterials used within a product can thus either be a direct and definable benefit to the consumer, such as by providing better protection in sunscreens (Cole *et al*., 2016); or they could aid the effective manufacture of the product, for instance by increasing the dispersion of an active ingredient in a formula, such as in a medicine or in a cosmetic (de Barros *et al*., 2022).

Nanomaterials that are intentionally manufactured are usually referred to as engineered nanomaterials. There are two main routes to manufacturing nanomaterials. The first is the top-down approach in which a material is broken down to generate a nanomaterial. The processes used can include milling, etching or grinding a material into smaller sizes. The second approach is bottom-up, where smaller structures such as atoms or molecules are used as building blocks to synthesise nanomaterials. Bottom-up approaches usually provide more control over the final shape, size and surface structure of the nanomaterial (Parvez *et al*., 2012).

Table 3 provides some common examples of the types of nanomaterials that may be used in consumer products and the reasons for their use.

Table 3. Examples of nanomaterials used in consumer products and their functionalities.

Nanomaterial	**Example of functional property**	**Examples of use in products**
Titanium dioxide (TiO_2)	Increase the UVA and UVB absorption due to higher specific surface area compared to larger than nano-sized TiO_2 without leaving a white residue. Nano TiO_2 is transparent because, due to its small size, it hardly scatters visible light. (SCCS, 2018c).	Sunscreen and cosmetics
Silver (Ag) nanoparticles	Anti-bacterial effects due to direct release of silver ions, which permeate the cells, produce reactive oxygen species and interfere with RNA replication. (SCCS, 2018b, Kędziora *et al*., 2021)	Stain-resistant textiles
Carbon black (CB)	Active colour that provides an absolute black colour effect. Carbon black is generally used because it is a cheap and cost-effective material. (SCCS, 2013).	Cosmetics such as mascara, eye shadows and lipsticks
Zinc oxide (ZnO)	Absorbs and scatters UVA and UVB rays remaining	Sunscreen

Nanomaterial	Example of functional property	Examples of use in products
	transparent. Nano ZnO provides high UV light absorption but due to their small particle size they become transparent in visible light.[4]	
Copper (Cu) nanoparticles	Anti-microbial effects through the destabilisation of the cellular membranes due to the presence of $Cu^{(2+)}$, which further induces DNA degradation, lipid peroxidation and generation of reactive oxygen species. (Chatterjee *et al*., 2014).	Self-cleaning coatings for textiles

Products that have an action or function that relies upon the properties of a nanoscale component are described as nano-enabled products. Nano-enabled products may only have a low concentration of nanomaterials used in their design, but the nanomaterial will serve a function in the product. Some products may only use one type of nanomaterial, whist others will have more than one. The nanomaterial in a nano-enabled product may not impart the main functionality or be the main function of that product, but they may give the overall product some additional functionality that would not otherwise be apparent.

To learn more about nanomaterials and the science and technology behind them, the following resources can, by way of examples, be referred to:

- *Comprehensive Nanoscience and Nanotechnology* 2nd Edition - 2019 David Andrews, Thomas Nann, Robert Lipson Elsevier ISBN: 9780128122952
- *Bionanotechnology: Concepts and Applications* 2021 by Ljiljana Fruk and Antonina Kerbs Cambridge University Press *ISBN: 9781108452908*
- *Nanotechnology for Dummies* 2nd edition 2011 E Boysen John Wiley & Sons Inc ISBN: 9780470891919
- https://www.nano.gov/
- https://ec.europa.eu/environment/chemicals/nanotech/index_en.htm

[4] https://ec.europa.eu/health/scientific_committees/opinions_layman/zinc-oxide/fr/l-3/2.htm

2 Introduction to the study

This chapter introduces the project and gives some background to its design and purpose. It outlines the reasons why the study has been undertaken and its scope.

Over the last two decades there has been a growth in the number of consumer products that contain nanomaterials. This can be shown by the number of products listed in the Nanotechnology Consumer Products Index (CPI) of the Woodrow Wilson International Centre for Scholars' Project on Emerging Nanotechnologies. This database grew from listing 54 products in 2005 to 1,814 products in its revised inventory of 2013 (Vance *et al.*, 2015). Similarly, the Danish Nanodatabase[5] developed by the Technical University of Denmark (DTU) Department of Environment, the Danish Ecological Council and the Danish Consumer Council has grown from 1,206 products in 2012 to 5,224 products in 2021 (see Figure 1 below). The Nanodatabase is composed of products that have a claim, usually made by the manufacturer, that they contain nanomaterials or are based upon nanotechnology. Anyone can submit a product for inclusion in the Nanodatabase by uploading a picture as well as basic information on the product name and manufacturer, via an online form on the Nanodatabase website. Submissions are then reviewed by the DTU before a product is included in the Nanodatabase. With only limited regulatory or legislative requirements, such as in respect of cosmetic ingredients, that obligate manufacturers to label products as containing nanomaterials or to register them, the Nanodatabase may underestimate the number of products in the global market. Equally, with some manufacturers using nano as a positive marketing label for their products, there may indeed be an overestimation of the number of products that do contain nanomaterials (Hansen *et al.*, 2016).

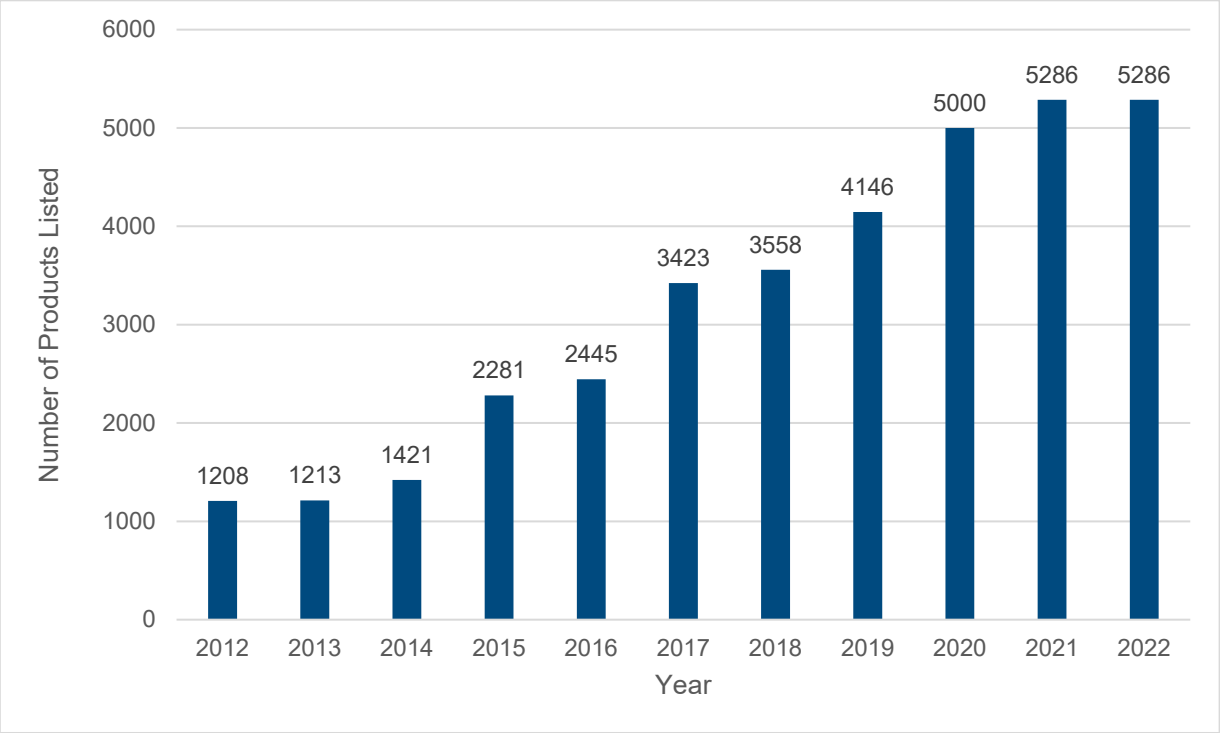

Figure 1. Number of consumer products containing nanomaterials by year listed in Danish Nanodatabase (source https://nanodb.dk/en/analysis/consumer-products/#chartHashsection).

[5] https://nanodb.dk/en/analysis/consumer-products/#chartHashsection

The increased use of nanomaterials in consumer products can be explained partly by the specific, unique properties of the nanomaterials that have been used in consumer products to effect a functionality. For example, in sunscreens the mineral ZnO) has been used as a physical barrier to UVA radiation, to offer protection against the effects of the sun on the skin. However, the disadvantage of ZnO use in sunscreen is the white chalky appearance on the skin. Reducing the size of the ZnO particles to the nanosize can improve its cosmetic appeal whilst retaining its ability to protect against UV radiation (Smijs *et al*., 2011).

The increased availability of nanomaterials has certainly offered consumer product manufacturers the opportunity to add these materials into their products, therefore benefitting from their functional properties. To some extent, the nanomaterials that appear in consumer products are those that are freely available on the market. The claim of 'use of nanotechnology' in products has also often been employed as a sales strategy for consumer goods as a means of increasing market desirability. Adding new functionalities to products can help companies market their products at a premium price.

Despite the growth in the number of available nano-enabled products, nanomaterials are still a relatively new class of materials and there is still ongoing research to understand their properties. As early as 2004, there were some concerns expressed regarding the safe use of nanomaterials. In the Royal Society and Royal Academy of Engineering report of that year, it was concluded that whilst many applications of nanotechnology do not introduce new health or environmental challenges, it was necessary to manage the risks posed by nanomaterials (Royal Society, 2004). Since then, much research has been undertaken looking at both a wide range of nanomaterials and their impact in human health and the environment, as will be presented in this report.

Despite the growth in research of nanomaterials and their increased use in both industrial and consumer products, there remain several challenges to be addressed. Firstly, it is difficult to identify specific products that contain nanomaterials. A large part of this is because, with very limited exceptions, for example use of nanomaterials as ingredients in cosmetics, manufacturers are not obliged to disclose the use of nanomaterials in their products. In cosmetics, ingredients that are nanoscale must be listed as such on the label by adding '(nano)' after the relevant ingredient. But in other products for use by consumers, short of the rare exception such as in respect of biocidal products, the lack of provision for disclosing use of nanomaterials makes it difficult to trace the use of nanomaterials in consumer products.

Furthermore, there are no comprehensive lists of consumer products containing nanomaterials. The datasets that are currently available are not complete and, in part, rely on crowdsourcing, e.g., the Danish Nanodatabase.[6] Many of the datasets have several weaknesses as follows.

1. **Datasets are not always regularly updated.**

The datasets that are available have been established by private entities, and sometimes have relied upon external funding for their initiation and ongoing maintenance. Without continued financial support, these datasets can soon become outdated. The Consumer Product Index, for example, was initiated in 2005. It last underwent a major update in 2013 but does not currently appear to be regularly updated. The Danish Nanodatabase claims to be updated daily as required, but between 2021 and 2022 the number of products it lists has remained the same at 5,286.

[6] See https://nanodb.dk/en/report-product/, which invites people to help report products "in which the word nano occurs on the packaging or on the product itself".

2. Products may no longer be available.

Over time manufacturers can go out of business, change their product offerings or the formulation of their products. During this study, a significant number of products were seen to be no longer available on the market and are effectively 'dead' (or discontinued) products. This has also been noted by the datasets themselves. (Vance *et al*., 2015, Hansen *et al*., 2016)

3. Useful data is often absent for products.

The Danish Nanodatabase recognises that one of its greatest weaknesses is the lack of confirmed product data and the nanomaterials that they contain. In 2016, the Nanodatabase team acknowledged that nanomaterials used in products were not reported for almost 50% of the products listed (Hansen *et al*., 2016). Beyond knowing with certainty whether nanomaterials are used in a product, it would also be useful to know more about the specific nanomaterials and their characteristics, such as their physical/chemical properties, size and shape, coatings, surface chemistry, and other characteristics that drive toxicological properties.

4. Nano claims are often unverified.

The datasets do not independently investigate the veracity of the claims made around the products containing nanomaterials and rely upon the accuracy of the claims made by manufacturers or by those providing data through crowdsourcing. The datasets have accepted that there is an inherent risk that manufacturers' claims that a product contains nanomaterials are both difficult to verify and may skew the number of products that are listed as being nano-enabled. However, even when a manufacturer makes a claim for the presence of nanomaterials in their product, the claim should be treated with caution. As an early study from the National Institute for Public Health and the Environment (RIVM) in The Netherlands indicated, '*products without a claim can contain nanomaterials, whereas products with a claim [do] not always contain nanomaterials*.' (Oomen *et al*., 2011)

5. Datasets can have a restricted geographical focus.

The CPI dataset focuses on products that are or were available in the USA, whilst the Danish Nanodatabase tends to focus on products marketed in the EU. This is probably to be expected owing to the location of the organisations that established these datasets, and the scope of their data collection. There is no dataset that is specifically focussed on the UK market that can be easily used to identify which consumer products contain nanomaterials, meaning that there is a need to use the existing datasets to identify the products with a claim to contain nanomaterials and check if those products are available to UK consumers.

Despite these limitations, the datasets used in this study are useful to give an indication of products available to consumers which claim to contain nanomaterials. The fact that there is no central register of nano-enabled products makes it challenging to find reliable data for which consumer products contain nanomaterials. Even in countries such as France and Belgium, which have established compulsory nanomaterials registers, it is the nanomaterials themselves that must be registered rather than the products in which they are used. Similarly, though cosmetics containing nanomaterials must have nano ingredients labelled, there is no central register of cosmetics that contain nanomaterials.

Another challenge is the apparent decline in the marketing strategy to claim that a product contains nanomaterials to help show that it is 'advanced' and 'high-tech'. During the early part of the twenty-first century, there was a tendency for manufacturers of consumer products containing nanomaterials to clearly state this in their marketing of the products (EUON, 2020). This aided the compilation of the earlier datasets of nanomaterial containing

consumer products, which relied upon manufacturers' claims in order to identify products. It is difficult to gauge to what extent the reduction in the use of the term 'nano' in describing products is due to consumer fears about nanomaterials, and to what extent it is instead because this marketing strategy may not actually help increase sales. Consumer attitudes have been studied in different EU countries to understand their reactions to products that use nanomaterials, but these are outside of the scope of this report. The use of 'nano' to describe some consumer products in earlier periods was also sometimes used regardless of whether these products contained nanomaterials or not, leading to the difficulties mentioned in identifying the actual presence or absence of materials at the nanoscale.

2.1 Scope of this report

This study explores the use of nanomaterials in the following consumer product areas regulated by the Office of Product Safety and Standards (OPSS), which are widely accepted to be those most likely to contain nanomaterials in select products:

- cosmetics;
- toys;
- nightwear; and
- personal protective equipment (PPE).

The study will aim to identify the most prevalent nanomaterials that are being used in these product areas on the UK market, and then to provide a targeted analysis of the safety of identified nanomaterial use in the product areas of interest. The regulatory and industrial standards governing the selected product areas was also examined, with consideration as to how nanomaterials can be characterised and the required exposure and toxicological analysis.

Specifically, the research questions addressed were as follows:

1. What is the prevalence of metal and non-metal nanomaterials in consumer products on the UK market?
2. What are the potential physical and chemical safety issues relating to the use of metal and non-metal nanomaterials in consumer products on/to be placed on the UK market and the associated risks?
3. What are manufacturers' responsibilities and relied upon industrial standards when characterising and performing toxicological assessment of metal and non-metal nanomaterials for use in consumer products on the UK market?

Addressing these research questions will help manufacturers introduce new technology in consumer products on the UK market, whilst also protecting UK consumers by ensuring that nanomaterials are used safely in consumer products. The report also highlights the gaps in existing research with respect to potential safety concerns of nanomaterials in consumer products in the UK market, allowing future research to focus on these areas.

2.2 Nanomaterial definition

This section provides a brief introduction to the nanomaterial definitions used during this project and some of the shortcomings and considerations. Further discussion will be presented throughout this report, but a full appraisal is beyond the scope of the project. To identify nanomaterials in consumer products it is important to work to a standard definition. The standard to work towards was therefore defined without prejudice at the start of the project. This allows consistent identification of materials without bias. When a specific

definition is not available under the regulatory framework under analysis, the definition provided in the following legislation will be used:

Nanoform definition under REACH Regulation and REACH Regulation (GB)

'a form of a natural or manufactured substance containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm, including also by derogation fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm.'

Sector specific definitions were used as available to accurately contextualise the results and future actions.

The REACH Regulation and REACH Regulation (GB) definition was chosen for the wider scope of the project definition as it is the most widely accepted definition in both the UK and the EU, and has clear parameters for defining nanomaterials. These parameters can be measured, and as such, it is possible to identify nanomaterials through measure, as guided by the Joint Research Centre (JRC) (Rauscher *et al*., 2019).

However, it is of note that specific regulations deviate from this definition. For example, under the Cosmetics Regulation and Cosmetics Regulation (GB) , a nanomaterial is defined as seen below.

Nanomaterial definition under the Cosmetics Regulation and Cosmetics Regulation (GB)

[a nanomaterial is an] 'insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100nm.' (UK Statutory Guidance, 2022)

To help identify nanomaterials under the Cosmetics Regulation, the SCCS provided an EU level guidance document (SCCS, 2019) where insoluble falls under the categories termed as 'practically insoluble', 'very slightly soluble', 'slightly soluble' or 'sparingly soluble' following the EU Pharmacopoeia (EU Pharmacopoeia, 2019); USP38 and USP38 NF33[7] as shown in Table 4.

[7] https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-commentary/approvals-usp38-2s.pdf

Table 4. Solubility definitions as per EU Pharmacopoeia; USP38 and USP38 NF33.

Term	Parts of solvent required for 1 part of solute	Solubility defined in g/L
Very soluble	Less than 1 part	>1000
Freely soluble	10 to 30 parts	33.3 -100
Sparingly soluble	30 to 100 parts	10 -33.3
Slightly soluble	100 to 1000 parts	1 -10
Very slightly soluble	1000 to 10000 parts	0.1 -1
Insoluble*	>10000 parts	<0.1

* The European Pharmacopeia makes use of the alternative term, 'practically insoluble'.

Further information regarding terminology of nanomaterials can be found in ISO/TS 80004-2:2015 Nanotechnologies — Vocabulary — Part 2: Nano-objects (ISO, 2015).

A definition for biopersistency is not introduced in the guidance, though the OECD has produced relevant documentation of how to assess biodurability (OECD, 2018), which may provide indications to biopersistency. Likewise, the guideline does not define intentionally produced. The concepts of biopersistence and insolubility will be covered further in Section 6.2.1.

The definition deviation, in some instances, is relevant to the uses and exposure scenarios governed by the regulation or more simply as no definition was available during the authoring of the legislative text, as it was not available until 2011. It also seeks to simplify how nanomaterials are defined and includes specificity for different nanomaterial shapes which were previously lacking, e.g., rods and platelets.

In the Cosmetics Regulation (and Cosmetics Regulation (GB)), the nanomaterial definition was considered to adequately address possible nano-specific hazard. It was considered that if the material was no longer a nanomaterial when in contact with the consumer, or, quickly transformed into a non-nanomaterial, then the hazard is appropriately addressed using information on the molecule or bulk form itself. Unfortunately, this does not account for possible 'trojan horse' mechanisms of toxicity, wherein a particle is internalised within cells and then releases high levels of toxic ions; this may lead to higher toxicity.

Though, the UK and EC definitions are used or referred to in many instances, including by the UK Government Health and Safety Executive[8], the definition itself has undergone scrutiny and has been the subject of update over the past several years. This update sought further clarity on, for example, whether the 50% particle number size distribution was adequate for purpose.

2.3 Availability of consumer products definitions

This study is concerned with the potential safety aspects of nanomaterial use in consumer products on the UK market. It is therefore important to define which products were considered in terms of their availability to UK consumers.

Due to the complex landscape with respect to online trade, the breadth of retailers selling products to UK consumers is ever changing, as such, two types of product categories are

[8] https://www.hse.gov.uk/nanotechnology/what.htm#regulatory-definition; last accessed 20/02/2023

set out below as, i) available products on the UK market and, ii) available products to the UK consumer.

Readily available products on the UK market

The consumer products primarily within project scope are those that are readily available on the UK market, as defined below.

Readily available products on the UK market

Products available within the UK, through retail outlets actively trading in the UK. To be in scope, products needed to be:

- Delivered to mainland UK addresses without customs fees;
- Advertised for sale in Pounds Sterling; and
- Product must be sold as new and not second-hand.

This definition was selected on the basis that these products were considered more likely to be purchased by UK consumers and are therefore of particular relevance. Using products on a well-known online platform, only products available on its UK site were considered, whilst products on the international site were discounted.

The retailers were selected to sample the UK market. They have searchable websites and represent the main/popular retailers in their categories of supermarket chains, chemist chains, main retailers and department stores.

Available products to the UK consumer:

It is however acknowledged that consumers may seek to source products globally, e.g., a consumer product available in the USA or China could be purchased by a UK consumer, using generic trading sites. Consequently, a brief secondary search was conducted to consider products available to UK consumers through three popular aggregate websites, agreed with OPSS.

For the purposes of this research, available products to the UK consumer are defined as seen below.

Available products to the UK consumer

Products that the UK consumer may procure through retail outlets that might be perceived as not primarily targeting the UK market. To be in scope, products need to be:

- purchased by the consumer who acts as the importer of the product and pays customs fees; and/or
- paid for in a currency other than Pounds Sterling.

3. Prevalence of nanomaterials in consumer products on the UK market

3.1 Consumer product searching

A number of databases were used to identify consumer products in the categories covered in this project, the methodology is provided in Appendix 1. The databases list products under different categories, highlighted in Table 5. An initial search of said databases returned the results for the selected product categories.

Table 5. Summary of number products claimed to contain nanomaterials by product category and source database.

Category	Sub-category (where applicable)	Source database	Number of products	Notes
Children's toys		Nanodatabase	84	Products categorised as 'Goods for Children'
		PEN	38	Products categorised as 'Goods for Children'
Cosmetic		Nanodatabase	385	Using keyword search 'cosmetic'
		French Registry	1113	products categorised as cosmetics, care products personal
		PEN	174	Products categorised as Cosmetics
	Sunscreen	PEN	40	Products categorised as Sunscreen
PPE		Nanodatabase	1	Using keyword search 'PPE'
		Nanowerk	51	Global Nanotechnology

Category	Sub-category (where applicable)	Source database	Number of products	Notes
				Face Mask Database
Nightwear (with search broadened to furniture and textiles)	Furniture	Nanodatabase	40	Using keyword ‘furniture’
	Textile	Nanodatabase	998	Using keyword ‘textile’
	Clothing	PEN	216	Products categorised as Clothing
	Nightwear	Nanodatabase	0	Using keywords ’nightwear’, ‘pyjamas’, "’PJs’,
	Home Furnishing	PEN	50	Products categorised as Home Furnishings

The different databases use different product catergories for the products that they list. The most likely product categories were selected, alongside some keyword searches. The figures in the table above gave an intial indication of the number of products found in each product category, and informed whether a different search strategy would be needed to identify products that contain nanomaterials.

Textiles is a very broad category and search returns included both textile products and treatments for textile products, such as for cleaning or coating applications. The term ‘textiles’ can also be used interchangeably, and can both mean final products, such as clothes and components of products, such as textiles used in upholstered furniture. Similarly, the furniture category search returned post-sales applications, such as cleaning or protective coatings. So, it was necessary to make some decisions around which products were identified in these categories to ensure that they were within the scope of the survey.

There were some caveats to note:

1. **The appearance of a product in one of the databases does not necessarily mean that it contains nanomaterials**, but rather a claim has been made by either the manufacturer or a third party, i.e., it is stated that the product contains nanomaterials. These claims have been taken at face value in this project, as further physical examination of products would be required to verify the claims.

2. **There can be a high turnover of products by manufacturers,** i.e., databases become outdated, and products are discontinued. Also, some manufacturers are no longer trading, thus their products are not available. This can be seen in the number of discontinued products identified in the searches made and is also noted by the team

behind the Nanodatabase (Hansen *et al*., 2016).

3. **New products can come to the market between any of the databases undergoing updates**, which makes it easy to overlook products that have not been added to the databases. Similarly, it is possible that products that no longer use nanomaterials or products for which the claim to use nanomaterials has been proven to be false, for them to be removed from the datasets.

4. **There can be difficulties in attributing the exact nano containing product listed in the database to a product available from a retailer**. In other words, manufacturers can change the branding or even the brand name of products, making it difficult to ensure that the product found in the database is the same as the one found to be available to a UK consumer. Alongside this, manufacturers can also change materials they use within their products, so where there are doubts as to the veracity of the claim that a product still uses nanomaterials, the approach taken was to describe the product shown as not containing nanomaterials so as not to incorrectly inflate the number of products containing nanomaterials.

Despite these limitations, it is possible to use the product data to draw some conclusions about which products containing nanomaterials are available to UK consumers, and also around the nanomaterials that are most commonly used in consumer products.

The category with the greatest number of consumer products using nanomaterials is cosmetics. This may be due to the direct consumer benefit nanomaterials may impart, and therefore marketing their presence could be an advantage, or because companies in the UK and EU must label any nanomaterials used in their products, making them easier to identify. Excluding cosmetics, it is more likely that nanomaterials that provide the main functionality or offer a marketing opportunity for the product will be captured in the databases. It may be that the product containing nanomaterials is consequently easier to find and identify, which may especially be true as both the CPI and Nanodatabase use crowd sourcing to gather recommendations of products to include. For example, textile products that are marketed as using nanomaterials to impart stain resistance have a higher likelihood of database incorporation. In contrast, some furniture components use nanomaterials, such as adhesives, but because the product is not marketed or promoted for this functionality, only the manufacturer may be aware of their use.

Using the search criteria outlined in Appendix 1, a total of 613 products with a nanomaterial use claim were identified. These products were then searched for to see if they were either readily available in the UK (228 products) or available to UK consumers (an additional 52 products), meaning that 280 products with a claim to use nanomaterials could be available to UK consumers. Of the 280 products, the majority (66%) were in the

cosmetics category (see Section 3).

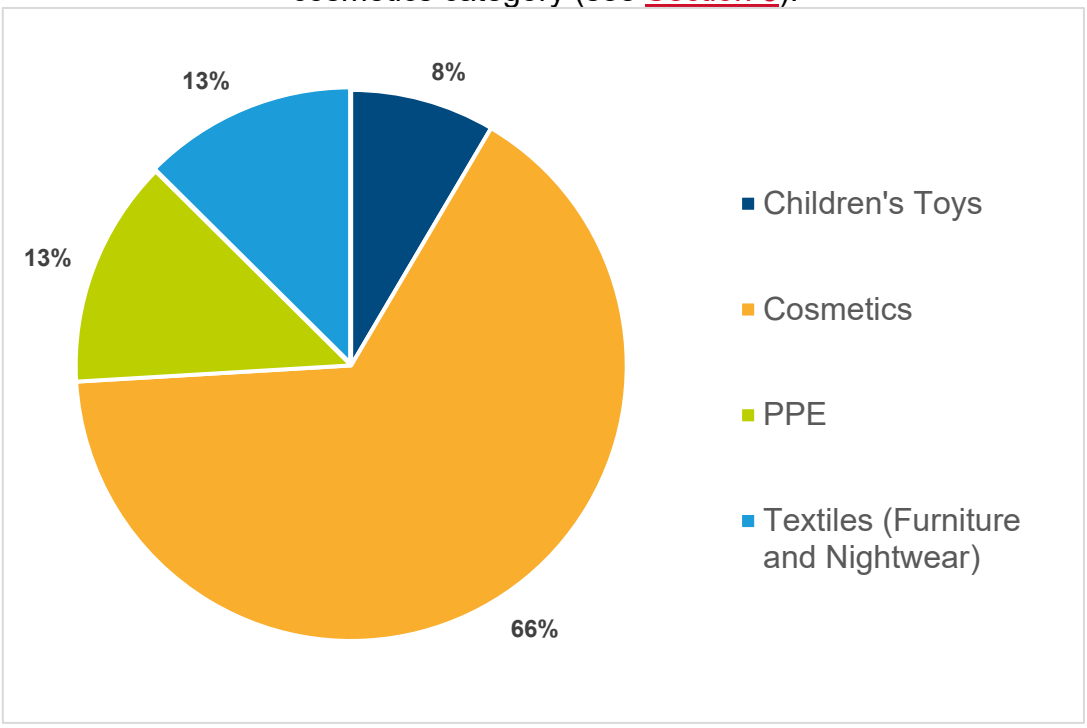

Figure 2. All available products to the UK consumer with a claim to use nanomaterials by consumer category.

Of the products with a nanomaterial use claim that were readily available on the UK market or available to UK consumers, there were 269 products where the nanomaterials that were used is known and can be identified (see Table 6). Of the remaining 344 products, the nanomaterial being used is unknown. The percentage of products for which the nanomaterial used is known varied among product category, ranging between 13% and 50%; on average the nanomaterial used was identified in only 44% of products.

Table 6. Total number of products found that claim to use nanomaterials and total number of products in which a positively identified nanomaterial (known nanomaterial) was used.

Product Category	**Total number of products that have a nanomaterial claim**	**Nanomaterial known?**		
		No	**Yes**	**Percentage of total number of products**
Children's Toys	52	45	7	13%
Cosmetics	402	200	202	50%
PPE	82	45	37	45%
Textiles (Furniture and Nightwear)	77	54	23	30%
Total	**613**	**344**	**269**	**44%**

In the cosmetics category, 200 out of 402 readily available products on the UK market the nanomaterial used is unknown. This is an obvious gap in the data available, as it should be possible from the list of ingredients to identify the nanomaterial used in cosmetics.

Table 7. Number of products readily available in the UK through UK retailers, or available to UK consumers via non-UK retailers containing a positively identified nanomaterial (known nanomaterial).

Product Category	Total number of products	Number of products readily available from UK retailers	Number of products available to UK consumers from non-UK retailers
Children's Toys	7	0	7
Cosmetics	202	99	103
PPE	37	10	27
Textiles (Furniture and Nightwear)	23	1	22
Total products that use known nanomaterials	269	110	159

Of the products in which the nanomaterial used is known, the most commonly incorporated nanomaterials were TiO_2 (85 products), silver (42) and bisoctrizole (23), with a further 6 nanomaterials used in 5 to 20 products available to UK consumers (Table 8). It is noteworthy that of the top three commonly found products containing nanomaterials, those containing silver nanomaterials were predominantly only available to UK consumers from retailers based outside of the UK. The converse is true for TiO_2 and bisoctrizole, which were available through UK based retailers. Of course, it must be stated here that the small selection of online retailers, representing products available to the UK consumer from outside the UK, may have skewed some of the analysis but it does give some indication as these are some of the most popular online retailers used by UK consumers.

Table 8. Number of Products readily Available in the UK through UK retailers, or available to UK consumers via non-UK retailers, only, containing a positively identified nanomaterial (known nanomaterial).

Nanomaterial	Total number of products	Number of products readily available from UK retailers	Number of products available to UK consumers from non-UK retailers
Titanium dioxide	85	45	40
Silver	42	4	38
Bisoctrizole	23	18	5
Silicon dioxide	20	14	6
Carbon black	16	5	11
Zinc oxide	15	5	10
Gold	10	8	2
Copper	8	0	8
Silicon	5	0	5

The results from the survey of prevalence of nanomaterials in consumer products readily available (through UK retailers) in the UK and available to UK consumers (via non-UK retailers) has informed the following sections of this report which examine the safety of consumer products using nanomaterials and the manufacturers' responsibilities, regulations, and standards. Only nanomaterials identified in the database were followed in this study, this does not exclude that other nanomaterials may be present in consumer products but not reported as nanomaterials by the manufacturer or not easily identified in the available databases. Such examples would be nanocellulose and nano-hydroxyapatite, which are both available in cosmetics such as emulsifications and toothpastes. These could be missing due to either measuring the cellulose 'as produced', which for cellulose may lead to hydration and swelling beyond the nanomaterial form, or poor supply communications for hydroxyapatite. In both instances, it could also be a failure to accurately measure particle size. Moreover, substances (chemicals) can often have many synonyms, and this may dilute the overall prevalence into many pseudo-substances though all referring to the same one. For example, hydroxyapatite is also known as pentacalcium hydroxide triphosphate, calcium hydroxyapatite, calcium phosphate tribasic, pentacalcium monohydroxyorthophosphate and pentacalcium hydroxide tris(orthophosphate) to give only a few examples. The constituent of the formulation may also be hidden behind trade names to protect intellectual property. Again, a few examples of trade names for hydroxyapatite are; alveograf, periograf, interpore-200 and osprovit, again the list is not exhaustive.

