Nanomaterials as part of society

Towards a safe future of nanotechnology

REPORTS AND MEMORANDUMS OF THE MINISTRY OF SOCIAL AFFAIRS AND HEALTH 2022:26

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Abstract

The review contains information on the use of nanomaterials and safety issues, regulation and research related to nanomaterials in Finland. Nanomaterials have at least one dimension between 1–100 nanometers. At the nanoscale, materials can exhibit unique chemical, physical, electronic and mechanical properties. Nanotechnology is used to improve the properties of materials. Manufactured nanomaterials are used in nearly all industrial sectors. As a result of human activity, nanoparticles are also generated unintentionally through various processes and combustion. The impact that nanomaterials have on health or the environment is not yet fully understood. The assessment of health and environmental risks is based on information on the hazardous properties and exposure levels of nanomaterials. Exposure to manufactured nanomaterials may occur during the production process or the use of these products. However, as a rule, the risk of exposure to manufactured nanomaterials in consumer products is minimal. The regulation of nanomaterials builds on EU and national legislation concerning chemicals, food and medicines. The EU also has sector-specific legislation on the safe use of nanomaterials. The European Commission is directing more and more funding to the research on the safety of nanomaterials. In Finland, universities and government research institutes conduct valuable safety and material-related research on nanomaterials.

Keywords	nanotechnology, ambient air, nanomaterials, nanosciences, nanotechnique, nanoparticles, chemicals, health impact, environmental impact, research and development, research funding, occupational health and safety, food safety, medicines
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Nanomateriaalit osana yhteiskuntaa
Kohti turvallista nanoteknologian tulevaisuutta

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Tiivistelmä

Katsaus sisältää tietoa nanomateriaalien käytöstä, turvallisuuteen liittyvistä kysymyksistä, sääntelystä, sekä tutkimuksesta Suomessa. Nanomateriaalit ovat materiaaleja, joissa vähintään yksi ulottuvuus on välillä 1–100 nanometriä. Aineella voi nanokoossa olla kemiallisia, fysikaalisia, sähköisiä ja mekaanisia erityisominaisuuksia. Nanoteknologiaa käytetään tuotteiden ominaisuuksien parantamiseen. Teollisesti tuotettuja nanomateriaaleja käytetään lähes kaikilla teollisuuden aloilla. Ihmistoiminnan seurauksena syntyy myös tahattomasti poltto- ja prosessiperäisiä nanohiukkasia. Nanomateriaalien terveydelle tai ympäristölle aiheuttamia vaikutuksia ei vielä täysin tunneta. Terveys- ja ympäristöriskien arviointi perustuu tietoihin nanomateriaalien vaaraominaisuuksista ja altistumistasoista. Teollisesti tuotetuille nanomateriaaleille on mahdollista altistua valmistuksessa ja käytössä. Altistuminen kuluttajatuotteista on pääsääntöisesti vähäistä. Nanomateriaalien sääntelyssä sovelletaan EU- ja kansallisia säädöksiä, jotka koskevat kemikaaleja, elintarvikkeita tai lääkkeitä. Lisäksi EU:ssa on sektorikohtaisia säädöksiä nanomateriaalien turvalliselle käytölle. Euroopan komissio rahoittaa yhä enemmän nanomateriaalien turvallisuuteen liittyvää tutkimista. Suomen yliopistoissa ja valtion tutkimuslaitoksissa tehdään ansiokasta nanomateriaaleja koskevaa materiaali- ja turvallisuustutkimusta.

Asiasanat	nanoteknologia, yhdyskuntailma, nanomateriaalit, nanotieteet, nanotekniikka, nanohiukkaset, kemikaalit, terveysvaikutukset, ympäristövaikutukset, tutkimus- ja kehittämistoiminta, tutkimusrahoitus, työsuojelu, elintarviketurvallisuus, lääkkeet

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Nanomaterial som en del av samhället
Vägen till en trygg framtid för nanoteknologi

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Denna översikt innehåller information om användningen av nanomaterial i Finland och om säkerhetsfrågor, reglering och forskning som gäller nanomaterial. Med nanomaterial avses material med minst en dimension i storleksintervallet 1–100 nanometer. Ämnen i nanostorlek kan ha kemiska, fysikaliska, elektriska och mekaniska egenskaper. Nanoteknologi används för att förbättra egenskaperna hos olika produkter. Industriellt framställt nanomaterial används inom nästan alla industrisektorer. Till följd av mänsklig verksamhet uppstår det också oavsiktligt nanopartiklar vid förbränning och processer. Man känner ännu inte helt till vilken effekt nanomaterial har på hälsan och miljön. Bedömningen av hälso- och miljörisker grundar sig på uppgifter om nanomaterialens farliga egenskaper och exponeringsnivåer. Det är möjligt att man vid tillverkning och användning exponeras för industriellt framställt nanomaterial. Exponeringen för nanomaterial i konsumentprodukter är i regel liten. Nanomaterial regleras genom EU-rättsakter och nationella författningar som gäller kemikalier, livsmedel eller läkemedel. Dessutom finns det sektorspecifika EU-bestämmelser om trygg användning av nanomaterial. Europeiska kommissionen finansierar i allt högre grad forskning kring säkerheten hos nanomaterial. Finlands universitet och statliga forskningsinstitut bedriver förtjänstfull forskning kring nanomaterial och säkerheten hos nanomaterial.

Nyckelord	nanoteknologi, luftmiljön i samhället, nanomaterial, nanovetenskaper, nanoteknik, nanopartiklar, kemikalier, hälsoeffekter, miljöeffekter, forskning och utveckling, forskningsfinansiering, arbetarskydd, livsmedelssäkerhet, läkemedel
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Contents

FOREWORD

This review was drawn up by the nanosafety network coordinated by the Ministry of Social Affairs and Health. One of the tasks of the network is to provide information on the applications and safety of nanotechnology with an eye to the needs of administration, research and development, and private individuals. The idea of writing a review on nanomaterials and nanotechnology stemmed from the need to give a comprehensive overview of this exceptionally broad and cross-sectoral field, with emphasis on the Finnish perspective.

The review was written during the course of 18 months, from the autumn of 2020 to the spring of 2022, and completely by remote means due to the COVID-19 pandemic. During the writing process, the network held a total of five review workshops (in October 2020, March 2021, May 2021, August 2021, and November 2021). The network also organised an open webinar entitled ‘Nanomaterials as part of society’ in the autumn of 2021, with presentations based on the review theme.

Alongside the network members, contributions to the review were also provided by experts from their background organisations. Towards the end of the writing process, the review was also submitted for comments by a broader group of experts within the writers’ background organisations. For the chapter on nanomaterials research in Finland, the network requested universities and research institutes to provide their own descriptions.

The review was written by the following network members and experts: Kukka Aimonen, Anna-Kaisa Viitanen (currently from Tampere University) and Piia Taxell from the Finnish Institute of Occupational Health; Taina Siponen, Merja Korkalainen, Tarja Yli-Tuomi and Päivi Ruokojärvi from the Finnish Institute for Health and Welfare; Elina Rydman, Hanna Lindberg, Riitta Leinonen and Elina Ekokoski from the Finnish Safety and Chemicals Agency; Sari Kauppi and Petrus Kautto from the Finnish Environment Institute; Tiina Palomäki, Anne Paavola, Tita-Maria Muhonen and Risto Joro from the Finnish Medicines Agency Fimea; Pertti Koivisto and Anna Mizrahi from the Finnish Food Authority; Ulla Forsström and Heli Kangas from VTT Technical

Research Centre of Finland Ltd; Minna Räisänen and Samuli Hemming from the Academy of Finland; Sanna Viljakainen, Elina Pahkala and Anna Lemström from the Ministry of Agriculture and Forestry; Hinni Papponen and Tuulia Toikka from the Ministry of the Environment; and Sirkku Saarikoski, Anneli Törrönen and Hanna Korhonen from the Ministry of Social Affairs and Health.

The following universities and research institutes submitted descriptions of their research on nanomaterials: VTT Technical Research Centre of Finland Ltd, Aalto University, University of Jyväskylä, University of Eastern Finland, University of Oulu, Tampere University, University of Helsinki, and University of Turku.

Comments to the review were provided by Tiina Santonen, Arto Säämänen, Tomi Kanerva, Mikko Poikkimäki and Kirsi Siivola from the Finnish Institute of Occupational Health; Markus Sillanpää and Niko Karvosenoja from the Finnish Environment Institute; Merja Virtanen from the Finnish Food Authority; Eeva Saarisalo and Tove Jern from the Ministry of Agriculture and Forestry; and Kirsi Kyrkkö and Tuija Metsävainio from the Ministry of Social Affairs and Health.

As the coordinator of the writing process, I would like to extend my greatest thanks to all authors and all those who were involved in drawing up descriptions from universities and research institutes and providing comments on the review for their expertise, commitment and enthusiasm, and for their hard work. I am very proud of this network achievement and I hope that the review will receive the interest and appreciation that it deserves.

Elina Ekokoski, deputy chair of the nanosafety network,
Finnish Safety and Chemicals Agency Tukes
May 2022

Abbreviations

ALD	Atomic Layer Deposition
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail; French Agency for Food, Environmental and Occupational Health and Safety
AOP	Adverse outcome pathway
ASA register	Finnish register of people exposed to carcinogenic substances and methods and to mutagenic substances at work
BNCT	OECD Working Party on Biotechnology, Nanotechnology and Converging Technologies
CAS	Chemical Abstracts Service; a system of identifiers for chemicals
CEN	European Committee for Standardisation
CLP	Classification, labelling and packaging of chemicals; Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures
CMR substances	Carcinogenic, mutagenic or reprotoxic substances; substances that can cause or promote cancer or induce heritable mutations in the germ cells or induce adverse effects on the reproductive process
CoRAP	Community Rolling Action Plan; action plan for evaluating substances under the REACH Regulation
COVID	Coronavirus disease
DNA	Deoxyribonucleic acid
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
EUON	European Union Observatory for Nanomaterials
EU-OSHA	European Agency for Safety and Health at Work
GHS	UN Globally Harmonised System of Classification and Labelling of Chemicals
HPV	Human papilloma virus
IATA	Integrated approach to testing and assessment

IPRP	International Pharmaceutical Regulators Programme
ISO	International Organization for Standardisation
JRC	Joint Research Centre of the European Commission
LNP	Lipid nanoparticle
MOA	Mode of action
mRNA	Messenger RNA
NANONetwork	Nanotechnology expert group of the European Food Safety Authority
NMEG	Nanomaterials Expert Group of the European Chemicals Agency
NSC	Nanoscience Center of the University of Jyväskylä
NWG	Nanomedicines Working Group; working group under the International Pharmaceutical Regulators Programme (IPRP)
OECD	Organisation for Economic Co-operation and Development
PEG	Polyethylene glycol
PIC	Prior Informed Consent Regulation; Regulation (EU) No 649/2012 of the European Parliament and of the Council concerning the export and import of hazardous chemicals
PM_{10}	Particulate matter; inhalable particles with aerodynamic diameter of 10 µm or less
$PM_{2.5}$	Particulate matter; fine particles with aerodynamic diameter of 2.5 µm or less
RAC	Risk Assessment Committee of the European Chemicals Agency
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals; Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	Rijksinstituut voor Volksgezondheid en Milieu; Dutch National Institute for Public Health and the Environment
RNA	Ribonucleic acid
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks (currently SCHEER)

SCHEER	Scientific Committee on Health, Environmental and Emerging Risks (formerly SCENIHR)
SSbD	Safe and sustainable by design; a product design approach taking account of safety and sustainability perspectives
SYKE	Finnish Environment Institute
THL	Finnish Institute for Health and Welfare
Tukes	Finnish Safety and Chemicals Agency
UN	United Nations
UV	Ultraviolet
VLP	Virus-like particle
VTT	VTT Technical Research Centre of Finland Ltd
WHO	World Health Organization
WPMN	Working Party of Manufactured Nanomaterials; OECD working group on the safety of manufactured nanomaterials

1 Introduction

1.1 Benefits and challenges of nanomaterials and nanotechnology

‘Nanomaterial’ is a generic word for materials composed of very fine, nanoscale particles that are invisible to the human eye. One nanometre equals to one millionth of a millimetre. ‘Nanotechnology’, in turn, refers to a branch of science and technology that makes it possible to manufacture and use nanosized materials.

Nanomaterials and nanotechnology-enabled applications are already part of our everyday lives. We use sunscreen containing nano zinc oxide, paint the walls of our homes using paint that contains pigment in nanoform, play tennis with rackets reinforced with carbon nanotubes, and wear waterproof hiking jackets coated with nanosilica to keep us dry during autumn showers. We also eat food packaged in plastic containing nano titanium nitride, drive cars with tyres reinforced with carbon black, tap away on smartphones powered by semiconductor chips that are coated using nanotechnology, and use electricity generated by wind turbine blades made from carbon nanotubes to reduce weight. Nanomaterials and nanotechnology have become an integral part of society, to the extent that we do not always even notice or realise all the ways in which nanomaterials are already being used.

Nanotechnology allows us to make materials that are stronger, lighter, more durable, reactive or electroconductive, on top of many other properties. Indeed, nanotechnology is used to improve product properties. Nanotechnology applications are used in an increasing range of industries, such as the chemical industry, consumer products, energy production and electronics. Likewise, nanotechnology is already being widely used in the field of medicine. Nanotechnology helps target medicines more effectively, reducing their adverse effects.

There is an increasing number of nanotechnology applications of considerable technical and economic importance. It is clear that the use of nanomaterials and nanotechnology provides society with substantial benefits from the perspective of both consumers and industries. Nanotechnology has indeed been identified by the European Commission as one of six key enabling technologies. These technologies are expected to help develop and deploy new solutions to societal challenges, such as health, energy and climate.

While the increasing use of nanomaterials has improved the quality of our lives, there are also growing concerns about the potential adverse effects caused by such materials. The impact that nanomaterials have on health or the environment, particularly in the long term, is not yet fully understood. Our current knowledge of health and environmental impacts is based on nanomaterials that have been used for a longer period of time. As the number of applications and uses of nanomaterials increases, it would be advisable to expand knowledge of the potential health and environmental risks of different nanomaterials accordingly. The rapid product development of materials also poses challenges in terms of their regulation. We can expect to see more and more advanced materials entering the market, potentially introducing new types of properties. It may be unclear whether such materials fall within the scope of existing legislation.

A new development is the aim to take the considerations relating to the safety and sustainability of materials and products more effectively into account as early as during their development stage. This approach is also supported by the European Green Deal of the European Union (EU), which includes the new EU chemicals strategy published in the autumn of 2020 under the title ‘Chemicals Strategy for Sustainability – Towards a Toxic-Free Environment’. The strategy introduces many actions to promote the consideration of safety and sustainability starting from the product development stage. (EU Commission, 2020a.)

Although nanomaterials are already widely used in many everyday consumer products, there is limited public awareness of their properties and characteristics. This was discovered through a questionnaire survey conducted by the European Chemicals Agency (ECHA), which involved 5,000 respondents from Austria, Bulgaria, Poland, France and Finland. The survey showed that outreach towards citizens should be improved in order for consumers to gain a better understanding of the ways in which nanomaterials and nanotechnology are used in different products and the types of benefits and risks involved. (ECHA, 2020.)

While this review mainly focuses on intentionally produced nanomaterials, exposure assessment should also take account of nanoparticles resulting unintentionally from natural processes and human activity. Nanosized particles are released into air from traffic, industry and energy production, such as burning of wood. In the workplace, nanosized particles can be generated as a result of hot processes, such as welding and use of diesel engines. Products containing nanomaterials may release nanoparticles into the environment and microplastics may degrade into nanoplastics in the environment.

1.2 Objective and implementation of the review

This review examines nanomaterials and their use, safety and regulation in general terms, highlighting the Finnish perspective in particular. While the review is primarily intended for experts, it was drawn up with a view to ensuring that its contents would also benefit citizens and consumers.

The review will describe:

- what nanomaterials are;
- where they are used;
- how exposure to them may occur;
- what is known about their potential health and environmental impact;
- how they are regulated;
- what kinds of safety and material-related research is conducted in Finland; and
- what types of nanotechnology research have received public funding in Finland.

The review was drawn up by the nanosafety network appointed by the Ministry of Social Affairs and Health. The network is a national cross-sectoral working group, which has operated since 2011 (Gateway to Information on Government Projects). The network is composed of experts from key ministries and various agencies and institutes in their administrative branches. In addition to the Ministry of Social Affairs and Health, the network currently includes representatives from the Ministry of the Environment, Ministry of Agriculture and Forestry, Ministry of Economic Affairs and Employment, Ministry for Foreign Affairs, Finnish Safety and Chemicals Agency (Tukes), Finnish Environment Institute (SYKE), Finnish Food Authority, Finnish Institute of Occupational Health, Finnish Institute for Health and Welfare (THL), Academy of Finland, and VTT Technical Research Centre of Finland Ltd. Each term of the nanosafety network lasts three years and it is chaired by a representative from the Ministry of Social Affairs and Health. The role of the nanosafety network is to provide a channel for exchanging information to maintain debate on legislation relevant to nanotechnology, any potential legislative reform needs and scientific advancements.

2 What are nanomaterials?

Nanomaterials have already been produced industrially for decades because their special characteristics make them suitable for a wide variety of applications. Manufactured nanomaterials are used in several different sectors while interest in their use is growing rapidly. Nanomaterials can help to improve the properties of existing products, including building materials, cosmetics and foods, and to create completely new technological applications, such as foldable touch screens and printed electronics. They can be used in industrial and consumer chemicals, plant protection products and fertilisers, as feed and food additives, biocides and human and veterinary medicinal products, and in cosmetics and other consumer products.

As distinct from manufactured nanomaterials, nanoscale (ultrafine) particles also arise as part of natural phenomena and as unintended byproducts of human activity, such as industrial and combustion processes (unintentionally produced nanoparticles, process-generated nanoparticles). In Finland, the leading local sources of nanoparticles unintentionally released into ambient air through human activity include exhaust emissions from road transport and small-scale combustion of wood. Other sources of nanoparticles in ambient air include mobile machinery, industrial processes, power plants, waste incineration plants, and agriculture (EU Commission, 2011a).

Definition of nanomaterial

In 2011, the European Commission issued Recommendation 2011/696/EU on the definition of nanomaterial (EU Commission, 2011b), which reads as follows:

'Nanomaterial' means a natural, incidental or manufactured material 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.

In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%.Furthermore, in derogation from the above provisions, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.

The definition of nanomaterial describes certain parameters on the basis of which a material either is or is not a nanomaterial, without regard to its hazard properties or risks. The Commission prepared its recommendation to ensure that nanomaterials

would be consistently identified in all pieces of relevant legislation. However, the recommendation has so far only been incorporated into REACH Regulation (EC) No 1907/2006, Biocidal Products Regulation (EU) No 528/2012, and Medical Devices Regulation (EU) No 2017/745.

At the time when the recommendation was issued, the Cosmetics Regulation already included a specific definition which differed from the Commission's recommendation. In accordance with Cosmetics Regulation (EC) No 1223/2009:

'nanomaterial' means 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.

Furthermore, a specific definition for 'engineered nanomaterial' has also been introduced in food law (Novel Foods Regulation (EU) No 2015/2283), according to which:

'engineered nanomaterial' means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale.

Properties that are characteristic of the nanoscale include:

i) those related to the large specific surface area of the materials considered; and/or

ii) specific physico-chemical properties that are different from those of the non-nanoform of the same material.

An engineered nanomaterial under the Novel Foods Regulation specifically differs from the general definition of nanomaterial in that it must be intentionally produced and that there is no number size distribution threshold of 50%.

The Commission Recommendation has been reviewed on the basis of the work carried out by the European Commission's Joint Research Centre (JRC) and the results of an EU-funded NanoDefine project, among other sources (JRC, 2014a, 2014b, 2015; Mech et al., 2020). A public consultation on a potential amendment to

the definition was held in 2021. The Commission published an updated Recommendation in June 2022 (2022/C 229/01) which reads:

'Nanomaterial' means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50 % or more of these particles in the number-based size distribution fulfil at least one of the following conditions:

(a) one or more external dimensions of the particle are in the size range 1 nm to 100 nm;

(b) the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm;

(c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm.

In the determination of the particle number-based size distribution, particles with at least two orthogonal external dimensions larger than 100 µm need not be considered. However, a material with a specific surface area by volume of < 6 m^2 /cm^3 shall not be considered a nanomaterial.

In keeping with the new EU Chemicals Strategy, the Commission's updated recommendation for the definition will be consolidated into relevant legal instruments to ensure consistency. The definitions of at least the Novel Foods Regulation and the Cosmetics Regulation will be reviewed after the general definition of nanomaterial has been updated.

2.1 Most commonly used nanomaterials

Within the European Union, all nanomaterials produced or imported in annual quantities exceeding a thousand kilograms per operator must be registered in accordance with the REACH Regulation. ECHA and the European Union Observatory for Nanomaterials (EUON, https://euon.echa.europa.eu/en/) collect information about nanomaterials and maintain various registers on nanoforms, the quantities used and the companies using nanomaterials.

In nanoform, a substance may have different and unique chemical, physical, electrical and mechanical properties when compared with the ordinary form of the same substance, known as the 'bulk form'. The same nanomaterial may also take different

forms, depending on particle size, morphology or surface treatment. Nanomaterials can be grouped in many different ways and the principles of grouping nanomaterials have been studied in several research projects. However, it has not yet been possible to form a harmonised grouping for nanomaterials. The following passages present the most common types of nanomaterials available on the market. (Ealias & Saravanakumar, 2017; Jeevanandam et al., 2018; Saleh, 2020.)

Carbon-based nanomaterials can take a round (fullerenes), tubular (carbon nanotubes) or flaky (graphene) form. As their structures are very lightweight but durable, they are widely used to reinforce structures in various composite materials. Due to their electroconductivity, they are also used in electronics and battery technology. Carbon nanotubes are also used in paints and coatings and in various filters.