4. Literature search results

Table 9 presents an overview of the literature searches and critical review; all stages of the evaluation are recorded in the Supplementary Information. Approximately 1,500 manuscripts were identified in the literature search for Research Question 1: '*What is the prevalence of metal and non-metal nanomaterials in consumer products on the UK market?*'. However, 1,415 manuscripts were dismissed as not being relevant during the rapid relevance reviews (see A1.2 Literature search methodology) as they did not indicate the availability of specific consumer products in the UK (indicative of prevalence), and/or they were duplicates. Manual searches were also conducted in parallel. Broadly speaking, the literature search was conducted to achieve sufficient coverage of different evidence sources and to gain background information. The limited number of results was not a concern, as literature searching was not the main method for retrieving prevalence data, which was identified using the product searches as reported in the section above (Section 3). There were two manuscripts relevant to research question 1.

Approximately 4,500 manuscripts were identified in the literature searches for Research Question 2: '*What are the potential physical and chemical safety issues relating to the use of metal and non-metal nanomaterials in consumer products on/to be placed on the UK market and the associated risks?*'. After the rapid relevance review, which focused on the most prevalent nanomaterials on the UK market (Section 3), following duplicate removal, approximately 300 manuscripts remained. Due to the large number of manuscripts and that several of them had useful *in vivo* data from, e.g., the ECHA dissemination page and from the sourced manuscripts, *in vivo* data was the initial focus of this review. When effects *in vivo* were identified, the critical review subsequently focused on in vitro studies to elucidate specific physical chemical linked (e.g., size dependent toxicity) hazards and modes of action. This methodology established whether there were nano-specific effects or general effects of the bulk substance. Exceptions were made for relevant *in vitro* data on well-known regulatory accepted test systems such as in vitro methods for genotoxicity and/or skin sensitisation. The purpose for including such studies relate to the manufacturer's responsibilities and how they will fulfil them, i.e., Research Question 3, seen in Section 6.

Table 9. Overview of the literature searches and critical review.

Organism group	Number of identified manuscripts	Number of manuscripts identified as potentially relevant from title/abstract	Number of manuscripts containing relevant and reliable data for use
Research question 1	1,417	2	0
Research question 2	4,592	337	293

N.B.: See A1.2 Literature search methodology for further method details.

5. Nanomaterial enabled consumer product safety

The safety profile of nanomaterials used in consumer products is of the utmost importance. This is due to the wide-dispersive nature of use, and subsequent potential to impact the consumer and the environment. It is essential to note that wide-dispersive use and prevalence are not synonymous with high-volume usage. Crucially, the eventual exposure is dependent on the amount required for the ingredient to execute its function in the product, and the likelihood and pattern of release. As such, it is obvious to note the importance of the safety of products containing nanomaterials when direct product contact (e.g., toys, furniture, and cosmetics) is part of the end use.

Initial concerns around the safety profile of nanomaterials were largely due to their novel characteristics when compared to their bulk form and, where the particle contains metal, their ionic forms (e.g., metallic nanomaterials suspended in culture medium or other liquids can dissolve to form metal ions, with a potentially different hazard profile) (Royal Society, 2004). For example, due to the size range in which these materials occupy (1-100 nm), they:

- have a large surface area to volume, lending themselves to higher levels of reactivity; and
- are able to penetrate surfaces and varying cellular channels larger particles cannot via passive diffusion (e.g., they can cross the blood-brain, blood-testis and placental barriers).

Furthermore, at the lower end of the size distribution (around 10 nm and smaller), nanomaterials can become governed by quantum mechanics (referred to as the quantum confinement effect, which describes properties of the electrons within the particle), which may affect such behaviours as chemical reactivity, fluorescence, and electrical conductivity (Kumar *et al*., 2018).

The point of departure (to eliciting effects, whether adverse or not) of the safety profile of any given nanomaterial (in comparison to its other forms) may be related to its physical-chemical characteristics, such as size and shape. Thus, much focus in recent years has been on deciphering not only the effect of the substance, i.e., the element or compound of elements (e.g., silver, gold and TiO_2) but also if there are specific toxicity drivers related to the nano-specific physicochemical properties.

Indeed, links between nanomaterial size and toxicity have already been made. For example, decreasing the size of uncoated ZnO nanomaterials leads to increasing toxicity to the aquatic environment (Yung *et al*., 2015). This is due to increased surface area which subsequently increases the rapidity with which these nanomaterials dissolve into the more toxic Zn^{2+} ions. It could also be with increased surface area that there is increased reactivity, regardless of dissolution, dependent on nanomaterial type. Conversely, for other nanomaterials such as amorphous SiO_2, the relationship is far more ambiguous. Briefly, for SiO_2 it is thought that reactivity, or toxicity, may directly relate to manufacturing process or release of ions after uptake. Amorphous SiO_2 is neither rapidly soluble nor crystalline. Moreover, as many sources of amorphous SiO_2 on the market are highly aggregated the surface areas are often lower than would be expected based on the discrete particle size, so reactivity in relation to this is difficult to determine. Due to its amorphous nature, the exact process of any exerted toxicity is less well defined, in comparison to e.g., crystalline silica, which after inhalation can cause health complications through increased inflammation. The further complication, and worthy of note here, is that for the most part many studies

conducted on amorphous SiO_2 for regulatory purpose shows little hazard to the extent that it is currently not classified for human health hazards. Thus, any hazard and the mechanisms of action linked to this are only being recently highlighted, if at all.

Ultimately, safety of any product is a balance between the potential hazard (the inherent potential of the constituent parts or whole nanomaterials to cause harm), the known threshold where the hazard is likely to present and the exposure to the end user and/or the environment. Therefore, to establish a safety profile, it is integral to understand:

- the hazard of the nanomaterial;
- the amount of the nanomaterial used; and
- the use pattern.

To inform this, qualitative and quantitative safety assessment can be undertaken. A quantitative safety assessment is carried out by comparing the estimated exposure levels for relevant exposure scenarios with the critical threshold value indicative of no toxicological effect, e.g., derived no effect levels. This is done separately for each relevant exposure pattern considering the population exposed (e.g., consumers, workers etc.) and exposure route, i.e., inhalation, dermal and oral. A qualitative safety assessment assesses the likelihood that effects are avoided when the substance or product is used in an expected scenario (i.e., an intended use), often known as exposure scenarios. It is important to note that it is impractical to try to assess accidental use/release and unintended uses of products. Therefore, in this sense, only expected and appropriate use patterns as defined within regulatory applications are accounted for.

From the prevalence data presented above it can be seen the two most prevalent product categories in the UK are cosmetics and PPE. This section will focus on these uses to advance understanding of the possible hazards and risks to humans during use. Moreover, the most prevalent nanomaterials within these products were also noted. In order of most prevalent to least (across products readily available on the UK market and to UK consumers, based on information available at the time of writing) these were: TiO_2, silver, bisoctrizole, SiO_2, carbon black, ZnO, gold, copper, and silicon. The section will therefore focus on TiO_2, silver and bisoctrizole.

Detailed information on how safety is assessed according to various regulations is discussed within the subsequent section of this report (Section 6). Below, a hazard profile for three of the most prevalent nanomaterials on the market (Bisoctrizole, Silver and TiO_2) is outlined, as evidenced by the previous section of this report (Section 3). These were selected not only based on their widespread use, but because they represent differing types of material and likely different modalities by which they cause toxic insult, if at all.TiO_2 is insoluble, silver can dissolve and dissociate to ions, and bisoctrizole is organic. Any hazard of TiO_2 is often therefore linked to size, aspect ratio and crystallinity rather than its dissolved form. For silver, though the latter can also be true, often for rapidly dissolving nanoforms (after or before uptake) hazard can be linked to the dissolved fraction. Then, the organic nanoform bisoctrizole does not fit the traditional paradigm of toxicity for inorganic nanomaterials which have been more widely researched.

5.1 Bisoctrizole

Bisoctrizole (EC name 2,2'-methylene-bis-(6(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol; CAS No. 103597-45-1; INCI name methylene bis-benzotriazolyl tetramethylbutylphenol) is a phenolic benzotriazole which is capable of absorbing both UVA and UVB rays (Figure 3). As such, it is added to sunscreens to absorb UV rays. In its nano

form, its primary use is as UV filter in sunscreens, whereas in day care products and skin lightening products it is used at a maximum concentration of 10% in both the UK and EU.[9,10] It is known to be on the European Economic Area (EEA) market in nano form, as highlighted by the European Union Observatory on Nanomaterials (EUON)[11], and is also registered in the French[12] and Belgian[13] national inventories of nanomaterials on the market.

Nano-bisoctrizole is prepared by micronisation; physical milling of its bulk form. In one process describing preparation of a formulation including nanoform bisoctrizole, pre-milling was undertaken with a corundum disc mill followed by the main milling step, conducted with a ball mill (Hetrzog *et al*., 2004). The process was performed in deionised water using decyl glucoside as dispersant. After micronisation, xanthan gum was added to the dispersion to prevent particle sedimentation (SCCS, 2015).

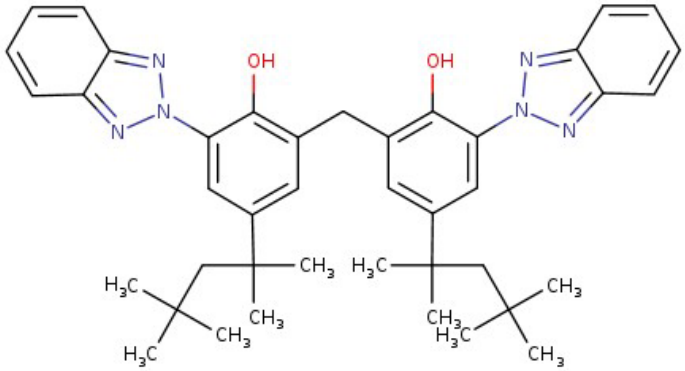

Figure 3. Chemical structure of bisoctrizole, CAS 103597-45-1, EC 403-800-1.

5.1.1 Safety profile

5.1.1.1 Regulatory registration

Bisoctrizole has 14 active registrations under REACH Regulation[14], its highest tonnage band is 100-1000 tonnes per annum. It is registered for use by consumers, in articles, by professional workers (widespread uses), in formulation or re-packing and at industrial sites. It is also listed as being used in cosmetics and personal care products (Table 11).

Although ECHA's substance infocard highlights that the substance is known to be on the EEA market in nano form, there were no nano-specific registrations available to view at the time of this review. As a nanomaterial, it is registered with the EU cosmetics inventory, the Belgian nano inventory (no annual tonnage specified) and the French nano inventory (≥ 10

[9] Regulation (EC) No 1223/2009 on Cosmetic Products, as amended by the Product Safety and Metrology etc. (Amendment etc.) (EU Exit) Regulations 2019
[10] Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products
[11] https://euon.echa.europa.eu
[12] https://www.r-nano.fr/?locale=en
[13] https://www.health.belgium.be/en/environment/chemical-substances/nanomaterials/register
[14] Active registrations of bisoctrizole according to the ECHA website, as of February 2023. Accessed at https://echa.europa.eu/information-on-chemicals/registered-substances/-/disreg/substance/100.100.550 (Feb 2023)

to < 100 tonnes per annum)[15]. It is also included within Annex VI of both the Cosmetics Regulation and Cosmetics Regulation (GB), see Table 10[16,17].

[15] https://euon.echa.europa.eu/search-for-nanomaterials - bisoctrizole nanomaterial entry, last accessed 15 Feb 2023
[16] Regulation (EC) No 1223/2009 on Cosmetic Products, as amended by the Product Safety and Metrology etc. (Amendment etc.) (EU Exit) Regulations 2019
[17] Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products

Table 10. Excerpt of bisoctrizole entry as UV filter allowed in cosmetic products within Annex VI of the Cosmetics Regulation (GB) and Cosmetics Regulation

Reference number	Substance identification				Conditions			Update date
	Chemical name / INN / ZAN	Name of common ingredients glossary	CAS number	EC number	Product type, body parts	Maximum concentration in ready for use preparation	Other	
No data	Sulisobenzone							
23	2,2'-Methylene bis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) / Bisoctrizole	METHYLENE BIS-BENZOTRIAZOLYL TETRAMETHYLBUTYLPHENOL	103597-45-1	403-800-1		10%		27/07/2020
23a	Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (nano)	METHYLENE BIS-BENZOTRIAZOLYL TETRAMETHYLBUTYLPHENOL (NANO)	103597-45-1	403-800-1		10%(*) (*) In case of combined use of Methylene Bis-Benzotryazolyl Tetramethylbutylphenol and Methylene Bis-Benzotryazolyl Tetramethylbutylphenol (nano), the sum shall not exceed the limit given in column g.*.	Not to be used in applications that may lead to exposure of the end user's lungs by inhalation. Only nanomaterials having the following characteristics are allowed: – Purity # 98,5 %, with 2,2#-methylene-bis-(6(2H-benzotriazol-2-yl)-4-(isooctyl)phenol) isomer fraction not exceeding 1,5 %; – Solubility < 5 ng/L in water at 25°C; – Partition coefficient (Log Pow): 12,7 at 25°C; – Uncoated; – Median particle size D50 (50 % of the number below this diameter); # 120 nm of mass	06/08/2020

							distribution and/or # 60 nm of number size distribution.	

Table 11. Use profile for bisoctrizole bulk and nanomaterial forms.

Uses information		
	Bulk form[18]	**Nanomaterial form**[19]
Environmental release category	Formulation into mixtures	Formulation of preparations Wide dispersive* indoor use of processing aids in open systems
Article Category	Plastic articles	Plastic articles
Product Category	Cosmetics, personal care products	Cosmetics, personal care products

[18] Data compiled from EU REACH disseminated dossier for biscotrizole (tonnage band ≥100 tonnes per year), last updated 22/11/2022. Accessed at: https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/5321/7/4/3 (last accessed, Feb 2023).

[19] Data compiled from 2014 dataset including both nano and bulk data. Studies summaries sourced from revision of SCCS opinion on 2,2'-Methylene-bis-(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3- tetramethylbutyl)phenol) (nano form), COLIPA n° S79 (2015).

Process Category	Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition Mixing or blending in batch processes Transfer of substance or mixture (charging and discharging) at non-dedicated facilities Transfer of substance or mixture (charging and discharging) at dedicated facilities Transfer of substance or mixture into small containers (dedicated filling line, including weighing) Use as laboratory reagent	Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition Chemical production where opportunity for exposure arises Mixing or blending in batch processes Transfer of substance or mixture (charging and discharging) at non-dedicated facilities Transfer of substance or mixture (charging and discharging) at dedicated facilities Transfer of substance or mixture into small containers (dedicated filling line, including weighing) Use as laboratory reagent

Uses information		
	Bulk form[18]	**Nanomaterial form**[19]
Sector of Use		Formulation [mixing] of preparations and/or re-packaging (excluding alloys) Health services Manufacture of fine chemicals
Belgian Inventory Uses (NACE)	N/A	None listed

*A wide dispersive use means widespread (i.e. used by many sites or by many users) with potential release to the environment or for human exposure.

5.1.1.2 Classification & Labelling and Persistent, Bioaccumulative and Toxic (PBT) assessment

Bulk form bisoctrizole is classified as toxic to the aquatic environment following long-term exposure (aquatic chronic 4, H413: may cause long lasting harmful effects to aquatic life). It is not currently classified for physical or health hazards under the Globally Harmonized System for Classification & Labelling. It is not considered to be persistent or bioaccumulative. No nano-specific classifications exist at the time of writing.

5.1.1.3 Relevant commentary on physicochemical properties and toxicological profile

Table 12 outlines some of the pertinent endpoints of relevance to building a safety profile for nanoforms, and the available information for each, using data from both bulk and nanoform registrations of bisoctrizole.

Table 12. Comparative data for bulk- and nanoform 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) (bisoctrizole). All studies are good laboratory practice (GLP) compliant unless specified otherwise. Data have been compiled from publicly disseminated dossiers; the bulk form column is populated from the disseminated dossier for the bulk chemical registration and the nano form column from the disseminated dossier for the nanoform under the Cosmetics Regulation and Cosmetics Regulation (GB). Please reference the glossary of terms for definitions of relevant endpoints included for hazard assessment.

Endpoint	**Registration dataset 1 (bulk)[20]**	**Registration dataset 2 (nano and bulk)[21]**
Chemical identity		
Name	2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)	2,2'-Methylene-bis-(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)
Trade names	ADK STAB LA-31RG Eversorb 78 Lowilite 36 MPI Milestab UV-360 Mixxim BB/100 THASORB UV-360 Tinuvin 360 UV-360	UV-absorbing ingredient (UV filter) (also referred to as MBBT): Bulk: MBBT, Tinosorb®, MBBT FAT 75714B, CGF-C002089, TKA 40027, CG 30-1881* Nano-MBBT: Tinosorb® M, FAT 75'634 * additional trade names are on the market
EC number	403-800-1	403-800-1
Appearance	Solid powder	Yellowish powder (MBBT) Viscous white dispersion (nano-MBBT)

[20] Data compiled from EU REACH disseminated dossier for biscotrizole (tonnage band ≥100 tonnes per year), last updated 22/11/2022. Accessed at: https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/5321/7/4/3 (last accessed, Feb 2023).
[21] Data compiled from 2014 dataset including both nano and bulk data. Studies summaries sourced from revision of SCCS opinion on 2,2'-Methylene-bis-(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3- tetramethylbutyl)phenol) (nano form), COLIPA n° S79 (2015).

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
Particle size distribution (Granulometry)	D90 = 69.8 µm	Bulk form: mean particle d(0.5) size of 207±70µm (n=3) with a range of 142–281µm. Medial particle size ≥120 nm (number based). Nanoform: mean particle size d(0.5) of 122 ± 0.005 nm (n = 32) with a range of 115 – 129 nm Median particle size ≥60nm (number based)
Water solubility	0.007 mg/L at 20 °C	MBBT has extremely low solubility in water (< 5 ng/L at 25 °C) which increases when formulated in a sunscreen lotion (1.0 – 3.2 mg/L, temp. unspecified). The nano-formulation is dispersible in water, and soluble in polar cosmetic oils.
Partition coefficient (n-octanol / water)	4.2 at 20 °C	12.7 at 25 °C (calculated value) determined according to OECD 107 (MBBT). No data for formulated micronized form, but it is expected to be similar.
pH	N/A (solid)	
UV/visible light absorption spectrum	N/A	D(0.5) = 169nm
Additional physicochemical properties of nanomaterials –Nanoform type	N/A	Mean specific surface area: Bulk form: 0.21 ± 0.03 m^2/cm^3 (n = 3) (range 0.19 - 0.25 m^2/cm^3).

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
–Crystallinity Structure –Shape category –Specific surface area –Surface treatment / functionalisation –Surface treating agent ID		Nano form: 56.0 ± 2.9 m^2/g (n = 32) (range 52 - 67 m^2/g) Zeta potential: -25 mV at neutral pH (Tinosorb® containing 10 % UV-absorbing ingredient MBBT in micronised form). Crystalline structure: N/A
Toxicological information		
Toxicokinetics (relevant information from absorption, distribution, metabolism and excretion studies)	Basic toxicokinetic study according to accepted OECD test guideline (OECD 417) referenced, but no results reported. A 2002 skin absorption study (undertaken according to OECD 427 using semi-occlusive exposure) reported minimal absorption (≤ 0.8%)	An OECD 417 toxicokinetic study is reported following oral administration or dermal application of the non-micronised (non-nano) form in the rat. It reported negligible systemic availability following oral administration, with the substance being quantitatively and rapidly excreted as parent compound via the faeces. A 2007 dermal penetration study *in vitro* (OECD 438, non-occluded) on intact skin using a suspension of nanoform 14C-FAT 75714/B (particle size d(0.5) <100 nm) reported penetration at extremely low rates and to a very limited extent through rat and human split thickness skin membranes. The penetration through rat skin membranes was higher than through human skin membranes, although it was notable that recovery for human samples was lower than in rat.

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
		A 2009 *in vitro* dermal penetration study on damaged skin according to OECD 428 (non-occluded) using nanoform Tinosorb® M (particle size d(0.5)= 87 and 91 nm) reported penetration at an extremely low rate through pre-damaged human skin membranes.
Skin irritation/corrosion and Eye irritation	Not irritating to the skin (OECD 404, 1991). Substance applied neat to 3 animals (rabbit). Not irritating to the eyes (OECD 405, 2013). Substance applied neat to 3 animals (rabbit).	No skin irritation studies with nano-sized material. Eye irritation *in vitro:* No eye irritation was identified in two isolated bovine cornea eye irritation tests (2010, OECD 437) on different batches of the formulated micronised UV filter (Tinosorb® M). *NB. SCCS opinion noted that the particle size distribution nor purity were provided in the study report. Based on historical data, the d(0.5) value was estimated by the applicant as 110-130 nm.* Eye irritation *in vivo*: the formulated micronised UV filter Tinosorb® M pH = 11.6 Was slightly irritating to the rabbit eye when tested according to OECD 405 (2010), based on slight conjunctival redness and slight chemosis up to 24 hours after application. *NB. the SCCS opinion noted that one of the batches tested was pH 11.6, as such,*

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
		under REACH it would be considered corrosive Category 1 and further testing for corrosivity/irritation waived (Annex VII, 8.1, column 2). Under the cosmetics regulations a substance should be considered as corrosive a priori if there are no other formulant in the medium that can provide buffering capacity. In the in vivo study report, no justification was provided for testing of a high pH substance on animals (study undertaken as part of Japanese quasi-drug registration).
Sensitisation	Not sensitising (OECD 406, 1991)	No studies with nano-sized material.
Acute toxicity	Very low Oral and Dermal acute toxicity (both studies reported LD_{50} >2000 mg/kg bw in rats). No inhalation acute toxicity study reported.	No Oral or Dermal acute studies reported. Inhalation: In a 4h acute inhalation toxicity in rats (OECD 403), the lethal concentration 50 (LC_{50}) was greater than the highest technically achievable aerosol concentration of the formulated micronised UV filter (Tinosorb® M), generated from a 20 % aqueous dilution. The LC_{50} of the UV-absorbing ingredient MBBT in micronised form was therefore > 0.488 mg/L. Transient pulmonary effects noted on day 2 of the observation period were considered to be test item-related and indicative of an acute pulmonary

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
		clearance reaction associated with an inflammatory response.
Repeated dose toxicity	Low repeated dose toxicity (RDT). A 1998 28-day sub-acute study in rats via the oral route (OECD 407) reported no adverse effects to the highest level tested (1000 mg/kg bw/day). A 2002 sub-chronic study in rats by the dermal route (OECD 411) reported no adverse effects to the highest level tested (1000 mg/kg bw/day). No chronic studies reported.	A 2003 exploratory dermal RDT study was undertaken in rats using non-nano bisoctrizole (Tinosorb® M, FAT 75'634/B - d(05) = 128 nm) suspended in water or base ointment. Following dosing days 1-17, animals given 1000, 1500 or 2000 mg/kg bw/day showed dermal intolerance & pain in a dose-related manner. After a 5-day treatment holiday, dosing was continued for 29 further days at levels of 100, 400 and 800 mg/kg bw/day, with no effects observed (locally or systemically). The results of this study were used to inform further dermal studies (chronic exposure and carcinogenicity). *NB: this data is based on the non-nano form of bisoctrizole. Base ointment composition nor batch pH were not provided in the report. Based on the high pH reported in the irritation studies, it can't be ruled out that this was a contributing factor to low tolerance at the higher dose levels.* A 2006 non-guideline sub-chronic (39 week) dermal study in mini-pigs compared bulk (MBBT) or nanoform (Tinosorb® M, FAT 75'634/B) bisoctrizole suspended in hydrophilic ointment at doses up to 2000

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
		mg/kg bw/day. No toxicity from the nanoform, nor evidence of significant systemic exposure was identified. In the high dose group for the bulk form, detectable plasma concentrations were observed in 1 male and 1 female. The NOAEL for the nanoform was therefore greater than the bulk form (NOAEL bulk = 1000 mg/kg bw/day, NOAEL nanoform = 2000 mg/kg bw/day). No chronic studies reported.
Carcinogenicity	No studies reported.	A 2006 OECD 451 carcinogenicity study in rats using formulated micronised UV filter Tinosorb® (d(0.5) = 128 nm) exposed dermally for 104 weeks reported no carcinogenic properties at up to 400 mg/kg bw/day. *NB. SCCS' review of the study noted a lack of consideration re. non-dose response related findings (increased frequency of malignant tumours with metastasis in the low dose and high dose male rats). Further, issues with a lack of positive control data and evidence on dermal carcinogenicity studies in the performing lab led the SCCS to conclude the study was not of value.* A 12 month Photo-co-carcinogenicity study to determine the influence of Tinosorb® M (FAT 75'634 in base

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
		ointment formulations) on photocarcinogenesis in hairless mice showed a dose-dependent reduction in UV irradiation-induced skin tumour development.
Genetic toxicity	Bacterial: No adverse effect identified in 1991 Ames genetic toxicity study in bacteria (OECD 471), In vitro: No adverse effect was reported in a 1991 mammalian chromosome aberration test (OECD 473) In vivo: 2002 *in vivo* micronucleus test in mammalian somatic cells in mouse (OECD 474). Overall: no concern for genetic toxicity via gene mutation or chromosome mediated effects.	Bacterial: No study reported. This is to be expected, as bacterial reverse mutation mutagenicity assays are not recommended for nanomaterials (OECD 2014)[22]. In vitro: Two 2014 micronucleus tests *in vitro* (OECD 487) undertaken using i) nanoform (Tinosorb® M pH= 10,5 - 49.1% MBBT in aqueous solution) and ii) bulk form (Tinosorb® M, not micronized - 54.7% MBBT in aqueous solution) reported no biologically relevant increase in the number of micronucleated cells either with or without metabolic activation (S9), regardless of dose applied or exposure time. However, higher cytotoxicity was reported in experiment ii. As such, no clastogenic or aneugenic potential was identified. An *Hrpt* gene mutation assay (OECD 476) was also undertaken using the same nanoform and bulk forms for comparison. No biologically relevant increase in the

[22] ECHA Guidance on information requirements and chemical safety assessment, Appendix R7-1 for nanomaterials applicable to Chapter R7a Endpoint specific guidance, Section 2.2.3.1, Version 4.0, December 2022

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
		number of mutant colonies was observed either +/- S9 mix, regardless of the dose applied or exposure time. As such, no mutagenic potential was identified. *All studies reported investigations on particle size distribution in culture media (pre- and main tests). However, no evidence to support cell uptake was provided, nor was there confirmation of exposure of cells in culture to the nanosized form.* In vivo: no studies reported.
Developmental and Reproductive toxicity (DART)	A 1998 prenatal developmental toxicity study (OECD 414) identified no potential for developmental toxicity up to the limit dose (highest possible for this test type) in rats (parental and developmental NOAELs ≥ 1000 mg/kg bw/day). A 2005 one-generation reproductive toxicity study (test guideline not specified) reported no effects up to the limit dose in rats (NOEL ≥ 1000 mg/kg bw/day).	No studies reported.
Endocrine Disruption	No studies reported.	No studies reported.
Human Data	No studies reported.	A 1998 *in vivo* phototoxicity patch test on humans using micronised UV filter Tinosorb® M (10 %) in white cream base applied the test item occluded for 24h then exposed the skin to UVA/UVB radiation in

Endpoint	Registration dataset 1 (bulk)[20]	Registration dataset 2 (nano and bulk)[21]
		a controlled manner. The irradiated test item-treated sites exhibited lower skin reactions than the irradiated vehicle control and saline treatment sites. In a 1998 *in vivo* human repeated insult patch test (HRIPT) using bulk form MBBT and nanoform Tinosorb® M in white cream base, test item was applied occluded then exposed to UVA/UVB radiation as per the previous study. After a 2-week rest period, a challenge experiment was undertaken. Neither substance was photosensitising or sensitising to human skin. In 2x 2001 human patch tests (non-GLP, non-test guideline) using nanoform Tinosorb® M, no potency to cause reactions on human skin was identified. *NB. Data is supporting only due to lack of GLP/guideline compliance*.

5.1.1.4 Additional information on safety profile

Whilst the registered dossier for bisoctrizole does not include any information from endocrine disruption (ED) screening studies, Ashby *et al*. (2001) report a lack of binding to oestrogen or androgen receptors in the rat uterotrophic assay. When placed alongside the lack of relevant effects identified from repeated dose and reproductive toxicity studies, there is no concern for endocrine disruption raised.

No further specific information on the safety profile of bisoctrizole was identified from the literature search.

5.1.1.5 Comparison of bulk and nanoform hazard profiles

There is a reasonable data coverage across the two registrations, with the MBBT and nano-MBBT dataset providing a greater range of studies than the generic bulk chemical dataset available as a disseminated dossier under REACH Regulation and REACH Regulation (GB). For endpoints where studies are not reported for bulk bisoctrizole, it is because they are not required by the information requirements for the annual tonnage of the registration. The data allows for some subtle differences in hazard profile between bulk and nano form to be highlighted. These are discussed in brief below.

Physicochemical properties: examination of key physicochemical properties can provide a 'first impression' on how any substance may act within a biological system, for example with regard to its potential absorption, distribution, metabolism and excretion (ADME) or toxicokinetic profile. In this case, it was possible to identify some relevant information with which to build a physicochemical profile for a specific nanoform of bisoctrizole (namely Tinosorb® M, FAT 75'634), and to place this alongside multiple sources of data for the bulk form. All data was generated to fulfil information requirements of the regulation under which the nanoforms were registered, therefore there are some differences in data coverage between the datasets.

No study on toxicokinetics (TK) specific to nanoform bisoctrizole exists. However, comparable findings between nano and bulk form for dermal penetration were realised (extremely low in intact and damaged skin). As such, based on the current information, it can be expected that the TK profile for nanoform bisoctrizole will be similar to that of bulk form following dermal exposure.

Although there is an ISO technical document in existence which offers considerations for performing toxicokinetic studies with nanomaterials (ISO, 2019), the existing OECD test guideline for toxicokinetics is not applicable for nanoforms at the current time for several reasons. There are no specific provisions for nanomaterials, nor is there sufficient advice on their administration via certain routes of exposure (e.g., inhalation). In addition, it's recognised that nanomaterials will rapidly be removed from the circulation by the mononuclear phagocytic system, making monitoring exposure via blood plasma unreliable. A new test guideline on toxicokinetics specific to nanoforms is under development (April 2020) and is expected to be finalised in 2025 (ECHA, 2017b). This is being further supported by European projects such as NanoHarmony, which aims to support development of test guidelines and guidance document for nanomaterials[23]. As these efforts come to fruition, it is hoped that generation of relevant, reliable, and reproducible ADME data for nanomaterials will be easily achieved.

The acute inhalation study (see Table 12 above) on nanoform bisoctrizole reported noteworthy findings. Rats were exposed in a limit test to a single dose of nanoform

[23] https://nanoharmony.eu

bisoctrizole in formulation (as FAT 75'634) for 4 hours and then observed for 15 days. There were no clinical signs or adverse effects on body weight reported. However, on day 2 of follow-up, various observations were made in the treatment group as compared with the placebo control group, including:

- increases of total cell count (neutrophil numbers);
- increases in total protein in broncho alveolar lavage fluid (BALF, taken as part of a diagnostic check for function of the lower lung);
- increase in lung weight;
- presence of diffuse alveolar histiocytosis (increase in the number of immune cells called histiocytes); and
- alveolar lining cell activation.

These findings were consistent with marginally higher inflammatory cytokine levels (special inflammatory proteins which facilitate cell to cell communication, including TNFα and IL-6) in BALF seen in test item exposed females relative to placebo control females. At the end of the observation period, histopathology confirmed reversal of the effects.

In short, these findings are indicative of a pulmonary inflammatory response similar to that seen with other inhaled ultrafine and nano particles (Elder *et al*., 2000). It is widely acknowledged that particle size influences persistence and clearance of aerosolized particles, with nanoparticles in the smaller size range (e.g., <20 nm) having altered clearance from the lung following exposure due to altered interaction with alveolar macrophages, and reentrainment of nanoparticles from the interstitium to the luminal side of the lung epithelium (Oberdorster *et al*., 1994; Semmler-Behnke *et al*., 2007). As the nanoform bisoctrizole is not in such a size range, it could be postulated that the effect may not be dissimilar to that following exposure to aerosolised bulk form. However, there is no data on acute inhalation toxicity for bulk form bisoctrizole, it is not possible to draw clear conclusions regarding the similarities or differences in hazard profile for this endpoint.