Metal and metal oxide nanomaterials are round or cylindrical, have a large surface area and are often reactive. Nanoscale particles and their oxides (e.g. zinc oxide, ZnO, and titanium dioxide, TiO_2) can be made from almost any metal. Metal and metal oxide nanomaterials are used in electronics, antibacterial and self-cleaning coatings, cosmetics, etc.

Organic and bio-based nanomaterials include branched dendrimers and nanocelluloses, as well as hollow micelles and liposomes, which are usually biodegradable. Nanocapsules with a hollow structure are used in cosmetics, for example. In the pharmaceutical industry, they can be used to deliver drugs to targeted organs. In Finland, nanocellulose materials are used in packaging products, manufacturing of clothing fibres, and in various products developed for medical purposes.

However, this rough grouping excludes many nanomaterials. As increasingly advanced, functional nanomaterials are entering the market, their classification requires different parameters from those used to classify the ‘traditional’ nanomaterials discussed above. Nanocomposite materials combine several different nanomaterials or nanomaterials and microsized materials in order to produce desired properties.

2.2 Where are nanomaterials used?

A study commissioned by the European Commission indicates that, in 2013–2017, nanomaterials were used across almost all industrial sectors and product categories, such as electronics, cosmetics, industrial chemicals and medicines (Table 1)

(NanoData). Nanomaterials can also be used in foods and in materials and articles intended to come into contact with food, but these uses are less common.

Table 1. Number and percentage share of products using nanomaterials by sector on the EU market in 2013–2017 according to a study commissioned by the European Commission (table based on data from the EUON – NanoData website).

Sector	Percentage share (number of products)
Transport	30.8% (175)
Energy	19.5% (111)
Manufacturing and production	15.6% (89)
Construction	14.9% (85)
Health and wellbeing	12.7% (72)
Information and communications technology (ICT)	3.0% (17)
Photonics	2.3% (13)
Environment	1.2% (7)

Nanoscale materials that have not been intentionally produced in nanoform have been used for a long time and are still the most commonly used nanomaterials. These materials include carbon black used in vehicle tyres and amorphous silicon oxide with a wide variety of applications as a filler and reinforcing agent and as an additive in the food industry. Nanomaterials have been used to develop new properties in many consumer products and the number of consumer products containing nanomaterials is growing rapidly. Nanomaterials used in consumer products may consist of single elements (e.g. metals), compounds (e.g. metal oxides) or composites.

In **electronic devices**, nanotechnology is applied to reduce the size and energy consumption of touch screens and increase computer speed and storage capacity. Nanomaterials are added to pigments used in inkjet printers to prevent printer nozzles from clogging and improve the end result of printed colours.

In the **plastics industry**, nanotechnology is widely used to reinforce plastic polymers. Thermoplastics reinforced with nanomaterials are heat-resistant, flame-retardant,

stable and electroconductive. In rubber products, such as vehicle tyres, nanomaterials are used to reinforce rubber, thus prolonging the wear resistance of tyres.

In the **textiles industry**, nanomaterials are used in finishing and as coatings, fibres and composites. Nanomaterials help to improve the abrasion resistance of textiles, eliminate bacteria, protect users from UV radiation, enhance fire-retardant properties, prevent humidity issues and protect textiles from stains.

In **sports products**, nanomaterials are used, among other things, to reduce the weight of tennis rackets, golf clubs and bicycle frames while also making them more rigid.

In **cosmetic products**, nanomaterials are used to improve the functionality and aesthetic appeal of products and the stability, targetability and controlled release of cosmetic ingredients, among other things. About 40,000 of the 2.5 million cosmetic products available on the EU market contain nanomaterials, corresponding to 1.5% of all products (EU Commission, 2021). The most common applications of nanomaterials in cosmetics are as pigments or UV filters. Nanomaterials are most frequently used in sunscreen products, nail polishes, oxidising hair care products, foundation makeup and lip products.

In **food products**, nanotechnology is applied to pursue a wide variety of benefits, such as improving nutritional value, reducing the amount of additives, enhancing colour, taste and flavour (e.g. nanoform colouring and flavouring agents), and improving the uptake and delivery of nutrients to the body (e.g. improving the solubility of water-insoluble substances by means of nanoencapsulation). The use of nanotechnology in the food industry is currently very limited. No food products containing intentionally manufactured nanomaterials have so far been approved for the EU market. However, foods do contain particles that are nanosized by nature, such as sugars, amino acids, proteins and fat micelles. A study commissioned by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) identified more than 30 food additives that contain or may contain nanoscale particles (https://www.anses.fr/en/system/files/ERCA2016SA0226Ra.pdf).

In **food packaging**, the antimicrobial properties of nanomaterials are utilised in prevention of microbial growth, aiming to extend the shelf life of products (Huang et al., 2018). Nanomaterials may also be used with a view to developing lighter, stronger and more durable food packaging and materials (e.g. plastic containers and bottles or oven-safe surfaces); preventing food spoilage, extending shelf life, or improving quality (e.g. preventing light and gases from penetrating containers or antimicrobial properties of active packaging); replacing plastic in paper and cardboard coatings

(e.g. cellulose films); smart packaging (with nanosized sensors monitoring the condition of food and informing consumers of product quality); and reducing waste.

In **paints and coatings**, nanomaterials are applied to enhance durability and develop new properties, such as preventing microbial growth and scratching and making water- and dirt-repellent products that are easy to clean. Due to the fast-evolving COVID-19 pandemic in the spring of 2020, the popularity of antiviral and antimicrobial nanocoatings also increased significantly among consumers. As a result of the pandemic, research has also been geared towards exploiting the antiviral properties of nanomaterials, which is challenging due to the diverse and variable structures of viruses (Imani et al., 2020). Pigments – a number of which are nanomaterials – are insoluble chemicals, whether organic or inorganic, that are used as colourants. Nanomaterial pigments can be found in paints, coatings, printing inks, cosmetics and tattoo inks (Høgsberg et al., 2011; Serup et al., 2015).

Nanomedicine makes use of the physical, chemical and biological properties of nanoscale raw materials in detecting, diagnosing, treating and preventing diseases. Nanomedicines are often developed to improve the solubility and absorption of poorly absorbed drugs, to control the duration or potency of their effects, or to reduce adverse effects. Using nanotechnology in medicine delivery helps target the drug more effectively at a certain organ or tissue area. This also makes it possible to control the penetration of the drug through the body's biological membranous structures, reducing the required dosage and causing fewer potential adverse effects when compared with the dose of medicine that would normally be required.

With regard to **medical devices**, applications of nanomaterials include bone reconstruction cements (carbon nanotubes), bone fillers (nanopastes), nanopolymers (dental fillers), antibacterial agents used in wound dressings (nanosilver), suppressing tumour cells with iron oxide nanoparticles (destroying tumour cells with radiation or an external magnetic field with the aid of nanomaterials), coatings of implants and catheters, and polycrystalline nanoceramics in dentistry.

SUMMARY

In nanoform, a substance may have special chemical, physical, electronic and mechanical properties and specific applications related to these. The same nanomaterial may also take different forms, depending on particle size, morphology or surface treatment. Manufactured nanomaterials are used across almost all industrial sectors while interest in their use is growing rapidly. Furthermore, nanoparticles are generated unintentionally through combustion and various processes as a result of human activity. The recommendation on the definition of nanomaterial issued by the European Commission in 2011 has been updated and the updated definition is to be consolidated into all legal instruments relevant to nanomaterials.

3 Safety

The assessment of health and environmental risks of nanomaterials is based on information on the hazardous properties (toxicity) and exposure levels of materials. Exposure to manufactured nanomaterials should be examined from the perspectives of consumers, public health, workers' health and the environment throughout the life cycle of the nanomaterials. In addition, indoor and outdoor air always contains some nanoparticles from natural sources and typically also some process-generated (unintentionally produced) nanoparticles.

People may be exposed to nanoparticles through inhalation, skin absorption or ingestion. With regard to adverse effects, the respiratory tract is generally considered the most significant exposure route, as it is expected to result in the highest internal dose. In this context, 'internal dose' refers to the quantity of nanomaterial that reaches the circulatory system, tissues and organs. To assess human exposure to nanoparticles from different sources, it is necessary to have data on both the environmental status (e.g. presence and concentrations of nanomaterials in breathing air) and actual human exposure (concentrations in the body).

Assessing the effects of exposure on health requires information on the chemical composition and morphology of nanoparticles and on their adverse effects. The solubility of nanoparticles is a key metric in assessment of health risks. The adverse effects of dissolved chemical forms (ions) are mainly well known. The tendency of nanoparticles to join in larger clusters (agglomeration and aggregation) must be taken into account when determining adverse effects and measuring exposure. Nanoparticles may also be carriers of chemical exposure agents and environmental contaminants, advancing their penetration into cells and tissues. (Zielinska et al., 2020.)

As the properties harmful to human health vary between nanomaterials, their health risks cannot be assessed as a single group. In many cases, a specific challenge for risk assessment is the lack of sufficiently detailed research evidence, particularly on any potential health effects associated with more chronic exposure. As information is incomplete, the aim is to apply the precautionary principle to nanomaterial risk management. The 'precautionary principle' means that measures must be taken to protect health or the environment if there are grounds for concern that an activity would cause serious harm to health or the environment, even in the absence of full scientific certainty (EU Commission, 2000). This means, among other things, minimising exposure to as low a level as technically possible.

Different nanoforms of a substance may behave differently in the environment due to the specific properties of the nanoform. In many cases, the physicochemical properties of nanomaterials, especially water solubility, can be used to assess whether a nanoform requires specific studies or whether it is safe to assume that the environmental fate of the nanoform will be more or less the same as that of the non-nano form of the substance. The environmental fate of a nanomaterial is also affected by its potential surface treatment or coating. Scientific research is rapidly evolving in this area.

3.1 Health effects and related research

The health effects of nanomaterials have been studied extensively and a relatively large body of toxicological research is already available. However, as the number of different nanomaterials is constantly increasing and as they do not form a single uniform group in terms of health effects, it is not possible to know the health effects of all nanomaterials. The majority of studies on potential health effects have been carried out using cellular and animal testing models. To date, human subject research on the effects of nanomaterials only covers a few materials. Likewise, data available on the concentrations of nanomaterials in the human body (biomonitoring) is currently very limited.

Nanoparticles in ambient air and nanosized particles unintentionally generated in industrial processes may differ from those produced by industry in terms of size distribution and composition, but there are similarities in their health effects. The effects of both manufactured and process-generated nanoparticles on the body result from the same biological mechanisms, oxidative stress and inflammatory reactions (Stone et al., 2017). By way of example, occupational exposure is often mixed exposure to manufactured nanomaterials and to nanoparticles resulting from processes and those present in ambient air.

3.1.1 Health effects of nanomaterials

The health effects of nanomaterials differ from those of larger particles and chemicals for a variety of reasons. The smaller the particle, the larger the share of molecules or atoms located on its surface and the ratio between its surface area and volume become. A large surface area increases reactivity, which makes a substance unusually reactive with biomolecules, such as proteins, lipids or nucleic acids. Due to their small size, nanoparticles penetrate the body’s membranous structures more readily than larger particles and migrate deeper into the lungs, for example. In

addition to nano-specific properties, many other material properties (e.g., surface charge, coating, functional groups and shape) have a bearing on the migration of nanoparticles and their interactions with the body's cells. Even minor changes in individual properties may lead to different physiological effects.

When entering the body, the surface molecules of a nanoparticle interact with the molecules of body fluids, forming a biocorona around the particle. The biocorona changes the properties of the nanoparticle. Nanoparticles also have the tendency to join in larger clusters, forming agglomerates (weak bond) or aggregates (strong bond). It is not usually possible to predict the dose threshold for adverse health effects solely on the basis of the mass of nanoparticles, as it may be related to their surface area or to the area-to-mass ratio.

The health effects of nanoparticles depend on the exposure route, i.e., the pathway through which nanoparticles enter the body. The lungs are a key exposure route. The body's defence system actively destroys and eliminates foreign particles from lungs by means such as enzymes and macrophages, i.e., phagocytes, on the surfaces of mucus and pulmonary cells. Besides macrophages, the lungs continuously have multiple defence cells involved in identification and elimination of contaminants. Some nanoparticles are removed from the body by means of its normal defence mechanisms. Problems occur if nanoparticles are transported by the circulatory system and lymphatic fluids to and accumulate in tissues, or if the body cannot remove particles at all or if they are eliminated too slowly relative to exposure.

Research indicates that it is particularly difficult for the body to eliminate certain types of fibrous nanomaterials, such as carbon nanotubes, from lungs. Nanoparticles accumulated in tissues will typically trigger an inflammatory reaction, which may, if prolonged or repeated, result in a very wide variety of health hazards, including gas exchange issues, elevated blood pressure, elevated asthma susceptibility, and eventually in an elevated risk of cardiovascular diseases and cancer development. Not all health effects from nanomaterials are directly linked to contact between cells or organs and a nanomaterial itself; instead, the effects may also occur by way of low-grade inflammation. Understanding the long-term effects of nanomaterials is therefore a major challenge.

Nanoparticles may also enter the body through the skin or the digestive system. In light of current knowledge, nanoparticles are not readily absorbed through healthy skin. However, the skin's permeability may change due to atopic dermatitis or other skin damage. In some cases, dermal exposure may cause allergic symptoms. Oral and pharyngeal exposure, in turn, may lead to local irritation symptoms in the gastrointestinal tract. As the intestinal lining is generally not easily permeable to nanoparticles, the majority of the particles are passed naturally. Nanoparticles that

have entered the body through the skin and digestive tract may pass through circulation into secondary target organs, such as the liver, spleen and brain, where they may cause inflammatory reactions or other health hazards mentioned above, if the body is unable to break them down or eliminate them.

As nanomaterials may also affect the human genome (DNA), establishing their genotoxic effects forms an important part of assessing their hazardous properties. Nanomaterials may damage the genome through multiple routes. If a nanomaterial penetrates a cell nucleus, it may react directly with the DNA or other molecules required in cell division, such as the nuclear spindle. On the other hand, nanomaterials may damage the genome indirectly by causing oxygen radical formation, which may lead to DNA damage associated with cellular oxidative stress. Cells are generally capable of repairing damaged DNA, but cumulative damage to the DNA may lead to many adverse effects, such as cell and organ dysfunction, impaired immune response and cancer development.

Epidemiological studies have found evidence indicating that exposure to ambient nanoparticles weakens lung function, accelerates inflammatory processes and has adverse effects on cardiovascular function (Downward et al., 2018; Ohlwein et al., 2019; Samoli et al., 2020; Schraufnagel, 2020; Strak et al., 2012). However, the precise role of these particles in development of different diseases is unclear. The daily variation in the nanoparticulate concentrations in ambient air has also been linked to total mortality and cardiorespiratory mortality, albeit the body of research is limited (Cassee et al., 2019; Rückerl et al., 2011, Wichmann & Peters, 2000). Even fewer studies are available on the adverse effects of chronic exposure and the relative importance of different particle sizes in ambient air on disease development remains unclear. Research has recently become increasingly focused on the effects of nanoparticles on brain health, albeit the effects are still poorly understood. Overall, the assessment of adverse health effects caused by nanoparticles is hindered by the scarcity of research, differences and difficulties in exposure assessment, and the insufficient number of consistent results, particularly on the adverse effects of chronic exposure (Kumar et al., 2014; Ohlwein et al., 2019).

3.1.2 Research into health effects

Nanotoxicological research aims to increase our understanding of how nanosized materials interact with cells and tissues in the human body. Researchers are particularly interested in identifying the properties of nanomaterials that are related to their potential health hazards. Should we be able to identify the most critical properties, we could predict the toxicological effects of nanomaterials simply by

examining the material properties. Critical properties would also make it possible to assign nanomaterials to different hazard classes and to design and modify nanomaterials so as to make them safer. Besides basic research carried out at universities and research institutes and as part of product development, legislation also requires information about the nanomaterials available on the market and their health effects. For further information on legal requirements, see Chapter 4.

In addition to computational models, research into health hazards caused by nanomaterials (hazard assessment) makes use of both *in vitro* methods based on cell cultures and *in vivo* tests carried out on animals. *In vitro* methods have the advantage of being less expensive and faster to perform when compared with animal testing. However, cell cultures are only limited to studying the direct cytotoxic effects and primary genotoxicity of nanomaterials. Co-cultures of several different types of cells have been developed to reveal inflammatory effects and related secondary genotoxicity. Nevertheless, the most common way to study the more complex adverse health effects of nanomaterials, such as their effects on the immune system or secondary genotoxicity, is still based on *in vivo* studies. In *in vivo* studies, exposure is generally effected through either the respiratory tract or the digestive system. This is also the only way to study the transport and accumulation of nanomaterials in the body. Likewise, the information on dose–response relationships required for risk assessment cannot be obtained without animal testing models.

Research carried out at universities and research institutes is always driven by a specific research question and aims to comply with the OECD Test Guidelines for assessment of the health and environmental hazards of chemicals (OECD Test Guidelines and guidance documents) whenever possible. Statutory hazard assessment of nanomaterials, in turn, always aims to adhere to these Test Guidelines. However, some of the testing methods used for traditional chemicals are not suited to testing nanomaterials as such, which is why methodological development is important (Rasmussen et al., 2019). Established under the auspices of the OECD in 2006, the Working Party of Manufactured Nanomaterials (WPMN, OECD Nanosafety) aims to update OECD guidelines to accommodate nanomaterials. The legislative validation process of many testing methods is still underway. Likewise, the OECD Test Guidelines and methods conforming to ISO/CEN standards are also used for assessing nanomaterials in the food supply chain (EFSA, 2021).

In addition to animal testing models, unintentionally produced nanoparticles in ambient air and in the workplace have also been studied in epidemiological population surveys. According to its traditional definition, ‘epidemiology’ is the study of the incidence of disease and its contributory factors. Studies about the health effects of ambient particles mainly use exposure data based on variation in concentrations obtained from urban measuring stations, which is combined with health data available

from registers. Register-based studies can also be used to investigate the health effects of exposure at work.

3.2 Exposure at work

As the production volumes and use of nanomaterials increase in a growing number of industries, potential occupational exposure to nanomaterials is also going up. Workers form a significant group exposed to nanomaterials, as occupational exposure is generally prolonged and repeated. Exposure to manufactured nanomaterials is possible in many industrial sectors that produce or use nanoparticles, such as research and development, and the construction, chemical, electronics, textiles and pharmaceutical industries (EU-OSHA, 2009; Savolainen, 2016). Workers may be exposed at different stages of the nanomaterial life cycle from production through to waste treatment and recycling processes (Savolainen, 2016; Brouwer, 2010).

Occupational exposure to nanomaterials primarily occurs through respiration, but dermal and digestive exposure is also possible. The likelihood of exposure is higher in connection with handling powdered materials when compared with liquids, pastes or nanomaterials bound in a matrix, because a dusty powder spreads easily in the air (Kuijpers et al., 2017). Exposure may be particularly significant in cleaning and maintenance work, especially with the use of compressed air or dry-brushing (Fonseca et al., 2015; Kuijpers et al., 2017). Attention should also be paid to accident prevention and action taken in such situations. The requirement for materials to be recycled poses challenges for safeguarding the health of circular economy workers as they handle products containing nanomaterials.

In addition to manufactured nanomaterials, workers in many sectors can also be exposed to nanoparticles generated unintentionally through processes (Viitanen et al., 2017). Nanoparticles are generated by combustion engines, various industrial processes as well as ordinary office equipment, such as laser printers. High concentrations of process-generated nanoparticles have especially been measured in welding work and in the metal industry. Workers can also be exposed to nanoparticles generated by human activity and natural particles in outdoor air both in outdoor work assignments and indoors through ventilation.

3.2.1 Assessing exposure and risks

Assessing workers' exposure to nanomaterials is generally based on a tiered approach: gathering background information on contributory factors to exposure;

determining exposure levels; and assessing exposure by means of measurements (OECD, 2015; CEN, 2018).

The limitations of the measurement technique should be taken into account in exposure assessment. It is possible to measure nanoparticles as small as one nanometre in the air. The measuring instruments typically used for this purpose are based on measuring the electrical or optical properties of particles. However, instruments measuring nanoparticulate concentrations in the air are not capable of distinguishing between nanoparticles from different sources. Consequently, the measuring result also includes nanoparticles arising from natural sources and those unintentionally generated in various work processes, such as welding and paint fumes. In order to assess exposure to manufactured nanoparticles, it is also necessary to measure the background concentrations of particles in the workspace to establish the concentrations of natural and process-generated particles and to supplement the measurements by microscopic methods as required (e.g., Fonseca et al., 2015). The chemical composition of particles can be analysed using a mass spectrometer. There are active efforts to study and develop the suitability of biomonitoring methods used to assess chemical exposure for assessing and monitoring nanomaterial exposure.

Workplace risk assessment of chemical exposure agents generally makes use of (health-based) limit and reference values to which the results of exposure measurements are compared. No occupational exposure limit values have thus far been determined for nanomaterials at the EU level, nor have any national limit values been set in Finland or other EU countries. However, efforts are underway in Denmark and the Netherlands, among others, to determine health-based occupational exposure limit values for nanomaterials. Some countries, such as Germany, the Netherlands and the United Kingdom, have already introduced reference values for nanomaterials based on the precautionary principle. In 2013, the Finnish Institute of Occupational Health published recommendations based on German and Dutch reference values for the target levels of nanomaterials in the workplace (Table 2; Finnish Institute of Occupational Health, 2013). The purpose of the target levels is to help the workplace to identify high-exposure work stages and target risk assessment and management and they do not describe the threshold between health risk and absence of risk.

Safety data sheets for products are an important tool for assessing and managing chemical risks in the workplace. Workplaces should be provided with safety data sheets for nanomaterials whenever a product is classified as hazardous under the CLP Regulation (EC) No 1272/2008, or contains components classified as hazardous, for example. As of 2021, the safety data sheets for products containing nanomaterials have been required to indicate that the substance is in nanoform and include certain data on the properties of the nanoforms (see Section 4.1.1). The data provided in a

safety data sheet should describe the product's hazardous properties and any points to consider for its safe handling.

Table 2. Target levels of the Finnish Institute of Occupational Health for manufactured nanomaterials (eight-hour time-weighted average concentration).