5.1.1.6 Relevance (biological plausibility/hazard to risk translation)

The SCCS opinion on the approval of nano-bisoctrizole for cosmetic uses, calculates a conservative Margin of Safety (MoS) (i.e., a ratio of no-observed adverse-effect levels derived from animal studies to the predicted/estimated human exposure levels, which are based on the 'worst case scenario' to ensure that as much risk as possible is taken into account) for the dermal route of exposure, as the route most likely to be used in sunscreen formulations. The value is based on a comparison of internal dose between the rat (the most commonly used species for hazard assessment) and humans, calculated using repeated dose toxicity data for the bulk form of bisoctrizole. However, given the 39-week dermal study in pigs revealed no effects up to the highest dose tested (1000 mg a.i./kg bw/day), there appears to be little concern for systemic (whole body) effects from dermal exposure to bisoctrizole.

5.1.1.7 Other areas of research interest

Aside from the already discussed gaps in biological response following inhalation exposure, no further areas of research interest were identified during the review of available literature and regulatory registrations.

5.1.2 Summary and key knowledge gaps

It is to be expected that other versions of nanoform bisoctrizole (e.g., produced by different companies, using variations on production method, instrument, or source 'bulk' material) will hold different physicochemical properties, within a range. As such, caution should be urged in assuming that the properties summarised in this document are representative of all

nanoforms of bisoctrizole. In future, better representation for other forms, and where these have similarities (or differences) would be useful to build a more complete picture. For example, this would help to define 'sets' of nanoforms (as seen within the REACH Regulation and REACH Regulation (GB)) with identical physicochemical, toxicological and ecotoxicological hazards, and where it is possible to use grouping of the nanoform with the bulk form in order to allow read-across between the two. Unfortunately, as there appears to be no publicly available registration of the substance under REACH Regulation (and REACH Regulation (GB)) it is not possible to elicit whether further information exists.

A primary gap in relation to bisoctrizole is the lack of a nano-specific toxicological data for some endpoints (for example, reproductive and developmental toxicity). Furthermore, clarification on issues identified within those studies already undertaken, e.g., a lack of data on particle size provided in some studies, or a lack of evidence to support cellular exposure or uptake in studies undertaken *in vitro* would be beneficial, as it would provide clarity on exposure to nano bisoctrizole in each study, and as such, the reliability of the reported results.

Some transient effects were noted following inhalation exposure to nano bisoctrizole, which were linked to an inflammatory response. As such, generation of further data on the potential for consumers to be exposed to inhalable bisoctrizole is desirable. In the case that exposure is possible, further evidence on both TK and hazard profile following inhalation would be beneficial. At the current time, it is noted that the Cosmetics Regulation and Cosmetics Regulation (GB) do not allow uses which may lead to inhalation exposure. However, no such conclusion appears to be in place for other end uses e.g., PPE, or indeed (although not relevant to consumers) in workers during the processing of nanobisoctrizole.

In relation to establishing potential risk from nanobisoctrizole exposure, a lack of clarity on the most appropriate dose metric for hazard and exposure characterisation of nanoforms is a key theme for establishing safety of all nanomaterials. This remains under discussion.

However, the safety profile of bisoctrizole appears to be relatively favourable as directed for dermal use (with inhalation exposure avoided).

5.2 Nanosilver

According to the European Commission and based on the Cosing cosmetic database, silver (nano) is used in cosmetics in its nano uncoated form both in leave-on and rinse-off oral cosmetics products including toothpastes and skin care products with a maximum reported concentration limit of 1% with a function of abrasive, bulking and emulsion stabilising[24].

Silver (nano) has been reported to be used in biocides, where it is being reviewed for use in the EEA and/or Switzerland regarding disinfection, food and animal feeds, drinking water or as a preserving substance for liquid systems[25]. Silver (nano) may be used in metals and welding/soldering products, where release to the environment is likely to occur[26].

Release of silver (nano) in the environment may occur from indoor use in long life materials with low release (e.g., flooring, furniture, toys, construction materials, curtains, footwear, leather products, paper and cardboard products, electronic equipment) and outdoor use in long-life materials with low release rate (e.g., metal, wooden and plastic construction and

[24]Scientific Committee on Consumer Safety SCCS OPINION ON Colloidal Silver (nano) 2018

[25] https://echa.europa.eu/substance-information/-/substanceinfo/100.028.301 (visited February 2023)

[26] Chesar (ECHA) Exposure scenario 9: Use at industrial sites - Use of silver in the production of other silver compounds

building materials). It may also be found in complex articles, with no release intended: machinery, mechanical appliances and electrical/electronic products (e.g., computers, cameras, lamps, refrigerators, washing machines), electrical batteries and accumulators and vehicles and may also be found in products made of materials based on metals (cutlery, pots, toys, jewellery)[24].

Regarding silver (nano) use by professional workers, it may be found in welding and soldering products, metals, metal surface treatment products, semiconductors, adhesives and sealants, coating products, laboratory chemicals, lubricants and greases, metal working fluids, pharmaceuticals and biocides (e.g., disinfectants, and pest control products). It may also be used in health services and to manufacture machinery and vehicles. Release to the environment may also take place due to professional use in the production of articles and from machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners[24].

Table 13, Use profile for silver bulk and nano forms.[24]

Uses information		
	Bulk form	**Nano form**
Environmental release category (ERC)	Industrial use or wide dispersive professional use of substance intended to become part of an article Industrial use of substances intended to become part of an article Disperse indoor use of articles with high release ERC 1: Manufacture of the substance	Widespread use leading to inclusion into/onto article (indoor) Widespread use leading to inclusion into/onto article (outdoor)
Article Category (AC)	Fabrics, textiles and apparel: bedding and clothing, consumer fabrics, textiles and apparel: curtains, upholstery, carpeting/flooring, rugs, Metal products: toys Metal products: furniture	Metal articles
Product Category (PC)	Textile dyes, finishing and impregnating products; including bleaches and other processing aids	Base metals and alloys Welding and soldering products, flux products

Process Category (PROC)	High mechanical work up of massive metals, substances bound in materials or articles Raw material handling Powder handling Handling of solutions/suspensions Wet process Hot process Mechanical processes Spraying Packaging Cleaning and maintenance	Raw material handling Powder handling Handling of solutions/suspensions Wet process Hot process Mechanical processes Spraying Packaging Cleaning and maintenance
Sector of Use (SU)	Manufacturing of fine chemicals	Manufacturing of fine chemicals

5.2.1 Safety profile

The European Chemicals Agency's Risk Assessment Committee (RAC) recommends classifying all forms of silver (massive, powder and nano) for reproductive toxicity category 2 and systemic target organ toxicity via repeated exposure (STOT-RE) category 2 as well as to classify only the silver powder and silver nano as aquatic acute 1 and aquatic chronic 1.

5.2.1.1 Regulatory registration

Silver (EC number 231-131-3) is registered under the REACH Regulation and is manufactured in and/or imported to the European Economic Area, at ≥10 000 to <100 000 tonnes per annum. There are currently 87 active registrants under REACH Regulation, and the substance is known to be on the EEA market in the nanoform, with two compositions under the infocard in the nanosize (<100 nm).

5.2.1.2 Classification & labelling and PBT assessment

According to the classification provided by companies to ECHA under REACH registrations this substance is very toxic to aquatic life (H400), is very toxic to aquatic life with long lasting effects (H410) and may damage the unborn child (H360D). The PBT and vPvB criteria of Annex XIII to the REACH Regulation do not apply to inorganic substances, such as silver.

5.2.1.3 Relevant commentary on physicochemical properties and toxicological profile

Table 14 outlines some of the pertinent endpoints of relevance to building a safety profile for nanoforms, and the available information for each, using data from both bulk and nano form registrations of silver.

Table 14. Comparative data for bulk- and nanoform silver. Capital letters next to trade names are used as reference regarding characteristics of those substances in the different sections of the table. Blanks indicate no data.

Endpoint	Bulk form	Nanoform
Chemical identity		
Name		Silver colloidal
Trade names	Silver	A. Silver Water nano-TECH B. Silver Water nano-TECH C. Silver Water nano-TECH D. Silver Water nano-TECH E. Premium Heritage Colloidal Silver) F. Nanosrebro G. Nanosrebro H. Nanocolloidal Silver (H2O Ag) Non-Chemical I. Ag 100 Koloidné striebro J. Silver Water nano-TECH K. Silver Water nano-TECH L. Silver Water nano-TECH
EC number	7440-22-4	7440-22-4
Structural Formula	Ag	Ag Ag^0 H_20 H_2O Ag
Appearance	Solid	Water dispersion (colloid) of silver nanoparticles; it is a clear liquid with no odour

Endpoint	Bulk form	Nanoform
Particle size distribution (Granulometry)	Silver powder 1: D10: 12 µm, D50: 30 µm, D90: 50 µm, MMAD: 30.1 µm Silver powder 2: D10: 0.8 µm, D50: 2 µm, D90: 11 µm, MMAD: 25.4 µm (Parr, 2009)	(A, B, D, J, K, L) .3-5 nm (80-85%), 5-100nm (15-20%) (F, G) Lowest cut-off 1.56 nm, Number weighted median 5.79 nm (I) 39 nm
Water solubility	Massive silver: <0.02 µg/L (LOD) after 7 and 28 days and a loading of 3 and 9 mg/L. At a loading of 27 mg/L one out of three replicates gave a measurable solubility after 28 days (0.11 µg/L) giving a mean of 0.03 µg/L over all three replicates. All tests done at pH 8 (ECHA, 2013). Silver powder (>100 nm), silver dissolution: pH 6. 1.25-37.4 µg/l at 1-100 mg/L loading and 7 days. 3.55 µg/l after 28 days at 1 mg/l loading pH 8 2.55-26.03 at 1-100 mg/L loading and 7 days. 5.71 µg/l after 28 days at 1 mg/l loading (CIMM, 2009). Silver flakes (>100 nm), pH 6, silver dissolution: 1.79-38.1 µg/l at 1-100 mg/L 3.60 µg/l after 28 days at 1 mg/l loading (ECTX, 2010)	Solubility in water is unlimited (A, B, C, D, J, K, L).
Partition coefficient (*n*-octanol / water)	Not applicable	Not applicable
pH		(A,B.C,D, J, K L) 5-7 (6-7.5) (100 ppm) (H) 5.5 – 7 (max 0.015%) (I) 7.33 (at 23.1 ˚C)

Endpoint	Bulk form	Nanoform
UV/visible light absorption spectrum		(I) no significant absorption peaks over 250 nm.
Melting point	961.8°C (CRC, 2003)	(E) 960˚C
Boiling point	2162°C[27]	(A,B.C,D, J, K, L) Approx. 100 ˚C (E) 2212 ˚C (I) 99.5 ˚C
Density	10.5 g/cm^3 [28]	(A,B,C,D,J,K,L) 0.99-1.01 g/cm3 1.00 kg/l (at 20.0˚C) (I) 0.997504 g/cm3 at 24.0˚C
Viscosity	Not applicable	(A,B,C,D,J,K,L) 1000 x 10-6 Pa x s (100 ppm)
Conductivity	Highest of all metals	(A,B,C,D,J,K,L) 5.0-50.0 µS/cm 23.07 µS (I) 0.5 µS/cm
Turbidity	Not applicable	(A,B,C,D,J,K,L) max 8 NTU
Colour	Metallic grey	(A,B,C,D,J,K,L) max 5 Pt/l
Toxicological information		

[27] Nano-TECH Material safety data sheet
[28] Nano-TECH Material safety data sheet

Endpoint	Bulk form	Nanoform
Acute oral toxicity	There is no robust data available for massive silver or powder consisting of particles in sizes larger than nanoscale. Based on the results from a non-GLP study, an oral dose of 240 mg colloidal silver/kg bw was well-tolerated by rats (ECHA, 2016).	The oral LD50 (rats, guinea pigs) of (colloidal) silver is > 5000 mg/kg (material A, B, C, D, J, K, L)[29,30,31,32,33,34,35,36,37,38] OECD test guidelines (TG) 420, LD50 (rat) >2000 mg/kg, no symptoms of toxicity (material F, G)[39,40] Oral LD50 (mice) of (colloidal) silver is > 10000 mg/kg (material H)[35] Oral LD50 for mice is 100 mg/kg (material F)[39]
Acute dermal toxicity	No data	(G) OECD 402, LD50 >2000 mg/kg, no symptoms of toxicity (material G)[40]
Acute inhalation toxicity	No data	No data
Skin irritation and corrosivity	No data	(A, B, C, D, J, K, and L) do not exert specific irritation[29,41]. (E) no data (G) Irritation index (PII=0,34), classified as “neglectable” following OECD T404[40]. (F) no effect on skin irritation (rabbit, 0,5 g/ 5 ml H_2O for 4h)[39].

[29] Nano-TECH Material safety data sheet
[30] Nano-TECH Material safety data sheet
[31] Nano-TECH Material safety data sheet
[32] Nano-TECH Material safety data sheet
[33] UK Colloidal Silver Ltd. Safety data sheet
[34] UK Colloidal Silver Ltd. Safety data sheet
[35] Cosmetic product safety report No. 275a/06/2015/ENG
[32] UK Colloidal Silver Ltd. Safety data sheet
[37] MSDS-Ag-Eng
[34] MSDS-Ag-Eng

[39] Component Nanosilver (colloidal) Toxicity file
[40] For Health safety file (in Polish).
[41] Purity determination of colloidal silver Ag 100

Endpoint	Bulk form	Nanoform
Mucous membrane irritation and eye irritation	GLP OECD 405 study on 3 New Zeland white rabbits with silver. No corneal or iridial effects were noted during the study. No ocular effects were noted 24, 48 or 72 hours after treatment. However, no information on test item purity was provided	(A, B, C, D, J, K, and L) irritation of eye can result from extended contact[29,37]. Two references (18, 19, colloidal silver dispersion (F, G) no irritating potential on eyes. One of them is based on OECD TG 405 (refers to G)[39], the other on a study using 180 mg of nanosilver in rabbits (18, colloidal silver dispersion (F)[40]. (H) possibility of eye irritation[35] and (E) no data available.
Airway irritation	No data	No data
Sensitisation	Several studies on silver-containing active substances concluded that the test items were non-sensitising. Substances tested were Silver(I) docosanoate (ECHA, 2013), Citric acid / silver(I) citrate mixture (containing 3.2% silver dihydrogen citrate monohydrate[42], Silver zeolite (SZ)[43], Silver thiosulphate (Prinsen, 1995), Silver sodium hydrogen zirconium phosphate[44], Silver zeolite[45], Silver zinc zeolite (SZZ)[46], Silver zinc zeolite (SZZ)[47], Silver copper zeolite[48], Silver copper zeolite[47], A mixture of silver (2438 ppm Ag+), citric acid, and sodium lauryl sulfate (Moore, 1999)	Colloidal silver dispersions do not exert specific sensitisation potential and do not contain any of the 36 allergens[29,49,39]. Furthermore, there are no data on respiratory sensitisation. It is further stated that results of tests in volunteers with the finished product have shown no sensitisation or allergenicity. “The tests were performed with carefully selected volunteers, with the use of the dermatological patch test method according to the semi-open Declaration of Helsinki with the later subsequent additions, the EU and the Republic of Poland rules and the guidelines of the Cosmetic Europe”[35].

[42] RCC 2006 RCC Ltd, CH-4452 Itingen. Study Number A79255 (18 August 2006). FAT 81034/E - Local Lymph Node Assay (LLNA) in Mice (Identification of Contact Allergens).
[43] IIIA 6.1.5-01
[44] IIIA 6.1.5-06 (2000)
[45] IIIA 6.1.5-08 (2006)
[46] IIIA 6.1.5-09 (2002)
[47] IIIA 6.1.5-03 (1989)

[49] UK Colloidal Silver Ltd. Safety data sheet. (57700_safety_file_2013-9-20-19-1-21.pdf)

Endpoint	Bulk form	Nanoform
Repeated dose toxicity	Silver nitrate. No effects observed. Only pigmentation of organs or tissues after repeated oral exposure due to the presence of silver ions	In a 90-day study minimal hepatocellular vacuolation was found in livers of treated animals[50], bile duct hyperplasia and focal, multifocal or lobular liver necrosis.
Mutagenicity/genotoxicity	No in vivo or in vitro reliable studies	No good quality data. Results published in peer review publications indicate that a genotoxic potential of nanosilver both in vitro and in vivo (Awasthi, 2015, Al Gurabi, 2015)
Carcinogenicity	One study using silver zinc zeolite (2.3% Ag, 12.5% Zn) showed statistical positive trends for leukaemia[51]	No good quality data. Results from published in vitro data indicate that nanosilver may have tumour-promoting properties (Schmahl and Steinhoff, 1960), however there is a lack of robust studies
Developmental and Reproductive toxicity (DART)	The evaluation of reproductive toxicity of silver metal (massive and powder) was performed via the weight of evidence approach, which demonstrated that the adverse effects on fertility and reproduction after repeated exposure to nanosilver and soluble silver salts are not expected for silver metal (massive and powder) based on the bioavailability considerations and its direct interaction with the Cu-depletion mode of action[52].	Published studies indicate that nanoparticles of silver can be transferred in milk to the foetus[53] Published studies performed via the oral route and referred to in a review of reproductive and developmental toxicity describe adverse effects on sexual function and fertility (Makoto, 2017), results showed sperm, ovarian and embryonic toxicity

[50] IIIA, 6.8.2-10
[51] IIIA 6.5-06 (1992b)
[52] https://echa.europa.eu/registration-dossier/-/registered-dossier/16155/7/9/1 (last visited 02.12.2022)
[53] IIIB, 6.8.2-17

Endpoint	Bulk form	Nanoform
Toxicokinetics **Distribution and secretion**	Silver nitrate. Available studies are very old. According to information available in the open literature, the silver absorbed from silver nitrate undergoes a first-pass effect in the liver and is excreted into bile after being conjugated to glutathione. The biliary excretion appears to vary between species and the mechanism seems to be saturated at higher doses, at least in the rat (Scott and Hamilton, 1950). The silver absorbed from silver nitrate appears to be widely distributed in the rat. The previously mentioned study observed that the highest amount of silver after an intramuscular dose of silver nitrate was found in the GI tract followed by liver, blood, kidney, skin, muscle, bone, heart, lungs and spleen. Microscopic analyses of tissues from rats orally exposed to silver nitrate and silver chloride in sodium thiosulphate is presented in another publication (Olcott, 1948). Silver was regularly found in histiocytes of lymph nodes and liver, in association with the reticulum fibrils of the sinuses of the lymph nodes and the periphery of the malpihian bodies of the spleen and in close approximation to blood vessels (between endothelium and epithelium of thyroid, choroid of the brain and the glomeruli and tubules of the kidney). It was also found near or in fine blood vessels of pancreas, adrenal medulla, pituitary body (in pars nervosa), choroid of the eye and in striated muscle. A few black granules were observed in the bone marrow	Rats Sprague-Dawley Male Six-week-old Average weight 245g 5/group 2 control groups, 3 experimental groups. $AgNO_3$ Silver nanoparticles. Main target organs for AgNPs and AgNO3: liver and spleen, followed by the testis, kidney, brain, and lungs, without differences in the distribution pattern between the two different AgNPs, or the $AgNO_3$ exposed animals. Higher uptake of silver in blood and organs of $AgNO_3$ exposed rats. Elimination of silver occurred at an extremely slow rate in brain and testis, which still contained high concentrations of silver two months after the final exposure (Van der Zande, 2012). Published information states that the ability of particles to cross the gut epithelium is limited and ion uptake is thus likely the main route to systemic circulation. Results from a 28-day study in rats indicate a similar distribution pattern between silver nitrate and nanoparticles of silver following oral exposure with a higher uptake of silver in animals treated with silver nitrate (Van der Zande 2012). In this study, the proportions of silver uptake from the fraction of soluble silver was similar between the Ag nanoparticles (< 20 nm) and the silver nitrate treated animals (apart from testis and spleen where Ag nanoparticles contributed to higher silver content than silver nitrate) indicating that silver is probably bioavailable mainly in the ionic form. However, since all measured silver could not be accounted for in blood, testis, and spleen solely by the fraction of soluble silver alone, the authors state that a small fraction of particles might still be bioavailable.

Endpoint	Bulk form	Nanoform
	but it was not possible to determine whether or not this was silver and the bone marrow of rats exposed to either silver or water appeared the same. Consequently, it is not possible to conclude whether or not the substance is distributed to the bone marrow.**Error! Bookmark not defined.**	Since silver-containing nanoparticles were detected in liver, spleen, and lungs also in $AgNO_3$ exposed animals, nanoparticles form in vivo from silver ions.
Endocrine Disruption	No studies reported.	
Human Data	According to the summary prepared by the Agency for Toxic Substances and Disease Registry it is not known whether silver causes developmental toxicity in humans. There were no studies found regarding developmental effects in humans after exposure to silver but the document refers to a study by Robkin et al. (1973) in which the possibility of a relationship between the concentration of silver in foetal tissues and the occurrence of developmental abnormalities was investigated. The authors reported that the concentration of silver in the foetal liver of 12 anencephalic human foetuses was higher (0.75±0.15 mg/kg) than the values from 12 foetuses obtained either through therapeutic abortions (0.23±0.05 mg/kg), or in 14 spontaneously aborted foetuses (0.21±0.05 mg/kg). The concentration in 9 premature infants was 0.68±0.22 mg/kg. According to a pesticide re-registration document for silver prepared by US EPA	Testing of the toxicological effects of the product[54] was performed according to Colipa Guidelines on a group of volunteers. All participants fulfilled all the criteria for being assigned to the study, were clearly informed and gave their written consent before participation. The product was applied undiluted on the back of the volunteers repeatedly. All of the volunteers were visually controlled in periodical intervals after application. Volunteers subjectively commented product properties like unpleasant feelings, itching and burning on application area. Mild to moderate skin changes on the application area were reported, like redness, for example. In addition, a dermatological assessment has been conducted in a contact patch semi-occlusive test testing a dispersion called demineralised water "PPUH PAWEŁ" with silver colloid Ago at a concentration of 10 ppm. Twenty volunteers (18 women, 2 men) were selected for the study, including 20 people with a positive allergic history. No allergic reaction was

[54] Cosmetic product safety report. No. 032/1/2013. 32936_safety_file_2016-7-11-14-52-12.pdf

Endpoint	Bulk form	Nanoform
	(EPA, 1981), excessive industrial and/or medicinal exposures to silver have been associated with arteriosclerosis and lesions of the lungs and kidneys. Exposure to industrial dusts containing high levels of silver nitrate and/or silver oxide may cause breathing problems, lung and throat infections and abdominal pain. Skin contact with certain silver compounds may cause mild allergic reactions such as rash, swelling and inflammation in sensitive people	observed in the entire study group (including the persons with positive allergic interview), which indicates that the preparation did not exhibit irritating and sensitising properties[55]. A document on silver prepared by US EPA Integrated Risk Information System refers to a publication by Gaul and Staud (1935) reporting 70 cases of generalized argyria following organic and colloidal silver medication, including 13 cases of generalized argyria following intravenous silver arsphenamine injection therapy. The authors concluded that argyria may become clinically apparent after a total accumulated i.v. dose of approximately 8 g of silver arsphenamine.

[55] srebro-dermatologia

5.1.2.4 Additional information on safety profile

Whilst the registered dossier for silver did not include any information on endocrine disruption studies, Chang *et al.,* (2006) recorded a case study of a 59-year-old man who had ingested colloidal silver two to three times per year for two years and showed endocrine disruptions such as hyperlipidemia, hypertension, and diabetes as well as blue-grey skin (argyria). Considering the noted distribution (e.g., can be found in the testes) of silver the endocrine system may warrant further study and has been the topic during more recent ECHA ED expert group meetings.

5.1.2.5 Comparison of bulk and nanoform hazard profiles

Soluble nanoparticles, such as silver, release ions in solution as they dissolve, released ions produce inflammation, oxidative stress and ultimately cell death (Johnston *et al*., 2010). Hence toxicity has been linked to ion release, which in turn is linked to surface area, with several studies having reported that smaller particles are more toxic (Katsumiti *et al*., 2015, Batchelor-McAuley *et al*., 2014). When this occurs, the hazard displayed and effects in general between bulk and nanoforms are highly similar, with both being driven by the ionic fraction. However, when the silver nanomaterials do not dissolve there is potential for nanospecific effects to occur.

5.1.2.6 Relevance (biological plausibility/hazard to risk translation)

The large amount of data found on different types of nanosilver, in particular regarding genotoxicity clashes with the SCCS opinion on colloidal silica which states that with the data provided it is not possible to draw conclusions on the safety of colloidal silver. The SCCS also recommends a maximum concentration of 1% of colloidal silver used in toothpaste and cosmetic products.

5.1.2.7 Other areas of research interest

The following information regarding silver in the environment was also identified[56]:

- organisms can accumulate silver. Some groups, like algae or small crustaceans, can accumulate silver to very high levels;
- bioconcentration and bioaccumulation are species-specific and controlled by physiological processes rather than physical partitioning. Therefore, (the Bioconcentration factor (BCFs) are not meaningful tools for the risk assessment of silver;
- digestive intake is an important route of uptake, in particular in sediment-associated invertebrates;
- silver bound to sulphides can become available through the ingestion of sediment or detritus;
- bioaccumulation is highly variable, species-specific, and depends on geochemical as well as biological factors;
- there is no general relationship between bioaccumulation and toxicity. Storage of silver in tissues can be a means of detoxification; and
- trophic transfer can be an important route of exposure, but evidence of significant biomagnification is lacking.

It is not meaningful to quantify the accumulation of silver in organisms based solely on intrinsic physico-chemical properties of silver. Furthermore, if accumulated, the possible consequences for toxicity cannot be assessed. This strongly supports the use of conservative assumptions and assessment factors generally, and in particular for benthic

[56] CLH report Proposal for Harmonised Classification and Labelling

invertebrates. Alternatively, chronic toxicity tests with relevant sensitive organisms that include all significant uptake pathways, as well as studies covering several trophic levels, need to be conducted.

Theoretically, by using kinetic modelling and worst-case assumptions (high assimilation rates, high filtration or ingestion rates and low elimination rates), a worst-case bioaccumulation factor could possibly be calculated. However, Rapporteur Member States (RMS) do not consider this meaningful because the resulting factor will still not be useful for the risk assessment, since a general correlation of body burden with toxicity does not exist. Currently, the only way forward would be to include bioaccumulation in an adequately designed toxicity test or mesocosm study.

5.2.2 Summary and key knowledge gaps

Long-term exposure to silver leads to argyria a staining caused by silver deposits in the skin which may not be associated with other adverse effects.

Several studies have been reported using different types of silver nanoparticles, although unfortunately a proper characterisation of the materials was lacking in several of those studies. Sample preparation also poses challenges, but it is highly relevant to allow for study comparison, this information was not always available.

Since particle effects depend on physicochemical properties, characterisation in relevant biological media is of utmost importance to understand different outcomes in reported studies. There is very limited data on silver nanoparticle toxicokinetic properties, particularly metabolism and clearance; although several studies have shown organ distribution, it is not yet clear whether such distribution and the effects observed were due to their nanoform, ionic forms, or a combination of both forms or the formation of secondary particles due to the protein corona.

There is also a lack of studies on the exposure to silver of susceptible populations such as individuals suffering from pulmonary disorders, obesity, hypertension, and diabetes.

5.3 Titanium dioxide

TiO_2 is an inorganic oxide. It has three naturally occurring crystallographic forms: anatase, brookite, and rutile (Figure 4). The rutile is the most common and stable form of the bulk material. However, anatase is commonly used in many applications relevant to this study (e.g., as a coating or in sunscreens) as it is colourless, whilst rutile is dark red in appearance.

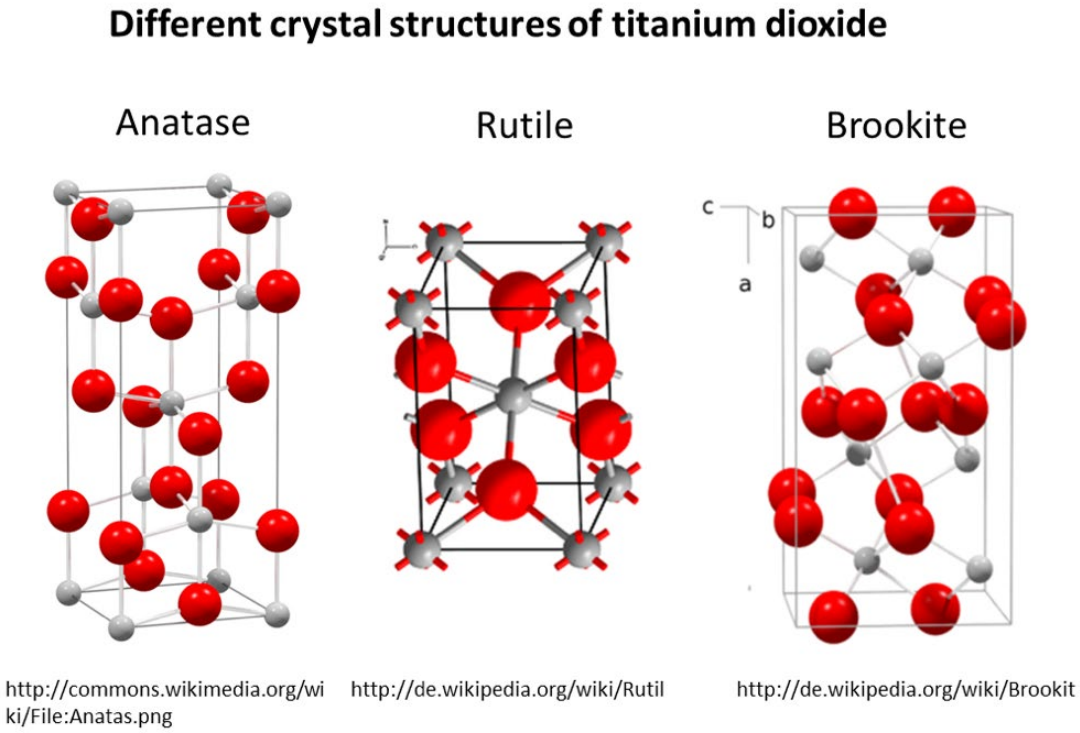

Figure 4. Crystallographic forms of titanium dioxide.

It is known to be on the EEA market in nano form, as highlighted by the European Union Observatory on Nanomaterials (EUON)[57], and is also registered in the French[58] and Belgian[59] national inventories of nanomaterials. According to the European Commission and based on the Cosing cosmetic database, TiO_2 is used as a colourant, opacifier, UV absorber and UV filter.

The nano form of TiO_2 may be prepared using the sol-gel process, chemical vapor deposition (CVD), milling from the bulk form and the hydrothermal method, amongst others.

5.3.1 Safety profile

5.3.1.1 Regulatory registrations

TiO_2 has over 100 active registrations under REACH Regulation[60], its highest tonnage band is ≥1,000,000 tonnes per annum. It is registered for use by consumers (widespread uses in cosmetics, foods, plant protection products, lubricants, biocides, inks, adhesives, pharmaceuticals, dyes and paints), in multiple articles, by professional workers (widespread uses), in formulation or re-packing and at industrial sites (Table 15).

ECHA's substance infocard highlights that the substance is known to be on the EEA market in nanomaterial form, although no stand-alone nano-specific dossier was available at the time of review (data is presented within the general TiO_2 dossier). As a nanomaterial, it is registered with the EU cosmetics inventory, the Belgian nano inventory (≥ 1 to ≤ 10 tonnes per annum) and the French nano inventory (≥ 10,000 tonnes per annum)[61]. It is included within Annex IV and VI of both the Cosmetics Regulation and Cosmetics Regulation (GB).

[57] https://euon.echa.europa.eu
[58] https://www.r-nano.fr/?locale=en
[59] https://www.health.belgium.be/en/environment/chemical-substances/nanomaterials/register
[60] Active registrations of biscotrizole according to the ECHA website, as of February 2023. Accessed at https://echa.europa.eu/information-on-chemicals/registered-substances/-/disreg/substance/100.100.550 (Feb 2023)
[61] https://euon.echa.europa.eu/search-for-nanomaterials - bisoctrizole nanomaterial entry, last accessed 15 Feb 2023

Table 15. Use profile for titanium dioxide nano forms.

Uses information	
	Nano form[62]
Environmental release category	Formulation of preparations Formulation in materials Industrial use resulting in inclusion into or onto a matrix Industrial use resulting in manufacture of another substance (use of intermediates) Industrial use of substances in closed systems Wide dispersive indoor use of processing aids in open systems Wide dispersive indoor use resulting in inclusion into or onto a matrix
Article Category	Plastic articles Machinery, mechanical appliances, electrical/electronic articles Metal articles
Product Category	Adhesives, sealants Metal surface treatment products Ink and toners Adsorbents Products such as ph-regulators, flocculants, precipitants, neutralisation agents Laboratory chemicals Pharmaceuticals Photo-chemicals Washing and cleaning products Cosmetics, personal care products Coatings and paints, thinners, paint removes Fillers, putties, plasters, modelling clay

[62] Use profile built from publicly disseminated dossier on nano TiO_2: https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.033.327

Process Category	Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions Roller application or brushing Tabletting, compression, extrusion, pelletisation, granulation Use as laboratory reagent Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions Potentially closed processing operations with minerals/metals at elevated temperature. Industrial setting Handling of solid inorganic substances at ambient temperature Chemical production where opportunity for exposure arises Mixing or blending in batch processes Transfer of substance or mixture (charging and discharging) at non-dedicated facilities Transfer of substance or mixture (charging and discharging) at dedicated facilities Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
Sector of Use	Formulation [mixing] of preparations and/or re-packaging (excluding alloys) Manufacture of rubber products Manufacture of fabricated metal products, except machinery and equipment General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment Building and construction work Scientific research and development Manufacture of food products Manufacture of bulk, large scale chemicals (including petroleum products) Manufacture of fine chemicals
Belgian Inventory Uses (NACE)	2030 4675101

5.3.1.2 Classification & labelling and PBT assessment

TiO_2, TiO_2; [in powder form containing 1 % or more of particles with aerodynamic diameter ≤ 10 µm], is classified as carcinogenic via inhalation (category 2, H351: Suspected of causing cancer). It is not considered to be persistent or bioaccumulative. In a guide, issued in September 2021, ECHA provided the following guidance on classification and labelling requirements for TiO_2:

'*The substance TiO_2 must be classified as carcinogen if inhaled (Carc. 2, H351 (inhalation) when supplied on its own or in mixtures, where the substance or mixture contains 1 % or more of TiO_2 particles with an aerodynamic diameter ≤10 µm. In addition, mixtures*

containing TiO_2 must be labelled with the supplemental label element 'Hazardous respirable dust may be formed when used. Do not breathe dust' (EUH212).

Non-classified solid mixtures must also be labelled with the EUH212 supplemental labelling element if they contain at least 1% of TiO_2, regardless of their form, or particle size.

Liquid mixtures containing TiO_2 do not require Carc. 2 classification. However, if they contain at least 1% of TiO_2 particles with an aerodynamic diameter ≤10 µm, then they need to be labelled with the supplemental label element 'Hazardous respirable droplets may be formed when sprayed. Do not breathe spray or mist' (EUH211).'

5.3.1.2.1 Regulatory developments related to Classification & Labelling

Over recent years, both bulk and nano form TiO_2 have been subject to intense scrutiny and discussion in the regulatory arena. In 2011, the International Agency for Research on Cancer (IARC) classified TiO_2 dust as an IARC Group 2B carcinogen, meaning it is possibly carcinogenic to humans (IARC, 2010). In May 2016, a report from the French Member State Competent Authority ANSES proposed to ECHA that TiO_2 'in all phases and phase combinations; particles in all sizes/morphologies' be classified as Carc. 1B, H350i. The proposal stated that the available data show that TiO_2 holds carcinogenic properties that justify a harmonised classification and labelling according to Article 36 of CLP Regulation[63].

In 2017, ECHA's Committee for Risk Assessment (RAC) concluded that the available scientific evidence met the criteria in the CLP Regulation to classify TiO_2 (in powder form containing 1% or more of particles with an aerodynamic diameter of ≤10µm) as a category 2 carcinogen: a substance suspected of causing cancer (via the inhalation route) in Delegated Regulation (EU) 2020/217[64] (ECHA, 2017). However, there was insufficient evidence to classify TiO_2 in the more severe category for carcinogenicity (Category 1B), as was originally proposed by the dossier submitter, France.

In 2018, TiO_2 was added to the Community Rolling Action Plan (CoRAP) for further evaluation. Under the cosmetic regulations, a request for its use in cosmetic product as an exception was submitted. The European Food Safety Authority (EFSA) also reaffirmed the safety of TiO_2 as a food additive (E171), following a request on 22 March 2018 from the European Commission for a scientific opinion.

Following publication of SCCS/1617/20 opinion on TiO_2 used in cosmetic products on October 6, 2020, a further change to use according to the Cosmetics Regulation was agreed (SCCS, 2020). From October 1, 2021, TiO_2 (in powder form containing 1% or more of particles with aerodynamic diameter of ≤10µm) was allowed in face products in loose powder form and in hair aerosol spray products (Table 16). Its restriction was therefore added into Annex III to the Cosmetics Regulation. EU exit took place during this period: the change was not reflected in the Cosmetic Regulation (GB).

In 2021, EFSA published an updated safety assessment on the food additive TiO_2 (E171) based on new relevant scientific evidence considered by the panel to be reliable. This included 'data obtained with TiO_2 nanoparticles (NPs) and data from an extended one-generation reproductive toxicity (EOGRT) study'. Observations of potential immunotoxicity and inflammation with E171 and potential neurotoxicity with nano TiO_2 were highlighted, along with a concern for genotoxicity which could not be ruled out. It should be noted that

[63] ANSES (on behalf of the French MSCA), CLH report, Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, Substance Name: Titanium dioxide, Version 2, May 2016

[64] https://www.sgs.com/en/news/2021/07/safeguards-10021-eu-amends-cosmetics-regulation-in-response-to-cmr-substances

less than 50% of constituent particles by number in E171 have a minimum external dimension <100 nm. EFSA noted that no appropriately designed study was available to investigate the potential carcinogenic effects of TiO_2 in nano form. Based on the available evidence, the Panel concluded that E 171 can no longer be considered as safe when used as a food additive (EFSA, 2021). Based on this review, as of 7 February 2022, TiO_2 (E171) has been removed from Annexes II and III of Regulation (EC) No 1333/2008 (the 'Food Additives Regulation').[65]

In the UK, the UK Committee on Toxicity (COT) and Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) undertook a review of the EFSA opinion. The COM assessment is ongoing at the time of writing, but thus far has noted that a lack of quality in the available evidence did not support definitive conclusions to be drawn. The COT considered that the weight-of-evidence did not support the conclusions of EFSA, citing significant weaknesses with reliability of source data. Based on this, the Food Standards Agency confirmed that no safety concerns were identified and as such, no change to regulation in England and Wales is planned. Food Standards Scotland (FSS) also reached the same conclusion.

Importantly, in November 2022, the General Court of the European Union passed a decision to annul the Commission Delegation Regulation of 2022 as regards to the classification and labelling of '*titanium dioxide mixtures in powder form containing 1% or more of titanium dioxide which is in the form of or incorporated in particles with aerodynamic diameter ≤10 µm*' as a carcinogenic category 2 substance by inhalation.[66] In its judgment, the General Court ruled that the Commission made a manifest error in its assessment of the reliability, relevance, and adequacy of the study on which the classification was based, and incorrectly applied the classification criteria as laid down by the CLP Regulation to a substance that has the intrinsic property to cause cancer[67].

On 8th February 2023, the French Government announced that it was appealing the EU General Court's decision to annul the delegated regulation of the European Commission concerning the classification and labelling of TiO_2 as a suspected carcinogen (category 2) by inhalation for certain powder forms. The appeal suspends the court's decision, and as such, the harmonized classification and labelling will continue to apply until the appeal is decided.

Although the REACH Regulation (GB) and CLP Regulation (GB) are distinct from the REACH Regulation and CLP Regulation respectively, these ruling highlights the clear and relevant concern around basing a critical decision on a single study unless there is absolute certainty in its interpretation. At the time of writing, it remains to be seen what the outcome will be in the EU of this change in classification, or how it may be echoed by CLP Regulation (GB), or how these feeds into the GB Mandatory Classification Labelling of the substance.

[65] COMMISSION REGULATION (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E 171); https://eur-lex.europa.eu/eli/reg/2022/63/oj

[66] Commission Delegated Regulation (EU) 2020/217 of October 4, 2019, to amend and correct Regulation (EC) 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures (CLP Regulation)

[67] CJEU Press Release No. 190/22, Luxembourg, November 2022

Table 16. Annex VI of the Cosmetics Regulation (GB), including reference to Annex IV of the Cosmetics Regulation (GB). Where there are differences between the information current within the Cosmetics Regulation and the Cosmetics Regulation (GB), these are highlighted in the 'update date' column.

Substance Identification		**Conditions**			**Update date**
Name of Common Ingredients Glossary	**CAS Number**	**Maximum concentration in ready for use preparation**	**Other**	**Wording of conditions of use and warnings**	
TITANIUM DIOXIDE (cosmetic ingredient, Annex VI)	13463-67-7[1]/ 1317-70-0[2]/ 1317-80-2[3]	25%* *: In case of combined use of TiO_2 and TiO_2 (nano), the sum shall not exceed the limit given in column g (Maximum concentration in ready for use preparation)	TiO_2 in powder form containing 1 % or more of particles with aerodynamic diameter # 10 µm, to be used in compliance with Annex III, No 321. For the product types under letter (c) of column (f) in Annex III, No 321, the maximum concentration in ready for use preparation provided in column (g) of this entry applies. (For use as a colourant, see Annex IV, No 143)		21/06/2021 (details in the 'other' column are currently implemented in the EU but they are not currently reflected in the Cosmetic Regulation (GB) Annexes)
TITANIUM DIOXIDE/CI 77891 (colourant, Annex IV)			Purity criteria as set out in Commission Directive 95/45/E (E 171) TiO_2 in powder form containing 1 % or more of particles with aerodynamic diameter # 10 µm, to be	Purity criteria as set out in Commission Directive 95/45/EC (E 171)	21/06/2021 (current for both UK and EU Annex IV)

			used in compliance with Annex III, No 321 (For use as a UV filter, see Annex VI, No 27)		
TITANIUM DIOXIDE (NANO) (cosmetic ingredient, Annex VI)	13463-67-7[1]/ 1317-70-0[2]/ 1317-80-2[3]		25% - In case of combined use of TiO_2 and TiO_2 (nano), the sum shall not exceed the limit of 25%.	Not to be used in applications that may lead to exposure of the end-user's lungs by inhalation Only nanomaterials having the following characteristics are allowed: purity # 99 %, rutile form, or rutile with up to 5 % anatase, with crystalline structure and physical appearance as clusters of spherical, needle, or lanceolate shapes, Median particle size based on number size distribution # 30 nm, Aspect ratio from 1 to 4,5, and volume specific surface area # 460 m2/cm3, Coated with: Silica, Hydrated Silica, Alumina, Aluminium Hydroxide, Aluminium Stearate, Stearic Acid, Trimethoxycapr ylylsilane, Glycerin, Dimethicone, Hydrogen Dimethicone, Simethicone; or coated with one of the follow-ing combinations: Silica at a maximum concen-tration of 16 % and Cetyl	28/07/2020 (current for both UK and EU Annex VI)

				Phosphate at a maximum concentration of 6 %. Alumina at a maximum concentration of 7 % and Manganese Dioxide at a maximum concentration of 0,7 % (not to be used in lip products). Alumina at a maximum concentration of 3 % and Triethoxycapryl ylsilane at a maximum concentration of 9 %, photocatalytic activity ≤ 10 % compared to corresponding non-coated or non-doped reference, nanoparticles are photostable in the final formulation.	

5.3.1.3 Relevant commentary on physicochemical and toxicological profile

Table 17 outlines some of the pertinent endpoints of relevance to building a safety profile for nanoforms, and the available information for each, using data from both bulk and nanoform registrations of titanium dioxide.

Table 17. Comparative data for bulk- and nano- titanium dioxide. All studies are GLP compliant unless specified otherwise. Data have been compiled from publicly disseminated dossiers; the bulk form column is populated from the information available for the bulk chemical registration and the nano column from the information available on for the nanoform. In this instance, the header information on names is shared, as these are not separated within the disseminated dossier. Please reference the glossary of terms for definitions of endpoints included for hazard assessment. Use profile built from publicly disseminated dossier on nano TiO_2.[68]

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
Chemical identity		
Name	Titanium Dioxide	Titanium Dioxide
Trade names	titanium white "TYTANPOL" AERODISP® AEROPERL AEROXIDE TiO2 AEROXIDE® TiO2 Anatase Anatase Titanium Dioxide C47051 C475001 CSB CSP CathayCoat White TA41, TA42, TA45, TA46, TA49 Cristal DHA-100 DHA-130 Dwutlenek tytanu FerroTint White F31 HOMBITAN HTR-100AP	TTO-S-3 TTO-S-4 Tego Ti-Catalyst C-94 Ti-Pure® Ti-Pure™ TiOx TiOx-220 TiOx-230 TiOx-270 TiOx-271 TiOx-280 Tiona Tiona(r) Tipure Titandioxid KA 100 (Anatase) Titandioxid R-Z (Rutile) Titanium Dioxide Titanium Dioxide Cotiox KA 100 Titanium bioxide enamel grade GZ Titanium bioxide enamel grade LNB

[68] https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.033.327

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	HTR-100SA	Titanium dioxide
	HTR-100W	Titanium dioxide anatase
	HTR-15Z	Tronox
	High Purity Titanium dioxide F31(B)HP	ULTRA FINE TITANIUM DIOXIDE ST-101T
	Hombitan FF-pharma	ULTRA FINE TITANIUM DIOXIDE ST-4
	KA-100	ULTRA FINE TITANIUM DIOXIDE ST-410WB
	KR-1000	ULTRA FINE TITANIUM DIOXIDE ST-450
	KR-2000	ULTRA FINE TITANIUM DIOXIDE ST-450EC
	KRONOS TITANIUM DIOXIDE KA-10	ULTRA FINE TITANIUM DIOXIDE ST-450SA
	KRONOS TITANIUM DIOXIDE KR-310	ULTRA FINE TITANIUM DIOXIDE ST-450WD
	KRONOS Titanium dioxide	ULTRA FINE TITANIUM DIOXIDE ST-455
	Kronos 1171	ULTRA FINE TITANIUM DIOXIDE ST-455WB
	Kronos 2071	ULTRA FINE TITANIUM DIOXIDE ST-455WS
	Kronox	ULTRA FINE TITANIUM DIOXIDE ST-457SA
	Lavanya Chaandani	ULTRA FINE TITANIUM DIOXIDE ST-457WD
	MPT-350	ULTRA FINE TITANIUM DIOXIDE ST-485SA15
	MT(Micro Titanium Dioxide)	ULTRA FINE TITANIUM DIOXIDE ST-486EFS
	MTW	ULTRA FINE TITANIUM DIOXIDE ST-495MC
	No specific trade name	ULTRA FINE TITANIUM DIOXIDE ST-500
	PF-671	ULTRA FINE TITANIUM DIOXIDE ST-550
	RFC	ULTRA FINE TITANIUM DIOXIDE ST-550R
	Rutile	ULTRA FINE TITANIUM DIOXIDE ST-570
	Rutile Titanium Dioxide	ULTRA FINE TITANIUM DIOXIDE ST-6
	SACHTLEBEN	ULTRA FINE TITANIUM DIOXIDE STT-100H
	SHT-R114	ULTRA FINE TITANIUM DIOXIDE STT-300
	SHT-R420	ULTRA FINE TITANIUM DIOXIDE STT-30A-I
	SHT-R422	
	SHT-R610	
	SHT-R615	

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	SHT-R621 SHT-R722 SSP STR STR-100C STR-100C-LF STR-40C SUMTITAN SUMTITAN R-202 SUMTITAN R-203 SUMTITAN R-204 SUMTITAN R-206 T-Lite TIO2 TITANIUM DIOXIDE TITANIUM DIOXIDE 3328 USP TITANIUM DIOXIDE ST-705SA TITANIUM DIOXIDE ST-705WD TITANIUM DIOXIDE ST-710EC TITANIUM DIOXIDE ST-710WD TITANIUM DIOXIDE ST-750EC TITANIX TITONE TTO-55(A)	ULTRA FINE TITANIUM DIOXIDE STT-30A-I-FS10 ULTRA FINE TITANIUM DIOXIDE STT-30A-I-FS5 ULTRA FINE TITANIUM DIOXIDE STT-30S ULTRA FINE TITANIUM DIOXIDE STV-455 UV TITAN biel tytanowa titanium dioxide
EC number	236-675-5	236-675-5
Appearance	Solid, crystalline, white, odourless inorganic substance.	
Particle size distribution (Granulometry)	A number of dustiness studies are reported under the ‘particle size distribution’ endpoint.	A number of dustiness studies are reported under the ‘nanomaterial dustiness’ endpoint.

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	These use method EN15051-2 “Workplace Exposure: Measurement of dustiness of bulk materials – Part 2: Rotating drum method”. They report that that content of particles with aerodynamic diameter ≤ 10 µm was 0.01-0.08 % wt. Further, they demonstrate that TiO_2 bulk has a variable dustiness depending on form, with inhalable, thoracic and respirable dustiness varying between the samples tested. Inhalable dustiness: Low to Moderate (516 - 711 mg/kg) Thoracic dustiness: Very low to Moderate (<80 - 941 mg/kg) Respirable dustiness: Very low to high (<10 - 224 mg/kg)	These use method EN15051-2 “Workplace Exposure: Measurement of dustiness of bulk materials – Part 2: Rotating drum method”. They report that that content of particles with aerodynamic diameter ≤ 10 µm was 0.01-0.61 % wt. Further, they demonstrate that TiO_2 nano has a variable dustiness depending on form, with inhalable, thoracic and respirable dustiness varying between the samples tested. Inhalable dustiness: Moderate to high (2290 - 15330 mg/kg) Thoracic dustiness: Very low to very high (172 - 6148 mg/kg) Respirable dustiness: Very low to high (<10 - 2364 mg/kg) The flavouring E171-E (which has both bulk and nano fractions) was reported to have content of particles with aerodynamic diameter ≤ 10 µm was 0.01 % wt, with moderate (711 mg/kg) inhalable dustiness, a very low (<80 mg/kg) thoracic dustiness and a very low (<10 mg/kg) respirable dustiness.
Water solubility	Microsized TiO_2 does not dissolve to any relevant extent under regular environmental conditions. Water solubility determined according to OECD TG 105 in ultrapure water. Under the conditions of this test (flask method, mean loading of 500.6 mg/L), a solubility equilibrium	Nanosized TiO_2 does not dissolve to any relevant extent under regular environmental conditions. Transformation/dissolution (T/D) testing of three TiO_2 materials ranging in their particle size from 19 to 23 nm and specific surface area from 50.4 to 82.0 m^2/g was tested according to

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	was not observed during the test. Mean background-corrected dissolved Ti concentrations of test solutions in samples (operationally defined as fraction < 2.1 nm, i.e. after filtration through a 0.2 µm membrane and centrifugal filtration) ranged from 0.024 µg Ti/L to 0.172 µg Ti/L, which corresponds to 0.04 to 0.287 µg TiO2/L.	OECD Series No. 29. Measured dissolved Ti concentrations after 28 d at a loading of 1 mg/L at pH 6 and pH 8 were below the limit of detection / quantification (LOD/LOQ) (<0.11 / <0.34 µg Ti/L). After 28 d and at a loading of 1 mg/L, suspended Ti concentrations were below the LOD/LOQ (<0.11/<0.34 µg Ti/L) at pH 8, whereas at pH 6 they ranged from below the LOQ (<0.34 µg Ti/L) to 5.72 µg/L during the 28-day test.
Partition coefficient (n-octanol / water)	N/A – substance is inorganic	N/A – substance is inorganic
pH	No specific study reported.	A number of combined (non-guideline) pH and conductivity studies on 5 different nanoforms of TiO_2 prepared as a dispersion (1% w/w TiO_2 powder in deionised water) found the equilibrium pH and conductivity of TiO_2 to range from: - pH: 2.8 - 8.8 - conductivity: 22.4 µS/cm - 890.3 µS/cm
Additional physicochemical properties of nanomaterials –Nanoform type –Crystallinity Structure –Shape category –Specific surface area –Surface treatment / functionalisation –Surface treating agent ID	N/A	Zeta potential: 5 experimental results were reported for nanoforms of TiO_2. Within these, the approximate isoelectric point was identified to range from 2.5 – 7.5 (in a dispersion (0.01% w/w) in 10-3 M KCl), depending on specific nanoform. For ‘Nanomaterial dustiness’ see ‘Particle size distribution’
Toxicological information		

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
Toxicokinetics (relevant information from absorption, distribution, metabolism and excretion (ADME) studies)	A number of guideline and non-guideline studies are presented within the dataset. Throughout, precise quantification of TiO_2 is hampered by issues such as high background levels of titanium (as an abundant element), poor oral bioavailability, lack of sensitivity of analytical techniques to detect TiO_2. Because it has very low water solubility, an assumption that there will be no dissolution in the gastrointestinal tract could be warranted, although some studies' data suggests that some may occur. Dermal absorption studies on TiO_2 have demonstrated negligible absorption via this route.	A number of academic papers investigating the ADME profile of nano TiO_2 are described within the dataset. Unfortunately, due to significant differences in study design and nanoforms used, it is very difficult to compare between studies in order to draw out themes or conclusions. However, notable are three studies comparing the toxicokinetics of 48V-radiolabeled, pure TiO_2 anatase nanoparticles ([48V]TiO2NP) with a median aggregate/agglomerate size of 70 nm in aqueous suspension after intravenous injection as well as intratracheal and oral administration in female Wistar rats (Kreyling et al 2017a, 2017b, 2017c). Through these studies, it was demonstrated that the toxicokinetic distribution and kinetics after intratracheal instillation and gavage administration were similar, but were distinctly different from the pattern after intravenous injection, disproving the latter to be a suitable surrogate of the former applications.
Skin irritation/corrosion and Eye irritation	Skin irritation/corrosion: A mixture of OECD guideline and well-reported non-guideline studies using pigment grade (bulk) TiO_2 found that it is not irritating to the skin (*in vitro* and *in vivo*). Eye irritation: a 2006 study according to OECD 405 (3 rabbits) found that TiO_2 is not irritating to the eye. A 2004 study exposed 3 rabbits to	Skin irritation/corrosion: *in vitro* and *in vivo* guideline studies with ultrafine and nano TiO_2 report no evidence of irritation. Eye irritation: Two studies using ultrafine TiO_2, according to OECD 405 (3 rabbits) found it not to be irritating.

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	silanised TiO_2. This was not found to be irritating.	
Sensitisation	Three studies conducted with pigment-grade (bulk) TiO_2 show negative results. The tests were conducted according to the Bühler method in guinea pigs, with some deviations from the guideline relating to the numbers of animals used, and grading scale applied. Although there were deficiencies in design and data interpretation, the studies do support a lack of skin sensitising properties when considered together as a weight-of-evidence.	Studies with ultrafine TiO_2 do not report any skin sensitising properties. This is evidenced by a local lymph node assay (LLNA, OECD 429) using mice (25 animals) and a guinea pig Bühler test according to OECD 406 (20 animals). Two further LLNA studies conducted in 2012 and 2015 using nano TiO_2 (15 nm) also report no sensitising properties.
Acute toxicity	Oral: Two acute oral toxicity studies with pigment-grade TiO_2 are available, conducted according to OECD 401 or equivalent. In rats (5/group, 1996) the LD50 was reported to be >2,000 mg/kg bw. In mice (10 male and 10 female/group, 2007) the LD50 was reported to be ≥5,000 mg/kg bw. Inhalation: In acute inhalation toxicity studies with TiO_2 dust (pigment grade and ultrafine), rats were head and nose only exposed for 4 hours with up to 6.82 mg/L air. During the conduct of the studies no mortalities occurred. Therefore, the LC50 inhalation, rat was derived to be > 6.82 mg/L air. Dermal: no studies reported.	Oral: Several non-guideline acute oral toxicity studies with ultrafine or nano TiO_2 are available. In a 2006 study exposing rats (1 or 3/group) to ultrafine TiO_2, the LD50 was reported to be >5,000 mg/kg bw. In a 2007 study using mice (10 male and 10 female/group) were exposed to 80 or 25 nm TiO_2. The LD50 was reported to be ≥5,000 mg/kg bw. Inhalation: A 1989 limit (highest dose only) study using OECD 403 exposed rats (5 male and 5 female /group) to ultrafine TiO_2 nose only with 5.09 mg/L for 4 hours. No toxicity was identified. A number of studies evaluated inflammatory and immune responses within animals' lungs following acute exposure to nano TiO_2. The reliability of the studies for hazard identification was limited due to their design (non-test

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
		guideline, deficiencies in description of methods or reporting of results). As such, the results are not specified here. Dermal: no studies reported.
Repeated dose toxicity (oral)	Although several studies are reported, none are considered within the dataset to be sufficient for hazard and risk assessment alone. Therefore, the endpoint is concluded using weight-of-evidence, including information from two chronic oral toxicity studies, a 90-day subchronic and a 28-day subacute study. In one chronic toxicity study (carcinogenicity study), F344 rats (m/f, 8w old, 50 animals/group) and B6C3F1 mice (m/f, 36d old, 50 animals/group) were fed a diet containing 2% corn oil and 25,000 or 50,000 ppm TiO_2 (anatase) for 103 weeks (7 days per week). The only effects were of spleen haematopoiesis (considered to be incidental), liver necrosis (proposed to be non-test item related), uterus/endometrium hyperplasia (concluded to be within strain historical control levels) and kidney inflammation (proposed to be related to chronic infection rather than TiO_2. In the 90-day repeated dose toxicity study according to OECD 408 (rats 10 animals/sex/dose exposed via oral gavage) reported no observed adverse effects levels (NOAEL) at the highest dose tested in both male and female animals (1000 mg/kg bw/day	Numerous studies using oral exposure to nano TiO_2 have been reported. Many of these are summarised within the existing EU registration dataset, with in depth discussion of their findings and weaknesses. Only two are described in detail here, as they relate to E171, and hold particular relevance to the discussion around classification. A non-test guideline 2017 study evaluated the impact of food-grade TiO_2 (E171) and standardised reference nano TiO_2 (NM-105) on rats in a 7- and 100-day oral toxicity study. Adult male Wistar rats were exposed to E171 or the TiO_2 nano reference substance NM-105 by intragastric gavage in a concentration of 10 mg/kg bw/day for seven days, before sacrifice and testing for tissue inflammation and gut permeability changes. Two further groups of rats were treated with either 1,2-Dimethylhydrazine (DMH) to induce colon carcinogenesis, or vehicle. Seven days later these rats were exposed to E171 at 200 µg/kg bw/day or 10 mg/kg bw/day for 100 days via drinking water. The authors concluded that food-grade TiO_2 impairs intestinal and systemic immune

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	nominal, pigment grade rutile phase), due to the lack of substance related effects on any parameter. These findings were supported by a guideline 28-day toxicity study (OECD 407, 5 males/dose at 0 and 24,000 ppm/day, pigment grade rutile phase). In summary, the dataset concludes that due to a complete lack of adverse effects in all repeated dose toxicity studies with oral route of administration reviewed in the weight of evidence approach, it is concluded that no hazard is identified for TiO_2 in pigment of ultrafine grade for the endpoint repeated dose toxicity (oral).	homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon. It should be noted that there were significant methodological deficiencies in study design and parameters included test item identification, delivery system (water), and assay kits used to for evaluation which are indicative of a lowered reliability in the results reported. In follow-up, a 2019 mechanistic study was undertaken to test the reproducibility of the 2017 reporting that food-grade TiO_2 induces immunologic and carcinogenic effects. Wistar rats received food containing 0, 40, 400 or 5000 ppm food-grade E171 TiO_2 in the diet for either 7 or 100 days. The 100-day study included pre-treatment using the genotoxic carcinogen dimethylhydrazine (DMH) at 180 mg/kg bw or vehicle only (via i.p. injection). In contrast to previous studies, no inflammatory or immune effects were observed, and as such the NOAEL was set at the highest dose of 5000 ppm (236-300 mg/kg bw/day).
Repeated dose toxicity (inhalation)	Due to the extensive evidence available, this endpoint is represented by a comprehensive literature review. For both systemic and local effects, due to deficiencies in all studies, the endpoint is presented as a weight-of-evidence evaluation. Within this, studies administering TiO_2 via inhalation or intratracheal instillation were assessed. The primary effects observed were	Within the dataset, 8 studies relevant to nano TiO_2 are presented. Four studies on the effect of TiO_2 nanoparticles and/or microparticles were outlined. The TiO_2 was administered by whole-body, head-nose or nose-only exposure to mice and rats. From these, a number of observations were highlighted within the dataset:

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	inflammatory and fibrotic responses. There did not appear to be any significant differences in the inflammatory response following single or repeated administration of hydrophobically coated compared with hydrophilically coated TiO_2. Within the dataset, a firm conclusion could not be drawn due to various shortcomings in the available literature. It is noted that the data and findings from three sub-chronic, 90-day interspecies rodent inhalation studies provide convincing mechanistic justifications to better understand the distinct differences in cellular responses to particle overload exposures when comparing rats to either mice or hamsters. Furthermore, the dataset concludes that the studies therein support the understanding that the rat is a uniquely sensitive species in its pulmonary responses to sub-chronic or chronic exposures to high doses of inhaled low solubility dusts, leading to inflammation, the development of fibroproliferative effects, and eventually lung tumour formation. It goes on to conclude that the pulmonary effects observed in rats (inflammatory and fibrotic responses), are also not observed in large mammals such as nonhuman primates and humans, nor through epidemiology studies on TiO_2 exposed workers. As such, the dataset concludes there is no causal link between TiO_2 exposure and the risk of non-malignant respiratory disease in humans.	i) that in vivo inhalation exposure produced upregulation of lung neurotrophils in weanling (2-weeks-old) and newborn (2-day-old) rats but not in adult (12-weeks-old) animals; ii) that signs of dose-dependent partial reversible inflammatory response were observed; iii) that SiO_2-coated rutile TiO2 nanoparticles ($cnTiO_2$) was the only sample that elicited clear-cut pulmonary neutrophilia (uncoated rutile and anatase did not); iv) that pulmonary neutrophilia was accompanied by increased expression of tumour necrosis factor-alpha (TNF-a) and neutrophil-attracting chemokine CXCL1 in the lung tissue; v) that TiO_2 particles accumulated almost exclusively in the alveolar macrophages; vi) that no marked differences between behaviour and elicited lung effects of nanoscale and fine particles were detectable, that particle deposition was similar in both groups, and that no particles were found in cell organelles. As such, no significant difference in the translocation and deposition behaviour of nanoparticles, compared to fine particles, was observed; vii) no difference in toxic potential between TiO_2 nanoparticles and fine particles was found.

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
		Four further studies on the effects of TiO_2 nanoparticles were identified. The TiO_2 was administered by either intratracheal or intranasal to mice at different dose levels and during different time periods. From these, a number of observations were highlighted in the dataset: i) the instilled TiO_2 could induce lung damage, and change the permeability of alveolar-capillary barrier. ii) TiO_2 was able to get access to blood circulation and reach extrapulmonary tissues, then lead to injury at the different level, such as liver and kidney; iii) nanoparticles administration causes inflammatory cell infiltrate and inhibits lung development, but does not significantly affect lung function or pulmonary vascular remodelling; iv) nanoparticle administration increases gene expression and protein amounts of specific cytokines in lung homogenates; v) inhaled TiO_2 nanoparticles could be translocated to and deposited in murine brain after absorbing by nasal mucosa, and further influence the releases and metabolism of monoaminergic neurotransmitters in brain. Although the findings above offer interesting insights to how nano TiO_2 may compare in profile to its bulk counterpart, none of the studies were considered to be relevant for

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
		hazard assessment due to deficiencies in study design or characterisation of the TiO_2 tested.
Repeated dose toxicity (dermal)	Limited information is presented for repeated dose toxicity via dermal exposure. From the information present, the dataset concludes that TiO_2 does not produce local dermal effects after prolonged exposure. Furthermore, due to its poor percutaneous absorption, systemic availability is not expected to occur after prolonged dermal exposure. This is supported by a review of the Scientific Committee on cosmetic products and non-food products[69] and which concluded: "extensive tests…indicate that [percutaneous] absorption does not occur, either with coated or uncoated material […] The toxicological profile of this material does not give rise to concern in human use, since the substance is not absorbed through the skin."	Some references are present in the dataset, representing *in vivo* mechanistic investigations in rats and mice, following repeated dermal administration of nano-size TiO_2. The study designs were not found to be in accordance with accepted guidelines and held multiple deficiencies (low animal numbers, missing dose response relationship, contradictory results etc). As such, the dataset concludes that the criteria for quality, reliability and adequacy of experimental data for the fulfilment of data requirements under REACH Regulation was not met.
Carcinogenicity	Two studies exist with pigment-grade TiO_2. In the first (1985), male and female CD rats were exposed to TiO_2 at concentrations of 10, 50, or 250 mg/m³ for six hours a day, five days a week. The majority of TiO_2 was of respirable size (95% of the particles were <10µm; average particle diameter was circa 1.5µm for high dose group). Findings of lung tumours were reported at the highest dose, although the study authors concluded that these were	No specific studies reported.