Nanomaterial	Target level (8h)	Examples
Rigid, biopersistent fibrous materials for which effects like those of asbestos cannot be excluded	0.01 fibres/cm^3	Carbon nanotubes, metal oxide fibres
Biopersistent, granular nanomaterials; density > 6,000 kg/m^3	20,000 particles/cm^3	Nanosized Ag, Au, CeO_2, CoO, Fe, Pb, SnO_2
Biopersistent, granular materials with density < 6,000 kg/m^3 and fibres without asbestos-like effects	40,000 particles/cm^3	Nanosized Al_2O_3, SiO_2, TiN, TiO_2, ZnO, nanoclays, dendrimers, C60, polystyrene
Biopersistent, granular nanomaterials mainly occurring as agglomerates (agglomerate diameter > 100 nm) 0.3 mg/m^3 (alveolar fraction)		E.g., agglomerates of granular nanomaterials mentioned above

3.2.2 Risk management

In risk management, the same principles apply to nanomaterials as to any other chemical exposure agents in the working environment. Primarily, an exposure agent is eliminated or substituted by a less hazardous product and, secondarily, emissions are precluded from being generated and spread by means of technical solutions. Nanoparticles can be prevented from spreading in a workspace by using compartments, casings and local exhaust ventilation. Worker orientation and training are key to managing exposure and risks. Personal protective equipment (PPE) is used if exposure cannot be adequately controlled by other means. Risk management

measures may be targeted at materials, processes, working methods and working environments alike (Buringh et al., 1992).

The likelihood of exposure is lower in connection with handling liquid or paste-like materials when compared with powdered materials (Fonseca et al., 2015; Kuijpers et al., 2017). However, exposure is more likely when spraying liquid nanomaterials, where special attention should be paid to exposure management. Current knowledge indicates that matrix-bound nanomaterials, such as nanocellulose or carbon nanotubes used in sports equipment, do not cause a significant exposure risk if the products containing nanomaterials are used for the intended purpose as determined by the manufacturer.

As no information is available on the potential health effects associated with chronic and repeated exposure for most nanomaterials, it is not possible to identify safe exposure levels. In such cases, exposure should be minimised in keeping with the precautionary principle. Active efforts should especially be taken to identify substitutes to nanomaterials classified as carcinogenic or mutagenic (CLP classification Carc. 1A/1B or Muta. 1A/1B). If substitution is not technically possible, exposure must be minimised. If exposure to nanomaterials classified as carcinogenic or mutagenic cannot be completely avoided at work, exposed workers should be reported to the ASA register of workers exposed to carcinogenic substances and methods at work (www.ttl.fi/asa, in Finnish).

Managing risks related to nanomaterials is part of workplace chemical risk management. Besides nanomaterials, many other chemical exposure agents can typically also be found in workplaces and their health risks must be determined. Due to their large surface area and porosity, nanoparticles may also be carriers of chemical exposure agents and environmental contaminants, advancing their penetration into cells and tissues (the ‘Trojan-horse phenomenon’, Naazs et al., 2018). Assessing the combined effects of various nanomaterials as well as nanomaterials and other chemicals poses a challenge for both public authorities and companies.

3.2.3 Tools and guidelines

The Finnish Institute of Occupational Health participates in the maintaining and developing of the Dutch Stoffenmanager tool for assessing chemical risks in working environments, which also includes a Nano Module developed for assessing the risks of nanomaterials (https://nano.stoffenmanager.com). Other similar risk assessment tools include NanoSafer (http://www.nanosafer.org), the Advanced Reach Tool (ART,

https://www.advancedreachtool.com/) and LICARA NanoScan (https://www.empa.ch/web/s506/licara). The Finnish Institute of Occupational Health has also published guidelines for workplace risk management of nanomaterials (Target levels for working environments, in Finnish; Model solutions for risk management in working environments, in Finnish). The concept of 'risk management' has recently been expanded into a more comprehensive concept of 'risk governance', considering not only the traditional risk management but also aspects such as social, economic and ethical risks complete with appropriate risk management methods and risk communications. Online services have been developed for use by companies and public authorities in support of risk governance, including the caLIBRAte Nano Risk Governance Portal (http://nanoriskgov-portal.org/Public/Index).

The World Health Organization (WHO) has published guidelines on protecting workers from potential risks of manufactured nanomaterials. The guidelines cover assessment of health hazards and occupational exposure as well as risk management. The Finnish Institute of Occupational Health has been involved in developing the WHO guidelines. The European Commission has published separate guidelines for employers (Guidance on the protection of the health and safety of workers from the potential risks related to nanomaterials at work) and for workers (Working Safely with Manufactured Nanomaterials). The European Agency for Safety and Health at Work (EU-OSHA) and the European Union Observatory for Nanomaterials (EUON) have websites available in several languages, including English, where they have produced and compiled plenty of guidelines for handling nanomaterials safely at the workplace (https://osha.europa.eu/en/emerging-risks/nanomaterials; https://euon.echa.europa.eu/en/nanomaterials-at-the-workplace).

3.3 Consumer exposure to manufactured nanomaterials

Little detailed information is available on the exposure of consumers to products containing nanomaterials, although international research teams have aimed to assess this (RIVM, 2009; WHO, 2013). Nanomaterials in nanotechnology-enabled consumer products are often bound in a matrix and, in light of current knowledge, therefore do not cause any major exposure risk to users (RIVM, 2009). As consumer products such as sports equipment only release small amounts of manufactured nanomaterials into the breathing air, consumers are mainly exposed to nanoparticles through dermal contact with cosmetics and possibly also from food products through the digestive tract (EUON, 2017).

People can be exposed to nanoparticles when using cosmetics that contain nanomaterials. However, the nanomaterials contained in sunscreens, such as titanium dioxide or zinc oxide, have not been found to be absorbed into the lowest skin layers in multiple studies conducted on human subjects and cells (Larese Filon et al., 2015; Nohynek & Dufour, 2012). In more general terms, nanoparticles do not readily pass through a healthy skin, but penetration becomes easier if the skin is damaged mechanically or due to skin disease. Skin is also a potential pathway for exposure to nanomaterials contained in textiles, such as metallic nanomaterials and metal oxides in direct skin contact (Saleem & Zaidi, 2018). Tattoo inks, which may contain nanosized particles and are specifically injected under the skin, are a case apart. Research evidence available on these is incomplete (Serup et al., 2015).

Nanosized particles are naturally found in foods, but they can also be added to food to improve its nutritional value, colour and taste, among other things. People may also be exposed to nanoparticles released from packaging materials through the gastrointestinal tract. While the exposure from consumer products via ingestion is limited, its role will likely increase in the future, as the use of nanomaterials in foods and their packaging materials becomes more prevalent.

Nanoparticles are mainly released from consumer products into the respiratory area when products containing nanomaterials are used in a sprayable form. The use of nanomaterials in sprayable forms is mainly prohibited in cosmetics, for example, if it may result in respiratory exposure. Textiles containing nanomaterials may also release small amounts of respirable particles into the air, but the level of respiratory exposure from consumer products is generally considered low. Exposure can be assessed by means of various tools. The OECD has compiled suitable tools for assessing consumer risks (OECD, 2021a).

The risk of exposure to nanomaterials contained in consumer products is low in everyday life, considering different exposure pathways and their combinations (RIVM, 2009). The majority of products containing manufactured nanomaterials used by consumers are probably safe and their safety is also regulated (see Section 4.1). However, there are also vulnerable groups among consumers, such as children and elderly people, who are known to be more sensitive to the effects of harmful chemicals, among other things. No information is currently available on whether this also applies to nanomaterials (WHO, 2013).

3.4 Nanomedicine and the safety of nanomedicines

Nanomedicine makes use of the physical, chemical and biological properties of nanoscale raw materials in detecting, diagnosing, treating and preventing diseases. Nanomedicinal products mostly consist of an active medicinal substance and its transporter. In a nanomedicinal product, the size of the active substance, its adjuvant or transporter has been engineered to the nanoscale by means of manufacturing technologies. Nanoapplications can be used to modify the chemical or physical properties of drug molecules. The aim is to improve the solubility and absorption of poorly absorbed drugs, to control the duration or potency of their effects, or to reduce adverse effects. Nanodelivery systems help target drugs more effectively at a certain organ or tissue area. It is also possible to control the penetration of drugs through the body's biological membranous structures, reducing the required dosage and causing fewer potential adverse effects when compared with the dose of medicine that would normally be required.

The market approval of medicines requires a marketing authorisation granted by competent authorities, which is based on the assessment of efficacy, safety, quality and the benefit–risk ratio. The efficacy and safety of all medicinal products on the market, including nanomedicines, has been proven by studies conforming to official requirements and their benefits exceed any potential risks involved. Any medicinal product made available on the market falls within official control and regulation both before and after its entry into the market. A product's risk assessment may be updated where necessary. The safety of medicines involves not only the safety of the medicinal product but also its safe and appropriate use. Safety data on medicinal products accumulates through research and use. Potential adverse effects are monitored in accordance with medicines legislation.

Nanomedicines for human and veterinary use have been on the market for more than 20 years. The first nanomedicines were authorised by the European Commission in the late 1990s. The majority of currently authorised nanoform medicines for human use are products for intradermal or intravenous injection, but orally administered nanomedicines are also available. The nanoforms used in medicinal products include colloidal chemical applications, such as liposomes, nanoparticles, micelles and nanoemulsions. Various polymeric complexes, biological membranes isolated from cells, and virus-like particles (VPLs) and lipid nanoparticles (LNPs) are also used.

Human medicines

Unlike most nanotechnology applications, human exposure to nanomedicines for human use is intentional. Assessing the safety of nanomedicines is therefore of particular importance. The safety of medicines is assessed very comprehensively prior to marketing authorisation, including safety studies to verify that a nanomedicine is safe to use at doses approved for the indication cited in the marketing authorisation. As most nanomedicines for human use are products injected in hospital settings, it is highly unlikely for a user to be accidentally or unknowingly exposed to a nanomedicine. The orally administered nanomedicinal products on the market are available by prescription only. No self-care nanomedicines are currently available on the Finnish market.

The pharmacological effects of medicines in the body are established through comprehensive studies using *in vitro* methods and *in vivo* clinical studies on animal and human subjects. Pharmacokinetic studies are used to determine the behaviour of medicinal products in the body, such as their absorption, migration and distribution into different tissues, their half-life and potential accumulation in and excretion from the body. Safety assessment covers extensive toxicological studies on animals, including general toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicology and local tolerance. Further studies, such as assessment of immunotoxicity and phototoxicity, may be carried out as required. Clinical studies involve assessing the safety of a medicine on human subjects through extensive, multi-phase trials. Furthermore, medicinal products available on the market are monitored throughout their life cycles, updating safety information based on any potential adverse effects and taking action as required.

Veterinary medicines

The safety studies of nanomedicines used for animals can be roughly divided into two parts. Pre-clinical studies examine aspects such as the effects of the ingredients of medicinal products on laboratory animal species, whereas clinical trials focus on the safety and efficacy of the products in the target animal species. Under Regulation (EU) 2021/805, safety studies focus on the target species but also assess the risk for consumers, users (people administering the medicine) and the environment.

Consumer safety is only studied for veterinary medicinal products intended for food-producing animals. This involves analysing any potential tissue residues of pharmacologically active excipients, including nanocomponents. The withdrawal period, i.e. the minimum period between the last administration of a medicinal product and the time when the foodstuffs are allowed to be supplied for consumption again, is set on the basis of residue depletion studies in accordance with Regulations (EC) No

470/2009 and (EU) 2019/6. This is to ensure that consumers are not exposed to nanomedicines through foodstuffs of animal origin.

User safety assessment involves modelling and analysing various exposure risk scenarios, including children's accidental exposure. The results are used to determine the required risk mitigation measures, which may include warnings and instructions in the summary of product characteristics or safety solutions on product packaging. User safety risk mitigation measures aim to minimise or prevent user exposure to a medicinal product or to related adverse effects under Regulation (EU) 2021/805.

Nanomedicines for veterinary use are also subject to specific requirements relating to risks associated with nanoparticles. Any veterinary medicinal products containing nanotechnology are required to have specific evidence of risks related to the ability to penetrate membranes such as the blood-brain barrier, the ability to form agglomerates, specific kinetic characteristics, cytotoxicity and immunogenicity under Regulation (EU) 2021/805. Under Veterinary Medicinal Products Regulation (EU) 2019/6, these requirements apply to veterinary medicinal products for which marketing authorisation is sought as of 2022.

3.5 Exposure to nanoparticles in ambient air

Nanoparticles, also known as 'ultrafine particles' in atmospheric sciences, are generated in natural processes (incl. forest fires and atmospheric reactions of hydrocarbon emissions from forests) and as a result of human activity (unintentionally produced nanoparticles). In Finland, the leading local sources of nanoparticles unintentionally released into ambient air include exhaust emissions from road transport and small-scale combustion of wood. In addition to high emission rates, these low-lying sources of emissions have a greater effect on general exposure than those released from tall chimney stacks, which have time to be diluted and transformed before reaching the breathing zone. Emissions rates and the chemical composition of particulate matter are influenced by both the fuel and the combustion conditions. Besides direct particulate emissions, combustion processes release into the air gases, which form new particles as they cool down. Nanoparticles transform rapidly in the atmosphere and their physical and chemical processes are influenced by many atmospheric processes. The shape, chemical composition and size distribution of ambient particles are, indeed, generally less well known than the properties of manufactured nanoparticles.

Exposure to nanoparticles in ambient air primarily occurs through the respiratory tract (Schraufnagel, 2020). Nanoparticles migrate deep into the respiratory tract and end

up on lung surfaces, causing local inflammation, and make their way into the epithelium and further on into circulation (Cassee et al., 2019). In addition to the respiratory tract, exposure to ambient nanoparticles also occurs through the digestive tract and skin, but there is less research evidence on these.

Assessment of exposure to particles found in ambient air is often based on the analysis of concentration at fixed air quality measuring stations, which does not necessarily describe actual exposure very effectively. Personal exposure is influenced by many factors, such as concentrations in outdoor air, particulate infiltration from outdoors to indoors, specific sources of particles in indoor spaces, and personal use of time (Pekkanen & Kulmala, 2010). Assessing exposure to nanosized particles is more demanding compared with exposure to fine particulate matter ($PM_{2.5}$; aerodynamic diameter less than 2.5 µm), as the number and size distribution of nanoparticles vary considerably in temporal and spatial terms and concentrations may vary substantially even within the distance of a few metres (Cassee et al., 2019; Kumar et al., 2014). The conditions in different seasons, such as temperature, relative humidity and sunlight, as well as concentrations of gaseous compounds, have an effect on the formation, growth process and concentration variations of particles (Salma et al., 2011). Tall, densely located buildings also have a major impact on particulate concentrations in the environment (Kumar et al., 2014). Due to the above-mentioned factors, modelling the concentrations and especially size distributions of nanoparticles is challenging (Gerling et al., 2021). Nanoscale particulate emissions of human origin have been assessed at the global level (Paasonen et al., 2016).

The limit values currently used to regulate particulate contaminants in ambient air are based on mass while official measurements assess fine particles and inhalable particles (PM_{10}; aerodynamic diameter less than 10 µm). The mass concentrations of nanoparticles are generally so small that they cannot be reliably determined using current methods. Conversely, nanoparticles are of great importance for air quality in terms of number or the surface area to air volume ratio. As measuring nanosized particles in ambient air is still based on scientific interest both in Finland and other parts of the world, no comprehensive long-term monitoring data is available. While the lower cut-off limit of the instrument plays a key role in terms of measuring results, no international or national recommendations exist for this. By way of example, the lower cut-off limit varied within the range of 3–250 nm in the studies published between 2011 and 2017 that were included in a review of the health effects of ultrafine particles by Ohlwein et al. (2019). As imprecision in exposure assessment makes it more difficult to determine health hazards, efforts should be made to develop measurements and models for both personal exposure and ambient air.

In its recent publication on reference values for outdoor and indoor air quality, the World Health Organization provided guidelines for good practice for measuring

number concentrations of particulate matter (WHO, 2021). For measurement purposes, the lower cut-off of particle diameter should not exceed 10 nm, whereas the largest size is not limited. As the number of particles with a diameter of over 100 nm plays a minor role in practical terms when compared with the number of nanoparticles, the guidelines can be considered to apply to nanoparticles. The number concentration of particles is low when the daily average is less than 1,000 particles per cm^3. Concentration is considered high when the daily average exceeds 10,000 particles per cm^3 or the hourly average exceeds 20,000 particles per cm^3.

3.6 Environmental exposure and environmental effects

Environmental exposure

Manufactured nanomaterials may be released into the environment from their production or their use for manufacturing various products through e.g., production plant effluents or ventilation. Products may also release nanomaterials at different stages of their life cycles, such as during use and waste stages. The wear and tear of products, such as paints and textiles, and the use of products containing nanomaterials, such as cosmetics, result in nanomaterials being transported mainly to waste or wastewater treatment plants. Nanomaterials may also end up in surface waters with storm waters, as atmospheric deposition and through washout from the soil. In many cases, the release of nanoparticles from treated surfaces or textiles has not been comprehensively established, but it has been reported that antibacterial silver particles are released from textiles during washing (Benn & Westerhoff, 2008) and titanium dioxide particles come off painted surfaces with rainwater (Kaegi et al., 2010).

Environmental exposure is assessed in terms of potential effects on the aquatic environment (including sediment), soil and air (greenhouse effect, effects on the ozone layer, acidification) and accumulation in the food chain. The assessment also involves analysing potential effects on the microbiological activity of wastewater treatment systems.

Nanomaterials may change in physical, chemical and biological terms in the environment. These changes are influenced by both the nature of nanomaterials and environmental conditions, which makes it difficult to understand and predict how nanomaterials behave (Lead et al., 2018). Studying nanomaterials is also hindered by

the potential effects of their surface treatment or coating on their environmental fate and behaviour.

Environmental exposure assessment estimates the concentration to which the environment may be exposed. It takes account of all the stages of a material's life cycle relating to its manufacturing and use.

The specific data required for manufactured nanomaterials includes the dissolution rates, aggregation and agglomeration of particles and changes in their surface chemistry. Aggregation means that nanoparticles are bonded to a solid cluster, whereas agglomeration refers to a group of nanoparticles clustered together by weak bonds. Solubility can be used to assess the stability of nanoparticles.

Aggregation reduces the number and total area of particles. It contributes to particle reactivity, bioavailability and toxicity. Aggregation is influenced by pH of water, ion content and composition, and organic matter. Sedimentation is a consequence of aggregation because gravity gains more importance as particle size increases. Sedimentation rate depends on the volume and shape of the particle and on the density of the dispersion medium. The sedimentation rate has a particular effect on the spread of nanoparticles into the environment. Highly aggregated particles are deposited close to the emission source, likely resulting in higher local concentrations than nanoparticles that spread wider. Sedimented particles may be later released back into the water (resuspension) (Sillanpää et al., 2014).

An integral part of studying the environmental impact of nanomaterials is development of test methods. The last decade has seen considerable progress in assessing the sources, environmental fate and effects of nanomaterials. Estimates based on modelling of environmental concentrations were recently confirmed by measurements (Bundschuch et al., 2018).

Environmental effects

The environmental risk of chemicals is assessed on the basis of the hazardous properties of and exposure to substances. Hazardous properties are generally studied by means of laboratory toxicity tests on organisms, which aim to use the OECD test guidelines or other established methods. Exposure can be assessed by means of various models or measurements carried out in the environment. If the exposure estimate indicates that the threshold of concentration harmful to an organism based on toxicity tests is exceeded, the use of the substance causes risk.

When testing nanomaterials, attention must be paid to determining concentrations and particle stability. The characteristics of the particles being studied should be described as precisely as possible for the purpose of comparing results. Test conditions will often need to be adjusted due to properties typical of nanoparticles, such as aggregation. Nanoparticles also interact with organisms in physical terms, which affects the growth and behaviour of the exposed organism. By attaching to a biological surface, they may affect photosynthesis, nutrient intake, mobility, etc. Nanoparticles also interact with pollutants.

By way of example, the toxicity of certain plant protection products and metal ions has been found to increase in the presence of certain nanomaterials, albeit there are results to the opposite as well. The relevance of such interactions is as yet unknown. (Bundschuh et al., 2018).

It is still challenging to measure manufactured nanoparticles in the environment or from environmental samples. By way of example, no methods currently exist for measuring several nanoplastics with sufficiently low limits of quantification for concentrations actually found in the environment. While metallic nanoparticles can be measured, it is not possible in practical terms to distinguish naturally occurring metallic nanoparticles from those manufactured. Conversely, more precise measuring results can be obtained in test conditions by making use of isotope-labelled nanoparticles, for example.

Toxicity tests have been conducted on several nanomaterials. A review published by the Finnish Environment Institute (Sillanpää et al., 2014) provides a summary of the results of research into the environmental impacts of certain manufactured nanomaterials. The review established several considerations relating to certain nanomaterials and their testing, which need to be borne in mind when planning tests, handling test material and interpreting test results, taking account of the specific characteristics of each nanomaterial. The treatment of test materials, for example, was found to have an effect on test results and their interpretation when examining carbon nanotubes, fullerene and titanium dioxide. The surface structure of a particle may also have a significant impact on its properties and potentially on its behaviour in test organisms, as was the case with fullerene, nanosilver and quantum dots. Furthermore, the adverse effects of certain nanomaterials, such as nanosilver and zinc oxide, were mainly or fully caused by dissolved ions. Nanocellulose was not shown to have any adverse effects in conventional toxicity tests.

Research into the environmental impacts of nanomaterials still involves gaps in knowledge to fill, which requires more advanced measuring techniques and data on environmental concentrations, systematic information on adverse effects and risks, life-cycle assessments, and assessment/valuation of advantages and disadvantages.

As the number of commercial products containing nanomaterials is growing rapidly, so is the amount of waste that contains nanomaterials. It is imperative to identify the types of waste and recycling processes in which nanomaterials of special concern may end up and to develop treatment and separation methods for nanomaterials to be recycled, removed and disposed of safely (non-toxic material cycle).