[69] SCCNFP/0005/98, 2000

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	of minimal biological relevance. Subsequent review by ECHA (EU)[70] and NIOSH (USA)[71] concluded that the study exceeded maximum tolerated dose (MTD) with a complete cessation of alveolar clearance, and clear demonstration of lung burden overload (even at the lowest dose). As such, the use of the study for classification purposes was not recommended. In a second study (1991), TiO_2 was used as a negative control dust in a two-year inhalation study with toner particles. Male and female rats were exposed (6 hr/day, 5 days/week) to 5 mg/m³ TiO_2 (rutile form) of 1.1µm Median mass aerodynamic diameter (MMAD) with a respirable fraction of 78%. Inhalation of TiO_2 showed no signs of toxicity. Fibrosis was present in the controls at a comparable rate to that of TiO_2 exposed rats, and there were no significant increases in lung tumours vs. control rats exposed for up to 24 months by whole body inhalation to TiO_2. A 1995 chronic study described female Wistar rats exposed via whole body inhalation to ultrafine TiO_2 (80% anatase: 20% rutile) at an average concentration of 10 mg/m³ for 24 months followed by 6 months without exposure. The particle size of the TiO_2 ranged	

[70] ECHA (2017): Committee for Risk Assessment RAC, Opinion proposing harmonised classification and labelling at EU level of Titanium dioxide, Document: CLH-O-0000001412-86-163/F

[71] NIOSH (2011): Current Intelligence Bulletin 63 – Occupational Exposure to Titanium Dioxide, NIOSH Dept of Health and Human Services

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	from 15-40nm with a MMAD of 0.8 mm (agglomerates of ultrafine particles). Bronchioalveolar hyperplasia (moderate to severe) and interstitial fibrosis (slight to moderate) of the lungs was present after 2 years of exposure. First lung tumours were found in serially sacrificed animals after 18 months of exposure; there were no lung tumours satellite groups after 6 and 12 months of exposure. 32/100 rats developed lung tumours after exposures to ultrafine TiO_2. These included benign squamous tumours, 3 squamous cell carcinomas, adenomas and 13 adenocarcinomas. Although there were again issues with exceeding MTD and excess lung burden, as well as interpretation standards and whether the study could be considered as guideline compliant, ECHA regarded the study as acceptable[72].	
Genetic toxicity	Bulk TiO_2 has been tested in bacterial reverse mutation assays, *in vitro* and *in vivo* gene mutation and clastogenicity tests. All show a negative response, thus TiO_2 does not require classification for mutagenic properties.	A large number of studies using ultrafine or nano forms of TiO_2 are presented within the dataset. A selection is included to illustrate. A 2017 non test guideline study investigated the potential for chromosome damage in HCT116 human colon adenocarcinoma cells, exposed to TiO_2 E171 at concentrations of 5, 10, 50 and 100 µg/cm² for 24 h. The study reported positive results (increase in micronuclei (MN)), and suggested that E171 interacts with the centromere region of

[72] ECHA (2017): Committee for Risk Assessment RAC, Opinion proposing harmonised classification and labelling at EU level of Titanium dioxide, Document: CLH-O-0000001412-86-163/F

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
		kinetochore poles during mitosis. However, it is notable that this study had some methodological deficiencies which mean its findings would not meet OECD validity criteria. A 2020 study using another human colon cancer cell line (HT29-MTX-E12) saw cells exposed to E171 at concentration levels of 0.5, 5.0, and 50 µg/mL for 48 hours. No change in MN formation was identified, although it was noted that E171 interferes with the scoring for MN, which combined with the use of a non-standard cell line brings the reliability of the study into some question. In a further non-guideline micronucleus test to establish effects on the number and structure of chromosomes induced by pigment size TiO_2, TiO_2 (NM100; crystalline phase: anatase; particle size distribution: 50-150 nm; surface area: 9.2 m^2/g) was tested via two different *in vitro* micronucleus test methods. No increase in formation of micronuclei was reported. However, as with the previous study, some notable methodological deficiencies were present which mean the findings are unlikely to meet the OECD's validity criteria for such a study. DNA damage was investigated in a number of studies using the alkaline comet assay, reporting mixed results. As the studies all had methodological or validation issues, no conclusion was drawn on the DNA damaging potential of TiO_2 in mammalian cells.

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
		Similar to the results reported *in vitro*, those studies undertaken *in vivo* (both investigating chromosome and DNA damage) reported a mix of results, alongside a wide range of reliability and relevance issues for many of the studies undertaken. Based on the studies considered to be reliable for hazard assessment, the conclusion within the dataset is that in none of the reliable *in vivo* data administering TiO_2 via physiological route in rats or mice was an increase of micronuclei observed. A similar outcome was identified for those studies investigating *in vivo* DNA damage. No reliable data was available on which to conclude about *in vivo* gene mutation.
Developmental and Reproductive toxicity (DART)	Within the dataset, eight references were identified representing studies on toxicity to reproduction, conducted either in mice or rats receiving ultrafine or pigment-grade TiO_2 via oral (gavage or diet), inhalation (whole body), subcutaneous or intravenous administration. The studies were reported as having varied reliability and relevance, with some including methodological or reporting issues which make them unsuitable for hazard assessment. Nonetheless, they report a range of effects. The definitive study to current guideline requirements using E171 and reported in 2020 (reported in the nano column) was used to address the variable findings in the data.	A number of studies are presented within this endpoint. However, the definitive study for hazard assessment is the Extended One Generation Reproductive Toxicity Study (EOGRTS, OECD 443) which was commissioned by the TiO_2 Manufactures Association (TDMA) in response to a request by the European Food Safety Authority (EFSA) on the re-evaluation of TiO_2 (E171) as a food additive[73]. The 2020 study used TiO_2 E171-E, dosing animals up to the limit (highest possible dose of 1000 mg/kg bw/day). It examined systemic and reproductive toxicity in parental animals (20/sex/group) exposed for 10 weeks through the diet, then through pairing for mating, gestation, lactation. The

[73] EFSA Scientific Opinion of 28 June 2016 (EFSA Journal 2016;14(9):4545)

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
	In relation to developmental toxicity, six studies via gavage in rats were reported in the dataset (according to OECD 414, and to GLP). Review of these allowed conclusion that there was no embryo-toxicity and no effect on the development of foetuses. No external visceral or skeletal malformations were observed and the incidence of variations was not different between treated and control groups.	study then assigned offspring to groups for assessment of reproductive/development endpoints (Cohort 1A/B), impact on the developing nervous system (Cohort 2A as adults and 2B as weanlings), and on the immune system (Cohort 3). A selected subgroup of animals (Cohort 1B) were dosed until postnatal day 90 and bred to form a 2nd generation of offspring, which were analysed for developmental toxicity on postnatal day 7. Further satellite animals (10/sex/group) were sacrificed after weaning and examined for presence of aberrant crypt foci (an early sign of pre-cancerous changes in the bowel). Further satellite animals were used for extensive hormone analysis, and whole blood and urine samples were also taken to determine TiO_2 levels. Across all endpoints measured, the study reported no test item related adverse outcomes to the highest dose tested. At the time of writing, some data on immune endpoints and analysis of titanium in whole blood and urine was yet to be reported.
Endocrine Disruption	No studies reported.	One non-guideline study (2020) is described in which *ex vivo* ovary culture is used for assessment of alterations to generation of steroid hormones following exposure to nano TiO_2 in Wistar rats via intraperitoneal (i.p.) exposure. Due to significant methodological deficiencies, the study was not considered to be sufficiently reliable or robust to contribute to hazard assessment. However, it is noted that

Endpoint	Registration dataset (bulk)	Registration dataset (nano)
		progesterone and oestradiol levels measured in the culture media did not differ between control and both nano TiO_2 treated groups.
Human Data	A review of epidemiological data for TiO_2 exposure is included within the dataset; based on three large cohort studies and two large case-control studies, no causative link between TiO_2 exposure and cancer risk was concluded.	No studies reported.

5.3.1.4 Additional information on safety profile
No further relevant information on safety profile was identified.

5.3.1.5 Comparison of bulk and nanoform hazard profiles
There is good data coverage across the bulk and nanoform registrations, with recent studies generally focussed on nano-TiO_2. As the TiO_2 registration from Europe (REACH Regulation was transferred to REACH Regulation (GB) in 2021, most of the data within the current EU dataset will also be within the UK Registration.

Physicochemical properties: In relation to particle size distribution and dustiness, for both bulk and nano the content of particles with an aerodynamic diameter ≤ 10 µm was sub 1%. However, of the nano TiO_2 forms tested, there was both a wider variation in results, and a higher potential for thoracic and respirable dustiness levels to be higher. Both bulk and nano TiO_2 have predictably low water solubility.

Toxicological profile: In relation to local endpoints (irritation, corrosion, sensitisation), there appear to be no differences between bulk and nano TiO_2. Likewise, a very similar profile is present for acute toxicity (oral and inhalation routes). The repeated dose toxicity datasets produce more of a divergence in findings. Although dermal exposure to bulk and nano TiO_2, and oral exposure to bulk TiO_2 produce no cause for concern, oral exposure to nano TiO_2 appears to lead to some more contentious results, which although hampered by method and characterisation issues which make their interpretation, comparison and repeatability difficult, were enough to cause requests for further testing. This was undertaken in the form of an OECD 443 EOGRTS study, which concluded that there were no adverse effects following exposure to E171 TiO_2 for any of the systemic, reproductive, developmental, neurodevelopmental or immune endpoints investigated. Repeated dose toxicity studies via the inhalation route also led to varied outcomes for both bulk and nano, with studies using bulk material reporting some inflammatory and fibrotic responses, and nano reporting a variety of inflammatory responses. In all studies, methodological and interpretation issues once again made reaching a clear conclusion on the hazard of inhalation of TiO_2 difficult. Studies on carcinogenicity reported for bulk form only appeared to echo the findings of the repeated dose inhalation studies as well as report an increased incidence of lung tumours, although once again, issues with excess lung burden and overly high doses brought into question the interpretation of these findings.

5.3.1.6 Relevance (biological plausibility/hazard to risk translation)
The data on repeated dose inhalation exposure to TiO_2 led to the initial proposal by France for classification of TiO_2 as a carcinogen. The subsequent timeline of events and status of this as an ongoing argument has already been outlined.

5.3.1.7 Other areas of research interest
Aside from the topics already discussed relating to carcinogenicity, no further areas of research interest were identified during the review of available literature and regulatory registrations.

5.3.2 Summary and key knowledge gaps

Varying physicochemical properties in bulk and nano-TiO_2 contribute to their hazard profile, evidenced in part by the number of ‘sets’ of nanoform included within the REACH Regulation and REACH Regulation (GB) adopted datasets. As with any nanomaterial, caution should therefore be exercised in application of the available data in a blanket manner; consideration should always be made for the individual properties of the nanoform being considered.

The key gap in understanding for TiO_2 clearly relates to its potential as a carcinogen via inhalation. This remains the focus of intensive discussions, and is clearly dividing the

scientific field, leading to a complex risk management landscape, where use is restricted or banned in some areas, and allowed in others.

6. Regulatory frameworks and industrial standards for the toxicological assessment consumer products

6.1 Regulatory frameworks

The UK left the EU on 31 January 2020 at the end of the transition period when Section 3(1)[74] of the European Union (Withdrawal) Act 2018 (EUWA) saved and converted into UK law most (but not all) directly applicable EU legislation (such as EU regulations), as they had effect in EU law immediately before the end of the transition period to become part of retained EU law. Brexit Statutory Instruments (SIs) amended the retained EU law to ensure it continues to operate. Any modifications to EU legislative instruments, thereafter, do not apply in Great Britain (GB) but will apply under and in accordance with Annex 2 of the Northern Ireland Protocol (as amended by and subject to the Windsor Framework). However, they may bear relevance for potential future application in GB legislation or consideration for adaptation and then implementation in GB. As such recent updates in the EU have been discussed in the following sections.

Before moving forward with specific responsibilities of manufacturers under the already noted areas in Section 2.1 (i.e., cosmetics, toys, nightwear and PPE) it is important to note, that while the authors appreciate some responsibilities are covered by derogation from broader regulations such as the REACH Regulation and REACH Regulation (GB), and the GPSR they are not covered in full here.

Firstly, the responsibilities under REACH Regulation and REACH Regulation (GB) only apply when manufacture or import exceed one tonne per year. With many nanomaterials being needed in smaller volumes to be effective in products there is often occasion where these regulations will not apply. Moreover, for such substances where classification and labelling may still be relevant, testing for the purpose of classification only is not encouraged by CLP Regulation or CLP Regulation (GB). Further, CLP Regulation and CLP Regulation (GB) are not under the remit of the OPSS and should be focused on by those who have direct responsibilities for them. For further information different sources are available e.g., NanoHarmony, EUON, ECHA Appendices to the Guidance on the Information Requirements and Chemical Safety Assessment and OECD guidance documents such as the Series on the Safety of Manufactured Nanomaterials. Also, REACH Regulation and REACH Regulation (GB) are regulations based on a per substance registration ethos. Products are often tested, exactly as that, products, and the responsibilities may differ. When substances do require analysis outside of whole product assessment, this is usually dealt with by using existing information or testing that is specific to the applicable regulation, not that of REACH Regulation or REACH Regulation (GB). For example, migration of substances during the use of toys.

GPSR provides the basis for ensuring the safety of consumer goods by setting requirements that apply in the absence of requirements imposed under sector specific regulations applying. GPSR also provides a range of provisions to secure compliance and enforcement with the GPSR requirements that apply. For example, GPSR imposes the following obligation on producers:

[74] https://www.legislation.gov.uk/ukpga/2018/16/section/3

'No producer shall place a product on the market unless the product is a safe product;

(1) No producer shall offer or agree to place a product on the market or expose or possess a product for placing on the market unless the product is a safe;
(2) No producer shall offer or agree to supply a product or expose or possess a product for supply unless the product is a safe product;
(3) No producer shall supply a product unless the product is a safe product.'

It should be noted that producers often demonstrate compliance by relying on the voluntary or inhouse standards, in line with the obligations of the specific regulations for the products noted e.g. PPE, Cosmetics and Toys. The exception is nightwear, for which the standards are mandatory and listed in the Nightwear (Safety) Regulations 1985. The Textile Products (Labelling and Fibre Composition) Regulations 2012 (the 'Textile Products Regulations') are a wider DBT responsibility also and not within the remit of OPSS. However, this section will not be dedicated to this broader regulation, regulations that relate regulations for specific substances or those outside the remit of the OPSS. It will also not explore those products and regulations that are under the remit of OPSS but are not the focus of this research.

6.2 Manufacturer's responsibilities

6.2.1 The Cosmetics Regulation and Cosmetics Regulation (GB): framework and knowledge gaps

As can be seen from answer to research Question 1: 'What is the prevalence of metal and non-metal nanomaterials in consumer products on the UK market?' (Section 3), there is a relatively high prevalence of nanomaterial use in cosmetics in the UK. In fact, cosmetics with nanomaterials accounts for 66 % of nanomaterials available on the consumer market in the UK (Section 3). The main nanomaterials used in cosmetics are the inorganic metal oxides, TiO_2 and SiO_2, as well as the organic nanomaterial bisoctrizole. The safety and prevalence have been covered in Section 5 and Section 3, respectively. Due to the prevalence and thus the availability of cosmetics containing nanomaterials in the UK market it is important to understand the obligations of the manufacturers or 'responsible persons. Moreover, it is of utmost importance to understand the challenges when trying to comply with these obligations, to address knowledge gaps and understand whether the current obligations sufficiently protect the consumer. The following provides a brief overview of the obligations for cosmetic manufacturers under the Cosmetics Regulation (GB) and critically analyses the regulatory framework and tools at the manufacturer's disposable to allow compliance.

There are specific provisions under the Cosmetics Regulation (GB) for nanomaterials. However, the definition used is not in line with the definition of a nanomaterial as presented by the European Commission (2011) as presented in Section 2.2. The definition of a nanomaterial under the Cosmetics Regulation (GB) is in line with its EU counterpart and as already noted in Section 2.2 is as follows:

> *'[A nanomaterial is] An insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.'*

When an ingredient fulfils this definition, it is subject to the nano-specific provisions under the regulation.

Within a regulation 'Articles' provide instruction on what provisions must be made in order to comply with the regulation and subsequently the ability to market a specific product. For the Cosmetics Regulation (GB) key Articles which contain requirements in respect of nanomaterial specificity include:

Article 13- Notification (https://www.legislation.gov.uk/eur/2009/1223/article/13#text%3Dnanomaterial),

Article 16- Notification of Nanomaterials (https://www.legislation.gov.uk/eur/2009/1223/article/16#text%3Dnanomaterial) and

Article 19- Labelling (https://www.legislation.gov.uk/eur/2009/1223/article/19#text%3Dnanomaterial). It is beyond the scope of this report to present these Articles in detail.

By considering the requirements contained in the Articles stated above, it is possible to highlight knowledge gaps and challenges therein, for compliance. Moreover, it is possible to highlight if further provisions will aid in consumer safety, without negatively influencing market competition.

Manufacturers need to understand if they utilise a nanomaterial in a product based on particle size, and whether the nanomaterial is (in)soluble and biopersistent (i.e., how long it lasts in the body).

6.2.1.1 Measuring size

There are major challenges for the manufacturer in positively identifying the presence of nanomaterials in their consumer products based on these criteria. Firstly, though the OECD TG 125 (OECD, 2022d), for the assessment of Nanomaterial Size and Size Distribution of Nanomaterials has been released, there are still several possible methodologies for the measurement of nanomaterial size. The manufacturer will be presented with this plethora of options from light scattering techniques to microscopy. However, not all methods are acceptable for all nanomaterials and selection of methods other than electron microscopy (which will be explained later) require prior knowledge of the nanomaterial's physical characteristics, e.g., shape, size, and agglomeration status (OECD, 2022d). Both the OECD TG 125 (2022d) and ISO 22412:2017 provide guidance on how to measure size via dynamic light scattering (DLS) but, DLS is not appropriate for nanomaterials that have a wide size range, that agglomerate/aggregate or that do not stay suspended in the testing medium. In general, such techniques are not recommended due to such shortcomings. It is also true that no one method is usually applicable to all nanomaterials and in fact it not only depends on the particle but also the purpose of the measurement i.e., all planes or perhaps the narrowest plane of a platelet. The myriad of methods causes difficulties when manufacturers attempt to comply with regulations and can lead to confusion. However, the OECD TG 125 (OECD, 2022d) goes some way to aiding the decision to ensure robust regulatory outcomes and correct method selection but does not fully cover nanomaterials that fall under the disc, platelet or flake definitions.

Another area of uncertainty as it pertains to the measurement of size, is the lack certified reference materials available for all nanomaterial types. Certified reference materials (CRMs) are simply materials with known properties that allow the verification of an experimental set-up. For example, if you know the reference material has a size of 10 nm, and your experiment also shows the measurement is 10 nm then your experiment is accurate and precise. This validates any results on the manufacturer's material. Again, the

OECD TG 125 expands on the useable CRMs by providing a list of materials that were not necessarily CRMs but were used to validate the contained methods within this guidance and considered suitable to validate inhouse experimental procedures. Again though, there is a total lack of any example platelet materials.

There are powerful microscopes, known as electron microscopes, which can measure the size of nanomaterials but for nanomaterials such as amorphous SiO_2 it can be difficult to isolate the perimeters of the individual particle to establish size distribution. This is because amorphous SiO_2 quickly aggregates to form apparent larger particles. These larger particles are in fact bound groups of nanoparticles, but due to the strong bridging at the boundaries of the original nanoparticles where the connections are formed are no longer identifiable. It is best to imagine holding two pieces of plasticine, when apart you can see the boundary of each piece. When pushed together, it forms one larger piece of the previous two with no recognisable boundary. Moreover, the end results a manufacturer gain will depend on how the particle was measured. As particles are often not spherical several measures can be taken such as the minimum Ferret diameter or maximum inscribed circle (see Glossary for definitions of these measurements). The JRC (2019) recommends the use of the aforementioned measurands for the implementation of definitions as they allow direct measurement of the particles' minimum external dimension. However, it is unclear if this is acceptable under the Cosmetics Regulatory framework that applies in Great Britain and Northern Ireland.

Before, the manufacturer enters the stage of deciding experimental methodology they must first find an appropriate facility to conduct the test. Many of the above highlighted size-determination techniques are not frequently available at commercial laboratories. Further, under the European Commission definition it is clear that if the percentage number of nanosized particles is less than 50 %, then the material is not defined as 'nano'. However, there is no percentage threshold for cosmetics under the Cosmetics Regulation (GB) and the Cosmetics Regulation. This could mean that something defined as a nanomaterial under one regulatory framework may not be under another. The SCCS in 2019, recommended that the European Commission definition be borne in mind during compliance with the Cosmetics Regulation. It therefore becomes difficult to say conclusively if a nanomaterial is in a product as there are no standard definitions that give quantitative direction to a materials designation as a nanomaterial.

Due to the changing nature of nanomaterials based on changing condition in their environment (media composition, pH, etc.), nanomaterials need to be characterised in their pristine state, after addition to the cosmetic formulation and as used in toxicity testing (cell culture media). The important parameters and methods for identification and characterisation of nanomaterials intended for use in cosmetic products, that should be provided as recommended by SCCS (2019), can be seen in Table 18 below.

Table 18. Relevant data provisions for nanomaterials to be used in cosmetics. Please note, abbreviations can be found in the Abbreviations section.

Parameter	**Method (non-exhaustive)**
Chemical identity	Analytical methods MS, AAS, ICP-MS, FTIR, NMR, Mössbauer spectroscopy, etc.
Chemical composition	Analytical methods UV-Vis, HPLC, GC/LC-MS, AAS, ICP-MS, FTIR, NMR, XRD,Mössbauer spectroscopy etc.
Particle size distribution	FFF, HDC, HPLC, Analytical ultracentrifugation, CLS disc

Parameter	Method (non-exhaustive)
	centrifugation, TEM, SEM, AFM, DLS, DMA, PTA/NTA
Morphology and shape	AFM, TEM, SEM, NMR, XRD
Structure	TEM, SEM, AFM
Crystallographic structure	XRD, TEM
Surface area	BET
Surface characteristics	LDE, SPM, XPS, MS, RS, FTIR, NMR, analytical ultracentrifugation (for surface composition), GE, SPM, LDE, Phase Analysis Light Scattering (for zeta potential), Nano SIMS, SERS, and Mössbauer spectroscopy.
Solubility	Solubility / dissolution rate in water and other relevant solvents.
Catalytic activity	Kinetic measurements of chemical, biochemical and/or catalysed reactions
Concentration	A wide range of analytical methods, including UV-Vis, HPLC, GC/LC-MS, AAS, ICP-MS, etc.
Dustiness	EN 15051:2006.
Density	ISO697:1981, EN ISO 60:1977
Redox potential	Potentiometric methods, X-ray absorption spectroscopy.
pH	pH in aqueous media
Stability	MS, HPLC, DLS, FTIR, NMR

Further, guidance is required on the acceptable techniques for measuring nanomaterial size, and what cut-offs (e.g., percentage of nanoparticles in a material) if any, are relevant to define the material as a nanomaterial. Guidance on the minimum requirements for characterisation, like those established by the SCCS, is of use. Otherwise, there may be inconsistency in the data provided and inaccurate material categorisation. At best, industry may be inclined to navigate these difficulties through use of the existing guidance for the EU legislative frameworks.

6.2.1.2 Measuring (in)solubility and biopersistence

The other factors for categorising a nanomaterial under the Cosmetics Regulation (GB) and Cosmetics Regulation are (in)solubility and biopersistence. Clarity with respect to how 'insoluble' and 'biopersistent' are defined would be of benefit. Again, although the SCCS provides opinions relevant for the EU legislative frameworks, which are of use to manufacturers in the UK, equivalent UK guidance is not currently available. According to an SCCS report from 2019 Solubility means: *'disintegration of a nanomaterial in an aqueous medium or biological environment into molecular components with the loss of nano features'*. Following the recommendations from the European Pharmacopea (Brayfield, 2023), the SCCS provided some guidance for manufacturers to address solubility according to Table 4 seen in Section 2.2

Even in respect of defining the solubility classifications, as above, there is still difficulty regarding solubility testing of a nanomaterial and how fast or slow it has to dissolve for it to

be classed as ‘not biopersistent’ or ‘biopersistant’, respectively. As stated in the OECD guidance document No. 318 ‘dissolution rates from nanomaterials are particularly important in determining risk/hazard since the rate of release of ions/molecules prior to interaction/complexation with ligands may be more important than equilibrium concentrations’ (OECD, 2021a).

It may be prudent at this time to perhaps unify thoughts with other jurisdictions and regulations to ease any understanding and regulatory compliance burden. Such moves make markets more accessible by being able to target more than one jurisdiction with any compliance strategy. For example, an option could be to unify terminology such as biopersistence by following the current EFSA and ECHA guidance. Said guidance indicates that a ‘highly soluble’ nanomaterial has a solubility in water of ≥33 g/L and a dissolution half-life (i.e., how long it takes 50 % of the material to dissolve) of <10 minutes (ECHA Appendix R.7-1, 2021). Some emerging work in nanomaterial dissolution includes nanomaterial dissolution in sweat thresholds noted in the EU project GRACIOUS (an EU project that worked towards methods for read-across, grouping and integrated testing strategies for nanomaterials), whereby a dissolution half-life of <1 hour would be considered as indicating that the nanomaterial specific effects do not require testing (Stone *et al*., 2020). Other such cut-offs relevant to other exposure routes should also be sought.

To highlight the complications in interpretation of nanomaterial persistence, an example is presented here. Though water soluble materials at the nanoscale are unlikely to be biopersistent, there are complex exceptions to this opinion. Interactions with body fluid may make for more persistent or less persistent nanomaterials and/or the dissolved fractions may in fact produce *in situ* nanomaterials (OECD, 2018a Series Number 86). This will depend on many things including material and the pH of the body environment where the nanomaterial may reach or persist. For example, protein coronas (a protein coating on a nanomaterial formed from body proteins) formed in the body may serve to both stabilise and destabilise a nanoform and the formation of a protein corona may depend on the coating of a nanomaterial (Akhter *et al*., 2021). It can reduce charge and lead to agglomeration and/or lead to better dispersion and reducing cell toxicity (Akhter *et al*., 2021 and Hu *et al*., 2011).

How exactly to measure the above parameters of biopersistence and solubility are other key issues. These are not just issues specific to this regulation and the challenges remain in academia and other regulations as highlighted by recent OECD guidance documents (OECD GD 318, 2021a).

The OECD have specific test guidelines for measuring non-nanomaterial solubility under the OECD test guideline number 105 (Water Solubility; OECD 105, 1995). Such test guidelines do not yet exist for nanomaterials. However, there is currently an ongoing OECD ’Working Group of National Co-ordinators of the TGs programme (WNT)’ project underway to address this globally. The result of this project will be an OECD test guideline on the Determination of Solubility and Dissolution Rate of Nanomaterials in Water and Relevant Synthetic Biological Media, aiming to provide harmonised approaches for testing solubility and dissolution rate of nanomaterials via static batch testing and dynamic flow-through methods. This is in conjunction with an EU project called NanoHarmony. NanoHarmony has the mission to support the development of Test Guidelines and Guidance Documents for eight endpoints where nanomaterial-adapted test methods have been identified as a regulatory priority.

Relevant sources of guidance and information may include NanoHarmony, the OECD guidance document 29 on Transformation/Dissolution of Metals and Metal Compounds in Aqueous Media (OECD GD 29, 2001) and guidance document 318, for the testing of

dissolution and dispersion stability of nanomaterials and the use of the data for further environmental testing and assessment strategies (OECD GD 318, 2021a).

Regardless, there are advantages and disadvantages to running either static or flow-through methodologies and a case-by-case decision must be made depending on regulatory purpose and the nanomaterial to be tested. For instance a static 24-hour screening study as prescribed by the OECD GD 29 (2001) can be useful to test the solubility limits of many nanomaterials and the dissolution rate of sparingly soluble and slow dissolving nanomaterials (OECD GD 318, 2021a), but would fail in accurately measuring the same endpoints for very fast dissolving materials where saturation of the test system may be reached quickly and skew the interpretation of dissolution rate. In the latter instance a flow-through system may be more appropriate, whereby fresh water is introduced and saturation is not reached in the medium due to this. All are complicated matters which require expert knowledge and interpretation.

Other methodological shortcomings relating to nanomaterial solubility testing, which may lead to false conclusions, may include using filtration devices (i.e., sieve like surfaces). Traditionally these devices are used to ensure all particulate is removed from water, to ensure that only the soluble fraction was measured. However, once dissolved, metals usually have a charge which can lead to the dissolved matter sticking to the filter. The solubility is therefore underestimated, and an incorrect material categorisation may be concluded. There are of course ways around this on some occasions, such as pre-exposure of the filter to the ions to reducing loss during testing by ‘filling’ adsorption sites so there is nowhere left for these ions to bind. This highlights the need for meticulous planning for nanomaterial testing.

At present, there are ISO reviews for persistency testing of nanomaterials (Nanotechnologies — Use and application of acellular *in vitro* tests and methodologies to assess nanomaterial biodurability, ISO/TR 19057:2017), but specific guidance on testing may be welcome.

Another consideration of biopersistence is whether this is simply related to the rapid dissolution of the nanomaterial or also complete and rapid excretion.

If the material is not biopersistent and/or dissolves rapidly and is highly soluble it is assumed that tests on the solute would be sufficient in addressing risk. However, if not nanospecific testing may be required to adequately assess the fate, exposure, and risk.

Once a material is categorised as a nanomaterial, and it is not considered that the nanomaterial rapidly dissolves, a nanomaterial specific risk assessment (i.e., exposure vs hazard) approach may be followed. The flow of this assessment is shown in Figure 5.

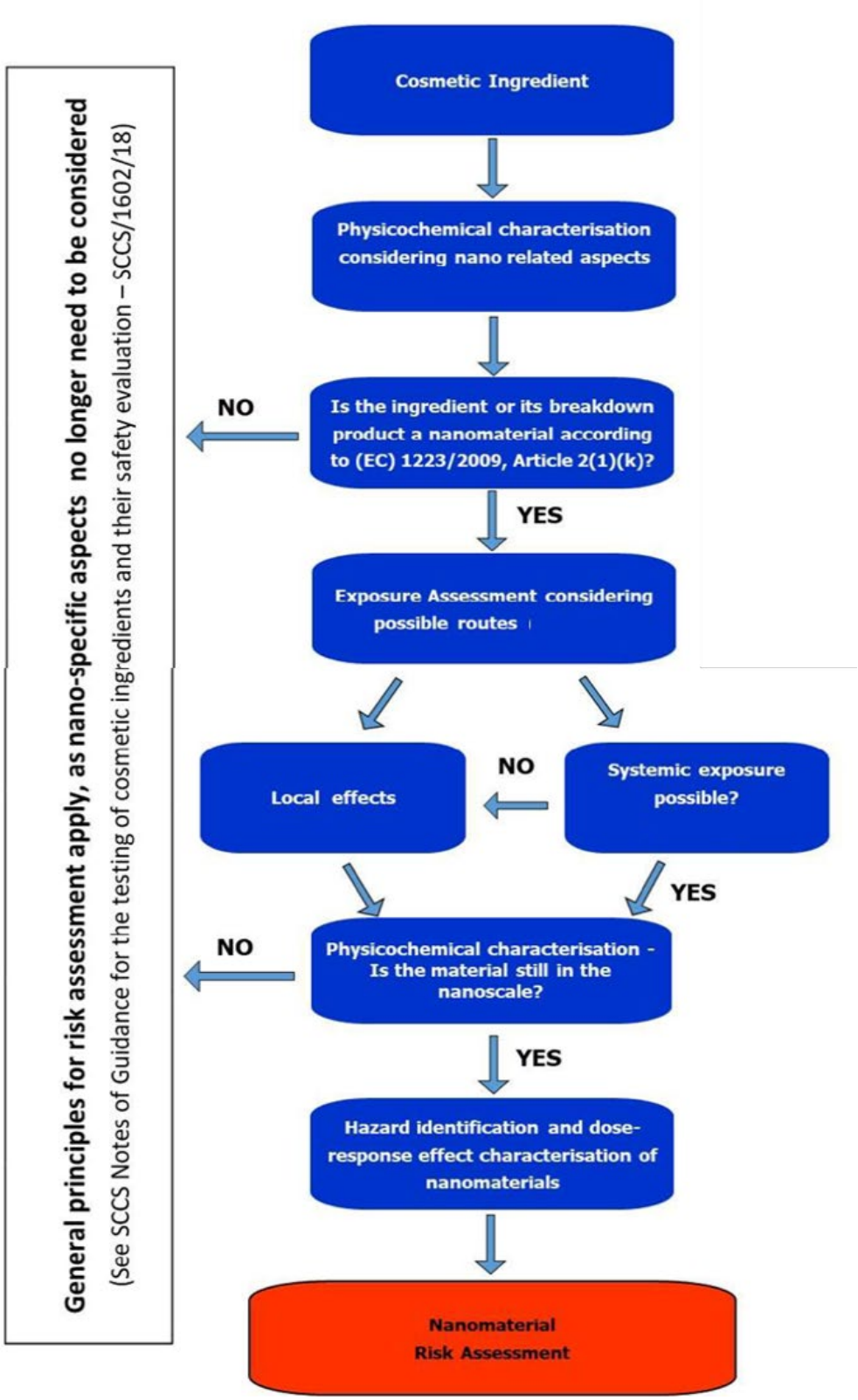

Figure 5. Schematic outline for the safety assessment of nanomaterials in cosmetic products (adapted from SCCS 2019).