Due to the specific characteristics of nanomaterials, special attention should be paid to the suitability of test conditions for certain nanomaterials when testing their environmental fate and effects and analysing the test results.

A review following studies on nanomaterials in the environment since 2008 found that, despite considerable progress made in assessing the environmental risks of nanomaterials, critical gaps in knowledge still exist due to the extensive scope and complexity of the subject. Studies have shown that the nanoform has a bearing on the environmental fate, bioavailability and toxicity of substances, but that this is not consistent across all nanomaterials, species or processes. Based on research materials collected, nanomaterials appear to be less toxic than equivalent dissolved materials but more toxic than equivalent non-nanomaterials. However, incomplete data poses challenges for regulation and procedures (Lead et al., 2018).

Environmental risk management is crucially affected by the lack of information about the uses, emissions, exposure risks, environmental effects and environmental behaviour of manufactured nanomaterials. Such information is expected to increase as a result of the updated information requirements of the REACH Regulation (see Section 4.1). EU-funded research projects aim to improve the available tools, such as models and test methods for environmental emissions and behaviour and techniques for measuring and monitoring nanomaterials found in the environment. These efforts will provide researchers and regulators with more reliable information for assessing the environmental risks of nanomaterials and will identify situations where additional risk management measures are required. In its recent publication, the OECD examined the feasibility of risk assessment tools for nanomaterials and identified six tools to be suitable for this purpose (OECD, 2021b).

SUMMARY

The safety of nanomaterials involves uncertainties because the impact that they have on health or the environment, particularly in the long term, is not yet fully understood. The assessment of health and environmental risks of nanomaterials is based on information on the hazardous properties and exposure levels of materials. Exposure to manufactured nanomaterials may occur during their production process or use in different industries. However, as a general rule, the risk of exposure to manufactured nanomaterials in consumer products is minimal. People and the environment are also exposed to nanoparticles unintentionally generated through human activity and natural processes. As different nanomaterials have different properties, their potential health and environmental risks cannot be assessed as a single uniform group; instead, assessment must take account of the composition, solubility and other properties of each material. Since research evidence on the effects of exposure to many nanomaterials, especially over a longer term, is as yet incomplete, their risk management is, as a general rule, subject to the precautionary principle. The approval of nanomaterials used in medicines is based on the assessment of efficacy, safety, quality and the benefit–risk ratio.

4 Regulation of manufactured nanomaterials and EU-level and international activities

Rather than being governed by specific legislation, nanomaterials are primarily regulated as part of other EU Community legislation applicable to chemicals, for example. Likewise, Finland does not have any specific national legislation on nanomaterials. The legal framework for sectors utilising nanomaterials consists of EU-level legislation mostly adopted as regulations or directives. EU regulations are directly binding on the Member States and do not need to be separately transposed into national law. Directives, in turn, will need to be implemented separately in each Member State within the national legal framework.

National regulation of nanomaterials in Finland involves different administrative branches. The key ministries in terms of the legislations covered by this review include the Ministry of Social Affairs and Health, the Ministry of the Environment and the Ministry of Agriculture and Forestry. The relevant fields of law within the administrative branch of the Ministry of Social Affairs and Health include industrial and consumer chemicals, cosmetic products, biocides, medicinal products for human and veterinary use, medical devices, and occupational health and safety. Legislation governing industrial and consumer chemicals and biocides is a shared responsibility between the Ministry of Social Affairs and Health, which is in charge of protecting human health, and the Ministry of the Environment, which deals with prevention of adverse effects on the environment. The administrative branch of the Ministry of Agriculture and Forestry especially focuses on regulating nanomaterials and nanotechnology used in foods (novel foods, food improvement agents and organic food) and materials that come into contact with food. However, the food supply chain also uses products such as feeds, fertilisers, plant protection products and veterinary medicines, which are governed by legislation that also includes provisions on nanomaterials and nanotechnology.

A significant part of preparatory work on nanosafety is carried out within the framework of international cooperation, where the key parties include EU-level organisations and the OECD.

4.1 Legislation

4.1.1 Chemicals legislation

Rather than specific national legislation on the safe use of nanomaterials or nanotechnology, legislation governing chemicals is based on EU Community legislation. The REACH and CLP Regulations are the cornerstones of chemicals legislation. Provisions on chemicals are also included in sectoral laws, such as the Biocidal Products, Plant Protection Products and Cosmetics Regulations. The EU legislative framework on chemicals is considered to cover nanomaterials, even if no specific reference were currently made to nanomaterials in all of the legal instruments (EU Commission, 2012a, b). While the principal concepts of chemical risk assessment have been found to be applicable to nanomaterials as well, it is also recognised that test methods and assessment tools will need to be rendered more suitable for nanomaterials.

The Finnish Safety and Chemicals Agency (Tukes) is the competent authority in Finland with regard to the REACH, CLP, Biocidal Products, Plant Protection Products and Cosmetics Regulations. Tukes controls the use of nanomaterials as part of chemicals safety. Tukes also supervises compliance with cosmetics legislation in cooperation with the Finnish Customs.

REACH Regulation

Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals applies to substances on their own and in mixtures and articles. The purpose of the Regulation is to ensure a high level of protection of human health and the environment. The Regulation covers a wide range of industrial and consumer chemicals used very widely in different product categories, which means that exposure to them is possible. The ‘no data no market’ principle of the Regulation places on industry the burden of managing risks posed by chemicals and providing safety data on substances prior to manufacturing or placing them on the market.

Under the Regulation, companies are required to collect data on the properties of substances and submit the information to the European Chemicals Agency (ECHA) by registering the substances manufactured or imported into the EU in quantities of one tonne or more per year. The higher the quantities in which a certain substance is manufactured or imported, the more comprehensive information that is required on it. Provisions on the information requirements for substances and on methods for

providing the information are laid down in the Annexes to the Regulation. In connection with registration, importers and manufacturers are required to provide information on the effects of each substance on human health and the environment and an estimate of exposure throughout the product life cycle. They are also required to demonstrate the safe use of the substance as part of registration. A chemical safety assessment is required for substances manufactured or imported in quantities of 10 tonnes or more. The assessment is carried out as part of the REACH registration process and it is a key source of information for chemical users by way of safety data sheets and exposure scenarios.

EU Member States evaluate certain registered substances in order to address concerns as regards human health or the environment. The competent authorities of the Member States and ECHA Scientific Committees work together to evaluate how to manage the risks involved in substances. The use of some substances may be restricted or made subject to authorisation.

The REACH Regulation requires substances, including nanomaterials, to be registered. The Regulation's Annexes on information requirements and chemical safety assessments were amended by Commission Regulation (EU) 2018/1881. The Regulation's restrictions and authorisation requirements also apply to nanomaterials as appropriate. The amendments aim to improve the management of health and environmental risks arising from nanomaterials. The new Annexes entered into force in January 2020. The Annex to the amending Regulation inserts the definitions for a nanoform of a substance and a set of similar nanoforms. The Regulation emphasises the appropriate characterisation of test material, documentation of test conditions, and scientific justification. Its new information requirements provide for precise characterisation of nanomaterials, including requirements for indicating at least their size, shape, surface area and any possible surface treatment. The information requirements have also been updated with regard to physicochemical properties (dissolution rate, dustiness) and those related to human health and the environment. As no tonnage limits for registrations were amended, the lowest threshold for registration remains unchanged (1 t/a), while nanomaterials can also be registered together with the so-called bulk form of the same substance. Earlier registrations will have to be updated if they include nanoforms of a substance.

The safety data sheets under the REACH Regulation include information about the properties and hazards of dangerous substances and mixtures containing such substances as well as advice on handling, disposal and transport, complete with information on first-aid, fire-fighting and exposure management measures. Safety data sheets are compiled by the manufacturers of substances and mixtures and their importers into the European Union. The provisions on safety data sheets are laid down in Annex II, which was expressly amended by Commission Regulation (EU)

2020/878 to better meet the specific requirements brought about by nanomaterials. The new requirements apply as of January 2021 and no later than at the end of the transitional period in 2023.

With the adaptations for nanomaterials made to the REACH Regulation, the focus has shifted from development to implementation of legislation. As a result of the new information requirements, it is likely that the REACH Regulation will produce more information on the health and environmental impacts of nanomaterials. Its effective implementation is of the utmost importance in order to obtain information on the properties, uses and risks of nanomaterials. While the registration requirements under the original REACH Regulation, which has been in force for over ten years, have been considered to cover nanomaterials, only 149 substances have so far been registered as nanomaterials, which falls below ECHA's expectations (about 300 nanoform substances on the EU market). It likewise remains to be seen whether information will also be obtained about nanomaterials manufactured or imported into the European Union in quantities not exceeding the minimum registration threshold of the REACH Regulation (1 t/a).

To date, a few nanomaterials have been evaluated by virtue of the REACH Regulation, including synthetic amorphous silicon dioxide, nanosilver and various multi-wall carbon nanotubes. Zinc oxide, cerium oxide, carbon black and titanium dioxide are currently being evaluated. So far, no restrictions or prohibitions have been imposed on the use of any nanomaterial.

ECHA has produced extensive guidance to support registration of nanomaterials (ECHA Guidance on Information Requirements and Chemical Safety Assessment at europa.eu). The guidance covers the characterisation and registration of nanoforms and sets of similar nanoforms, information requirements for nanomaterials with regard to human health and environmental protection, and the grouping of nanomaterials. Guidance on chemical safety assessment has been prepared for health impacts and there are plans to draw up guidance on environmental impacts during 2022. The guidance documents are very important for assessment, as no specific guidance on nanomaterials is currently available. ECHA has also commissioned a variety of reports on topics such as toxicological studies, next generation nanomaterials on the EU market, and consumer perceptions of nanomaterials and their safety in the EU (https://euon.echa.europa.eu/en/reports).

In addition to the Ministry of Social Affairs and Health and the Ministry of the Environment, Tukes is also responsible for effective implementation of legislation and advisory services at the national level as the competent authority under the REACH Regulation. Support for implementation is needed by small enterprises in particular, while consumers also require reliable information. As nanomaterials are used in an

increasing number of products, informed consumers need information about safety. Tukes experts are involved in the work of the ECHA Nanomaterials Expert Group (NMEG) and cooperate with other authorities, particularly at the Nordic level. The Nordic Nanomaterial Group (N-Nano) operating under the auspices of the Nordic Council of Ministers has produced a virtual e-REACHNano web tool to support the implementation of the REACH Regulation's obligations.

CLP Regulation

CLP Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures covers physical, health and environmental hazards.

Under the Regulation, substances and mixtures must be classified according to the criteria laid down therein and any chemical classified as hazardous must be labelled and packaged as appropriate to ensure that it does not present a hazard to human health or the environment. Substances classified as hazardous must also be notified to ECHA. The classification is based on the intrinsic hazardous properties of each substance or mixture without regard to any risk resulting from its use. Some substances are assigned a classification harmonised at the EU level, which must be used by operators. While the Regulation does not specifically refer to nanomaterials, it is considered to cover them as well (EU Commission, 2012a, b). At the national level, Tukes is the competent authority under the CLP Regulation.

The CLP Regulation is a crucial piece of legislation, which results in obligations in other legal instruments that apply CLP classifications. The wide use of CLP classifications in other legislation highlights the importance of proper hazard assessment and classification. In many cases, such classification is also the basis for risk assessment. As the CLP Regulation's classification criteria were drawn up for so-called conventional chemicals, their suitability for nanomaterials has not been examined in further detail. The CLP Regulation is based on the UN Globally Harmonised System of Classification and Labelling of Chemicals (https://unece.org/about-ghs). The system is being continuously updated by the UN's Sub-Committee of Experts on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS Sub-Committee), which has also examined its suitability for nanomaterials. Working in cooperation with the Nordic Classification Group, Tukes experts have produced two reviews on issues relating to the classification of nanomaterials for the needs of the GHS work. The first review surveyed the perceptions and experiences of nanomaterial classification among different stakeholders (Nordic Chemical Group, 2014) while the second one explored the applicability of the CLP/GHS criteria to four different types of nanomaterials (Nordic Chemical Group, 2019). Despite these reviews, the GHS work has failed to progress

to any significant extent, mainly due to insufficient resources relative to the complexity of the task.

Although the classification criteria have yet to be systematically reviewed, some harmonised classifications have been assigned to substances with nanoforms, such as titanium dioxide, all forms of which are classified as carcinogenic category 2, and silanamine (synthetic amorphous silicon dioxide, surface-treated silicon dioxide), which is classified in category 2 as toxic to lungs in repeated exposure. These evaluations are currently made on a case-by-case basis in the absence of guidance on classification. Some classification proposals on nanomaterials are also currently being considered. A proposed classification as carcinogenic has been submitted for multi-wall carbon tubes, including multi-wall carbon nanotubes, within the range of 30 nm to 3 µm in diameter, 5 µm or more in length and a ratio of >3:1. Likewise, the proposed classification for silver includes an environmental classification for its nanoforms.

Biocidal Products Regulation

Biocides are substances used to control or destroy harmful organisms. Biocidal products include:

- disinfectants for the skin, surfaces and drinking water;
- pesticides, such as rodenticides and insecticides;
- preservatives used by industry and for industrial products; and
- antifouling paints and other antifouling products, also known as antifoulants, on vessels and aquaculture equipment.

Biocidal Products Regulation (EU) No 528/2012 provides for the approval procedure for active substances in active biocidal substances and biocidal products. The purpose of the Regulation is to ensure a high level of protection of human health and the environment. In Finland, Tukes is the competent authority under the Biocidal Products Regulation.

As a general rule, biocides are hazardous chemicals and all biocidal products placed on the market require authorisation. Prior to product authorisation, its active substances are required to have been approved. Product authorisations are applied through a national authorisation procedure. National authorisations may be extended to other Member States via a mutual recognition procedure. If they so wish,

companies may also apply for an authorisation valid throughout the European Union (‘Union authorisation’), if the conditions of use are sufficiently similar throughout the Union.

Evaluations of active substances and biocidal products include hazards for human health and the environment, physicochemical hazards, and efficacy. In addition, human and environmental exposure due to the use of the products is assessed by calculations using various scenarios. Human exposure is assessed for both product users and those who may subsequently come into contact with the product. The risks of using the product are assessed on the basis of hazard and exposure.

The Biocidal Products Regulation includes a definition of nanomaterial based on the Commission Recommendation. Under the Regulation, the approval of an active substance does not include the nanomaterial form unless explicitly mentioned. As a general rule, any nanomaterial forms of active substances require a separate dossier that satisfies all information requirements. A specific risk assessment is likewise required whenever a nanomaterial form of an active or non-active substance is used in a biocidal product. The applicability of the tests used to assess the active substance or product must be proven or, where necessary, the test designs must be adjusted. The sales package labelling of biocidal products must specifically indicate any substances at the nanoscale and the risks involved. Furthermore, the labelling of any articles treated with a biocidal product containing nanomaterials must indicate the names of the nanomaterials, followed by the word ‘nano’ in brackets. No detailed technical guidance is currently available for evaluating nanomaterials. Active substances and products are classified in accordance with the CLP Regulation.

As at the end of 2020, only one active substance containing nanoparticles had been approved. However, as the active substance approved as an insecticide (pyrogenic, synthetic amorphous silicon dioxide, nano, surface treated, CAS No 7631-86-9) only contains nanoparticles in agglomerates of > 1 µm in size, a separate risk assessment was not required for its evaluation.

It is likely that nanomaterials will be used in biocidal products in the future. In disinfectants, for example, nanosilver is a potentially suitable nanomaterial for biocides.

Under the Finnish Chemicals Act (599/2013), the authorities supervising legislation relevant to biocides are Tukes, the Regional State Administrative Agencies (AVI Agencies), the Centres for Economic Development, Transport and the Environment (ELY Centres), municipal environmental protection authorities, and the Customs.

Plant Protection Products Regulation

Plant protection products are used to protect plants or plant products from plant pests, destroy harmful plants or parts of plants, or prevent harmful growth of plants. They can also influence the life processes of plants (plant growth regulators) and preservation of plant products. Plant protection products are mainly approved for professional users who have completed a qualification in plant protection products. Some of the products are also allowed for consumer use, such as for domestic gardens and indoor plants. Exposure to plant protection products mainly affects workers engaged in spraying work (e.g. opening a package, mixing, dilution, spraying, cleaning the sprayer and PPE). Those working in treated areas may likewise be exposed to plant protection products. Exposure is also possible among people with permanent residence and bystanders moving about in the vicinity of a spraying area. Consumers may be exposed to plant protection product residues through food products. As part of product authorisation, it must be verified that exposure remains at an acceptable level among all population groups. In addition to health risks, using the products may create risks for the environment (organisms, soil, groundwater and surface water), which is why it is also necessary to ensure their safe use from the environmental perspective as part of risk assessment. Plant protection products should only be used for proven needs in compliance with good application practice, which aims to ensure that plant protection products are applied safely to the intended site without causing risks to users, bystanders or the environment. The basics of good application practices are part of the plant protection product qualification, which includes guidance on regular testing, maintenance and calibration of application equipment, integrated plant protection and compliance with restrictions.

Plant Protection Products Regulation (EC) No 1107/2009 provides for a process for the authorisation of plant protection products and the approval of their active substances, which aims to ensure the appropriate and sustainable use of plant protection products. The risks of active substances in plant protection products are assessed and approved for a limited period within the EU, after which risks will need to be reassessed. Active substances must be approved within the EU before Member States can authorise the use of plant protection products containing them. Plant protection products must be authorised in each EU country in which they are to be used. At the national level, Tukes is the competent authority under the Plant Protection Products Regulation. Tukes authorises plant protection products for sale and use in Finland and determines the conditions for use.

The studies required for risk assessment of active substances and for plant protection products are determined in Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013, respectively. As the Plant Protection Products Regulation does not include specific provisions on nanomaterials, the approval process does not, as a general

rule, specifically consider any nanomaterials that a product may contain. The active substances of plant protection products approved in the EU have been compiled into a database, based on which no active substances at the nanoscale have currently been approved in the EU (EU Pesticides Database). Since no similar resource is available on plant protection products, it is unclear whether any products containing nanomaterials may have already been authorised within the EU. Nor have any nanosized ingredients been involved in the authorisation process of plant protection products in Finland, with the exception of one liquid product, which contained 1% or more of titanium dioxide particles with aerodynamic diameter equal to or below 10 µm as per Regulation (EU) 2020/217. Consequently, no further information is available on exposure to any nanomaterials that may be found in plant protection products.

Although few nanomaterial-based plant protection products are as yet available on the market, there is active development underway. Its aims include increasing the sustainability of these products, improve their efficiency and reduce undesirable environmental effects. While the Plant Protection Products Regulation does not specifically provide for nanomaterials, the European Food Safety Authority (EFSA) has already been monitoring advancements in nanotechnology since 2006 and published guidance for assessing the risks of nanomaterial applications used in food and feed products (including plant protection products) for human health (EFSA, 2018) and the environment (EFSA, 2020).

4.1.2 Cosmetics legislation

Cosmetics Regulation (EC) No 1223/2009, laying down provisions on the safety of cosmetic products only covers effects on human health. Any environmental concerns that may be caused by substances used in cosmetic products are considered by applying the REACH Regulation.

The definition of a nanomaterial included in the Cosmetics Regulation differs from the Commission Recommendation, as its adoption preceded the publication of the Recommendation. For the purposes of the Cosmetics Regulation, *'nanomaterial' means 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.* Hence, the definition does not cover soluble or biodegradable nanomaterials and excludes liposomes and emulsions, for example, from the scope of the Regulation.

Although the Regulation does not provide for any pre-market authorisation procedure for cosmetic products, certain substances used in the products, such as colourants, preservatives and UV filters, must still be submitted for EU-wide approval before they

can be used in cosmetics. Once approved, the substances are included in the positive list for each use category (colourants, UV filters, preservatives). The use of some substances may be restricted or completely prohibited. These substances include carcinogenic, mutagenic and reprotoxic substances (CMRs), classified in accordance with the CLP Regulation.

If a nanomaterial used in a product is not included in one of the above-mentioned use categories requiring prior approval, it must be notified to the Commission's database no later than six months prior to placing it on the market. Rather than being subject to EU-wide assessment, however, the safety of these nanomaterials is assessed by the operator. The Scientific Committee on Consumer Safety has produced guidance in support of safety assessment (SCCS, 2019).

The Regulation requires the Commission to publish a catalogue of all nanomaterials used in cosmetic products placed on the market (EU Commission, 2019a). The catalogue must indicate the categories of cosmetic products and the reasonably foreseeable exposure conditions. The catalogue is for information only and does not represent a list of authorised nanomaterials. The 2019 catalogue lists 29 nanomaterials, with the most commonly used being titanium dioxide, silicon dioxide compounds and carbon black.

Every cosmetic product has to indicate the list of its ingredients on its packaging. Like any other ingredient, nanoform ingredients must also be listed in the descending order of weight compared with other ingredients in the product. The ingredients present in the form of nanomaterials must be followed by the word 'nano' in brackets.

In the event that the Commission has concerns regarding the safety of a nanomaterial assessed by the operator, the Commission may request the Scientific Committee on Consumer Safety (SCCS) to carry out a risk assessment. A specific problem with some nanomaterials has been the inadequacy of the dossiers submitted by operators, which has prevented the Scientific Committee from providing its final opinion on the nanomaterials concerned. The Commission has considered that a general concern for the safety of a nanomaterial alone is not a sufficient reason to prohibit or restrict the use of a substance despite any shortcomings in a safety dossier. The Commission therefore requested the Scientific Committee to determine the aspects that can be considered to provide sufficient grounds for concern based on the nanomaterials published in the 2019 catalogue (EU Commission, 2020c). The aspects listed in the SCCS opinion completed in January 2021 as a basis for concern include physicochemical aspects (size, solubility, chemical composition, and toxicity, morphology, surface chemistry and coatings); exposure aspects (frequency and amount, potential for systemic exposure, accumulation); and other aspects (novel properties, activity of function, specific concern arising from the type of application

(SCCS, 2021). Further information is expected to become available as a result of the updated information requirements of the REACH Regulation, possibly also including information about nanomaterials used in cosmetics.

4.1.3 Occupational health and safety legislation

The requirements of occupational health and safety legislation for managing risks arising from nanomaterials are the same as for any other dangerous chemicals. Occupational health and safety legislation does not include any specific provisions on nanomaterials. Nanomaterials fall within the scope of EU Framework Directive 89/391/EEC and are subject to Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work and Directive 2004/37/EC, also known as the 'Cancer Directive', which specifies stricter obligations for the substances falling within its scope. Any nanoparticles unintentionally produced as part of work processes fall within the scope of these Directives. The Directives have been incorporated into Finnish legislation by the Government Decree on Chemical Agents at Work (715/2001), the Government Decree on the Prevention of Work-related Cancer Risks (1267/2019) and the Act on the List and Register of Workers Exposed to Carcinogenic Substances and Methods (452/2020).

Under the above-mentioned national legislation, employers are required to carry out an assessment of risks and take the necessary measures to reduce the risks. Employers must identify the hazards arising from chemical agents at work and assess the risks posed to workers. Risk assessment must consider aspects such as information on the hazardous properties of the exposure agent and the level and duration of exposure.

Employers are required to remove the hazards or reduce the risks to a minimum. Hazardous chemical agents must primarily be eliminated or substituted. If this is not possible, technical and work organisation measures (e.g. air-conditioning, local exhaust ventilation) must be taken. If exposure cannot be prevented by the means mentioned above, personal protective equipment (PPE) must be used. Employers must also provide employees with training and guidance on hazardous chemicals present in the workplace, the hazards caused by them and the appropriate precautions.

The Act on the List and Register of Workers Exposed to Carcinogenic Substances and Methods requires workers exposed to substances or mixtures that can be classified as carcinogenic or mutagenic (Carc. 1A/1B or Muta 1A/1B) under the CLP

Regulation to be reported to the ASA register maintained by the Finnish Institute of Occupational Health.

Besides actual occupational health and safety legislation, occupational health and safety obligations applicable to workplaces are also imposed within the framework of REACH legislation (see Section 4.1.1).

Handling of nanomaterials at work is supervised by the Occupational Health and Safety Divisions of the Regional State Administrative Agencies as part of other occupational health and safety supervision.

4.1.4 Legislation on the food supply chain

Legislation on the food supply chain covers the entire chain from primary production all through to the consumer's dinner table. It includes food products, any materials and supplies coming into contact with them, animal feeds, plant protection products, fertilisers and veterinary medicines.

Discussions on nanotechnology and food products should give priority to intentionally manufactured nanoparticles and nanomaterials. For the purposes of Novel Foods Regulation (EU) 2015/2283, *'engineered nanomaterial' means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale.*

Consumers should be informed of any engineered nanomaterials used in food products. According to Food Information Regulation (EU) No 1169/2011, all ingredients present in the form of engineered nanomaterials must be clearly indicated in the list of ingredients. The names of such ingredients must be followed by the word 'nano' in brackets. The labelling obligation applies to engineered nanomaterials as defined in Novel Foods Regulation (EU) 2015/2283.

To date, nanotechnology is still little used in foods, feeds and food contact materials because the safety of nanoform compounds is challenging to prove.

No specific legislation on nano-engineered food exists either in Finland or at the EU level; nor are there any plans for such legislation. However, foods, food contact materials and feeds fall within the scope of General Food Regulation (EC) No

178/2002 and are therefore subject to its general principles and safety requirements even in the absence of specific legislation on such products. In addition, EU law on novel foods, food improvement agents and food contact materials takes account of the use of nanotechnology as well. Nanomaterials and nanotechnology are also regulated by legislation on organic products, feeds, fertilising products, plant protection products and veterinary medicines.

As a general rule, the use of nanomaterials is subject to authorisation and the safety of use in foods (incl. food ingredients), food contact materials and feeds must be ensured as required by law. The authorisation processes for nanomaterials are mostly centralised, which means that authorisations for use are granted by the European Commission. The authorisations granted are valid throughout the EU. The Finnish Food Authority is the contact point and central authority for these authorisation processes in Finland. The European Food Safety Authority (EFSA) assesses the risks of using nanomaterials at the request of the European Commission prior to the granting of a marketing authorisation. The safety of nanomaterials already available on the market can also be reassessed. Not a single product compatible with the definition has been authorised as a food product within the European Union. EFSA received the first application for its consideration in 2021. EFSA assesses the safety of foods, feeds and food contact materials containing engineered nanomaterials as part of their authorisation procedures. The safety assessment is based on EFSA's own guidance on risk assessment of nanomaterials and nanotechnology used for foods, feeds and food contact materials (EFSA, 2021). Each field of food law has a working group led by the European Commission, consisting of representatives of EU Member States. The working groups discuss legislative proposals and proposals for decisions on pending authorisations and create and harmonise legal interpretations. Finnish representatives to the working groups mainly come from the Ministry of Agriculture and Forestry. Alongside the EU working groups, Finland has a national expert group under each jurisdiction, consisting of representatives from NGOs, industries and public authorities. Among other things, the national expert groups prepare Finland's positions on the matters discussed by the EU working groups.

Control of the use of nanomaterials in food products and food contact materials in Finland is part of the food control tasks of municipal food control authorities. Control is carried out in compliance with each municipality's own control plans and the Oiva evaluation guidelines prepared by the Finnish Food Authority. With regard to feeds, the use of nanomaterials is controlled by the Feed Division of the Finnish Food Authority. The Customs controls the use of nanomaterials in imported products falling within its control area.

Novel foods

Novel Foods Regulation (EU) 2015/2283 regulates food products consisting of or containing engineered nanomaterials and new production processes for nanosized food particles. The Novel Foods Regulation sets out the obligations concerning engineered nanomaterials, i.e. those intentionally manufactured to have certain properties. Any novel food will only be authorised for use in the European Union if it does not pose a risk for public health, is not nutritionally disadvantageous where intended to replace another, similar food, and does not mislead the consumer. Vitamins and minerals used in food supplements or to fortify foods fall within the scope of relevant specific legislation. They also come under the scope of the Novel Foods Regulation if the production processes or new sources give rise to significant changes in the composition or structure of a food, affecting its nutritional value, metabolism or level of undesirable substances. By way of example, the safety of nanoform vitamins and minerals is assessed as required by the Novel Foods Regulation. No nanoform food products have so far been authorised by virtue of the Novel Foods Regulation.

Food improvement agents

Food improvement agents include additives, flavourings and enzymes. Provisions on food improvement agents and their authorisation procedure are laid down in Regulations (EC) No 1331/2008, 1332/2008, 1333/2008 and 1334/2008 of the European Parliament and of the Council. There are also specific provisions on smoke flavourings, laid down in Regulation (EC) No 2065/2003, and on extraction solvents and processing aids used in food processes, laid down in Decree 1020/2011 of the Ministry of Agriculture and Forestry. Provisions on the re-evaluation of approved food additives are laid down in Regulation (EU) No 257/2010. In light of new toxicological information, all additives approved prior to 20 January 2009 must be re-evaluated taking account of additive intake from food. Where necessary, the safety of substances in nanoform is assessed in accordance with EFSA guidance on nanomaterials. In addition to the re-evaluation programme, the safety of additives must be reassessed if a food additive already included in and approved for the Union catalogue changes significantly in terms of particle size, for example. The Commission and/or a Member State may also request EFSA to re-evaluate an additive for other reasons. Based on such evaluation, it is possible to specify the technical and purity specifications of the additive, including the number and distribution of nanosized particles. Provisions on specifications for food additives are laid down in Regulation (EU) No 231/2012.

Some ingredients already approved and available on the market may contain nanoform particles, which may be related to the technological properties of such

ingredients. These include titanium dioxide, iron oxides and dioxides, ammonium ferric citrate, various silicate-containing compounds generally present as agglomerates, calcium and magnesium phosphates, and potassium and calcium fatty acid salts.

Food contact materials

The general safety requirements applicable to food contact materials are laid down in Regulation (EC) No 1935/2004. The Regulation applies to all materials and articles intended to come into contact with food. The Regulation does not contain any specific provisions on substances in nanoform. Consequently, their use is not categorically restricted, as long as the safety requirements of the Regulation are satisfied. According to the Food Contact Materials Regulation, substances must not transfer their constituents to food in quantities large enough to endanger human health. Nanoform compounds are used in coatings of contact materials, for example. Nano-compounds used in contact materials include titanium dioxide, certain silver compounds, titanium nitride, zinc oxide and nanoclay.

Certain contact materials are subject to specific legislation. EU Plastics Regulation (EU) No 10/2011 establishes specific requirements for the manufacture and marketing of plastic materials and articles. The Plastics Regulation only allows the use of nanoform substances in plastic food contact materials if specifically authorised. Only a few nanoform substances have so far been authorised for this purpose.

Provisions on the safety of food contact materials are laid down in Regulation (EC) No 450/2009 on active and intelligent materials. Similar to the Plastics Regulation, nanoform substances must always be authorised. The Regulation refers to substances deliberately engineered to particle size which exhibit functional physical and chemical properties that significantly differ from those with a larger particle size.

The European Commission is preparing an extensive revision of food contact materials legislation. The revision aims to improve the coverage and applicability of legislation, thus increasing the safety and ecological sustainability of food contact materials. Regulation of nano-compounds forms one of the areas of the Commission's inception impact assessment. Further information about the legislative revision is available on the Commission's website at: https://ec.europa.eu/food/safety/chemical_safety/food_contact_materials/specific-eu-policy-initiatives/evaluation-and-revision_en/.

There are also guideline level provisions on nanomaterials. The Council of Europe has developed guidelines for food contact materials not currently governed by Union-

level regulation. Its Resolution on food contact materials states that a specific risk assessment must always be carried out for substances in nanoform (Council of Europe, 2020).

Animal feed

In addition to the basic principles of the General Food Regulation, provisions on requirements for feeds are laid down in Regulation (EC) No 767/2009 on the placing on the market and use of feed and in Feed Additives Regulation (EC) No 1831/2003. These do not contain any specific requirements for nanomaterials or their labelling. As part of updating the requirements for feed additives applications under Regulation (EC) No 429/2008, new requirements for additives containing nanomaterials are being inserted into the guidelines. Iron oxide and titanium dioxide have already been authorised for use as colourants in feed additives years ago (for further details, see Section 6.1). The Finnish Feed Act (1263/2020) does not contain any specific provisions on nanomaterials.

Fertilising products

Neither the Finnish Fertiliser Product Act (539/2006) nor the Fertiliser Regulation (EC) No 2003/2003 or its replacement, Fertilising Products Regulation (EU) 2019/1009, includes any specific provisions on nanomaterials. Chemical fertilisers fall within the scope of REACH Regulation (EC) No 1907/2006 and are also subject to CLP Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures.

Although research is carried out on the use of nanotechnology, its use in fertilising products is currently very limited. In fertilising products, nanotechnology is applied with a view to enhancing the nutrient intake and absorption of plants, increasing growth, and improving resistance to stress and pathogens. Nanotechnology is also considered as a solution to environmental problems caused by nutrients in fertilising products.

Fertilising products are part of the EU Circular Economy Strategy and the use of waste-based components is increasing all the time. Waste-based raw materials, such as food waste and sewage sludge, may contain nanomaterials. New categories of component materials are considered by a Commission expert group on the basis of a report by the European Commission’s Joint Research Centre (JRC). In Finland, the Finnish Food Authority is responsible for controlling fertilising products and authorising new types of fertilisers, while general guidance and legislative development fall within the remit of the Ministry of Agriculture and Forestry. Finnish

legislation requires that fertiliser products must not cause risk to human, animal or plant health, safety or the environment.

Other legislation

Organic Products Regulation (EU) 2018/848 prohibits food containing, or consisting of, engineered nanomaterials. This Regulation applies as of 1 January 2022. The food supply chain also uses plant protection products and veterinary medicines, for example. Nanomaterials and nanotechnology are regulated by legislation governing these as well.

4.1.5 Medicines legislation

'Medicinal product' means any substance or combination of substances presented for treating, preventing or diagnosing disease in human beings or animals (Directive 2001/83/EC and Regulation (EU) 2019/6). Placing a medicinal product on the market requires a marketing authorisation, which is granted by the Finnish Medicines Agency Fimea at the national level and by the European Commission on proposal by the European Medicines Agency (EMA) at the EU level. Neither the Finnish Medicines Act (395/1987) nor Community legislation (Human Medicinal Products Directive 2001/83/EC) recognise any specific provisions on nanomaterials.

Nanomedicines for human use are regulated uniformly with other medicinal products and a marketing authorisation requires assessing the product's quality, efficacy and safety, covering physicochemical and biological studies, pharmacological and toxicological studies, clinical trials and a benefit–risk assessment.

EU Veterinary Medicinal Products Regulation (EU) 2019/6 imposes further requirements on nanomedicines for veterinary use. These focus on the risk characteristics associated with nanomedicines, such as small size or the ability to form agglomerates as provided in Regulation (EU) 2021/805.

In addition to guidance covering all medicinal products, the EMA has produced four guidelines for specific product categories, which include specific guidance for nanomedicines with regard to liposomal products, iron-based nano-colloidal products, block-copolymer-micelle medicinal products, and nano-transporters. Nanomedicines are also subject to the obligation imposed by the EMA in 2019 to identify medicinal products containing liposomes in the name and packaging. This aims to promote medication safety by avoiding any potential dosing errors that may arise from different forms of medicinal products.

Medicines are also controlled after placement on the market. Pharmacovigilance Directive 2010/84/EU was implemented in Finland by virtue of the Medicines Act, which imposes an obligation on the marketing authorisation holder to monitor the safety of the authorised medicinal product and take the necessary action in the event that any changes are detected in its risk–benefit ratio. An integral part of this process consists of monitoring adverse effects and taking risk management measures, which are the responsibility of pharmaceutical operators and authorities. Fimea supervises medicine safety at the national level and as part of the EU regulatory network of authorities.

In Finland, pharmaceutical authorisation and supervision falls within the remit of the Finnish Medicines Agency Fimea, a central government agency operating under the auspices of the Ministry of Social Affairs and Health. Fimea evaluates and controls medicinal products intended for both human and veterinary use, medical devices, and blood and tissue products, and is part of the European medicines regulatory network coordinated by the European Medicines Agency (EMA). Fimea's regulation and supervision cover the entire life cycle of medicinal products, from classification and preclinical and clinical studies and scientific assessment to distribution, pharmacovigilance by marketing authorisation holders, and pharmaceutical market supervision. Fimea's supervisory activities are based on national and European Union legislation. Fimea may also issue regulations binding on pharmaceutical operators. It is responsible for controlling veterinary medicinal products as well. Alongside Fimea, the Finnish Food Authority is also responsible for the duties assigned to national competent authorities under EU Veterinary Medicinal Products Regulation (EU) 2019/6.

Examples of nanomedicinal products

Active pharmaceutical ingredients in nanoform

An active pharmaceutical ingredient itself may be in nanoscale crystalline form, which can be made from a solid, powdered ingredient. By way of example, nanocrystalline tablet forms have been made from the immunosuppressive medicine sirolimus and the cholesterol medicine fenofibrate. Nanoemulsion technology has also been used to develop orally administered capsules of the antiviral ritonavir and the immunosuppressive ciclosporin. Some injectable medicinal products containing nanostructures are already available on the market, including psychotropic medicines olanzapine and paliperidone.

In certain cases, iron deficiency anaemia has been treated with intravenous, iron-based nano-complexes, where iron is in a more easily absorbed form.

Nanostructures in packing and transporting pharmaceutical ingredients

Liposomes are roundish structures composed of lipid bilayers formed by phospholipids, which can be packed with pharmaceutical ingredients. In Europe, liposomes have been used in certain anticancer medicinal products (e.g. doxorubicin and daunorubicin), etc.

Virus-like particles (VLPs) are nanosized ‘packaging’ structures consisting of the structural proteins of viruses and sometimes of lipids and are therefore used in vaccines, for example. Some of these products are already available on the market, including HPV, hepatitis B and malaria vaccines.

Lipid nanoparticles (LNPs) consist of various lipids and are used as carriers of RNA and DNA molecules, among others. Some of these products are also already available on the market, such as COVID-19 mRNA vaccines.

The properties of protein-based nanomedicinal products can be enhanced with a polyethylene glycol (PEG) component. Several pegylated protein medicines for various therapeutic indications are already available on the market, such as certolizumab pegol used to treat autoimmune diseases and interferons α2a and α2b acting on immune response.

In veterinary medicinal products, nanoparticles have been used in RNA virus vaccines since the 1990s. A matrix formed by saponin, cholesterol and phosphatidylcholine functions as an adjuvant and immunostimulant, leading to a better immune response in animals (Morein et al., 2004).

Drug–device interface

Nanomedicine applications may also contain combinations of medicines and medical devices and their share is growing as a result of new technologies. Their assessment requires cooperation between experts in medicines and medical devices and identification of legislative interfaces. Medical and diagnostic devices are governed by specific EU law. One of the aims of the EU’s Pharmaceutical Strategy for Europe, adopted in 2020, is to clarify legislative interfaces (EU Commission, 2020b). According to the strategy, it is necessary to revise and simplify pharmaceutical legislation and to streamline approval procedures. Furthermore, timely adaptation of technical requirements to scientific and technological developments is required in order to address the challenges relating to the interplay of medicines and devices.

4.1.6 Medical devices

Regulation (EU) 2017/745 on medical devices sets specific requirements for medical devices that use or contain nanomaterials. The definition and range of medical devices are quite broad, covering any instrument, apparatus, appliance, software, implant, reagent and material for medical purposes. The Regulation includes a definition of nanomaterial conforming to Commission Recommendation 2011/696/EU. According to the Regulation, special care should be taken in the design and manufacture of devices when using nanoparticles for which there is a high or medium potential for internal exposure.

Nanomaterials do not intrinsically entail any significant additional obligations on manufacturers solely on the grounds of their particle size. However, the Regulation does impose on manufacturers of medical devices an additional requirement to reduce any risk associated with the size and properties of nanoparticles that are or may be released into the user's body.

Devices are categorised into four risk classes depending on the risk to the human body, which determine the compulsory steps for placing them on the market (the higher the class, the stricter the obligations/requirements for placement on the market). The classification rules of Annex VIII to the Regulation on medical devices includes Rule 19, based on which any nanomaterials in a device influence its product class. Medical devices/products incorporating nanomaterials are always assigned at least Class IIa or higher. In the event of a high or medium potential for internal exposure of the human body, the devices are classified in the highest risk class (III). If they present a low or negligible potential for internal exposure, the risk class is correspondingly lower (IIb or IIa), which means that the assessment procedure is therefore less onerous. The product classes mentioned above (IIa or higher) always require an assessment by a notified body.

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has prepared a guidance document on the use of nanomaterials in medical devices, providing risk assessors with information on certain aspects to consider when assessing the safety of nanomaterials (SCENIHR, 2015).

4.2 EU measures, OECD work, EU Member States

In the European Union, matters related to nanotechnology and nanomaterials fall under several Directorates-General (DGs) in the European Commission. The REACH, CLP and Cosmetics Regulations are covered by the DGs for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW) and for the Environment (DG ENV); occupational health and safety by the DG for Employment, Social Affairs and Inclusion (DG EMPL); foods, feeds, biocides and medicines by the DG for Health and Food Safety (DG SANTE); and research, science and innovation matters by the DG for Research and Innovation (DG RTD).

The Commission has independent Scientific Committees, which it consults when drafting policies and proposals related to safety, health and the environment. The Committees are composed of named experts. The Scientific Committee on Health, Environmental and Emerging Risks (SCHEER; formerly SCENIHR) provides opinions on questions concerning emerging or newly identified health and environmental risks and on broad, complex or multidisciplinary issues that require a comprehensive assessment and are not covered by other European Union risk assessment bodies. The Scientific Committee on Consumer Safety (SCCS) provides opinions on health and safety risks (chemical, biological, mechanical and other physical risks) of cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products and services, for example. The Scientific Committee on Occupational Exposure Limits (SCOEL) ceased its activity as of the beginning of 2019 as its duties were transferred to the Risk Assessment Committee (RAC) operating under the auspices of the European Chemicals Agency (ECHA).

European Chemicals Agency (ECHA)

Situated in Helsinki, Finland, the European Chemicals Agency (ECHA) is responsible for uniform implementation of EU chemicals legislation relevant to chemicals safety. ECHA's remit covers the REACH, CLP, Biocidal Products and PIC Regulations.

ECHA has prepared guidance documents on REACH registration for industries in cooperation with experts from the Member States. They deal with the information requirements for and grouping of nanomaterials to facilitate registration. Working with the Member States, ECHA carries out compliance checks of registration dossiers with a view to ensuring that the information requirements are fulfilled. As a result of a check, ECHA may request additional information or tests from the registrant. ECHA and Member States also conduct evaluations of individual substances aiming to establish whether a specific substance poses a risk to human health or the

environment. ECHA may likewise request additional information or tests in order to establish whether there is cause for concern. The substances falling within this process are specified in the Community Rolling Action Plan (CoRAP) on substances to be evaluated.

The preparatory work on occupational chemical exposure limits, including nanomaterials, has been transferred to the Risk Assessment Committee (RAC) operating under ECHA.

ECHA's Nanomaterials Expert Group (NMEG) provides informal and non-binding scientific and technical advice on questions related to nanomaterials or nanoforms of substances in the frame of implementing the REACH, CLP and Biocidal Products Regulations. The NMEG's activities will not interfere with the formal regulatory processes of these Regulations. EU Member States and stakeholder organisations may nominate expert members to the group. Cooperation also involves the Commission (DG ENV, DG GROW, JRC) and EFSA.

ECHA has also set up the European Union Observatory for Nanomaterials (EUON, https://euon.echa.europa.eu/en/), a web portal serving all those requiring information on nanomaterials – authorities, companies and consumers. It provides information about the safety and uses of nanomaterials and about relevant research and innovation.