6.2.1.3 Exposure assessment

As can be seen in the Figure 5, once it is known that there is a nanomaterial, risk must be assessed. The risk assessment is an assessment of exposure vs. hazard as discussed previously. Either qualitative or quantitative exposure/hazard will allow for a qualitative or

quantitative risk assessment, respectively. Qualitative exposure assessments often rely on use patterns or physical chemical parameters, for example, the product is not intended for ingestion and therefore is not a risk via the oral route or, the material has low dustiness and therefore airborne particles and subsequent inhalation are of low concern.

6.2.1.3.1 Use pattern

With any ingredient or product it is important to identify the use of the product and subsequently the relevant exposure scenarios. This will allow for realistic and appropriate exposure estimations as well as selection of the most appropriate routes of exposure. For a cosmetic product, generally, both dermal and inhalation exposure routes are assessed because products are often sprayed onto, or applied to, the skin. Oral exposure is less relevant, however, such products which may lead to inadvertent ingestion (i.e., toothpaste, mouthwash or lipstick) must be assessed for the oral route.

The authors now look toward the SCCS Guidance on the Safety of Nanomaterials in Cosmetics (2019). The first aspect to be addressed is the specific nature of the nanomaterial when in contact with the consumer, which may be significantly different to the nanomaterial in its pristine form (e.g., as a raw material before incorporation in products). A comprehensive understanding of the material's physical characteristics is crucial, for example, it has been noted that nanomaterials >5 nm will not penetrate (in their particle form) viable (e.g., non-injured) layers of the skin above 1%, but those <3 nm may be readily absorbed (Stone *et al*., 2020). Assessing these characteristics in complex media, such as thick cosmetics or in human sweat, presents a huge challenge as they contain many other particles, or measurable units such as proteins, which can interfere or make it difficult to differentiate between the particles of interest and those present naturally.

Another issue as it concerns to exposure is selection of the appropriate way to measure hazard. For instance, it could be done by mass to body weight (mg/kg bw), or by particle number count to body weight (number of particles/kg bw). There is evidence that both ways to measure hazard can be relevant, and that which is selected depends on the toxicological mode of action, the exposure route, and organism. Moreover, these are not the only options to measure an exposed dose of nanomaterials (Delmaar *et al*., 2015). Choosing the correct dose metric rather comes down to the dose metric which shows the best, usually most monotonic (i.e., stepwise increases or decreases following a regular pattern), relationship with the toxicological response. In some cases, this is difficult to establish in advance. Therefore, in most instances, due to a lack of consensus, it is advised where possible to use all possible dose metrics to ensure longevity of any experimental results. This will ensure that the most relevant dose metric can be used when evidence arises in favour of one. It is also important that whatever the dose metric used, that the hazard assessment is also expressed in the same dose metric. For example, if exposure is expressed as particle number based, then the hazard for comparison must also be expressed as a particle number. The decision should be made based on practicability and evidence of appropriateness based on information for the nanomaterial in question, as well as the availability of exposure prediction tools for the dose metric where required.

6.2.1.3.2 Exposure modelling

Currently, there are no broadly accepted tools in the regulatory space to calculate exposure. That is not to say models do not exist but validation and acceptance are key issues. The OECD Working Party for Manufactured Nanomaterials (WPMN) has recently reported on the applicability of use for certain nano-sepcific and non-nano-specific models for the prediction of consumer exposure (OECD, 2021a-c). For example, inhalation can be modelled using Stoffenmanager Nano (https://nano.stoffenmanager.com). Beyond this, exposure assessment tools, such as ConsExpo Nano (https://www.consexponano.nl), are

available. The ConsExpo Nano tool provides an exposure estimation of a given nanomaterial and uses several different metrics to express exposure. From a list of over 32 tools for occupational and consumer exposure prediction only 7 were taken forward to assess performance. The performance testing assessed the predictive capability of the models/tools by comparing the output of these models/tools with direct measurement (monitoring) data of exposure. However, testing performance based on measured data in itself has limitations due to low availability of measurement data of suitable robustness for the performance testing of consumer exposure scenarios. In the work conducted by the OECD (2021a-c) the performance testing was limited to a few case studies. The project highlighted a knowledge gap and need for measured data for use in development, evaluation and implementing of models/tools to estimate exposure to nanomaterials for consumer exposure scenarios. Therefore, it is highly advised that as more data becomes available the performance of these tools is once again assessed. In fact, for any exposure tool continual re-validation is highly recommended as measured data becomes more widely available. From this project, the noted tools and what are considered acceptable uses of these models is as follows: the ENAE v1.0 tool, Boxall *et al*., 2007, GUIDEnano v3.0 and ConsExpo Nano v2.0 are suitable for quantitative exposure assessment of nanomaterials for consumer spray scenarios. Stoffenmanager Nano v1.0 and Swiss Precautionary Matrix v3.1 can be applied in prioritization of nanomaterials with respect to potential exposure. NanoSafer v1.1 can be used to estimate acute air concentration for consumer spray scenarios (OECD, 2021a-c).

6.2.1.3.3 Inhalation exposure

Beyond simple exposure estimation for inhalation consideration of biopersistence and characterisation of the nanomaterial in the lung need to be borne in mind. It is of note that simulant lung lining fluid is available that could allow for such an assessment *in vitro*. But the same challenges and uncertainties remain with regard to characterisation in complex matrices or how *in vitro* results relate to *in vivo* expectations (Akhter *et al*., 2021). Further, knowing the size of the particles is imperative to understanding how deeply into the lungs the particle may go. How deep a particle may go into the lungs has 3 main categories toxicologically speaking and these class the material as either i) inhalable, ii) thoracic or iii) respirable. The inhalable fraction is the mass fraction of total airborne particles which is inhaled through the nose and mouth. The thoracic fraction is the mass fraction of inhaled particles penetrating beyond the larynx. Finally, the respirable fraction is the mass fraction of inhaled particles penetrating to the unciliated airways. The amount of particles in each ’zone’ of the lung can be determined roughly by using their size and this is defined in the standards outlined in ISO 7708:1995, and is depicted in Figure 6.

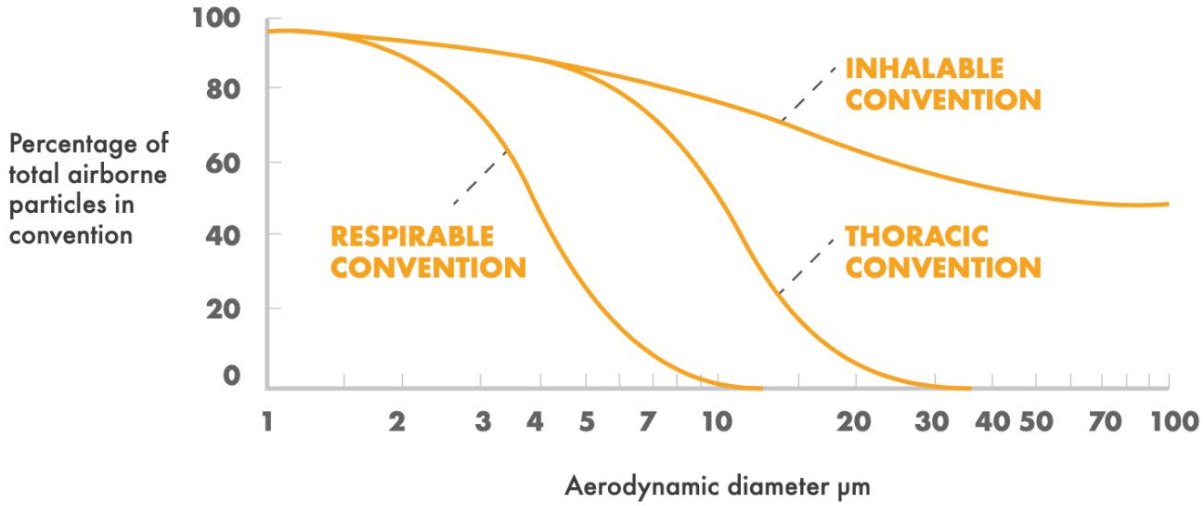

Figure 6. Schematic outline of particle deposition in the lungs versus particle size (µm). Image taken from: the NEPSi(O2) Good practice guide – Workers' Health Protection through the Good Handling and Use of Crystalline Silica and Products Containing it.

It can be seen in Figure 6, that, unless aggregated/agglomerated at greater 10 µm, all nanomaterials are respirable as by definition they are all less than 0.1 µm. Therefore, they will penetrate the deepest part of the lungs and may then be distributed around the whole body after uptake into the circulatory system. However, for most exposure models it is assumed that the whole dose/concentration is available locally/systemically. The assumption is worst-case and allows for a high level of protection. Thus the above discussion perhaps goes beyond predictive exposure and is more important for bridging concepts and proving similarity of nanomaterials for read-across.

6.2.1.3.4 Dermal exposure

Dermal exposure to nanomaterials can, in principle, be calculated as outlined in the SCCS Notes of Guidance (SCCS/1602/18; SCCS, 2018),[75] but this does not calculate particle number exposure which may be necessary if considered to be the better dose metric. Furthermore, since particle uptake depends on the size of the particles, it is necessary to consider the size distribution of the particles in the cosmetic product to allow calculation of internal exposure from external exposure. Internal exposure being those nanomaterials which can enter the skin cells and external being those particles which are on the surface. The size of the nanomaterial in the product can change drastically in comparison to the pristine form. Ideally, the model should account for exposure and likely absorption based on, for example. size. However, measuring size in a complex medium is highly challenging as already discussed. Therefore, inputting the correct parameters may be highly difficult in any model. As size of the material can have an impact on uptake and subsequently toxicity limitations in testing such a parameter will naturally limit model development, or at least one that is able to fully account for this factor. Again, though, perhaps worst-case principles should apply where 100% of exposure is assumed to be absorbed unless information is present to the contrary. It is of note that of the 7 consumer exposure models tested by the OECD (OECD, 2021a-c) none of these were dermal exposure models. Based on current literature it can be assumed that non-dissolving particles >5 nm will not penetrate the skin and thus systemic effects are unlikely to manifest, but for particles under 3 nm this may be

[75] https://health.ec.europa.eu/system/files/2019-02/sccs_o_224_0.pdf

possible. Again, how biological fluids may impact the size and dissolution of the nanomaterial must be accounted for in such statements.

6.2.1.4 Hazard assessment

With regard to hazard testing the first thing of utmost importance to note regarding the the Cosmetics Regulation and Cosmetics Regulation (GB) is that, in accordance with Article 18 of the respective regulations, the use of animals in the hazard assessment of cosmetics is prohibited. Therefore, alternative methods have to be used such as *in silico* methods (i.e., computer estimations of toxicity), *in vitro*/ *in chemico* methods (i.e., cell culture tests) and use of existing information. Another option is read-across, this is where data-requirements are fulfilled by using data from another substance which is structurally similar to the substance being registered by the manufacturer. Due to these structural similarities the effects are also assumed to be the same. To use read-across, similarity for the specific data-requirements must be proved and justified unequivocally.

The main hazard points that must be addressed for nanomaterials under the Cosmetics Regulation (GB) and Cosmetics Regulation are: toxicokinetics, acute toxicity, skin irritation and corrosivity, skin sensitisation, mutagenicity/genotoxicity, repeated dose toxicity, phototoxicity, reproductive toxicity, carcinogenicity, human data (when available) and any other relevant information that is available (SCCS, 2018).

The *in-silico* assessment of nanoforms is still in its infancy and is a difficult topic as the main drivers which may parametrise such models are still up for debate. However, new projects are focusing on how to utilise such methods with respect to nanoforms to promote effective nanomaterial screening, integrated testing strategy development and safe-by-design initiatives (e.g., NanoSolveIT, https://nanosolveit.eu).

Issues associated with building *in silico* predictive models for specific endpoints relates to data consistency and quality. The issue has caught much attention and specific EU level projects have tried to/are addressing this. For example, NanoCommons addresses this gap by creating a community framework and infrastructure for reproducible science, and in particular for *in silico* workflows for nanomaterials safety assessment and beyond (http://nanocommons.eu). Further, the regulatory acceptance and use of predictive models is not established, limiting the number of tools available to a registrant.

Though many *in vitro* methods exist, their applicability for nanomaterials is not yet fully elucidated in many instances.

For toxicokinetics, such methods as the Skin Absorption: *In Vitro* test (OECD TG 428, 2004) have been evaluated for their applicability to nanomaterials. It was considered that this test requires adaptation for the testing of nanomaterials, as there are many aspects which may not be suitable. In particular, the duration of the observation time, the sampling time, the influence of mechanical processes in particles translocation, the solubility and the compatibility of the receptor fluid all need to be further explored. An overview of nanoparticle toxicokinetics has been recently published by ISO (ISO/TR 22019:2019) 'Nanotechnologies-Considerations for performing toxicokinetic studies with nanomaterials'. Again, efforts are underway through NanoHarmony and the WPMN to validate toxicokinetic methods for nanomaterials but these methods are largely focusing on a harmonised approach for *in vivo* testing which is considered not applicable here (i.e., the OECD TG 417, 2010).

For skin irritation and corrosion many methods rely on spectrophotometric and spectrofluorometric (i.e., measures of light intensity) techniques and nanomaterials can interfere with light and lead to misinterpretation. In some instances, a nanomaterial (e.g., TiO_2 and cadmium selenide CdSe) can lead to underestimations in such assays (Ong *et al*.,

2014). The interreference in such assays is well-known and in order to prove the validity of such tests nanomaterial only controls and nanomaterial/analyte controls are considered to be appropriate. When interreference is seen in one method other methods should be sought.

More recently the (common) adverse outcome pathway which results in sensitisation has been elucidated. This has led to an advancement in non-animal testing methods such as those described by the OECD 442C to 442E series (OECD, 2022a-c). These tests are the Assays addressing the Adverse Outcome Pathway key event on covalent binding to proteins (OECD, 2022a), *In vitro* ARE-Nrf2 Luciferase Test Method (OECD, 2022b) and the *In Vitro* Skin Sensitisation assays addressing the Key Event on activation of dendritic cells on the Adverse Outcome Pathway for Skin Sensitisation (OECD, 2022c). Again, projects such as NanoHarmony are working toward the validation of *in vitro* methods for skin sensitisation. However, it should be noted that at least two of these tests must be applicable and then used in order to draw a conclusion on sensitisation of the substance and so far only one appears to have possible applicability to nanomaterials, the OECD 442D, e.g., ARE-Nrf2 Luciferase Test Method (OECD, 2022b). However, these methods have traditionally not been applicable for metals and many used nanomaterials are metals in cosmetic products (see Section 3, TiO_2 and ZnO prevalence). Moreover, the OECD TG 497 which defines a strategy for deriving skin sensitisation potency through non-animal methods uses the above methods and *in silico* tools. However, there are no relevant *in silico* tools to aid in such analysis meaning critical information on potency may not be possible without animal testing which is prohibited in accordance with Article 18 of the Cosmetics Regulation (GB) and Article 18 of the Cosmetics Regulation. The development of nano-specific adaptations to existing test methods or new test methods for skin sensitisation are currently required. Moreover, to use such frameworks as outlined in the OECD 497 (OECD, 2021e), *in silico* tools must also be developed.

It is widely known that a test for genetic toxicity, known as the AMES test (OECD 471; OECD, 2020) that uses bacteria is not appropriate for nanomaterials (OECD Series on the Safety of Manufactured Nanomaterials No. 85, 2018 and SCCS, 2018). This is because it has been found that many bacterial cells lack the ability to uptake nanomaterials through endocytosis and some nanomaterials have bactericidal activity. Other methods may be applicable, however. For example, the *in vitro* mammalian cell gene mutation tests (OECD TG 476; OECD, 2016a) is considered as an alternative for the bacterial reverse mutation test (OECD TG 471; OECD, 2020), as no identified specific limitations have been noted for nanomaterials at this time. Other assays may also be appropriate but it is noted that specific adaptations may be required e.g. OECD TG 487: *In Vitro* Mammalian Micronucleus Test (OECD, 2016b) and OECD TG 473 (OECD, 2016c): *In Vitro* Mammalian Chromosomal Aberration Test. One example where caution must be exercised for is in the *in vitro* micronucleus test where reagents/enzymes often used to inhibit cytokinesis, may inhibit endocytosis and may lead to false negative outcomes when particles are present. The appropriate adaptations required for these tests is not detailed in the test guidelines which may lead to uncertainty in their execution (OECD, 2018). In addition, the use of a metabolic activation system for nanomaterials is questionable. Many insoluble nanomaterials are not metabolised. Instead, the proteins present in a metabolic activation system may interfere with nanomaterials and alter their bioavailability, and thus reduce the sensitivity of the assay (SCCS, 2019; SCCS/1611/19). This again highlights that careful interpretation of the data is required.

For phototoxicity, this is of particular importance for those products used in e.g., sunscreens. The 3T3 Neutral Red Uptake Photo-toxicity Test (3T3 NRU PT) is a validated *in vitro* method, however, its applicability for nanomaterials has not been fully explored. If there is indication

of phototoxicity then it is prudent to also test for photo-mutagenicity/photo-genotoxicity. It has been noted that the addition of irradiation to the aforementioned genotoxicity tests does not significantly alter the protocol without irradiation and are therefore considered valid for this use. Therefore, it may be assumed that such tests are valid for nanomaterials when it has already been stated as such without radiation and that no interference is present. Considering the high prevalence of nanomaterial use in sunscreens (i.e., TiO_2, ZnO and bictrizole) and in fact that these are some of the most prevalent products and nanomaterials used, such tests for nanomaterials are of critical importance.

For repeated dose toxicity, no validated alternative methods are available to replace animal testing. This endpoint is hugely important as effects, which require a long latency period or which are cumulative are only identifiable in such tests (SCCS, 2019; SCCS/1611/19). This may be particularly the case for nanomaterials which often exert their effects through longer term mechanisms, if at all. At this time, it may be possible to build a weight of evidence using alternative test methods such as *in vitro* or in silico methods if available, but due to the complexities of interaction *in vivo* these may not entirely represent effects that will occur in the body. The need to develop surrogates for such tests, outside of the animal testing offerings, is not a challenge just from a nanomaterial perspective but for chemical hazard assessment as a whole. Work is needed to ensure, particularly for those chemicals which do not trigger animal testing under other regulations (e.g., REACH Regulation (GB) and Reach Regulation when substances are manufactured > 1 tonne), that sound test methodologies and suites of testing are available in order to lead to robust weights of evidence and conclusions. As more animal testing is done under other regulations it may also be possible to build predictive models, especially with machine learning techniques, and sophisticated *in vitro* surrogates.

For reproductive toxicity no validated animal alternative method is available. Though there are three alternative methods that, between them, cover large portions of embryotoxic mechanisms of action, this is only a small part of possible reproductive or developmental toxicity. The three tests are a) The Whole Embryo Culture test (WEC), b) The MicroMass test (MM), c) The Embryonic Stem Cell Test (SCCS, 2019; SCCS/1611/19). These are merely examples of what is likely available in the academic literature, describing all possible tests is beyond the scope of this document. Regardless, they must also be validated for nanomaterials prior to their use. Again, work is needed to ensure, particularly for those chemicals which do not trigger animal testing under other regulations (e.g., REACH Regulation (GB) and REACH Regulation when substances are manufactured >1 tonne), that sound test methodologies and suites of testing are available in order to lead to robust weights of evidence and conclusions for this endpoint. As more animal testing is done under other regulations it may also be possible to build more robust predictive models (including those which use machine learning) and more sophisticated *in vitro* tests. It is also of note that no method for testing endocrine disruption is currently validated for nanomaterials and again highlights a critical assessment gap for consumer products.

For carcinogenicity the recently adopted guidance for the cell transformation assays has been applied for several nanomaterials with some success, however, once again there is no validated method. There is definite need for caution here in particular when carcinogenicity is propagated from non-genotoxic mechanisms of action which would be missed by the suite of mutagenic/genotoxic tests. Under the current framework in the EU when a structural alert for carcinogenicity is present, or positive results are obtained in an *in vitro* mutagenicity tests, specific carcinogenicity tests may be needed. However, there is a lack of predictive models for predicting nanomaterial carcinogenicity and looking at chemical structure alone is perhaps less critical when considering nanomaterial specific toxicity where effects may be

due to the physical-chemical characteristics such as size, coating, surface charge and so forth rather than, for example, the materials ability to act as a nucleophile.

For all the above testing and implications such as relevant exposure schemes, a project that may be of use is that of PATROLS (Physiologically Anchored Tools for Realistic nanOmateriaL hazard aSsessment), which is developing advanced and realistic tools and methods for nanomaterial safety assessment. The Standard operating procedure (SOP) handbook is publicly available (https://www.patrols-h2020.eu/publications/sops/index.php) and covers preparation and test execution. For example, there is a method that deals with nanomaterial pre-treatment with simulant fluids to mimic oral and inhalation exposures for hazard assessment using 3D liver models *in vitro* and others dealing with specific endpoints, e.g., SOP Reverse Transcriptase PCR for Hepatocarcinogenicity Biomarkers in 3D HepG2 Liver Spheroids SU which focus on carcinogenesis. It should of course be cautioned that these are not necessarily validated or OECD methods but may provide data in weights of evidence or for the proof of nanomaterial similarity during read-across strategies. Potential toxicity from available or human data may be found for chemical components of a nanomaterial or the nanomaterial itself can be obtained by searching different databases; for example, Risctox (https://risctox.istas.net/en/); ECHA database for REACH Regulation registered substances (https://echa.europa.eu/information-on-chemicals/registered-substances). Note, a database for UK registrations of disseminated dossiers is not yet available. However, data availability will be reliant on the tonnage level being produced in the EU/UK. Those of a higher tonnage band will have more information as the REACH Regulation and REACH Regulation (GB) increases data demands with increasing manufacture or import. Other databases also include TOXNET database (available as part of ChemIDPlus: https://chem.nlm.nih.gov/chemidplus/). A database of nanomaterial safety (eNanoMapper: https://data.enanomapper.net/) is also available that may provide relevant toxicity information on some of the already tested nanomaterials. Use of databases supports recyclability of data, drastically reducing testing costs. However, it requires expert evaluation on whether these tests have been appropriately conducted and accounted for the nanomaterial in question, and whether the physical chemical parameters (e.g., size) of the nanomaterial tested are close enough to the nanomaterial being assessed to allow inference.

For read-across, there is a framework recently published from the GRACIOUS project (Stone *et al*., 2020) which may be of use, but some methods require regulatory validation or are undergoing development. However, these tests could prove a suitable weight of evidence in justifying a read-across approach. The GRACIOUS framework could be a powerful tool when deciding whether to use nanomaterial information or its dissolved or bulk counterpart for hazard assessment and future avoidance of animal testing.

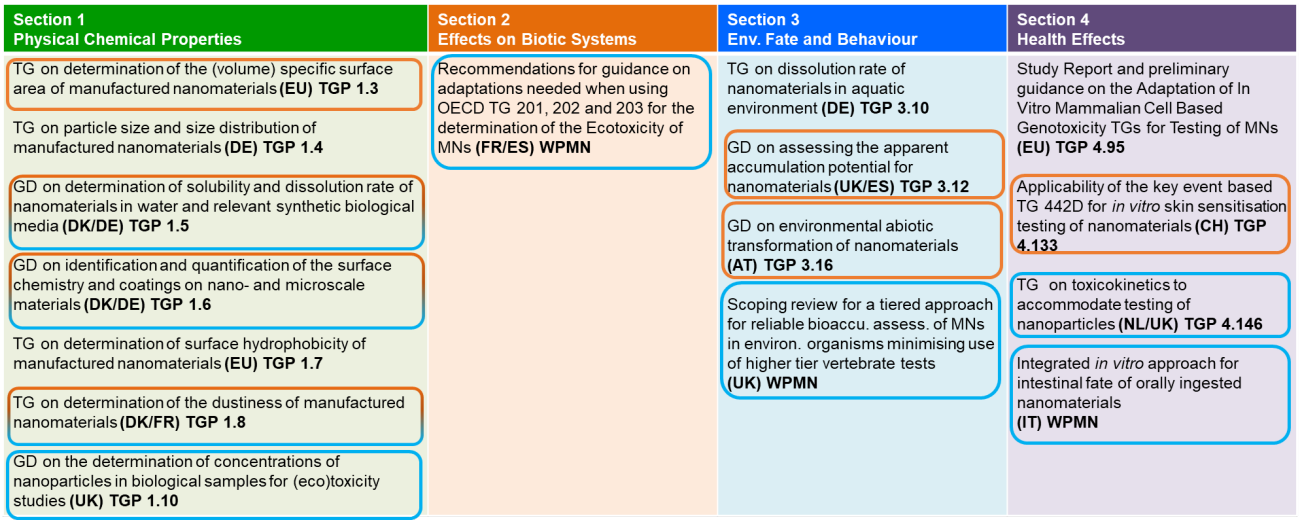

Figure 7. Current activities under the OECD WPMN on gap filling regarding adaptations of OECD guidelines to nanomaterials.

6.2.2 The Toys (Safety) Regulations 2011: framework and knowledge gaps

The purpose of the Toys (Safety) Regulations 2011 (herein the Toy Regulation) ensures safe products are placed on the market by requiring manufacturers to show how their toys meet the 'essential safety requirements' as denoted within the Toy Regulation and to ensure the safety during the toy's intended or foreseeable use, bearing in mind the behaviour of children. The Toy Regulation also includes lists of prohibited substances. For the banning of substances used in toys, a wide body of evidence concerning a particular hazard is required. Again, of note is that if there are test methods lacking to properly evaluate hazardous properties, such lists drawn up in their absence can be both over and under cautious. As highlighted under the Cosmetics Regulation and Cosmetics Regulation (GB), this further highlights the benefit of robust hazard testing methodologies. To assess a toy's safety the following should be available.

- **Bill of materials (BOM):** List of raw materials, intermediates and components used to manufacture the final toy, stating the quantities used;
- **Bill of substances (BOS):** List of chemical substances in each material, stating the substance CAS numbers and the concentrations in which the substances are present;
- **Safety Data Sheet (SDS):** Safety data sheets for chemicals used in the manufacturing process if required under REACH Regulation and REACH Regulation (GB) as applicable;
- **Test reports:** Results of chemical analyses documenting that the toy complies with relevant Toy Regulation.

To comply with the Toy Regulation, the toys should meet the relevant standards listed under the EN71 series (EN71-1 to EN71-14). The standards provide both methods for assessment and any applicable limits/restrictions for particular substances. However, there is no statutory requirement to carry out analyses in accordance with the standards. An analysis may therefore be unnecessary if it is probable that a substance covered by a standard cannot be/is not present in the toy material. The standards are as follows:

- EN 71-1: Mechanical and physical properties
- EN 71-2: Flammability
- EN 71-3: Specification for migration of certain elements
- EN 71-4: Experimental sets for chemistry and related activities
- EN 71-5: Chemical toys (sets) other than experimental sets

- EN 71-6: Graphical symbols for age warning labelling
- EN 71-7: Finger paints
- EN 71-8: Swings, slides and similar activity toys for indoor and outdoor family domestic use
- EN 71-9: Organic chemical compounds – Requirement
- EN 71-10: Organic chemical compounds – Sample preparation and extraction
- EN 71-11: Organic chemical compounds – Methods of analysis
- EN 71-12: N-Nitrosamines and N-Nitrosatable Substances
- EN 71-13: Olfactory board games, cosmetic kits and gustative games
- EN 71-14: Trampolines for domestic use

It is clear from the above list that many of these standards cover nanomaterials by derogation, or are simply not relevant to the constituent make-up of the toy but more its physical attributes. For example, although a nanomaterial may or may not give rise to a particular property, the property is still testable regardless of any adaptation toward the nanomaterial. If flammability was tested, the way it is tested does not change, though the property might. Insofar as nanomaterials are concerned the most relevant standards which may require adaptation or new test methodologies to be developed are:

- EN 71-3: Specification for migration of certain elements
- EN 71-4: Experimental sets for chemistry and related activities
- EN 71-5: Chemical toys (sets) other than experimental sets
- EN 71-7: Finger paints
- EN 71-9: Organic chemical compounds – Requirement
- EN 71-10: Organic chemical compounds – Sample preparation and extraction
- EN 71-11: Organic chemical compounds – Methods of analysis

It should be noted that EN71-9 to EN 71-11 though relevant for any organic nanomaterial, may currently be less of a focus for the UK market as the main prevalence on the UK market of nanomaterials (Section 3) was seen for inorganic nanomaterials where 100% of the known toys containing nanomaterials available to consumers were inorganic. Specifically, these were, (inorganic) carbon (n = 3), silver (n = 3), TiO_2 (n = 1) and unknown (n = 45), see Section 3 for more detail. Moreover, the only organic nanomaterial, which was found in 10% of products assessed as containing nanomaterials on the UK market, was only used in cosmetics and was not in toys in the UK though it can be used as an additive in polymers (Section 3). It should be noted that these are based on results of the current study and actual figures may vary due to the caveats set out in Section 3.

Regardless, the standards EN 71-3 to EN 71-11 have an aspect whereby analysis of the substance in the product, or its migration out of the product, is required. As discussed already, relevant to these standards are also the limits which can be contained in the toy or are allowed to migrate from the toy. This is on the basis of the prohibited and restricted list, i.e., those substances classified as a hazardous will usually have specific limits or prohibitions. For example, formaldehyde is only allowed in polymeric (e.g., rubbers/plastics) toys for ages <36 months if it meets the migration limit set by the Toy Regulation of 1.5 mg/L . As such it is critical to be able to have tools to analyse such migration. However, there is a point of departure as it concerns what factors are important to measure for a nanomaterial versus a traditional chemical. For non-nanomaterials it is sufficient to simply identify its presence/concentration, however, for nanomaterials it is not only important to identify its presence, but also what form it is migrating in, i.e., is it highly aggregated, is it non-nanomaterial (e.g., dissolved) or a nanomaterial, does it migrate as a pure aggregated form or with other materials? These are important questions because it is well known that for

some nanomaterials their hazardous properties are dictated by their physical attributes, and these relate to their particle specific toxicological profile. This can be very different when the nanomaterial is migrated from, for example, a toy compared with a nanomaterial is in pristine form. There is, therefore, the potential for divergence in how hazard and the migrated nanomaterial might be assessed in comparison to non-nanomaterials.