European Food Safety Authority (EFSA)

Situated in Parma, Italy, the European Food Safety Authority (EFSA) assesses the safety of nanomaterials potentially present in the food supply chain and provides Member States with scientific advice (https://www.efsa.europa.eu/en/topics/topic/nanotechnology). Since nanotechnology is a fairly new area of materials technology, it is challenging to establish the potential benefits and risks of these products. In 2011, EFSA prepared guidance for assessing the safety of potentially nanoform materials, which was updated in 2018. EFSA communicates with the European Chemicals Agency (ECHA) and the European Medicines Agency (EMA) on nanotechnology matters.

EFSA's NANO Network is an expert group that promotes cooperation and networking in nanosciences and nanotechnology with Member States as part of risk assessments of food and feed. The network facilitates exchange of information and expertise, increases dialogue and develops a mutual understanding of the principles of risk assessment between EFSA and the Member States. Cooperation also involves the Commission (DG SANTE) and ECHA, EMA and the JRC.

European Medicines Agency (EMA)

In the wake of Brexit, the European Medicines Agency (EMA) moved from London to Amsterdam. EMA plays an active role in the field of nanomedicine, providing expert regulatory guidance and scientific advice for developers of medicinal products, organising stakeholder meetings and drawing up guidelines. At the global level, the debate on regulating nanomedicine is coordinated by the Nanomedicines Working Group (NWG, http://www.iprp.global/working-group/nanomedicines) under the International Pharmaceutical Regulators Programme (IPRP), with a view to harmonising regulatory requirements for nanomedicine applications. EMA also cooperates with the IPRP Nanomedicines Working Group (NWG).

European Commission's Joint Research Centre (JRC)

The European Commission's Joint Research Centre (JRC) offers independent scientific advice and support for EU policies and procedures. The JRC has seven research facilities in five EU countries. It has a specific unit for nanotechnology in Ispra, Italy (JRC Nanobiotechnology Laboratory, https://ec.europa.eu/jrc/en/research-facility/nanobiotechnology-laboratory). The laboratory has facilities for studying and testing products. It also offers access to external parties to study their own materials. The JRC supports the Commission in areas such as definition and identification of nanomaterials and participates in standardisation (ISO and CEN Committees) and harmonisation (OECD cooperation) of methods relevant to nanomaterials.

EU Framework Programmes for Research

Research into nanotechnology and nanomaterials has been strongly driven by technology. However, attention is increasingly given to safety aspects, while research into the safety of nanotechnology and nanomaterials has also received funding. The European Commission has so far funded nanosafety research in several framework programmes.

Research into nanomaterial safety involves complex considerations, such as determining the physicochemical properties of nanomaterials (e.g. size, shape and solubility) and measuring these properties; the impact of nanomaterials on human health and the environment; exposure and exposure measurement and modelling; and the safe-by-design approach, i.e. taking safety aspects into account from the early stages of development.

The Commission's Seventh (2007–2013) and Eighth (2014–2020, entitled 'Horizon 2020') Framework Programmes for Research and Innovation covered projects

seeking scientific answers to regulatory issues in order to develop regulation. The outputs of these projects include an administrative framework and toolbox for assessing the safety of nanomaterials for the needs of industries and authorities (NANOREG, https://cordis.europa.eu/project/id/310584); a safe-by-design concept (NanoReg2, https://cordis.europa.eu/project/id/646221) and a white paper on the priorities that should be implemented and studied from the regulatory perspective (ProSafe, https://cordis.europa.eu/project/id/646325).

One of the objectives of the Horizon 2020 Framework Programme was to invest heavily in nanotechnology research and application development, harnessing this action to strengthen the EU's competitiveness and productivity, increase technological competences and promote sustainable development. At the same time, the programme also aimed to advance scientific research into the potential impact of nanotechnologies on health or the environment and to provide tools for risk assessment and management along the entire life cycle.

The EU is investing on graphene research through a major project. This Graphene Flagship (https://graphene-flagship.eu/) is a 10-year research project (2013–2023) with a budget of EUR 1 billion and involving 170 academic research teams from 22 countries, making it the largest research initiative of all time. The project aims to explore the opportunities brought about by graphene in various innovations across different sectors. One of the research topics is health and environmental impacts.

Within the new Horizon Europe Framework Programme (2021–2027), the measures of the 'Digital, Industry and Space' research cluster support key enabling technologies (KETs), which are strategically important for Europe's industrial future. The goals include global leadership in clean and climate-neutral industrial value chains and in the circular economy (https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/cluster-4-digital-industry-and-space_en). The research cluster's work programme for 2021–2022 includes development of characterisation methodologies to assess and predict the health and environmental risks of nanomaterials, among other topics.

NanoSafety Cluster

The EU NanoSafety Cluster (https://www.nanosafetycluster.eu/) is a platform for all EU-funded projects advancing the safety of nanomaterials. The cluster aims to maximise the synergies between projects and offer a platform for dialogue. The Finnish Institute of Occupational Health used to coordinate the NanoSafety Cluster, with responsibilities such as building a nanosafety strategy for the EU and producing

nanosafety roadmaps for the Commission. At present, the cluster is coordinated by its Steering Group.

Working on OECD Test Guidelines

The OECD Test Guidelines for Chemicals are a collection of the most significant test methods agreed at the international level and used by governments, industries and independent laboratories in order to assess the safety of chemicals. They are mainly used in official safety tests to satisfy regulatory requirements. The Test Guidelines are updated regularly according to scientific progress and national regulatory needs.

In 2006, a Programme of Work on 'Safety of Manufactured Nanomaterials' was launched under the OECD Environment Directorate and the Chemicals Committee (currently Chemicals and Biotechnology Committee) to ensure that the approaches for hazard, exposure and risk assessment for manufactured nanomaterials are of a high quality, science-based and internationally harmonised. In the same context, they set up the Working Party of Manufactured Nanomaterials (WPMN), consisting of experts from Member States and stakeholders. The WPMN has examined the applicability of the Test Guidelines for Chemicals and their guidance documents to nanomaterials while also considering the development of relevant risk assessment. This analysis concluded that the Test Guidelines and guidance documents concerning conventional chemical substances are mainly applicable to nanomaterials as well. However, they are not considered suitable for testing certain properties of nanomaterials, which means that the test guidelines will have to be modified and some new test guidelines will also be needed. ECHA and some EU Member States have been very active promoting this work, as its outcome will directly contribute to the implementation of the updated REACH Regulation. This specific item in the Programme of Work (the 'Malta project') is also funded by the European Commission.

The WPMN is also engaged in some cooperation with the OECD Working Party on Biotechnology, Nanotechnology and Converging Technologies (BNCT), which promotes the use of nanotechnology under the OECD Directorate for Science, Technology and Innovation (DSTI).

National registers of nanomaterials

In 2012, the European Commission issued a Communication on the Second Regulatory Review on Nanomaterials (EU Commission, 2012a, b). It assessed the adequacy and implementation of EU legislation for nanomaterials and responded to concerns raised by the European Parliament about the Commission's approach to the use and safety of nanomaterials that are already on the market. The Commission also

launched an impact assessment to identify and develop the most adequate means to increase transparency with regard to nanomaterials on the EU market. As a result of the assessment and a public consultation, the Commission concluded that there was no need for an EU-wide register of nanomaterials.

The Commission's decision not to establish an EU-wide register of nanomaterials and to launch the European Union Observatory for Nanomaterials (EUON) instead accelerated the establishment of national registers. The rationale for setting up these registers has been a desire to form an overview of the nanomaterials available on the market and their quantities. Registration is compulsory for industry in France, Belgium, Denmark and Sweden. In Norway, industry is required to declare any nanomaterials to the national register of chemical products. There have been no calls to establish a specific national register for nanomaterials in Finland due to reasons such as its potential overlap with the existing Chemical Products Register.

SUMMARY

The regulation of manufactured nanomaterials generally applies all of the EU and national legislation that also governs other chemicals, food and medicines. The EU also has sectoral legislation containing specific obligations for the safe use of nanomaterials. This specific legislation may determine a special authorisation process for the use of nanomaterials or make it conditional to a hazard and risk assessment by the operator. Any nanomaterials used in cosmetic, biocidal and food products must be indicated on the packaging. The regulation of nanomaterials is based on scientific evidence. Methods based on the OECD Test Guidelines are used to satisfy regulatory requirements. The European Commission's Framework Programmes for Research are directing more and more funding to research on the safety of nanomaterials.

5 Nanomaterials research in Finland

In Finland, universities and government research institutes conduct diverse nanoscience and nanotechnology research. Progress has been significant, especially since around 2005 when research and education in nanoscience were explored on the basis of a report by the Ministry of Education and Culture and a proposal was drawn up for a development programme for nanoscience (Ministry of Education and Culture, 2005). The concurrent FinNano programmes within the Academy of Finland and the Finnish Funding Agency for Innovation, Tekes, contributed to the progress (Academy of Finland, 2011).

While safety issues were still marginal in the 2005 report, an evaluation report of the Academy of Finland's research programme indicates that, by 2011, they had become an important topic of discussion alongside application development. As Finland had a high profile in the field of European nanosafety research, the European Commission awarded the task of coordinating the NanoSafety Cluster, an EU-funded consortium of projects to promote nanomaterial safety, to the Finnish Institute of Occupational Health in 2010. The Cluster covered about 30 research projects involving several hundred researchers, with the EU financial contribution totalling over EUR 100 million. However, national cuts in appropriations for education and research in the mid-2010s led to considerable reductions in nanosafety research at the Finnish Institute of Occupational Health, but the work has continued with support from EU funding programmes and national funding bodies and as part of business operations.

The following sections present current research relating to nanosciences and nanotechnology in Finland. The presentations are based on descriptions provided by universities and research institutes, which were requested in a centralised manner by sending an information request to each university registrar's office and, in individual cases, by contacting researchers directly. The descriptions do not cover the entire field of nanoscience and nanotechnology research and only include contributions from those who responded to the information request.

This chapter also examines the funding granted by the Academy of Finland for nanosciences and research into nanomaterial safety in 2011–2019. In addition to national funding, research projects have received funding from the EU Framework Programmes for Research.

5.1 Development of nanomaterials and their use in various products

VTT Technical Research Centre of Finland Ltd

VTT Technical Research Centre of Finland Ltd carries out research into new biomaterials and hybrid materials, including nanocellulose and nanolignin, and develops new high value-added functional products by means of biomaterials and other emerging materials (incl. graphene and other hybrid nanomaterials). A particular focus in the use of biomaterials is on substituting products made from fossil materials. More and more research is also carried out on the use of advanced functional materials in future product solutions, where a particular emphasis is on functional and intelligent products (various electronics and printed electronics solutions, including the Internet of Things, IoT).

The above-mentioned new hybrid and bio-nanomaterials are used as thin layers or additives in coatings as part of manufacturing end products. Emerging products are related to various packaging solutions, textiles, electronics, optoelectronics, diagnostics, construction, other consumer products, energy products, and air or water purification. Packaging research also covers the use of bio-nanomaterials as additives or thin layers in various food contact materials. In general terms, there is very little research on nanomaterials used in the food supply chain in Finland. Advanced materials are geared towards creating high-value products with functional properties, resource-efficiency and, as a result of their smaller environmental effects, achieving more sustainable development when compared with currently available products.

Research is carried out in cooperation with universities and research institutes with funding from both national bodies and the European Commission, including research initiatives such as the EU-funded Graphene Flagship (VTT, Aalto University, Finnish Institute of Occupational Health) and the Academy of Finland's FinnCERES Flagship (Aalto University, VTT; key projects listed in Appendix 8). As part of the Graphene Flagship initiative, VTT studies areas such as graphene-based printed electronics and sensor applications, which can be used as flexible textiles that support or promote health and wellbeing. Research within the FinnCERES Flagship focuses on topics such as the use of bio-nanomaterials for water and air purification applications with the aim of eliminating harmful particles or impurities (micro- and nanoplastics, hormones or pharmaceutical residues) and creating substitutes for packaging and other functional products, such as textile, electronics, and optoelectronics applications.

The projects developing new products take safety aspects into account from the outset, both in terms of the materials, processes and products used (safe-by-design principle, further information in Sections 4.2 and 5.2) and with regard to sustainability (economic, environmental and social impacts; sustainable-by-design principle; see Section 6.4). Assessment of the economic and environmental impacts as part of sustainability impact assessment and development of their methodologies are an important area of VTT's project activities. Research relevant to social impacts, including safety effects, are mainly carried out in individual EU-funded projects in cooperation with European research institutes.

Research into manufacturing products for the future aims at resource-efficient, sustainable processes. Resource efficiency covers material efficiency, recycling of used products and/or materials for reuse (circular economy), and reduction of energy and water consumption. In development work, online measurements, process adjustment and general automation play an essential role in terms of both reducing material consumption and stepping up new product development. Process development is geared towards achieving a high degree of automation by focusing on digital process control, data collection, processing and management, complete with utilising artificial intelligence (AI) through modelling. Stepping up development work in the future is based on the increasing amount of open access data and its use by modelling, which enables the development of both new properties and optimum solutions to be tested with less experimental work. Some solutions, especially for high-volume products, are also aimed at reusing products as new products and/or as recycling materials for new products, if there is a feasible and viable business case for collecting and reusing used products. While recycling of materials is very beneficial for both resource efficiency and the environment, it creates its own set of challenges for collecting, separation and reusing used materials in such a way that the processes are safe and harmful materials are not released into the environment.

These projects are in line with VTT's strategic goals and conform to the objectives of the European Commission's new Horizon Europe Programme: investing in bioeconomy, sustainable development, safety, digitalisation, and automation.

Nanomaterials research at the Aalto University School of Chemical Engineering

At the Aalto University School of Chemical Engineering, nanomaterials are studied extensively by two dozen research teams. One of the School's key research areas focuses on nanomaterials refined from biomaterials, as reflected by its co-leadership with VTT in the FinnCERES Flagship project funded by the Academy of Finland. The

FinnCERES Flagship develops new bio-based materials from lignocellulose (incl. nanolignin and nanocellulose), for example, and their new applications.

Functional materials are a key area of research for the Department of Chemistry and Materials Science in particular. Achieving functionality almost invariably involves nanomaterials, as their large specific area can be harnessed to increase functional chemical groups. The nano-dimension of the material structure makes it possible to adjust, not only electrical, optical and conductive properties, but also mechanical properties.

The range of nanomaterials studied is extensive, including carbon nanomaterials, metal and semiconducting nanoparticles and various lignocellulose-based materials. Significant nanomaterials research is carried out using thin-film techniques, among which the Department's Atomic Layer Deposition (ALD) is the most well-known on the global scale. ALD thin-film composite membranes contain inorganic, typically metal oxides and organic thin-film layers. The hybrid structure of organic and inorganic materials is a new, unique class of materials, which may have several revolutionary applications in the future. By way of example, the ALD technique has been used to demonstrate a functional solid-electrolyte battery structure relating to energy storage.

Nanomaterials are studied for several areas of application, with electricity storage and conversion being the Department's priority area. In this area, nanomaterials are mainly related to new types of catalysts. An example is a metal-carbon composite, where a graphene shell is processed onto the surface of a metal nanoparticle. This allows the metal's catalytic properties to function while the carbon layer protects the catalyst from chemical corrosion. Battery technology is living through a period of rapid development, where critical challenges include the environmental sustainability and recyclability and, first and foremost, functionality of battery raw materials. Nanostructures are important in battery materials in view of catalysis and transport phenomena.

Electrochemical surface properties are also studied as part of developing biomolecular sensors. These structures are mostly based on nanomaterials and are key to rapid assay techniques of pharmaceutical ingredients. Interactions between solid surfaces and fluids is a field of research in microfluidics, which makes use of the combination of material proportions and nano-/micro-dimensions and chemical surface functionalisation. Surface nanotopography has also been studied using light-activated polymers, allowing surface properties to be reversibly controlled in order to develop intelligent materials.

Managing the optical properties of materials is also a significant area of research with a key impact on development of solar energy, optical filters, decorative properties, etc.

The unit studies methods of synthesising nanomaterials, including various chemical, electrochemical, sol–gel, vacuum process, aerosol and Leidenfrost techniques. The synthetisation of nanostructured bulk materials is studied by means of pulsed electric current sintering (PECS).

The unit has linked extensive molecular dynamic modelling to experimental study of nanomaterials. This has elevated material synthesis and knowledge of structural properties to a completely new level.

University of Jyväskylä

The University of Jyväskylä Nanoscience Center (NSC) is an interdisciplinary research centre where physicists, chemists and biologists work together to study natural phenomena at the nanoscale. Research at the NSC is carried out in an international scientific community with extensive research projects spanning from basic research of nanostructures to commercial product development. The scientific centre's research is divided under five focus areas, including nanobiology, nanochemistry, experimental nanophysics, nanoscience of light and matter interaction, and theoretical nanoscience. Its key objectives concern health and wellbeing, sustainable society, the second quantum revolution, and appreciation of science in society.

The Nanoscience Center receives support for its research and innovation from the University of Jyväskylä services promoting commercialisation of research results. Indeed, new enterprises operating in the field of nanoscience are being established at a steady pace as a result of the NSC's activities. At present, NSC scientists are involved in developing antiviral materials from forest industry side streams, for example. Nanomaterials research and development form an integral part of NSC activities in other respects as well. Nanodevices and nanomaterials can be produced in dedicated clean rooms and nanoscale properties can also be examined in detail using the wide range of facilities available at the NSC.

One of the materials widely studied at the NSC is graphene. Graphene is an atom-thick carbon film, which is mechanically and chemically very durable, transparent, pliable and yet highly electroconductive. Due to its excellent properties, the use of graphene is studied in a vast range of application areas, such as flexible and transparent electronics, optoelectronics, biosensors and coatings. The discovery of graphene has been followed by several other ultra-thin, so-called 2D or single-layer materials and it can be expected that they will be used in many applications in the future. The NSC produces high-quality graphene while also mastering characterisation of materials and their transfer to various substrates. The NSC's Laser

Laboratory specialises in optical modification of graphene using laser radiation. This technique is used in a project to develop a nerve–machine interface from graphene. This is an example of how the special characteristics of graphene can lead to completely new solutions, which can improve people's lives. When electronics is combined with soft tissues, traditional solutions based on hard metals do not work because tissues tend to reject them. Graphene is a better match with tissues because it is flexible and pliable while also boasting excellent electrical properties, which make it possible to produce electronic devices. This research is related to a newly emerging field, bioelectronics, where nanomaterials have high potential.

University of Eastern Finland

The Kuopio Campus of the University of Eastern Finland is home to the Fine Particle and Aerosol Technology Laboratory, which studies and develops metal- and carbon-based nanomaterials. The material synthesis mainly uses aerosol methods based on the gas phase. In addition, high-temperature induction heating enables energy-efficient material treatment. The nanomaterials being manufactured comprise metal oxides, doped metal oxides, magnetic materials and carbon-based materials. By way of example, the flame synthesis and induction heating methods have been used to produce nano-based LTO and NMC anode and cathode materials and carbon-based silicon nanoparticles as anode materials for lithium-ion batteries. Titanium-based photocatalytic nanomaterials and recyclable, iron-based magnetic nanomaterials have been developed for water purification purposes. Doped zinc oxide nanoparticles have been synthesised for antiviral (SARS-CoV-2) coatings and water purification. Nanoform metals have also been extracted from fly ash with high metal content, which is generated as part of waste incineration processes.

Wood materials research carried out at the School of Forest Sciences deals with nanoparticles as part of development and applications of nanocellulose, nanolignin and mineral- or metal-bearing wood treatment products. In addition, the environmental effects of various nanomaterials are studied at the Department of Environmental and Biological Sciences. This is basic experimental ecotoxicological research on both terrestrial and aquatic environments.

University of Oulu

The University of Oulu conducts multidisciplinary research into the manufacture, analysis, applications and environmental and health impacts of nanoscale materials, particles and chemicals. This multidisciplinary research focuses on new bio-based nanomaterials and their synthesis methods compatible with green chemistry. Research areas include nanocellulose, nanochitosan/nanochitin and nanolignin,

biological and natural nanoparticles (incl. exosomes and aerosols) and inorganic carbon-based and mineral nanoparticles. Development of nanomaterial applications focuses on green and carbon-neutral technical materials and environmental applications, such as packaging, textile fibres, films, foams and catalytic materials, medical applications and diagnostics, as well as information and communications technology (ICT) and telecommunications applications. The University of Oulu is home to the Centre for Material Analysis (CMA), which offers centralised research and analysis services related to nanotechnology and materials science to university research teams and companies. The University of Oulu also serves as the national coordinator for the Swedish MAX IV synchrotron radiation facility, which offers a modern environment for nanomaterials research. The University also has expertise in the sustainability impact assessment of nanomaterials.

Tampere University

At Tampere University, nanomaterials research is carried out extensively within the Faculty of Engineering and Natural Sciences (ENS) and the Faculty of Medicine and Health Technology (MET). This research is funded by the Academy of Finland, the EU, Business Finland, domestic and international companies, corporations and foundations.

Within the Faculty of Engineering and Natural Sciences, nanomaterials are particularly studied in the fields of aerosol physics, photonics, chemistry and new materials and engineering materials science. Aerosol physics research focuses on fine particles and nanoparticles. Its fields of application include atmospheric phenomena from climate change to air quality research. The Aerosol Physics Laboratory has a broad experimental capacity for measuring aerosol particles and it also develops instruments. The focus areas of research into the yield of nanomaterials include the yield of multi-component nanoparticles at controlled particle size and composition. Photonics studies the use of light in energy technology applications, telecommunications, health technology applications and various imaging applications. Interactions between light and matter, at nanoscale in particular, play a significant role in development of various photonics materials, for example. Research is carried out with international partners and making use of the national PREIN Flagship platform for Photonics Research and Innovation. Nanomaterials research in the fields of chemistry and new materials focuses on the use of metal nanoparticles as part of developing *in vitro* breast cancer models; the manufacture and use of biomaterial-based fibres in optical sensing applications; the design, production and characterisation of perovskite nanocrystals, especially in optoelectronics applications; and the use of semiconductor quantum dots in activating photocatalytic reactions. In the field of engineering materials science, nanomaterials are studied in different applications by adding value to materials and structures through their

physicochemical properties. While materials are synthesised in the unit, proprietary materials are also used. Materials are also anchored to various substrates by both chemical and physical means. Structures and material properties are also studied through modelling and simulations.

Cellulose nanofibrils are studied for the needs of 3D cell and organoid culturing. The Protein Dynamics group studies how to improve the biocompatibility of cellulose nanofibrils by modifying fibrils with the aid of proteins and biomolecules. Research into cell culture systems makes use of the self-orientation of cellulose nanofibrils in producing cell culture substrates. The group also studies an electroconductive composite material made from nanocellulose and carbon nanotubes. Cell and tissue technology and biomaterials research, in turn, develops polymer-based nanoparticles and studies their use in drug delivery into cells and in cell modification. The research makes use of both synthetic and natural polymers. Biomaterials research also explores the synthesis of nanomaterials and manufacturing and behaviour of nanoparticles with different shapes in cell culture conditions. Nanoparticles are likewise used in research methods relating to the transport of materials, substances and gases. Part of the MET Faculty, the Finnish Hub for Development and Validation of Integrated Approaches (FHAIVE) is one of the six GLP-certified and EU-accredited reference laboratories in Finland. FHAIVE's nanotechnology research is related to testing the safety of nanomaterials and developing new, safe and environmentally friendly materials. Its methods are especially based on *in vitro* exposure models and toxicogenomics. FHAIVE also studies the immune-modifying properties of nanomaterials and the usability of these methods in development of new therapeutic methods.

University of Helsinki

The University of Helsinki Faculty of Science is home to the Institute for Atmospheric and Earth System Research (INAR), which studies nanomaterials, with focus on the formation, dynamics and properties of nanoparticles. INAR's spin-offs, Airmodus (https://airmodus.com/) and Karsa (http://karsa.fi/) are also related to nanomaterials.

The Nanomaterials Laboratory of the Faculty of Science provides facilities for forming nanostructures using ion and cluster beams. The structures, compositions and electrical properties of the samples and materials produced can be characterised using several methods. The main facilities available include a nanostructures production facility using cluster ion beams; an ion beam dry etching facility for nanostructuring and downsizing; an ion sputter deposition facility; ultra-high vacuum (UHV) variable temperature atomic force microscopy (AFM)/scanning tunnelling microscopy (STM); low energy electron diffraction (LEED); Auger electron

spectroscopy (AES); and a cryogen-free dilution refrigerator system (~10mK) for determining the electrical properties of nanostructures.

University of Turku

Research focuses on molecularly determined nucleic-acid-based (DNA/RNA) nanoparticles aimed at tissue-specific nucleic acid drug delivery. It is carried out in collaboration with Orion Corporation, the Turku PET Centre, the University of Helsinki, the University of Eastern Finland, Tampere University and the Finnish Red Cross Blood Service. The University of Turku is responsible for synthetics and structural analysis, while biology, intracellular transport, vesicle packaging and other areas of research are carried out elsewhere.

5.2 Safety research

Finnish Institute of Occupational Health

Research into nanotechnology and nanomaterials has been strongly driven by technology, but as the use of nanomaterials in industrial production and consumer products is becoming more prevalent, attention is increasingly focusing on their safety aspects as well. Research into nanomaterial safety must take account of material properties and measuring these properties; the impact of nanomaterials on human health and the environment; and exposure and exposure assessment by means of measurements and modelling. In Finland, research into the safety of nanotechnology is largely concentrated at the Finnish Institute of Occupational Health. The Finnish Institute of Occupational Health studies the health hazards of nanomaterials, such as genotoxicity and carcinogenicity, occupational exposure and risk management in working environments.

The main idea of nanosafety research at the Finnish Institute of Occupational Health is enhanced consideration for safety aspects from the early stages of the product development process, known as the ‘safe-by-design’ approach. The aim is to establish the health effects of new nanomaterials as early as possible, even before more large-scale industrial and consumer use, while risk management is extended to cover the entire life cycles of nanomaterials and products containing them. The effects of materials, particularly in terms of respiratory exposure, are assessed by *in vitro* tests based on cell cultures and, in the last resort, in *in vivo* exposure studies on test animals. Based on scientific evidence, it is also possible to set exposure limit values for nanomaterials.

Testing genotoxicity is an integral part of regulatory safety research. Genotoxic substances may cause cancer by damaging the DNA or affecting the cell division mechanisms. Some of the genotoxic effects may be indirectly transmitted by reactive oxygen radicals or ions released from the material. The genotoxicity tests currently available do not necessarily reveal the underlying mechanisms of the effects.

Since some nanomaterials may cause adverse health effects through many different mechanisms, a wide range of test methods are required to thoroughly establish their health effects. It is neither ethical nor economically possible to test all materials on animals, but test methods should make it possible to anticipate health hazards and determine the mechanisms related to adverse effects. Whenever possible, studies make use of the OECD Test Guidelines. The Finnish Institute of Occupational Health plays an active role in developing and validating new test methods.

Industries are already using a number of nanomaterials with different properties and product development is fast. More agile test methods are therefore required to ensure the safety of products and technologies placed on the market. Through development, test methods can either be simplified to save working hours and resources or enhanced to allow more parameters to be measured within the same test. Material toxicity studies require suitable fast, so-called *high throughput* methods based on cell cultures or co-cultures of several cell types, which make use of automation and increasingly sophisticated laboratory equipment and analytics software.

Advanced test methods produce more research results while data accumulated on the physicochemical properties and health and environmental effects of nanomaterials is being increasingly compiled into databases. Nanoinformatics aims to utilise the accumulated data resources in *in silico* studies assisted by databases and computer simulations for purposes such as classifying nanomaterials, creating algorithms that forecast health effects, and developing safe-by-design strategies. New approaches to assessing nanomaterial safety are developed by studying interactions between biological molecules and nanomaterials and combining various testing and modelling tools. The Integrated Approach to Testing and Assessment (IATA) aims to guide testing required for a new material so as to make it possible to demonstrate the likeliest adverse effect of the material and intended use concerned with as little testing as possible. In practical terms, the aim is to classify each nanomaterial in the same class with other materials with a similar mode of action (MOA), allowing the existing test results on other nanomaterials in the same group to be used in risk assessment. Besides physicochemical properties, classification also takes account of their characteristic adverse outcome pathways (AOP) and information about the likely exposure routes.

In silico methods could ideally streamline hazard assessment by eliminating the need to test all nanomaterials separately on animals or even cell cultures, as testing certain material properties or mechanisms of action chemically (*in chemico*) would suffice. In the future, AI-assisted computational methods may offer even more accurate forecasts than animal tests for the health effects of nanomaterials and be of significant help for assessing environmental impacts throughout a nanomaterial's life cycle.

The Finnish Institute of Occupational Health has strong cooperation networks with other European occupational health research institutes and the information produced as part of its research projects is also communicated to key stakeholders working with occupational health in both Finland and Europe. The European Commission has so far funded nanosafety research in several of its framework programmes.

The leading national funding body is the Finnish Work Environment Fund, which has recently supported research on the safety of carbon nanotubes, graphene and nanocellulose. National research has also focused on assessment of occupational exposure and development of risk management and measuring instruments needed in the workplace. The nano research projects currently ongoing at the Finnish Institute of Occupational Health are listed in Appendix 8.

Finnish Institute for Health and Welfare

The Finnish Institute for Health and Welfare conducts research into exposure to and health effects of ambient pollution at the population level. Its current research projects focus on emissions from transport and small-scale combustion of wood. Exposure to nanosized particles is mainly studied as part of other research projects relating to exposure and health hazards.

5.3 Research into nanomaterials and their safety in the Academy of Finland's funding activities

The Academy of Finland is an expert organisation in science and research that funds high-quality scientific research in Finland, acts as an expert in science and science policy, and strengthens the status of science and research. The Academy operates within the administrative branch of the Ministry of Education and Culture.

It supports high-quality, responsible and effective research in all fields of science and research and its utilisation for the good of society. In 2022, research funding amounts to EUR 468 million.

The tables below estimate the number of applications addressed to the Academy of Finland for funding research into nanomaterials and their safety and the Academy's funding for these areas. The table data was compiled by searching for key terms (about 170) relevant to nanomaterials research from public application descriptions. As the choice of key search terms has a significant impact on the results, the figures in the tables should be regarded as indicative estimates.

The number of applications addressed to the Academy is shown in Table 3. The 2010s was a very active period in applications made to the Academy for funding research related to nanomaterials, with about 100–200 applications relevant to this field submitted to the Academy every year. However, applications for nanomaterial safety research are submitted to the Academy at a clearly lower rate, as the average remains below ten per year.

Table 3. Funding applications to the Academy of Finland relating to research on nanomaterials and nanomaterial safety by year.

Year	2011	2012	2013	2014	2015	2016	2017	2018	2019
Applications relating to nanomaterials	183	177	179	179	178	209	163	125	144
Applications relating to nanomaterial safety	8	8	7	9	6	6	3	4	7

Table 4 shows the levels of funding granted by the Academy for research on nanomaterials and their safety. The statistics on funding decisions are listed by year of application. The distinct annual variation in the table figures is due to major programme-type funding decisions, such as centres of excellence in research, flagship projects and Academy programmes. At the annual level, about three to five per cent of the Academy's funding is allocated to nanomaterials research. The level of funding for nanomaterial safety research is clearly lower, but its share of funding is very close to that of applications.

Table 4. Academy funding decisions for research on nanomaterials and nanomaterial safety by year of application.

Year	2011	2012	2013	2014	2015	2016	2017	2018	2019
Funding for nanomaterials (EUR million)	15.7	18.4	16.9	20.8	11.1	27.8	9.7	21.3	9.4
Funding for nanomaterial safety (EUR million)	0.8	0.3	0.4	0.7	0.3	0.8	0.2	0.7	0.4

Academy funding received by different organisations between 2011 and 2019 is listed in Table 5. Aalto University has received the highest amount of funding for nanomaterials research by a significant margin. The University of Eastern Finland has received the highest share of funding for research on nanomaterial safety.

Table 5. Academy funding decisions for research on nanomaterials and nanomaterial safety in 2011–2019 by year of application. The funding decisions for the Tampere University of Technology have been combined with those granted to the University of Tampere due to their merger as Tampere University.

Organisation	Funding for nanomaterials (EUR million)	Funding for nanomaterial safety (EUR million)
Aalto University	57.3	0.0
University of Helsinki	19.4	0.5
Tampere University	17.4	0.7
VTT Technical Research Centre of Finland Ltd	11.8	0.0
University of Jyväskylä	10.6	0.0
University of Eastern Finland	9.5	2.2
University of Oulu	8.6	0.4
Åbo Akademi University	8.1	0.0
University of Turku	5.0	0.0
Lappeenranta–Lahti University of Technology	1.7	0.0
Finnish Institute of Occupational Health	0.7	0.7
Natural Resources Institute Finland	0.5	0.0
Geological Survey of Finland	0.3	0.0
Finnish Environment Institute	0.3	0.3

Table 6 shows funding by field of research in 2011–2019. The division into fields of research is based on the main field in the Academy's research field classification as reported by the applicants (https://www.aka.fi/en/research-funding/apply-for-funding/how-to-apply-for-funding/az-index-of-application-guidelines2/research-field-classification/). The bulk of funding for research relating to nanomaterials is allocated

to the fields of nanoscience and nanotechnology and materials science and technology. Some funding for nanomaterials research has also been granted for fields not shown in the table (totalling EUR 16.1 million), but the volumes of funding in these individual fields are fairly small (below EUR 0.3 million per field). The fields with the highest shares of funding for nanomaterial safety research are nanoscience and nanotechnology and systems biology and bioinformatics.

Table 6. Funding decisions by the Academy of Finland relating to research on nanomaterials and nanomaterial safety by primary field of research in 2011–2019.

Main research field	Funding for nanomaterials (EUR million)	Funding for nanomaterial safety (EUR million)
Nanoscience and nanotechnology	29.3	2.5
Materials science and technology	22.7	0.3
Physics	12.3	0.0
Optics, acoustics	11.5	0.0
Condensed matter physics	9.4	0.0
Physical chemistry	6.2	0.0
Chemistry	5.5	0.0
Biomaterials	5.4	0.0
Pharmacy	4.4	0.4
Inorganic chemistry	3.7	0.0
Electrical engineering and electronics	3.6	0.0
Polymer materials	3.6	0.4
Biomedicine	2.9	0.0
Biochemistry, biophysics	2.8	0.0

Main research field	Funding for nanomaterials (EUR million)	Funding for nanomaterial safety (EUR million)
Fuel cells, solar energy	2.0	0.0
Microbiology	1.7	0.0
Functional materials, semiconductors	1.5	0.0
Cellular and molecular biology	1.5	0.0
Wood and paper materials	1.2	0.0
Medical engineering	1.1	0.0
Biological and soft matter physics	1.1	0.0
Systems biology, bioinformatics	0.9	0.9
Environmental social science research	0.3	0.3
Environmental science	0.3	0.3
Other fields	16.1	0.0

SUMMARY

Finnish universities and research institutes carry out diverse materials and applied research aimed at creating functional materials, resource-efficient solutions and innovative initiatives for various needs of society. Finnish organisations also conduct valuable nanomaterial safety research on impacts on human health and the environment. There is significant research into fine and nanoparticles ranging from air quality to climate change. The European Commission is a key source of funding for research projects. Based on the analysis prepared for this review, annual funding provided by the Academy of Finland for research relating to nanomaterials accounted for 3–5% of its total funding during the period from 2011 to 2019. The share of funding granted by the Academy of Finland for nanomaterial safety research is very close to that of applications. The most important national source of funding for occupational safety research is the Finnish Work Environment Fund.

6 Current issues in nanomaterials

This chapter deals with a few topics relevant to nanomaterials, which are currently on the public agenda and may give rise to ideas and potential concerns. Section 6.1 focuses on titanium dioxide and its uses in different industries. The use of the substance will be subject to restrictions, which will also be reflected in consumer products. This section explores the reasons and background factors underlying the forthcoming changes. Section 6.2 deals with problems brought about by micro- and nanoplastics. The gradual degradation of plastics over time is known to result in microplastics, which may further break down into nanoplastics. Microplastics are widespread in the environment, causing growing concerns for both the environment and human health. The section covers the current understanding of their effects and relevant legislative initiatives. Section 6.3 examines product development involving nanomaterials and potential future challenges posed by novel materials. Nanotechnology can be used to create new types of materials, which can contribute to better achievement of solutions to societal problems and challenges. While innovations address the challenges involved in sustainability, climate and health, for example, they also lead to increasing complexity of materials and new potential safety concerns and regulatory challenges. Section 6.4 discusses the objectives of the European Union's European Green Deal and the strategies within its framework, with particular focus on the objectives of the Chemicals Strategy, and the actions proposed to solve climate and environmental challenges.

6.1 Titanium dioxide (TiO_2)

Titanium dioxide (TiO_2) is an interesting case study of the regulatory framework on chemicals. The case has shown that the regulation governing a chemical widely used in different sectors may be fragmented. At the same time, however, we have seen that it is possible to amend provisions at quite a fast pace in light of new information, with broad effects on other legislation and sectors.

The use of the poorly soluble titanium dioxide is widespread across industries, both in the conventional 'bulk' form and at the nanoscale. According to its REACH registration data, titanium dioxide is manufactured in or imported into the European Economic Area (EEA) at 1,000,000 tonnes per year (ECHA's Substance Infocard for TiO_2). Due to its whiteness, high opacity, brightness and colour endurance, the substance is used in paints, inks and toners, coatings and plastics. It is also used in cosmetics as a colourant and filler and in nanoform as a UV filter in sunscreen products. Food-grade titanium dioxide has been used as a food additive (E171) in sweets, pastries and

dietary supplements, in food contact materials and as a feed additive for colouring purposes. The E171 additive approved for food contact does not meet the definition of a nanomaterial, although it does contain nanoform particles. In medicines, titanium dioxide can be applied as an opacifier and colourant in oral solid and semi-solid products. The toy industry makes use of titanium dioxide in toys and toy materials, including coatings, chalks and powder coatings, clays and putties, and polymer materials. The writing instruments industry uses the substance in colouring pencils and crayons.

The regulatory framework governing titanium dioxide came onto the agenda in 2016, when a French authority responsible for chemicals law proposed a harmonised classification of the substance under the CLP Regulation as a carcinogen by inhalation in the strictest category 1 (or, more specifically, category 1B based on animal test data, as human epidemiological data did not provide a basis for classification in category 1A), covering all forms and sizes of the substance with the exception of fibrous forms or particles with modified surface chemistry. The substance did not have any prior classification based on health hazards. No reason was seen for its classification as carcinogenic through ingestion or dermal exposure or in terms of genotoxicity. The scientific Risk Assessment Committee (RAC) of the European Chemicals Agency assessed the proposed classification and arrived at a lower hazard category 2 in its opinion, as the evidence presented was not strong enough to warrant a higher category.

The classification established by the Commission was published in 2020 by Regulation (EU) 2020/217. The classification applies to titanium dioxide in powder form in which 1% or more of the particles have an aerodynamic diameter of ≤ 10 µm. Furthermore, substances placed on the market as fibres, as particles fulfilling the WHO fibre criteria, or as particles with modified surface chemistry should be evaluated to assess whether a higher category and additional routes of exposure should be applied. The harmonised classification has had to have been used since October 2021.

In 2017, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) stated that the use of titanium dioxide for food contact may potentially be linked to precancerous colon growth and called for further research. Within the framework of the food additives re-evaluation programme, the European Food Safety Authority (EFSA) re-evaluated the substance in 2016 and did not consider it a safety risk. Based on the research evidence provided by ANSES, the EU still saw no reason to change the 2016 evaluation in 2018. Nevertheless, France banned the use of titanium dioxide as a food additive at the national level as of January 2020. In 2021, EFSA further published another, exceptionally broad re-evaluation of titanium dioxide, applying its own guidance on risk assessment of

particles in nanoform for the first time. The evaluation indicated that genotoxic effects of titanium dioxide and its accumulation in the body could not be ruled out. As a result, it was decided to ban the use of titanium dioxide as a food additive on proposal by the European Commission, which adopted Regulation (EU)

2022/63 to this effect in January 2022. Due to its widespread use as a food additive, this will lead to considerable consequences for the food market.

Although titanium dioxide is prohibited as an additive in all foods, it will not be removed from the list of approved food additives, as the EU medicines law refers to food additives legislation. In order to allow the pharmaceutical market to replace titanium dioxide as a medical toner, the Commission has decided to revisit the issue in early 2024 following EMA's evaluation.

Titanium dioxide was authorised for use as a feed additive years ago. Similar to its use as a food additive, the use of titanium dioxide as a feed additive was prohibited for all animal species in the autumn of 2021 by Commission Regulation (EU) 2021/2090.

The repeal of the authorisation as an additive will also likely have a bearing on food contact materials, especially with regard to materials harmonised across the EU, such as plastics. The Commission has begun to investigate the status of titanium dioxide used in plastics.

It is fairly likely that the decisions made by the food sector, in particular, will have an influence on how titanium dioxide is regulated in cosmetic products, mainly in terms of oral or inhalation exposure. The use of titanium dioxide is currently allowed as a colourant (in bulk form), a UV filter (in bulk and nanoforms) and a filler (in bulk form). The substance must not be used in nanoform in products that may cause pulmonary exposure. The use of pigmentary titanium dioxide was already restricted by virtue of the CLP Regulation's classification by determining limits for safe concentrations of titanium dioxide in powder form in which 1% or more of the particles have an aerodynamic diameter of ≤ 10 µm in hair styling products and make-up cosmetics, and it must not be used in any other products that might cause exposure of the user's lungs (Regulation (EU) 2021/850).

Overall, the regulation of titanium dioxide in different sectors has underlined the weaknesses of the current, fairly fragmented approach with regard to substances widely used in different sectors. Such a way of operating wastes resources in terms of expensive toxicological, environmental or other impact assessments. Nevertheless, the situation is likely to improve as a result of the new EU Chemicals Strategy, as the

Commission is planning to move towards a more consistent approach by adopting the concept of 'one substance, one assessment' (EU Commission, 2020a). This initiative aims to improve the efficiency, effectiveness, consistency and transparency of chemicals safety assessments across legislation.

6.2 Micro- and nanoplastics

Micro- and nanoplastics are on the agenda in many forums due to their potential adverse effects on the environment and human health. Microplastics may be formed in the environment as a result of gradual degradation of larger pieces of plastic. They may break down further into nanosized particles (Wayman & Niemann, 2021; Gigault et al., 2021). Microplastics are also intentionally added to some products to achieve a certain property or functionality. At least one nanosized plastic is being used in some cosmetic products within the EU.

Microplastics are very slowly biodegradable particles consisting of mixtures of plastic polymers and additives. While microplastics have yet to be consistently defined, the term is generally used to refer to particles of less than 5 mm in size. Plastic particles smaller than 100 nm, in turn, are classified as nanoplastics (EFSA, 2016).

Potential sources of release of intentionally added microplastics include fertilisers, plant protection products, biocides (substances used to control harmful organisms), cosmetics, washing and cleaning agents, paints, coatings and printing inks, as well as medicinal products. However, the amount of microplastics in the environment is affected most by particles released from larger plastic products as a result of wear or over time. These sources of release include vehicle tyre dust, infill materials used in artificial turf pitches, washing of synthetic textiles, and plastic bags and bottles. As it is no longer possible to get rid of microplastics once they are released into the environment, their amount in the environment is cumulative.

The micro- and nanoplastics arising from wear and degradation form heterogeneous groups of particles of varying sizes. As nanoplastics differ from microplastics in terms such as size, reactivity, bioavailability and mobility, they should be distinguished from microplastics. Compared with manufactured nanomaterials, nanoplastics are also much more heterogeneous in terms of composition, surface properties and morphology (Gigault et al., 2021).