Before discussing this further, it is important to note how the hazard assessment is conducted for nanomaterials and under which regulation(s). Often, one of the drivers for hazard testing is for compliance with other regulations such as REACH Regulation (GB), the results of the testing then informs the classification and labelling under the CLP Regulation (GB). If there is limited testing the classification and labelling is still conducted if the substance is assumed hazardous but, is informed by existing or non-animal data. As it is well known that shape, size and surface coating etc. can change the properties and also hazard of a nanomaterial, it is possible that the classification and labelling may also be different when any of these factors change. For example, the smaller the size of a nanomaterial, the higher a surface area, and the quicker dissolution may occur. If the dissolved fraction is responsible for a toxicological effect, then the smaller nanomaterials may be more harmful, even if not directly. Another example would be when a particle shape increases toxicity, for example rigid nanomaterials with aspect ratios greater than 3:1 may lead to fibre specific toxicity. Briefly, this is caused by 'frustrated phagocytosis' where a bio-persistent material is taken up by a special cell in the body which aids in clearing anything unwanted from the body. However, due to the shape and persistence the cell is not able to breakdown the nanomaterial and it causes the cell to be misshapen. This leads to a feedback loop which increases inflammatory responses (Boyles *et al*., 2015 and Gualtieri, 2021). Under the REACH Regulation (GB) this change in nanomaterial profile with different physical-chemical attributes is accounted for by either allowing the manufacturer to assess nanomaterials as 'sets of similar nanoforms' or as individual nanoforms to show fate, exposure, hazard and risk are different from other 'sets of similar nanoforms' or other singularly registered nanoforms. What this means is that although many nanomaterials may be made of, for example, TiO_2, each nanoform or set of nanoforms can have different classification and labelling.

Ultimately, due to these differences it means that any analysis of a nanomaterial without also analysing its size or other characteristics can be rendered meaningless insofar as how to interpret the possible hazard. Of the identified nanomaterials used in toys copper and zinc and its compounds (which would include ZnO) are currently listed as being restricted for use in toys (paragraph 13, Part 3 of Schedule 2 to the Toy Regulation). However, these were not identified in any products in the UK (Section 3). It should be noted the list is not exhaustive and also those chemicals restricted on the market under other legislation such as REACH Regulation (GB) would also be banned for use in toys. These substances are often known as substances of concern – simply a restricted substance or a substance that has been identified as a potential safety concern.

6.2.2.1 Characterisation of nanomaterials and nanomaterial migration

Though there is a need to measure nanomaterial characterisers, methods to analyse nanomaterials and specifically their exact form in complex matrices, or the migrated form, are very much in their infancy or those that have been in development still present challenges. The most logical manner in which to analyse the nanomaterial in a complex matrix is to extract it from the matrices. However, rigorous chemical or physical extraction techniques can change the nanomaterial characteristics. This may be less of an issue for something migrated, but if it was co-migrated and the nanomaterial was accessible the same issues would arise. More recently, efforts have been made to extract nanomaterials from

such products as sunscreens (Philippe *et al*., 2018 and Nthwane *et al*., 2019) and a similar process could perhaps applied to viscous liquids such as paints. Even recent studies using these techniques note that more efforts are needed to standardise and develop approaches for such extraction (Lehutso *et al*., 2021). Lehutso *et al*., (2021) applied multiple methods in some instances to ensure that artifacts from extraction had not occurred, which for a manufacturer may prove impractical and costly. For nanomaterial socks (similar textiles can be used in toys), the same authors employed an ashing procedure, but noted that this can change the particle shape and charge compared to the pristine form. Without further information on exposure and effects of nanomaterial exposure from toys, as well as what effects integration of a nanomaterial (i.e., embedded in plastics or textiles) or extraction can have on its characteristics, the question around how nanomaterials should be defined and analysed, as they pertain to use in toys, is perhaps a potential opportunity for ongoing consideration.

Regardless of the ability to analyse the nanomaterial, if a nanomaterial is concluded to be hazardous, prohibition or restriction can be effected. It should be noted here, however, that it is difficult to predict toxicity of nanomaterial enabled products versus its pristine form. Some reports show that the nanomaterial's toxicity can be reduced once placed in a matrix or at least that the effects are no greater (Saber *et al*., 2018 and Smulders *et al*., 2014). But other reports show that nanomaterial toxicity may increase when not in pristine form, for example if present with other chemicals. For example, it is also known that nanomaterials can act as a transport aid for (more) toxic chemicals thereby helping in uptake and distribution (Naasz *et al*., 2018).

6.2.2.2 Risk assessment

Once, or more suitably if, a hazardous substance is known or found to be in the toy a risk assessment should be conducted. This will be based on either the overall concentration of the substance or the concentration of the substance that migrates. This will be identified by following, with or without modification, the standards previously listed. As a worst-case the first assumption would be that the entire amount of the substance is available to the child and the relevant exposure would then be assessed in line with specific defaults for that scenario (e.g., Existing Default Values and Recommendations for Exposure Assessment - A Nordic Exposure Group Project 2011 and Chemicals in Toys A general methodology for assessment of chemical safety of toys with a focus on elements RIVM, 2015). If there is an identified risk then further refinements can be made to add levels of realism, if not, no further assessment is needed. If the intention is for the toy maker or its supplier to model/predict an expected exposure some models may fall short and not be suitable for predicting nanomaterial exposure as previously mentioned. In fact, such models as ConsExpo have already been noted as not useable but the specific ConsExpo nano is suitable (OECD, 2021a-c). However, the latter is only usable if very specific information is available including weight fraction of the nanomaterial, nanomaterial density and nanomaterial particle diameter distribution. It is also only relevant to the inhalation route. Again, the same issues arise with accurately analysing nanomaterial properties in textiles or complex matrices and which particle diameter should be used, i.e., the pristine or as released form. Therefore, such an assessment may have to rely on monitored/experimental data. It should be noted that when the risk assessment begins to get complicated that it may be simpler for the toy maker to choose another substance or material supplier where the hazardous substance is not present, or one with known properties.

It should again be noted, that regardless of any new/adapted test methods being available there is still difficulty in finding a laboratory with the equipment and expertise to properly execute and interpret the data.

6.2.3 The Nightwear (Safety) Regulations 1985: framework and knowledge gaps

The Nightwear (Safety) Regulations 1985 (herein 'the Nightwear Regulations'), was specifically provided as a statutory instrument to prohibit '*the supply of children's nightwear, other than pyjamas, babies' garments, and cotton terry towelling bath robes, made of fabric of a kind not capable after having been washed of complying with the British Standard (BS) flammability performance requirements' (BS 5722:1984, https://knowledge.bsigroup.com/products/specification-for-flammability-performance-of-fabrics-and-fabric-assemblies-used-in-sleepwear-and-dressing-gowns?version=standard)*.

The Nightwear Regulations also outline the specific labelling and positioning of that labelling required for children's and adult's nightwear. There is no requirement in the legislation to refer on the label to the type of material that the garment is made from, or any additives. There are no nano-specific provisions as part of the regulations.

The main standards referenced in the Nightwear Regulations are the cleansing and wetting procedures (BS 5651:1978) and the Specification for flammability performance of fabrics and fabric assemblies used in sleepwear and dressing gowns (BS 5722:1984). The washing procedures are standard and state that, after washing, garments must still comply with the required flammability performance specifications. These do not require adaptation for the presence of nanomaterials. No analysis of the wash water or chemicals contained within it is required for this purpose, but only the test of the flammability. The flammability of the garment tested in accordance with BS 5722:1984, also does not have nano-specific provisions. However, there is not a need for such provisions as the flammability of the fabric used to make nightwear is tested and not the substances which are contained within it.

The requirements for the labelling of the substances which are contained within the garment, e.g., cotton, or even nanomaterials, is beyond the scope of the regulations. Also beyond its scope is the assessment of the possible exposures during skin contact of any leaching/migrating substance, for example nanomaterials, during normal wearing, or any materials that leach during a wash cycle. Indeed, enforced labelling of products with nanomaterials in, to indicate '(nano)', in line with the Cosmetics Regulation and Cosmetics Regulation (GB) could allow for easier prevalence assessment and allow easier highlighting of current regulatory needs for nanomaterials under specific statutory instruments.

Moreover, whether updates are required under the other regulations largely depends on the obligations contained within them and if, by derogation, they will ensure that all required information regarding nanomaterials is provided to ensure consumer safety. For example, in the Regulation (EU) No 1007/2011 on textile fibre names and related labelling and marking of the fibre composition of textile product ('Regulation (EU) No 1007/2011') Article 10(2) states *'metallic fibres and other fibres which are incorporated in order to obtain an antistatic effect and which do not exceed 2% of the weight of the finished product do not have to be taken into account in the fibre compositions'*. Whether this percentage is applicable to nanomaterials is unknown, including because it would seem more important to determine nanomaterials on the basis of safety and not weight. Moreover, the list of textile fibre names in Annex I of Regulation (EU) No 1007/2011 may be subject to change if it includes those fibres with nanomaterials incorporated into the fibre, or that are. nanomaterials, and whether marking and/or labelling should expressly refer to them. Again, the topic is outside the scope of this project. The change in Annex I of Regulation (EU) No 1007/2011 would by proxy ensure information is conveyed to a consumer for all textiles used in nightwear.

The Nightwear Regulations do not need to account for the possible nano-specific physical chemical properties which may lead to hazard or risk to the consumer, as these will be tested

for by derogation under the provisions laid out in the Nightwear Regulations and only concern flammability requirements and longevity of the anti-flammability of the garment. As such the presence of nanomaterials will not affect the safety of the garments for the consumer if tested and labelled in the manner which is outlined under the Nightwear Regulations.

6.2.4 The PPE Regulation and PPE Regulation (GB): framework and knowledge gaps

Firstly, it should be noted that this section deals with the PPE Regulation that sets out the essential health and safety requirements that must be met before PPE products can be placed on the UK market. The purpose of the legislation is to ensure safe and effective products are placed on the GB market by requiring manufacturers to show how their products meet the applicable 'essential health and safety requirements' imposed by the legislation on their product. The Personal Protective Equipment (Enforcement) Regulations 2018 provide a system for the enforcement of the PPE Regulation (GB). The PPE Regulation (GB) outlines the specific rules of conformity for PPE and labelling or 'marking' requirements. The PPE Regulation (GB) is largely about PPE conforming with essential health and safety requirements to show it is: i) safe for use (not prohibitive, doesn't endanger the user etc.) and ii) aids in the targeted protection goal. For example, manufacturers of gloves may wish their gloves to conform with standards that show they are imperviable to specific chemical substances. Although nanomaterials could perhaps enhance or give rise to desirable properties (e.g., more impervious properties) for the relevant PPE, the tests of efficacy and function may remain unchanged, and the product must still meet the required health and safety requirements. With regard to the nanomaterials found in PPE on the GB market it would appear the nanomaterials currently provide for two main purposes; i) increased functionality and ii) for biocidal properties. The nanomaterials found were varying carbon nanomaterials, copper, silver, TiO_2 and zinc. Carbon based nanomaterials are known for their adsorptive properties and can increase the surface area of filters during e.g. ventilation allowing more capture of harmful chemicals/bacteria/viruses. Silver and copper are well known for their biocidal properties and their use in medical PPE has obvious advantages (Blevens *et al*., 2021 and Palmieri *et al*., 2021). The efficacy of such uses or enhancing performance of PPE is subject to constant review and comparison with more 'traditional' technologies, and will not be further discussed. Carbon nanomaterials have been shown to exhibit excellent barrier function and antiviral effects against, for example, SARS-CoV-2 (Lee *et al*., 2021). (It is worth note that all testing and exposure modelling knowledge gaps are also true under the BPR Regulation.)

What is relevant under the PPE Regulation is that Annex II (the Essential Health and Safety Requirements) states that the PPE must be made of suitable constituent materials. This means that *'the materials of which the PPE is made, including any of their possible decomposition products, must not adversely affect the health or safety of users.'* Again, the difficulties previously noted still remain: i) Identification of nanomaterials, ii) Analysis of nanomaterial characteristics, iii) Different hazard profiles for the same nanomaterial type, iv) Difficulty in predicting an embedded/migrated nanomaterials hazard versus its pristine form and, v) What to best base hazard and risk assessment on (pristine, as used or as exposed) (see Section 6.2.1). On top of this, the fact the nanomaterial may be in contact with biological fluids (sweat) or in moist environments (face mask), further complicates interpretation (see Section 6.2.1). The same approach as suggested elsewhere is also encouraged here, i.e., use worst-case assumptions unless reliable data is available to allow specific assessment that is protective of the end-user.

There are no designated or harmonised standards that address the release/migration/use of nanoforms from or in PPE. However, some are under development, for example the ISO standard for measuring nano-objects released from face masks is under development (ISO/AWI TS 11353). Nonetheless, hazard presented by nanomaterials in PPE could be assessed by considering classification and labelling (C&L), and thus by adopting the same approach as for toys under the Toy Regulation. This approach entails searching for substances on various databases such as the ECHA database (https://echa.europa.eu) and their hazards ascertained from the relevant C&L. Where this becomes difficult is for nanomaterials where either different nanoforms have different C&L or the C&L differs from other forms.

For example, carbon black does not have specific health hazards and is not classified as such. However, some rigid carbon nanotubes possibly cause deleterious health effects. Note: the nanotubes must be rigid, inhaled and have a high aspect ratio for this to be true. The statement does not apply to all nanotubes and is here for purposes of providing an example. Growing evidence supports the idea that inhaled nanomaterials of >5 µm and with a high aspect ratio (3:1), like rod-like carbon nanotubes resembling asbestos-type shape, may cause pleural disease including mesothelioma (Barbarino *et al*., 2021). This is not an inherent chemical property but one related to the physical shape of the material and its biopersistence. The process (i.e., frustrated phagocytosis) was described in the toys regulation section and will not be covered again here. As such, it may be possible to use carbon-based nanomaterial technology for its high surface area and antimicrobial/anti-viral activity but, under the regulatory framework for PPE carbon materials that are rigid with a high aspect ratio should be avoided. Both would be detected as carbon, however, without analysis of shape and size it would be difficult to assess by an external reviewer which is acceptable or not. Here, again, the ability to accurately measure nanomaterials in the textile would be of key importance. Though understanding the hazard of a substance is important while making the PPE, assessing a substance's hazard that is used in PPE is not necessarily an integral part of PPE Regulation (GB). Simply, it is important to ensure non-hazardous materials are used, which can be scenario specific.

Although the PPE Regulation (GB) states that only safe materials should be used, the safety of these materials is assessed under other regulations. Regulations such as the EU Textile Products Regulations , REACH Regulation and REACH Regulation (GB), CLP Regulation and CLP Regulation (GB) and BPR Regulation may be relevant. All except the EU Textile Products Regulations have already been subject to much review on how to account for nanomaterials. The EU Textile Products Regulations(is outside of the project scope. How hazard is identified through nanomaterial testing and characterisation remains a common theme, therefore presenting a potential regulatory challenge.

7. Conclusions

7.1 Conclusion on the prevalence of nanomaterials

Over the last two decades, there has been a growth in the number of consumer products that use nanomaterials, as shown by the growth in products being listed by both the Consumer Products Inventory (CPI) and Nanodatabase datasets. There remains a challenge to positively identify the products that do contain nanomaterials and to then clarify if these are available in UK retailers or more generally available to UK consumers. As there is no requirement for manufacturers or retailers to register products that contain nanomaterials in publicly available databases, it is impossible to draw up a fully comprehensive list of consumer products that contain nanomaterials that could be purchased by UK consumers. Analysing the prevalence of nanomaterials in consumer products outside of cosmetics requires some claims to be taken at face value. This includes the manufacturers' claim that nanomaterials have been used in the product.

The largest category of consumer products in which nanomaterial use can be identified is currently cosmetics. This may be in part due to the requirement for manufacturers to indicate the nanomaterials used on the product's ingredients list, which makes it easier to identify nanomaterial use in these products.

Within the products containing nanomaterials found available in the UK market and available to UK consumers, the three top nanomaterials identified as being used are TiO_2, silver and bisoctrizole. However, in over half of the products identified as containing nanomaterials the actual nanomaterial used was unknown.

The amount of literature identified in answer to research questions 2 totalled over 5,000 available papers. Even limiting the study to the most prevalent nanomaterials identified in UK consumer products, such results make it difficult to undertake a fully comprehensive study.

With very few exceptions, the regulation in the UK with special provisions for nanomaterials is cosmetics. Other regulations relating to consumer safety make it a requirement for manufacturers to be aware of specific safety guidelines and guidance updates relating to the materials that they are using in making their products.

There are still gaps in the standards and test guidelines that are in place to aid manufacturers in complying with existing regulations. Further work is currently ongoing on developing test guidelines in both the OECD for regulations and ISO for industrial standards.

Tracking the prevalence and detecting or assessing nanomaterials in products is a huge challenge. Moreover, tools that reliably indicate which nanoforms are or are not hazard/risk concerns should also be considered.

7.2 Conclusion on nanomaterial enabled consumer product safety

The importance of establishing a safety profile for nanomaterials used within consumer products based on use of suitable tests to determine nano-specific physicochemical properties & hazard as well as relevant exposure profile is clear and is reflected within the regulatory requirements outlined for both the UK and other regions such as the EU.

Within this review, safety data on three of the nanomaterials identified as prevalent within the UK market (bisoctrizole, TiO_2 and silver) was summarised and evaluated.

For bisoctrizole, a lack of information (at a screening or more detailed level) was identified for some endpoints (e.g., reproductive toxicity and toxicokinetics). In addition, some of the previously conducted studies with nano bisoctrizole were lacking in information relating to particle size, or relevant demonstration of particle uptake, where relevant. This said, on the whole, the safety profile of bisoctrizole appears to be relatively favourable for its most widely used exposure route (dermal).

Nano silver is used in a range of scenarios relevant to consumers and workers, such as cosmetics, biocides and chemicals (across a huge range of end applications). Of the available data, some gaps in full characterisation of materials, the relevant biological media into which they were being added, and of toxicokinetic profile were identified. However, based on the existent data, the European Chemicals Agency's Risk Assessment Committee (RAC) has recently recommended that a harmonised human health classification is applied for all silver forms (massive, powder and nano) for reproductive toxicity (category 2 – fertility (H361F)) and Specific Target Organ Toxicity – Repeated Exposure (STOT RE category 2 (brain)). It remains to be seen whether a similar approach will be adopted within the UK.

In the case of TiO_2, for which there were the largest number of both bulk and nano form registrations under REACH Regulation, the primary safety concern is that relating to the potential for TiO_2 to be a carcinogen via inhalation. The discussion around whether this is indeed the case, and the practical application of such a classification under CLP Regulation and CLP Regulation (GB) remains ongoing.

For all the nanomaterials evaluated, there were clear themes in relation to establishing clearly the hazard profile of nano form vs. bulk form. These included a lack of i) sufficient characterisation (of the nanoparticle itself or the biological media into which it was being added), ii) ability to define the toxicokinetic profile for nano forms, and iii) an appropriate dose metric for hazard and exposure characterisation. As the use and application of nanomaterials continues to grow, the discussion on classification of hazards for known nanomaterials remains ongoing, further testing guidelines and guidance are developed to support generation and evaluation of quality hazard data, it remains hugely important for manufacturers to remain up to date with the latest information on the safety profile of nanomaterials. This is particularly relevant to those who are using nanomaterials in consumer products present within both the UK and wider areas such as Europe; even within the short time which has lapsed since the EU left the EU, differences are already emerging in direction of some key discussions.

7.3 Conclusion on Regulatory frameworks and industrial standards for the toxicological assessment of consumer products

When the UK withdrew from the EU, it was at a time of infancy for the formalised regulatory frameworks for nanomaterials. As such the landscape was, and still is, highly dynamic as industry, regulators and academics navigate compliance and knowledge gaps. Further, due to the timing, further work and advancements have been made in the EU regulations. This has forced a point of departure, whereby, decisions can be made on whether to follow the updates or whether a more specific approach may be needed based on the UK specific needs, which may be reflected in market share or prevalence of particular nanomaterials. However, it has been highlighted here that tracking the exact prevalence is highly challenging and there are several uncertainties. Here, cosmetic products using nanomaterials had two thirds of the market share of all nanomaterials on the market on an 'available product basis'. Also, the regulatory requirements in the cosmetics space are more

complex than some of the other product areas explored. Consequently, much focus was afforded to the cosmetics product type.

For the Cosmetics Regulation (GB)several challenges were highlighted. However, it is also true that the regulation has already gone some way in creating some divergence for compliance of nanomaterials in relation to 'normal' chemicals.

Complex matrix cosmetic products present difficulties around the identification of nanomaterials through measure. International work is ongoing with respect to development of guidance and testing procedures. Moreover, when measuring size, it could be noted if there would be benefit in identifying a preferred measurand (e.g., minimum Feret Diameter). An example would be the JRC guidance on the identification of nanomaterials through measure (Rauscher *et al*., 2019) or relevant OECD test guidelines. Regardless of tests employed there remain challenges regarding a lack of certified standard reference materials.

Specifically, for the Cosmetics Regulation (GB) it has been highlighted here that exactly how to test for, and define, biopersistence and insolubility are two areas that are open to further development/interpretation. A biopersistence definition might seek to include consideration of uptake, accumulation, and excretion. Regardless of uptake, cut-offs used should be monitored and updated as further advancements in the field are made and knowledge is gained in the area. For measuring solubility, there is still no widely accepted test guideline, though an OECD test guideline is expected to be released in the coming years.

For hazard assessment it is still unclear which dose-metric is most suitable and in fact this may be a case-by-case decision. At this time there may be general acceptance that all dose-metrics that can be measured should be measured, and the most suitable selected *post-hoc* based on that which presents the most logical relationship with any seen toxicological response.

Once hazard is identified in order to assess risk, exposure must be known or predicted. Several tools available for exposure prediction are highlighted throughout. It is important that the dose-metric used, and exposure concentration/dose predicted are comparable and that any estimate is conservative. The current recommended tools by the OECD (2022a-c) are mainly inhalation exposure estimation tools and they still only rely on small validation sets. As such any tools noted here should undergo continuous assessment especially as greater data-sets and knowledge are gained. For dermal exposure, models are sought and/or need to be updated, on the global stage, to allow appropriate assessment.

As it concerns to hazard for cosmetics, *in vivo* testing cannot be used, but there can be shortcomings and uncertainties when using *in vitro* methods. A more robust suite of *in vitro* testing may allow for more reliable conclusions on hazard without the need for existing data or the use of *in vivo* models. Testing strategies for skin sensitisation and development of methods for toxicokinetics, repeated dose and/or reproductive toxicity are also areas of ongoing consideration. Particularly when any potential toxicity of nanomaterials, if present, can often propagate longer term.

When data does not exist and cannot be generated, *in silico* methods or read-across could be used. Recent research under the GRACIOUS project has led to one framework for assessing and implementing read-across, but *in silico* methods are still in their infancy. With advances in knowledge of nanomaterial specific toxicology, increased data availability and machine learning, research into appropriate *in silico* tools or their development for regulatory purposes may aid regulations where *in vivo* testing is not allowed, as part of a weight of evidence or alone.

Many standards used to test the safety of toys either encompass nanomaterial usage considerations or are inherently not relevant to nanomaterial use. However, a major challenge remains on how to extract or track migration of nanomaterials. Over and above the simple analysis of concentration or amount of chemical migrated, nanomaterial characteristics such as size and coating may also need to be assessed due to their impact on, for example, toxicological profile. This means extraction or *post-hoc* chemical analysis cannot be destructive and/or leave artifacts from the process leading to misinterpretation. Without this knowledge decisions perhaps should be made on a worst-case form (e.g., nano, bulk, dissolved) of the material/substance in question based on hazard profiles 'as manufactured'. Caution here must be exercised and research into this type of worst-case application should be done to ensure that the assumptions remain protective. As noted, after being a matrix the toxicity may increase or decrease, and in the instance of the former there may be patterns that can be found in the literature where exception to the 'worst-case as manufactured form' should be avoided.

The other aspect, which is lacking, are relevant exposure tools and the pre-defined parameters which they would require as inputs to e.g., exposure models. For instance, what inputs of nano-characterisers as a minimum would be needed. Moreover, as already noted for cosmetics there is the lack of dermal exposure models.

There is currently no precedent to account for nanomaterials in nightwear under the Nightwear Regulations. Flammability, is a property of the entire fabric, including what is contained within it such as nanomaterials. The testing of flammability of a nanomaterial does not differ or need to differ. Therefore, the current flammability testing standards will cover any flammable properties imparted on a fabric by a nanomaterial. Full review of the related regulation, the EU Textile Products Regulation, in the context of its appropriateness for nanomaterials is outside the current scope but recommended.

For PPE there are no specific standards noted for the regulation, though an ISO standard for measuring nano-objects released from face masks is under development (ISO/AWI TS 11353). Regardless, the manufacturer must comply with a few key regulatory requirements. One being that:

'*The materials of which the PPE is made, including any of their possible decomposition products, must not adversely affect the health or safety of users.*'

Again, this sentence advocates the seeking of replacement materials when safety of a (nano)material is in doubt. However, what becomes difficult is what tools are available to measure safety in the first place, and which form should be tested: the 'as exposed/used' or the 'as manufactured'. Again, the noted difficulties previously still remain: 1. Identification of nanomaterials, 2. Analysis of nanomaterial characteristics, 3. Different hazard profiles for the same nanomaterial type, 4. Difficulty in predicting an embedded/migrated nanomaterials hazard versus its pristine form and, 5. What to best base hazard and risk assessment on (pristine, as used or as exposed). Moreover, although the PPE Regulation and PPE Regulation (GB) state that only safe materials should be used, the safety of these materials is assessed under other regulations. Regulations such as the REACH Regulation and REACH Regulation (GB), CLP Regulation and CLP Regulation (GB) and BPR Regulation may be relevant here to ensure the overall safety of the products outside the regulation directly itself.

One key aspect is that to understand possible risk it has to be known where nanomaterials are used and subsequently the exposure route. Highlighted here, is the difficulty of doing this without 1. Having formalised requirements to notify the presence of nanomaterials in all products and 2. The difficulty in proving a nanomaterial is in a product through testing.

Another difficulty comes as not all regulations define or use the same definition for nanomaterials. The use of different definitions also makes assessing prevalence a challenge. For example, in the EC recommendation (2011) it is stated that at least 50 % of the particles must be in the nano-range for it to be classed as nanomaterial. However, there is no such percentage cut-off for cosmetics and the other regulations lack an indication of which definition might be relevant. This could be due to uncertainties of each respective definition and the appropriateness of that definition under specific regulatory purpose. The EC recommendation has recently been updated, and the challenges of defining nanomaterials still remain and perhaps are worth further review on a case-by-case basis.

Appendix 1. Research methodology

A1.1 Consumer product searching methodology

Searches for relevant consumer products that may be either readily available products as available on the UK market or available products to UK consumers (refer to Section 2.3 for definitions of availability) were undertaken on a range of datasets. It should be noted that when a product is listed in a database of nano enabled products, it does not mean that the claim is physically validated by examination of the product in question. For the current study it is not possible to validate the nano-based claim made, so these have been taken at face value. However, it should be noted that previous research, both in the Netherlands and the UK, discovered that even when there is a nano-based claim made for a product, it is not always possible to verify that the products has been manufactured using nanomaterials (Oomen *et al*., 2011, Laycock *et al*., 2020). As has been made clear in an early RIVM study, "*products without a claim can contain nanomaterials, whereas products with a claim [do] not always contain nanomaterials*" (Oomen *et al*., 2011). There is difficulty in physically determining whether a product contains nanomaterials even when there is a verified nano-based claim, that the claim can be upheld and difficulties in accurately analysing consumer products (Contado *et al*., 2015). This is often because of the low concentrations of nanomaterials used in consumer products and the difficulty of identifying them when they are bound into products.

For the purposes of this study, to identify relevant consumer products that have a claim to use nanomaterials in their manufacture, a range of datasets were used, including:

- Project on Emerging Nanotechnologies (PEN): Consumer Products Inventory (CPI) (http://www.nanotechproject.tech/cpi/)

Established in 2005, the PEN database is based at the Woodrow Wilson Institute. It aims to show how nanotechnology enters the consumer products market (Vance 2015). The limitations of this dataset are partly due to its age and that it appears to be no longer regularly updated and that the claims made by manufacturers are not independently verified.

- Danish Nanodatabase (https://nanodb.dk/)

Established in 2012 by the Danish Technical University (DTU) Department of Environment, the Danish Ecological Council and the Danish Consumer Council, the Nanodatabase lists over 5,00 products that claim use of nanomaterials. There is an effort to encourage crowd sourcing of new products, with submitted claims being checked before inclusion. However, like the PEN database above, there is no scientific verification of manufacturers' claims.

- Nanowerk Global Nanotechnology Face Mask Database (https://www.nanowerk.com/nanotechnology-facemasks.php)

Provides a list of both commercially available facemasks and a number of research projects being run in academic institutions on nanomaterials use in face masks.

For the purposes of this study, the datasets were reviewed to identify the consumer product categories of interest. A list of all relevant products that were determined to use nanomaterials was compiled. Some other products that were found while undertaking product searches on UK retailers' websites (see below) were also added to the list of nano-products for completeness.

The following categories used by the datasets were used to help identify relevant consumer products in the sectors of interest, though it should be noted that the different databases categorise products differently:

- Goods for children
- Toys
- Cosmetic
- Sunscreen
- PPE
- Facemask
- Furniture
- Textile
- Clothing
- Nightwear
- Home furnishings

Once products were identified it was assessed whether these products were either readily available in the UK market using several common retailers' websites to see if these products were on sale to UK consumers or are available products to the UK consumers (refer to Section 2.3 for definitions of availability). A range of leading retailers' websites were chosen to be used to conduct the searches to cover the consumer product categories of interest. The sites were chosen to include general online retailers, UK supermarket chains, and catalogue retailers with a physical and online presence. The websites were searched using the product brand descriptions identified from the consumer product databases. If the product was found, then the search was stopped at that point and recorded as being available in UK retailers. If the product was not found on any of said websites, a further search was made to widen the search to more retail websites.

The criteria set for the product being readily available in UK retailers were as follows:

- delivered to mainland UK addresses without customs fees;
- advertised for sale in Pounds Sterling; and
- product must be sold as new and not second-hand

To supplement these UK retailers, a further search for products not identified as available through these outlets was undertaken. This was to ensure inclusivity and to help widen the search for products that may not be available in mainstream retailers, but may be available to consumers through aggregation sites..The criteria set for using these aggregation websiteswas as follows:

- Product must be sold as new and not second hand;
- Consumer must be able to purchase product using a UK bank account or credit card;
- Product must be able to be shipped to the UK, even if the consumer would be responsible for acting as the importer and be responsible for the payment of any customs dues.

These websites were searched using the product brand descriptions identified from the consumer product databases. If the product was found, then the search was stopped at that point and recorded as being available to consumers in the UK either as readily available product or as an available product to the UK consumer. If the product was not found on any of these aggregation websites, then it was recorded as not being available in the UK.

Using the criteria identified above, a master list of products with a claim to use nanomaterials was identified (see Supplementary Data). The list identifies the following information, as set out in Table 19.

Table 19. Categories used in product search.

Product name	Name under which the product is available
Product category	Category the product has been assigned to
Manufacturer	Manufacturer's name (if known)
Product nanoclaim	Whether it is claimed that the product contains nanomaterials
Nanoclaim source	Whether the claim is made by the manufacturer or by someone else
Known nanomaterials	Whether specific nanomaterials are identified in the nanoclaim
Nanomaterials used	List of any nanomaterials claimed to be in the product
Phys-chem data	Whether additional information is provided on these properties
Link	Weblink to the product at the time the search was performed
Available from UK Retailers	Whether the product can be bought in the UK (as verified on UK retailers' websites)
Available to UK consumers	Whether the product can be ordered online
Links to UK Retailers	Weblink to the product for UK retailers at the time the search was performed
Notes	Anything else of note

A1.2 Literature search methodology

The overall search and project methodology are similar to those outlined in the guidance on Quick Scoping Reviews as presented by Collins *et al.* (2015) and ECHA Chapter R.4 Guidance on information requirements and chemical safety assessment 'Evaluation of available information' v1.1 (2011). Briefly the steps in a quick scoping review which can be expanded to a more detailed analysis like within this document, are as follows:

1. Determine the question and identify the appropriate ER method;
2. Establish Steering Group and confirm method;
3. Establish a Review Team;
4. Hold an Inception Meeting;
5. Develop a Protocol;
6. Search for the evidence;
7. Screen the search results;
8. Extract evidence that relates to the research question;
9. Critical appraisal of evidence;
10. Synthesise/include the results;
11. Communicate findings; and
12. Sign off project.

For research question 1, when products with nanomaterials were identified, the nanomaterial type (e.g., TiO_2, silver) and the product were searched for at key retailers' websites to ratify the result.

For research question 2 as it concerns the reviewing of literature during critical appraisal (i.e., after Step 7 above), ECHA Chapter R.4 (2011, v1.1) presents a framework for the evaluation of relevant information. The framework is a widely accepted regulatory process and as such was used here. Briefly, the evaluation framework consists of:

1. Relevance assessment;
2. Reliability assessment;
3. Adequacy assessment; and
4. Data integration.

The evaluation used a Klimisch rating system as this is a widely recognised tool for data assessment (Klimisch, 1997) and a set of key quality criteria. The key quality criteria was approved by the entire project team, including the Office of Product Safety and Standards (OPSS).

The Klimisch system was adapted for the purpose of this research to allow evaluation of studies that are outside of the scope of the scoring system, namely, those studies that are not conducted to valid/internationally recognised guidelines, but are nonetheless useful. Moreover, it should be noted that the Klimisch system is used in a regulatory context for all studies, not just those of toxicological focus (e.g., physical chemical and environmental fate studies). The quality criteria and adapted Klimisch system can be seen in Table 21. The Klimisch and quality scoring process was not relevant for research question 1 where the basic step was to ensure robustness and validity of any prevalence research by e.g., checking primary source or (statistical) methods of data gathering.

The combined methodologies of these systems allows for a non-bias framework for literature review.

The focus of the literature searches as described above were research question one and two as defined in Section 2.1. Research question 3 is defined by the legislative/regulatory frameworks, and guidance therein, and is easily accessible and does not require a literature search. Key consumer goods that were the focus of these searches were cosmetics, furniture, toys, personal protective equipment and nightwear, as defined by the original project scope. These were identified by OPSS prior to execution of the project as those of most concern but are not exhaustive of OPSS's regulatory areas.

The literature search was conducted primarily in Web of Science. The databases/search engine was chosen as it provides access to current and retrospective multidisciplinary information from more than 10,400 of the most prestigious, high impact research journals in the world in the sciences, social sciences and arts and humanities – with coverage back to 1900 (sciences). It also provides access to multiple databases that provide reference and citation data from academic journals, conference proceedings, and other documents in various academic disciplines. The searches used specific Boolean search terms which included the list of products as previously mentioned, the term "nano" (plus its synonyms) and "U.K." (plus its synonyms). When no hits were found for specific products, broader terms were used e.g., product/consumer.

For research question 2 the term "U.K." was not used as the focus was on the potential effects of the nanomaterial which are not country specific. The terms used ensured relevance to nano-enabled consumer products and the U.K. market. A Boolean search is a type of search which combines keywords with operators (or modifiers) such as AND, NOT

and OR to further produce more relevant results. For example, a search could be “bed and breakfast” AND “Lake District”. This would limit the search results to only those sites/documents containing both keywords.

Exclusion terms were not included to ensure the broadest coverage and identify as many UK based products as possible to give the best reflection of product prevalence. In addition, searches involving key toxicological terminology such as “exposure”, “risk” and “hazard” were conducted to identify literature relevant to address research question 2. Secondary searches were also conducted to identify data from grey literature sources (e.g., reports by United States Environmental Protection Agency (USEPA), European Food Safety Agency (EFSA) conference outputs, industrial reports and theses). These were conducted in Google Scholar as well as, for example, the European Chemicals Agency (ECHA) and EFSA dissemination pages. Moreover, relevant industry bodies databases such as The Cosmetic, Toiletry and Perfumery Association, were also scanned for relevant results. This was to ensure unpublished, or literature that would not be captured by the Web of Science, that were still highly relevant, were not missed. Moreover, it allowed the retrieval of data from regulators, policy makers and industry. Example documents might be expert opinions or risk assessment reports from EFSA and national toxicology program (NTP) reports from the USEPA.

Initial search terms were established and only in cases where no literature or more than 2000 literature results were found were they refined. The search terms were approved with the project team, including OPSS before finalising the selected search strings (a list of words included during one search). All search terms and search term iterations can be seen in here in Table 22 to Table 29. A flow chart is also presented on how the search was conducted (Figure 8) when original search terms were not sufficient and shows the number of iterations required to achieve an appropriate search string.

Search results were collated into MSExcel® worksheets and any duplicate references were removed. Once in the MSExcel® worksheets an initial sift was conducted. This is a rapid assessment based on the title and abstract of the retrieved literature only. This screened references to ensure that the literature was relevant research question 1 and 2. The key terms looked for in research question 1 were, U.K., market, nano (any synonym) and consumer. If these were not present the literature was marked red and not carried forward for further review. For research question 2 again nano (any synonym) needed to be present and the title or abstract had to be specific to a toxicological response.

Moreover, based on research question 1 the literature for research question 2 was only carried forward if it contained information about a nanomaterial that is relevant to the UK market, these were TiO_2, ZnO, silver, carbon-based nanomaterials, bisoctrizole, gold, platinum, silicon and ceramics. Again, any literature that was not relevant was marked red and removed from further assessment. Those manuscripts still present after the initial sift were highlighted in green and potentially relevant literature was highlighted in yellow for critical appraisal. Those selected after critical appraisal were considered for inclusion in the presented research.

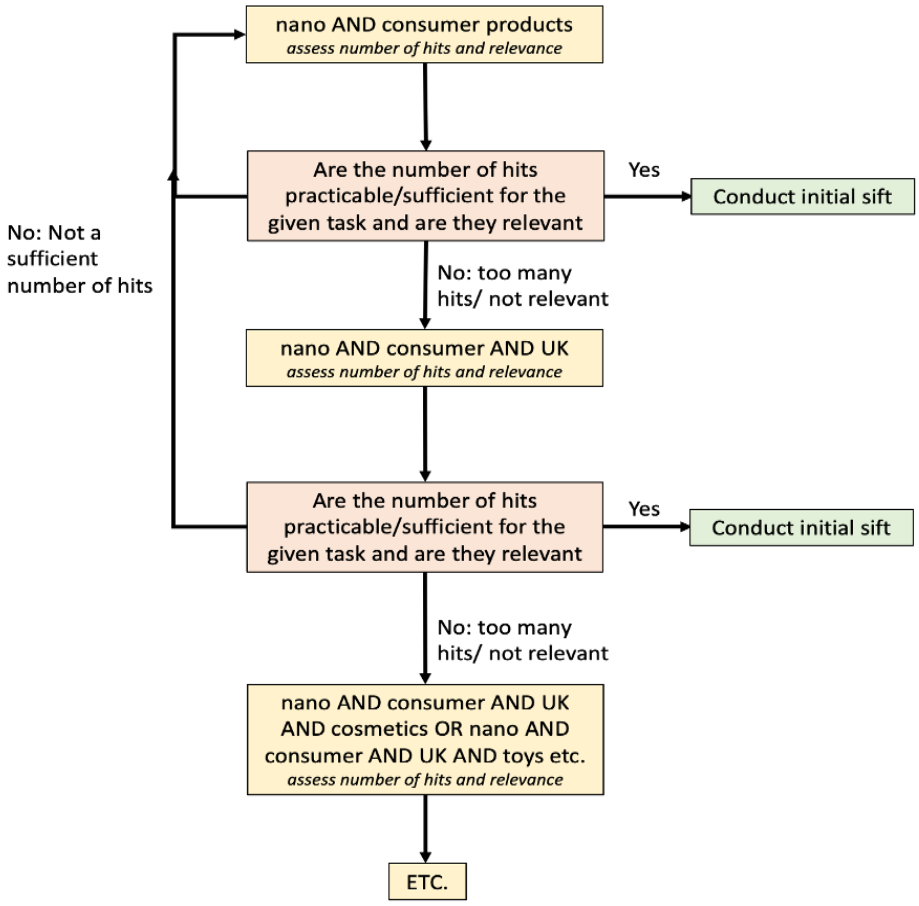

Figure 8. Literature search iterative strategy to ensure sufficient number, relevance and reliability of retrieved publications.

Table 20. Quality Criteria for research question 2 'What are the potential physical and chemical safety issues relating to the use of metal and non-metal nanomaterials in consumer products on/to be placed on the UK market and the associated risks?'

Quality criteria number	**Quality Criteria**
1.	Study is relevant for the exposure scenario or potential exposure route likely to be encountered by a consumer under the regulations stated in Section 6, i.e., if the material is imbedded inhalation may not be relevant.
2.	Well-defined primary test material, representative substance or transformation product ideally including purity/content for active ingredient or formulation details for product.*
3.	For laboratory studies, an acceptable dosing strategy is applied (e.g., exposure period, number of doses sufficient, suitable vehicle or medium are selected and dose volume is appropriate to the test system/species).**
4.	Exposure concentration is measured in the vehicle or medium unless otherwise justified (e.g., based on physical chemical properties).
5.	Sufficient information on test organisms/cohort/environment§ (e.g., age category) used
6.	Results are directly related to a useful endpoint that can be extrapolated to human effects caused by the test material in question, or the relevant exposure scenarios for consumers.
7.	The dosing and testing methodology used is clearly and transparently presented as well as robust.**
8.	For laboratory studies test organisms/cohort/environment§ have not been previously exposed to the test material or other contaminants or their history is well-known.
9.	Where individual data are not available, evidence that any statistical method used to derive the endpoint is acceptable and appropriate.
10	The methods used for measurements and analytical techniques are reliable and analytical techniques have been validated and verified.
11	Study authors are identified, and affiliations are transparent.
* When testing is directly on a product criterion 10 need only apply ** Dosing when testing products may not be applicable	§Environment means, media or surroundings of the product or material during tests of release or exposure in realistic scenarios. This does not need to relate to human effect but shows humans may be exposed.

Table 21. Adapted Klimisch rating* used for research question 2 ‘‘What are the potential physical and chemical safety issues relating to the use of metal and non-metal nanomaterials in consumer products on/to be placed on the UK market and the associated risks?’

Klimisch rating	**Description of requirements to meet the aligned Klimisch rating**
Klimisch 1 Reliable without restriction:	This includes studies or data from the literature or reports which meet quality criteria.
Klimisch 2 Reliable with restriction:	This includes studies or data from the literature, reports, which do not totally comply with the quality criteria (e.g., low organism numbers), but which are nevertheless well documented and scientifically acceptable.
Klimisch 3 Not reliable:	This includes studies or data from the literature/reports which do not meet most (≥ 5) of the quality criteria.
Klimisch 4 Not assignable:	This includes studies or data from the literature, which do not give sufficient experimental details (e.g., a paper citing data from another source) or which are only listed in short abstracts or secondary literature (books, reviews, etc.).

*The Klimisch ratings were adapted as the original ratings only included reference to internationally recognised or validated study designs. In order to include important work on e.g., mechanism of action the search was not restricted only to such studies but instead had to be studies with relevant robust and well-presented methods.

Table 22. Research question 1 search terms and number of literature papers identified prior to review process: Cosmetics.

Primary phrase	**AND**	**AND (separated by OR term)**	**WOS query (using all databases, all years)**	**No. of WOS results obtained (all databases)**
nano	cosmetic* OR "personal care product*" OR makeup OR "make up"	UK OR “U.K.” OR “United Kingdom"	**nano (Topic) and cosmetic* OR "personal care product*" OR makeup OR "make up" (Topic) and UK OR "U.K." OR "United Kingdom" (Topic)**	9
nano OR nano- OR nanomaterial* OR "nano material*"	cosmetic* OR "personal care product*" OR makeup OR "make up"	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **cosmetic* OR "personal care product*"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	13

Table 23. Research question 1 search terms and number of literature papers identified prior to review process: Furniture.

Primary phrase	**AND**	**AND (separated by OR term)**	**WOS query (using all databases, all years)**	**No. of WOS results obtained (all databases)**
nano	furniture	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **furniture** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	0
nano OR nano- OR nanomaterial* OR "nano material*"	Furniture	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*" (Topic) and furniture (Topic) and UK OR “U.K.” OR “United Kingdom" (Topic)**	0
nano	furniture OR table* OR desk* OR chair* OR handrail* OR "hand rail*"	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **furniture OR table* OR desk* OR chair* OR handrail* OR "hand rail*"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	6
nano OR nano- OR nanomaterial* OR "nano material*"	furniture OR table* OR desk* OR chair* OR handrail* OR "hand rail*"	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **furniture OR table* OR desk* OR chair* OR handrail* OR "hand rail*"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	10

When identified literature was 0, the key terms required refinement. Successful iterations can be seen directly below the cells where 0 literature was found.

Table 24. Research question 1 search terms and number of literature papers identified prior to review process: Toys.

Primary phrase	**AND**	**AND (separated by OR term)**	**WOS query (using all databases, all years)**	**No. of WOS results obtained (all databases)**
nano	toy*	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **toy*** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	0
nano OR nano- OR nanomaterial* OR "nano material*"	toy	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **toy*** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	0

There were no successful iterations and therefore generic consumer terms were also used. See Table 28.

Table 25. Research question 1 search terms and number of literature papers identified prior to review process: Nightwear/textiles.

Primary phrase	**AND**	**AND (separated by OR term)**	**WOS query (using all databases, all years)**	**No. of WOS results obtained (all databases)**
nano	nightwear OR "night wear"	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **nightwear OR "night wear"** (Topic) and **UK OR “U.K.” OR “United Kingdom"** (Topic)	0
nano OR nano- OR nanomaterial* OR "nano material*"	nightwear OR "night wear"	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **nightwear OR "night wear"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	0
nano OR nano- OR nanomaterial* OR "nano material*"	cloth*	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **cloth*** (Topic) and **UK OR “U.K.” OR “United Kingdom"** (Topic)	3
Nano* OR nano- OR nanomaterial*	Clothes OR clothing OR textile*	UK OR "U.K." OR UNITED KINGDOM	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) AND **Clothes OR clothing OR textile*** (Topic) AND **UK OR "U.K." OR UNITED KINGDOM** (Topic)	6

When identified literature was 0, the key terms required refinement. Successful iterations can be seen directly below the cells where 0 literature was found. Moreover, it was possible to further refine these searches based on the raw materials that would make the nightwear, e.g. cloth, textiles or synonyms for which it may fall under e.g. clothes and clothing

Table 26. Research question 1 search terms and number of literature papers identified prior to review process: Furniture.

Primary phrase	**AND**	**AND (separated by OR term)**	**WOS query (using all databases, all years)**	**No. of WOS results obtained (all databases)**
nano	furniture	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **furniture** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	0
nano OR nano- OR nanomaterial* OR "nano material*"	Furniture	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*" (Topic) and furniture (Topic) and UK OR “U.K.” OR “United Kingdom" (Topic)**	0
nano	furniture OR table* OR desk* OR chair* OR handrail* OR "hand rail*"	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **furniture OR table* OR desk* OR chair* OR handrail* OR "hand rail*"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	6
nano OR nano- OR nanomaterial* OR "nano material*"	furniture OR table* OR desk* OR chair* OR handrail* OR "hand rail*"	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **furniture OR table* OR desk* OR chair* OR handrail* OR "hand rail*"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	10

When identified literature was 0, the key terms required refinement. Successful iterations can be seen directly below the cells where 0 literature was found.

Table 27. Research question 1 search terms and number of literature papers identified prior to review process: PPE.

Primary phrase	**AND**	**AND (separated by OR term)**	**WOS query (using all databases, all years)**	**No. of WOS results obtained (all databases)**
nano	"personal protective equipment" OR PPE OR "safety equipment"	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **"personal protective equipment" OR PPE OR "safety equipment"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	0
nano OR nano- OR nanomaterial* OR "nano material*"	"personal protective equipment" OR PPE OR "safety equipment"	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **"personal protective equipment" OR PPE OR "safety equipment"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	0

There were no successful iterations and therefore generic consumer terms were also used. See Table 28.

Table 28. Research question 1 search terms and number of literature papers identified prior to review process: Generic consumer terms.

Primary phrase	**AND**	**AND (separated by OR term)**	**WOS query (using all databases, all years)**	**No. of WOS results obtained (all databases)**
nano	consumer	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **consumer** (Topic) and **UK OR “U.K.” OR “United Kingdom"** (Topic)	12
nano	product*	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **product*** (Topic) and **UK OR “U.K.” OR “United Kingdom"** (Topic)	115
nano	n/a	UK OR “U.K.” OR “United Kingdom"	**nano** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	388
nano OR nano- OR nanomaterial* OR "nano material*"	n/a	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **UK OR "U.K." OR "United Kingdom"** (Topic)	502
nano OR nano- OR nanomaterial* OR "nano material*"	Consumer	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **consumer** (Topic) and **UK OR “U.K.” OR “United Kingdom"** (Topic)	19
nano OR nano- OR nanomaterial* OR "nano material*"	product*	UK OR “U.K.” OR “United Kingdom"	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **product*** (Topic) and **UK OR “U.K.” OR “United Kingdom"** (Topic)	147
Nano* OR nano- OR nanomaterial*	Pigment* OR Paint* OR coating* OR dye*	UK OR "U.K." OR UNITED KINGDOM	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **Pigment* OR Paint* OR coating* OR dye*** (Topic) and **UK OR "U.K." OR UNITED KINGDOM** (Topic)	55

Primary phrase	**AND**	**AND (separated by OR term)**	**WOS query (using all databases, all years)**	**No. of WOS results obtained (all databases)**
Nano* OR nano- OR nanomaterial*	Antimicrobial* OR antiviral* or antibacterial* or anti*	UK OR "U.K." OR UNITED KINGDOM	**nano OR nano- OR nanomaterial* OR "nano material*"** (Topic) and **Antimicrobial* OR antiviral* or antibacterial* or anti*** (Topic) AND **UK OR "U.K." OR UNITED KINGDOM** (Topic)	138

*These terms may encompass several of the products areas specified and were used to ensure no possible consumer products in the UK were missed, especially when more specific searches failed to retrieve any results.

Table 29. Research question 2 search terms and number of literature papers identified prior to review process.

Primary phrase	AND	AND (separated by OR term)	WOS query (using all databases, all years)	No. of WOS results obtained (all databases)
Nano* OR nano- OR nanomaterial*	consumer safety	N/A	**nano* OR nano OR nano- OR nanomaterial* OR "nano material"*** (Topic) AND **consumer safety** (Topic) AND **UK OR "U.K." OR UNITED KINGDOM** (Topic)	3
Nano* OR nano- OR nanomaterial*	consumer safety	N/A	**nano* OR nano OR nano- OR nanomaterial* OR "nano material"*** (Topic) and **consumer safety** (Topic)	888
Nano* OR nano- OR nanomaterial*	consumer hazard	N/A	**nano* OR nano OR nano- OR nanomaterial* OR "nano material"*** (Topic) and **consumer hazard** (Topic)	238
Nano* OR nano- OR nanomaterial*	consumer health OR health and safety	N/A	**nano* OR nano OR nano- OR nanomaterial* OR "nano material"*** (Topic) and **consumer health OR health and safety** (Topic)	4559
Nano* OR nano- OR nanomaterial*	consumer health OR health and safety	UK OR "U.K." OR UNITED KINGDOM	**nano* OR nano OR nano- OR nanomaterial* OR "nano material"*** (Topic) and **consumer health OR health and safety** (Topic) and **UK OR "U.K." OR UNITED KINGDOM** (Topic)	26
Nano* OR nano- OR nanomaterial*	consumer risk	N/A	**nano* OR nano OR nano- OR nanomaterial* OR "nano material"*** (Topic) and **consumer risk** (Topic)	1043
Nano* OR nano- OR nanomaterial*	consumer impact	N/A	**nano* OR nano OR nano-* OR nanomaterial* OR "nano material"*** (Topic) and **consumer impact** (Topic)	993

Primary phrase	AND	AND (separated by OR term)	WOS query (using all databases, all years)	No. of WOS results obtained (all databases)
Nano* OR nano- OR nanomaterial*	consumer exposure	N/A	**nano* OR nano OR nano-* OR nanomaterial* OR "nano material"*** (Topic) and **consumer exposure** (Topic)	1401

When the identified literature was > 2000 refinement of search terms was conducted in order to reduce the number of hits. When the number of identified literature was < 5, refinement of the search terms was conducted in order to increase the number of literature retrieved. The next iterations can be directly below these cells, these were used as the search terms. As the search concerned consumer risk, health and safety and not specific modes of actions or toxicological endpoints, it was pertinent to focus on the UK consumer only for this search.

Appendix 2. Industrial standards frameworks

There are two main categories of industrial standards that can be discussed. Firstly, there are national standards (in the UK these are set by the British Standards institute (BSI)) and secondly, there are international standards, such as CEN (at an EU level) and ISO (at a global level). Standardisation activities regarding adaptation or development of novel guidelines and guidance to accommodate the particulars of the nanosize are currently running both world-wide (OECD and ISO) and at the European level (CEN). The OECD develops methods for regulatory testing, which are globally recognised for this purpose under the Mutual Acceptance of Data agreement (MAD)[76]. ISO and CEN develop standards for particular aspects regarding characterisation of nanotechnologies.

Standards may not be regulatory imposed methods but contribute to quality assessment of nanotechnologies and may be compulsory in some sectors (e.g., Medical Devices[77]).The needs to adapt current strategies to nanomaterials was already discussed at the OECD level back in the early 2000s and led to an initial publication already in 2009[78], and several EU and National initiatives followed on such activities which may be found under the NanoSafety Cluster[79].

A2.1 Relevant standards

A2.1.1 Activities under CEN

In 2010, the European Commission issued a mandate with the purpose to speed up standard development in the nanotechnology sector. Such mandate termed M46180 focuses on the following:

- Characterisation of and exposure from nanomaterials which includes the revision of existing standards (e.g. dustiness), methodologies for nanomaterial characterisation in the manufactured form and before toxicity and eco-toxicity testing, physicochemical properties relevant for hazard characterisation of nanomaterials (dynamics of dispersion, rate of dissolution, aggregation/agglomeration, surface area and the potential to adsorb substances onto nanomaterials' surfaces in the manufactured form and before toxicity and eco-toxicity testing).
- Guidance on safe handling and/or exposure avoidance of manufactured nanoparticles and other manufactured nanoscale entities (including selection of Personal Protective Equipment (PPE).
- Protocols for the characterisation of manufactured nanoparticles from aerosols and from environmental sources, including sampling, sample stabilization, agglomeration, aggregation, etc.

Several nanotechnology related standards are currently being developed under the following CEN groups and are enumerated below:

[76] http://www.oecd.org/env/ehs/mutualacceptanceofdatamad.htm
[77] REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
[78] OECD. (2009). Guidance Manual for the testing of Manufactured Nanomaterials. OECD´s Sponsorship program; 1 Revision.
[79] https://www.nanosafetycluster.eu/
[80] https://ec.europa.eu/growth/tools-databases/mandates/index.cfm?fuseaction=search.detail&id=443

CEN/TC 352:

- prCEN/TS (PWI 00352043) “Nanotechnologies - Guidance on the determination of aggregation and agglomeration state of nano-objects”
- prCEN/TS (PWI 00352047) Nanotechnologies - Safe-by-Design concept dedicated for nano scale materials (MNM) and products containing nanomaterials
- prCEN/TS (PWI 00352040) Nanotechnologies - Quick start guide for deploying a relevant nano health and safety risk management
- prCEN/TS (PWI 00352044) Nanotechnologies - Guidelines for the characterization of nanoobjects-containing additives in food products

CEN/TC 137 WG3:

- EN 17289-1:2020 Characterization of bulk materials - Determination of a size-weighted fine fraction and crystalline silica content - Part 1: General information and choice of test methods
- EN 17289-2:2020 Characterization of bulk materials - Determination of a size-weighted fine fraction and crystalline silica content - Part 2: Calculation method
- EN 17289-3:2020 Characterization of bulk materials - Determination of a size-weighted fine fraction and crystalline silica content - Part 3: Sedimentation method
- WI 137067: prEN 481 REV Workplace exposure – Size fraction definitions for measurement of airborne particles (together with ISO 7708)
- prEN 15051-1:2013 Workplace exposure - Measurement of the dustiness of bulk materials - Part 1: Requirements and choice of test methods (revision)
- prEN 15051-2:2013 Workplace exposure - Measurement of the dustiness of bulk materials - Part 2: Rotating drum method (revision)
- prEN 15051-3:2013 Workplace exposure - Measurement of the dustiness of bulk materials - Part 3: Continuous drop method (revision)
- EN 17199-1:2019 Workplace exposure – Measurement of dustiness of bulk materials that contain or release respirable NOAA and other respirable particles – Part 1: Requirements and choice of test methods
- EN 17199-2:2019 Workplace exposure – Measurement of dustiness of bulk materials that contain or release respirable NOAA and other respirable particles – Part 2: Rotating drum method
- EN 17199-3:2019 Workplace exposure – Measurement of dustiness of bulk materials that contain or release respirable NOAA and other respirable particles – Part 3: Continuous drop method
- EN 17199-4:2019 Workplace exposure – Measurement of dustiness of bulk materials that contain or release respirable NOAA and other respirable particles – Part 4: Small rotating drum method
- EN 17199-5:2019 Workplace exposure – Measurement of dustiness of bulk materials that contain or release respirable NOAA and other respirable particles – Part 5: Vortex shaker method
- WI 137085: Workplace exposure - Sampling of nano-objects and their agglomerates and aggregates in the workplace for electron microscopy (CEN/TS)
- WI 137086: Workplace exposure - Counting rules for the characterization of airborne nano-objects and their agglomerates and aggregates for scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (European Standard)

- WI 137087: Workplace exposure - Application of direct-reading low-cost sensors for measuring NOAA in the workplace (CEN/TS)
- CEN/TC 137 WG6:
- CEN ISO/TS 21623:2018 Workplace exposure – Assessment of dermal exposure to nano-objects and their aggregates and agglomerates (NOAA)

A2.1.2 Activities under ISO

- The most relevant ISO standards regarding Nanotechnologies are being developed under ISO/TC 22981. Currently the following new documents are being developed
- ISO/AWI TS 4958 Nanotechnologies — Liposomes terminology
- ISO/AWI TS 4971 Nanotechnologies — Performance evaluation of nanosuspensions containing clay nanoplates for quorum quenching
- ISO/DTS 4988 Nanotechnologies — Toxicity assessment and bioassimilation of manufactured nano-objects in suspension using the unicellular organism Tetrahymena sp.
- ISO/WD TS 5094 Nanotechnologies — Assessment of peroxidase-like activity of metal and metal oxide nanoparticles
- ISO/WD TR 5387 Nanotechnologies: Lung burden measurement of nanomaterials for inhalation toxicity studies
- ISO/AWI TS 7833 Extraction method of nanomaterials from organs by the proteinase K digestion
- ISO/WD TS 22298 Nanotechnologies — Silica nanomaterials — Specifications of characteristics and measurement methods for nanostructured porous silica samples with ordered nanopore array
- ISO/WD TS 23361 Nanotechnologies — Crystallinity of cellulose nanomaterials by powder X-ray diffraction (Ruland-Rietveld analysis)
- ISO/WD TS 23366 Nanotechnologies — Performance evaluation requirements for quantifying biomolecules using fluorescent nanoparticles in immunohistochemistry
- ISO/WD TS 23367 Nanotechnologies — Performance characteristics of nanosensors for chemical and biomolecule detection
- ISO/WD TR 23652 Nanotechnologies — Considerations for radiolabelling methods of nanomaterials for performance evaluation
- ISO/WD TS 23878 Nanotechnologies — Positron annihilation lifetime measurement for nanopore evaluation in materials
- ISO/DTR 24672 Nanotechnologies — Guidance on the measurement of nanoparticle number concentration
- ASTM E3025-16 Standard Guide for Tiered Approach to Detection and Characterization of Silver Nanomaterials in Textiles (https://www.astm.org/e3025-16.htm l)
- ASTM E3171-21a Standard Test Method for Determination of Total Silver in Textiles by ICP-OES or ICP-MS Analysis (https://www.astm.org/e3171-21a.html)

81 https://www.iso.org/committee/381983.html

A2.1.3 Activities under the OECD Test Guidelines Programme of the Working Party of Manufacture Nanomaterials (WPMN)

The OECD created the Working Party on Manufactured Nanomaterials (WPMN) in 2006 to promote international co-operation in human health and environmental safety aspects of manufactured nanomaterials. Under this group the OECD launched the Sponsorship Programme for the Testing of Manufactured Nanomaterials (Testing Programme) in November 2007. This Testing Programme verifies the testing methods used on Manufactured Nanomaterials through the expertise of OECD member countries, non-member countries and other stakeholders willing to contribute with funding to the Testing Programme. Initially a list of 11 Manufactured Nanomaterials was selected based on commercial use, results have been published in the form of Dossiers and are freely available82. Currently such activities are being funded either by countries themselves or under different EU initiatives such as Gov4nano[83] and NanoHarmony[84].

The following reports were published in the past two years:

- No. 103 - Important Issues on Risk Assessment of Manufactured Nanomaterials
- No. 101- Evaluation of Tools and Models for Assessing Occupational and Consumer Exposure to Manufactured Nanomaterials; Part III: Performance testing results of tools/models for consumer exposure
- No. 100 - Evaluation of Tools and Models for Assessing Occupational and Consumer Exposure to Manufactured Nanomaterials; Part II: Performance testing results of tools/models for occupational exposure (Annex 1)
- No. 99 - Evaluation of Tools and Models for Assessing Occupational and Consumer Exposure to Manufactured Nanomaterials; Part I: Compilation of tools/models and analysis for further evaluation
- No. 98 - Evaluation of Tools and Models Used for Assessing Environmental Exposure to Manufactured Nanomaterials; Functional Assessment and Statistical Analysis of Nano-Specific Environmental Exposure Tools and Models; Annex 1
- No. 96 - Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products
- No. 95 - Advancing Adverse Outcome Pathway (AOP) Development for Nanomaterial Risk Assessment and Categorisation/ PART3: Workshop Report and Recommendations
- No. 94 - Advancing Adverse Outcome Pathway (AOP) Development for Nanomaterial Risk Assessment and Categorisation/ PART2: Case Study on Tissue Injury
- No. 93 - Advancing Adverse Outcome Pathway (AOP) Development for Nanomaterial Risk Assessment and Categorisation/ PART1: Final Project Report and Recommendations with Methodology to Prioritise Key Events (KEs) Relevant for Manufactured Nanomaterials
- No. 92 - Ability of biopersistent/biodurable manufactured nanomaterials (MNs) to induce lysosomal membrane permeabilization (LMP) as a prediction of their long-term toxic effects

[82] https://www.oecd.org/chemicalsafety/nanosafety/testing-programme-manufactured-nanomaterials.htm
[83] https://www.gov4nano.eu/
[84] https://nanoharmony.eu/

- TG 125 for the Testing of Chemicals Particle Size and Particle Size Distribution of Nanomaterials
- TG 124 on the Determination of the Volume Specific Surface Area of Manufactured Nanomaterials

The following Test Guidelines and Guidance Documents are currently being updated/developed:

- Guidance on Sample Preparation and Dosimetry
- Test No. 305: Bioaccumulation in Fish: Aqueous and Dietary Exposure
- To support Guidance Document on aquatic and sediment toxicological testing of nanomaterials GD 317
- WNT1.3_TG on Determination of the volume Specific Surface Area of NMs (EU)
- WNT1.4 _TG on particle size distribution of NM (Ger)
- WNT1.5_GD on Determination of solubility and dissolution rate of NMs in water and relevant synthetic biological media (DNK/GER)
- WNT1.6_GD on identification and quantification of the surface chemistry and coatings on nano and microscale materials (DNK/GER)
- WNT 1.8_TG on Determination of Surface Hydrophobicity of NMs (JRC)
- WNT 1.9_TG on Determination of Dustiness of NMs (DNK/FRA)
- WPMN_Adaptation of OECD guidelines 201, 202 and 203 for the determination of ecotoxicity of nanomaterials (FR, ESP)
- WNT 3.10_TG on dissolution rate of NMs in aquatic environment (GER)
- WNT3.11_TG for nanomaterial removal from wastewater (US)
- WNT3.12_GD on assessing the apparent accumulation potential for NMs (Spain)
- WNT3.14_ GD to support implementation of TG312 for nanomaterials safety testing (CAN/GER)
- WNT 3.16_GD Environmental abiotic transformation of NMs (AT)
- WPMN_Scoping review for a tiered approach for reliable bioaccumulation assessment of MNs in environmental organisms minimising the use of higher tier vertebrate tests (UK)
- WNT 4.95_GD Document on the adaptation of in vitro mammalian cell-based genotoxicity testing guidelines for testing nanomaterials (EU)
- WNT 4.133_Applicability of the key event-based Test Guideline 442D for in vitro skin sensitisation testing of NMs (Switzerland)
- WNT 4.146_TG on toxicokinetics to accommodate testing of nanoparticles (NED/UK)
- WPMN_Integrated in vivo approach for intestinal fate or orally ingested NMs (IT)
- WPMN_GD on the determination of concentrations of nanoparticles in biological samples for (eco)toxicity studies (UK)

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