In the environment, microplastics have been found in sea and fresh waters, sediments, wastewater, soil, and indoor and outdoor air. Waterborne microplastics may be carried long distances, eventually ending up on seashores and in deeper

layers of sediment. Microplastics are released into the soil from sewage sludge, which contains the bulk of microplastics entering wastewater treatment plants. No precise calculations are available on airborne particle deposition to the environment, but it can be a significant source. Research indicates that concentrations of airborne microplastics are higher in urban environments (Prata et al., 2018).

Microplastics have been found widely in marine organisms and animals at different levels of the food chain, known as ‘trophic levels’. When ingested, microplastics may cause blockages and damage in marine animals. They may also cause starvation by reducing the absorption of consumed food and creating a false feeling of fullness. Chemicals added to plastics or contaminants that accumulate from the environment may also have harmful effects. Microplastics accumulated in marine organisms may be transferred through the food chain to fish, seals, etc., and further on to food-producing animals through feed made from fish.

The presence of microplastics in the environment also indicates the presence of nanoplastics. However, nanoplastics were not found in a marine environment until 2017 because methods of detecting and quantifying environmental nanoplastics have only been developed recently (Wayman & Niemann, 2021). Experimental studies on nanoscale polystyrene particles have shown that different organisms, such as water flea, molluscs, zooplankton and algae can actively ingest nanoplastic particles or absorb them onto their surfaces. However, current understanding of the potential hazards and risks involved in nanoplastics in the environment is still incomplete (Gigault et al., 2021).

People may be exposed to micro- and nanoplastics on a daily basis through food and the air they breathe, as well as through skin contact. Microplastics have been found around the world in several everyday foods and beverages, but Finnish sources of intake have only been examined in one preliminary study on microplastics contained in drinking water. The study carried out by the Finnish Environment Institute (SYKE) found only a few plastic particles per litre in tap and bottled water (Sillanpää et al., 2018). The largest individual concentrations of microplastics have been found in molluscs and crustaceans, but also in bottled water, honey, beer, dairy products, sugar and common salt (EFSA, 2016; Prata et al., 2020; Pironti et al., 2021; Zarus et al., 2021). Microplastics may also enter food or drink from take-away packages and plastic containers due to incorrect manufacturing methods or during storage (Du et al., 2020; Li et al., 2020). Sources of microplastics in indoor air include fleece and synthetic clothing, soft furnishings and upholstery fabrics (Zarus et al., 2021).

In light of current knowledge, it is unlikely that microplastic particles of cosmetic products penetrate undamaged skin (BfR, 2019). Nanosized plastic particles may potentially be absorbed through the skin, but there is little evidence at present to

suggest that particles over 100 nm in size could penetrate healthy skin (Lehner et al., 2019). On the other hand, if nanoplastics intentionally added to a cosmetic product meet the definition of a nanomaterial under the Cosmetics Regulation, they are subject to the safety provisions applicable to nanomaterials. Measurements of indoor and outdoor air indicate that the concentrations of microplastics found in the air are likely too low to be harmful to human health (Lehner et al., 2019).

The most significant pathway for human exposure to microplastics is the digestive tract (Lehner et al., 2019). As the bulk of all microplastic particles ingested are removed in faeces, less than one per cent are estimated to be able to be absorbed through intestinal mucosa into our bodies (EFSA, 2016). However, it is suspected that smaller nanoparticles are absorbed more readily into the circulation through intestinal and pulmonary mucosa (EFSA, 2016; Ragusa et al., 2021; Yee et al., 2021). In humans, microplastics have been found in the lungs, placenta and blood (Amato-Lourenço et al., 2021; Ragusa et al., 2021; Leslie et al., 2022). In faeces studies, microplastics have been found in the samples of all subjects (Schwabl et al., 2019). A small sample study collecting samples from newborn infants, one-year-old babies and adults found the highest concentrations in the faeces of one-year-old babies (Zhang et al., 2021). Babies may be exposed to micro- and nanoplastics while crawling on floors and through plastic toys and cutlery.

Little is currently known about the effects of micro- and nanoplastics on human health and data on potential adverse effects is based on laboratory studies. Animal tests and cell models indicate that potential toxicological effects include oxidative stress, cell toxicity, increased inflammation, metabolic dysfunctions and transfer of plastics into tissues. However, exposure studies on laboratory animals have used very high microplastic concentrations and virgin plastics, which does not match the usual human intake of microplastics. The toxicity caused by micro- and nanoplastics is influenced by the properties of plastic particles, such as size, shape, solubility, chemical characteristics, coatings applied to plastics, and functional groups, as well as chemicals and microbes that have accumulated on them from the environment. This particle diversity complicates research, as change in any single parameter may lead to a different physiological effect.

Evidence available to date on the potential effects of microplastics on human health is sparse and remarkably uncertain (SAM, 2019; SAPEA, 2019; WHO, 2019). Based on current knowledge, however, microplastic pollution does not at present pose any extensive risk to humans (BfR, 2019; Lim, 2021; SAM, 2019), but a reliable assessment of health risks requires further research on the levels and potential health effects of exposure. Workers exposed to dust containing micro- and nanoplastics in plastic manufacturing processes and in the synthetic textile industry, for example,

have exhibited respiratory symptoms and diseases (Prata et al., 2018; Zarus et al., 2021).

Even less is known about the effects of nanoplastics on human health, since they have not been studied until recently. The Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) recently identified nanoplastics as an emerging concern, noting the need for further research (SCHEER, 2022). Despite the increasing number of research projects, no suitable and validated analytical methods are currently available for sampling, identification and quantification of micro- and nanoplastics. Information is also required on the levels and health effects of exposure for risk assessment purposes.

In order to manage the risks arising from microplastics, the European Chemicals Agency (ECHA) published a proposal to restrict intentionally added microplastics by virtue of the REACH Regulation in January 2019 (https://echa.europa.eu/hot-topics/microplastics). If adopted, the proposal is expected to reduce the release of microplastics intentionally added to products within the EU by up to 400,000 tonnes over the next 20 years. The restriction proposal would prohibit microplastics in applications such as agriculture and horticulture, cosmetics, detergents, medical devices, paints and coatings, as well as medicines. The Commission is expected to present its proposal to amend the REACH Regulation to the REACH Committee (Monitoring Committee) during the spring of 2022. Following the Committee vote on the restriction proposal, the European Parliament and the Council will review the proposal before the restrictive measure is ready for adoption.

In February 2018, a citizens' initiative was launched in Finland to ban the use of microplastics in cosmetics by law, and the initiative proceeded to Parliament in the autumn of 2019. Although both the Ministry of the Environment and the Ministry of Social Affairs and Health, as well as several stakeholders, noted that the restriction would be warranted in substantive terms, they did not support the citizens' initiative, as it would have overlapped with the REACH restriction proposal. The Parliamentary Environment Committee likewise considered that the drafting of the pending EU legislation was at the time a sufficient legislative measure to address the adverse effects of microplastics. (Report of the Environment Committee, 2019; *in Finnish*.)

The restriction on microplastics issued by virtue of the EU's REACH Regulation does not cover intentionally added nanoplastics if the minimum size of microplastics is set at 100 nm. Furthermore, the REACH Regulation includes an exemption for registration of polymers. Although this exemption is currently being reviewed, it remains to be seen whether any potential new registration obligations will also cover the types of polymers that impact plastic pollution the most. A recent article discusses whether nanoplastics should be regulated as microplastics, polymers or

nanomaterials (Monikh et al., 2022). Its authors conclude by suggesting that the most practical solution would be to include nanoplastics in the regulatory framework governing nanomaterials due to the vast amount of work already done to modify the REACH Regulation relevant to nanomaterials.

6.3 Next-generation nanomaterials

Existing nanomaterials generally refer to so-called passive materials, which have already been available on the market for a long time or are nanoforms of pre-existing materials or substances. The passive property means that the nanomaterial is stable and that its presence alone is enough to add value to the application for which it is used. Publications predicting the future of nanomaterials have outlined next-generation nanomaterials and their properties such that their complexity increases with each new generation, and that they will include active nanostructures and nanosystems in fields such as biotechnology (Tour, 2007; Subramanian et al., 2010; Roco, 2011). The concept of 'next-generation nanomaterials' has never been defined very precisely; nor is there any commonly agreed terminology for them. At the same time, however, they have been invoked to demand that the legislative framework for information and testing requirements and risk assessment should also take account of future requirements. For these reasons, the European Chemicals Agency commissioned a study with a view to collecting and analysing the definitions of 'generations' of nanomaterials and proposing refinements for these, while also exploring whether any second- or higher-generation nanomaterials are available on the EU market (ECHA, 2019).

The analysis of the study indicates that the earlier concepts of 'generations' were introduced to highlight the possibilities of nanotechnology and attract investments, rather than with regulatory purposes in mind. As a term, 'nanomaterials' referred to nanotechnology products, including objects, such as nanostructures and nanostructured materials, although these fall outside the scope of the Commission's definition of nanomaterial.

The study proposes that the previous concepts of generations be refined to take account also of the concepts of energy, work and thermodynamic equilibrium. According to the proposal, first-generation nanotechnology applications cover passive nanomaterials, nanostructures and nanostructured materials. The constituent parts of these materials are in the nanoscale, exist in thermodynamic metastable equilibrium with the surrounding system and do not involve any changes beyond agglomeration or aggregation.

Second-generation applications are (re)active nanomaterials, nanostructures and nanostructured materials. These materials, with constituent parts in the nanoscale, are responsive to stimuli and absorb, receive or harvest energy from their surroundings and transduce it to engage in a variety of non-equilibrium activities, such as motility, growth or replication. This often results in a change in the system's energy level and conformation/molecular structure.

Third-generation applications are multifunctional nanosystems composed of stimuli-responsive nanoparticles and nanostructures. These are the building blocks for constructing complex chemical reaction networks and synthetic life-like systems and materials. They are characterised by an increased integration between organic and inorganic components. Multifunctional nanosystems aim to mimic living cells and may use some of their components, such as proteins and nucleic acids. At this level, nanotechnology converges with synthetic biology.

The study indicates that 48 active (second-generation) nanomaterials, nanostructures or nanostructured materials are already on the EU market or expected to enter the market within the next five to ten years. These are mainly medical and electronics applications, such as gold silica, superparamagnetic iron oxide nanoparticles and quantum dots. A further eight third-generation nanotechnology applications were also identified, but these were still at the research phase.

Advanced materials

'Advanced materials' refer to a very heterogeneous group of new or performance-enhanced materials. Advanced materials are very diverse and often multicomponent materials, which may combine organic and inorganic components. They may contain or consist of nanosized materials, which may be important in terms of their 3D structure. Advanced materials apply rational design processes to achieve and optimise material properties by means of a variety of techniques to organise and build even individual molecules. They are used in high-performance applications and are regarded as high-value products. They have considerable potential for application in various sectors, such as renewable energy, electro-mobility, digitalisation, healthcare or resource conservation. They are considered important enablers of technological innovations in applications that promote the circular economy and energy transition, for example.

The field of advanced materials overlaps with nanomaterials as an area of research and nanomaterials are considered a sub-group of advanced materials. There is currently no single consensus definition for 'advanced materials'. German chemicals safety authorities have produced a report aimed at identifying advanced materials

relevant to chemicals safety (UBA, 2020). The report divides advanced materials into clusters to facilitate consideration and gain an overview. The clusters of materials are listed below:

- biopolymers (DNA-, RNA-, protein-, lipid- and sugar-based);
- composites (macroscopic, fibre-reinforced, particle-reinforced, and hybrid materials, i.e. combinations of organic and inorganic materials);
- porous materials (microporous, mesoporous, macroporous);
- metamaterials (photonic, acoustic, electromagnetic);
- particle systems (quantum dots, supraparticles, graphene, nanoflowers);
- advanced fibres (organic, carbon-based, inorganic);
- advanced polymers (electro-active, magneto-active, electrorheological fluids, self-repairing polymers, copolymers);
- advanced alloys (metal alloys comprising more than two components with at least two components that have a large share in the final material).

Smart nanomaterials

The so-called smart nanomaterials represent a certain type of innovative materials, which are often composed of multiple components and can respond to stimuli. Smart materials can be considered as part of a broader class of advanced materials. Based on the classification of the 2019 ECHA study, smart nanomaterials are second- and third-generation nanotechnology applications (Gottardo et al., 2021). Besides having complex structures, smart nanomaterials are dynamic and can transform in response to external stimuli. Such external stimuli may include pH, temperature and light changes, or there may be multiple stimuli (Gottardo et al., 2021). Smart nanomaterials provide a basis for many new applications, including wearable and printed electronics, nanophotonics, quantum computing, artificial intelligence, optogenetics, smart coatings and thin films. They can be used in many industrial sectors, such as agriculture, medicine, cosmetics and food packaging.

Challenges involved in future nanomaterials

Although the regulatory status of nanomaterials has been clarified by means such as revising the REACH Regulation, it is unclear whether the current chemicals safety legislation also covers future nanomaterials, as the current information requirements for substances were developed with first-generation passive nanomaterials in mind. At the same time, however, it is recognised that the current regulatory frameworks generally appear adequate and appropriate to take account of the safety of advanced materials and smart nanomaterials. (UBA, 2021; Gottardo et al., 2021.)

Some of the novel materials can be expected to entail risk assessment and regulatory challenges similar to those affecting nanomaterials. The potential risk to human health or the environment is not necessarily caused by their chemical properties alone, but also by their physical and morphological properties. A well-known example of a hazard relating to morphology is asbestos, which showed that a fibrous form combined with high biopersistence may lead to a carcinogenic effect, which is difficult to predict by means of conventional toxicological test methods. In other words, the current chemicals legislation, which applies to substances and mixtures, fails to cover hazardous morphological properties to a sufficient extent. Some advanced materials may also pose significant challenges for sustainable development, including recycling and waste treatment. (UBA, 2021.)

One of the challenges in current legislation is the applicability of existing definitions to novel materials. ECHA's study (2019) analysed the extent to which the definitions of 'substance', 'mixture' and 'article' set out in the REACH and CLP Regulations are appropriate for next-generation nanotechnology applications. The study found that most second-generation nanomaterials could be identified as the nanoforms of a substance. For certain nanocomposite structures, however, there may be room for interpretation as to whether these are substances or articles. A similar conclusion on the interfaces between definitions was drawn for advanced and smart materials (UBA, 2021; Mech et al., 2022). It has therefore been proposed that the guidance for interpreting the term 'article' as defined in the REACH Regulation should be complemented with examples of nanomaterials, including smart nanomaterials. Moreover, the identification and characterisation parameters of the REACH Regulation fail to capture the dynamic dimension (responsiveness to stimuli) of second- and third-generation nanotechnology applications, as they were created to identify and characterise the solid nanoparticles of substances (ECHA, 2019; Gottardo et al., 2021). Another significant challenge, albeit not exclusively relevant to nanomaterials, is the availability of test methods suitable for safety assessment. It is therefore necessary to develop test methods on a continuous basis.

Due to the complexity and variety of materials, it is important to reach a consensus on the definitions of smart and advanced nanomaterials for regulatory purposes (UBA, 2021; Mech et al., 2022). This would be vital to clarify the scopes of application of legal instruments. The German Environment Agency (UBA) has developed an unofficial definition for advanced materials (UBA, 2021), while the ISO/TC 229 Committee (Nanotechnologies) is discussing the definition of advanced materials.

Challenges involved in advanced materials have been identified by the OECD, among others, as its Working Party on Manufactured Nanomaterials has adopted advanced materials as part of its work programme. Issues of advanced materials have also been included in a research project commissioned by the German Environment Agency and funded by the Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMU). Three international conferences have been organised in 2019–2021 in cooperation within the OECD (UBA, 2022).

6.4 Safe- and sustainable-by-design nanomaterials

Europe is pursuing a sustainable future and economic transformation in keeping with the European Commission's European Green Deal (EU Commission, 2019b). The plan implements the Sustainable Development Goals of the UN 2030 Agenda for Sustainable Development as well as the Commission's other policy initiatives. The European Green Deal aims towards a climate-neutral, zero-pollution and sustainable economy and society, and protection of the European natural capital, laying out a number of policy responses to achieve these objectives. The policy responses include the Circular Economy Action Plan, the European industrial strategy and the Zero Pollution Action Plan for Air, Water and Soil.

The policy responses also cover the Chemicals Strategy for Sustainability, which describes action towards a zero-pollution and toxic-free environment (EU Commission,

2020a). The strategy notes that chemicals are important for human wellbeing and the green and digital transition of the European economy and society while also recognising the urgency of responding to the health and environmental challenges posed by the most harmful chemicals. One of the key objectives of the strategy is to develop criteria for safe- and sustainable-by-design (SSbD) chemicals. This objective aims to take account of the safety and sustainability of a chemical, material or product at the early stages of the design process, instead of retroactive mitigation of its effects

on human health and the environment by means of risk management and control. Further benefits identified for the concept include faster and more cost-efficient product development and innovation, as well as safer and functional products.

The ‘safe-by-design’ concept covers assessing safety at the earliest possible stage of the innovation process. The concept aims at an iterative process, where safety assessment is integrated into product development. In this context, ‘safety’ means safe materials and products, safe production, and safe use and waste stages (JRC, 2021).

The ‘safe and sustainable by-design’ (SSbD) concept promotes a holistic approach that integrates safety, circularity and functionality of chemicals, materials, products and processes throughout their entire life cycle, minimising their environmental footprint (JRC, 2022).

Sustainability is more complicated to assess than safety, as it entails characterisation of several aspects of the environmental, economic and social dimensions. As a concept, sustainability is also less well defined and there is no current consensus on what it means. The EU is developing safe- and sustainable-by-design criteria. Although sustainability as a concept also covers socioeconomic impact assessment, these are not yet examined as part of the EU’s work on the criteria (JRC, 2022).

Rather than being limited to nanomaterials, the development of SSbD criteria covers chemicals in a broad sense. However, this work has drawn on the information and tools already collected within EU projects focusing on the design of the manufacture and use of safe nano-enabled products (including NANoREG, NanoReg2, ProSafe).

Another key source of information is the work carried out within the OECD on safe innovation of nanomaterials (OECD, 2020). There are still a number of ongoing Horizon 2020 projects (e.g. NanoRigo, SUNSHINE, SAbyNA), which are expected to contribute to the development work. Projects dealing with the subject are also included in the Horizon Europe Framework Programme for Research (JRC, 2021). Among these, a network cooperation project of European authorities entitled ‘Partnership on the Assessment of Risks from Chemicals’ (PARC) supports the work of the European Commission by developing risk assessment tools for a circular economy built on safe chemicals and by implementing the SSbD concept. The design of SSbD products is geared towards identifying the risks and uncertainties for people and the environment as early as possible during the innovation process and product life cycle (Finnish Government, 2022).

Some tools are already available for assessing environmental sustainability. The life cycle assessment (LCA) approach analyses the environmental impact of products, from sourcing raw materials to the waste stage. Examples of noteworthy environmental impact categories include global warming, freshwater eutrophication, depletion of natural resources, toxicity, air pollution, and use of renewable and non-renewable energy. While the LCA is considered a suitable tool for assessing the environmental sustainability of nanomaterials and nano-enabled products, further information is required to describe nanomaterial releases and environmental exposure, for example (Nizam et al., 2021; Lee et al., 2022). Smart nanomaterials are likely to introduce their own set of challenges and their special characteristics should be taken into account in safety and sustainability assessment (Gottardo et al., 2021; Mech et al., 2022).

SUMMARY

Current issues in nanomaterials include the use of titanium dioxide in different products; health and environmental concerns arising from micro- and nanoplastics; new types of safety and regulatory challenges brought about by increasingly complex nanomaterials; and EU action to address health and environmental challenges posed by chemicals. Titanium dioxide is widely used in various products in both bulk and nanoform. The poorly soluble substance has been considered safe, but its potential adverse health effects have given rise to the need for regulatory action. The European Commission prohibited its use as a food and feed additive, as its genotoxic effects and accumulation in the body could not be ruled out. These decisions will have a wide impact on many sectors. The release of micro- and nanoplastics into the environment from different sources may have adverse effects on both the environment and human health. Further information is required on the levels and health effects of exposure for risk assessment purposes. There are plans to restrict the use of intentionally added microplastics at the EU level. As a result of nanotechnology innovations, materials used for different applications will become increasingly complex. This development poses challenges in terms of safety research and regulation. The strategies adopted as part of the EU's European Green Deal aim at a sustainable future and a toxic-free environment. One of the key objectives of the strategy is to develop criteria for safe- and sustainable-by-design chemicals.

7 Closing words

Nanomaterials and nanotechnology are used because the properties of substances can often change radically in nanoform. As the particle size decreases, its mass shrinks while its surface area grows, increasing its area-to-volume ratio. A large surface area is linked to reactivity. In nanoform, quantum effects enter the stage alongside the laws of classical physics. A particle's properties can be altered by adjusting its size. Harnessing the properties brought about by the nanoscale has enabled development of new inventions and applications.

The narrative of the development of nanotechnology includes the concept of manipulation of matter at the atomic level, created by the US physicist Richard Feynman in the 1950s. However, the golden age of nanoscience and nanotechnology only began in earnest in the 1980s with the discovery of fullerene, also known as 'carbon balls' or 'buckyballs', and carbon nanotubes and as a result of the development of tools allowing working at the nanoscale, such as the tunnelling microscope. The range of tools available also includes the Atomic Layer Deposition (ALD) method developed and patented by a team led by Tuomo Suntola in Finland in 1974, which makes it possible to create coatings the thickness of only one atom layer in a precisely controlled way (Nanowerk). This has enabled more efficient and smaller microprocessors and memory circuits and, consequently, the development of smartphones, for example (Wikipedia).

The field of nanotechnology is developing rapidly and involves revolutionary opportunities. The latest innovations include graphene, a substance with a thickness of one carbon atom layer, which was known to exist in theory but was not isolated until 2004. A major project of the European Union is currently exploring various potential applications for graphene, which are expected to offer significant technological and commercial breakthroughs. Some experts predict that graphene applications may have an impact at such a large scale that nothing comparable has been seen since the industrial revolution. At the same time, new and innovative bio-nanomaterials such as nanocellulose offset the declining demand for old successful bulk products such as cellulose. Finnish universities and research institutes carry out diverse materials and applied research aimed at creating functional materials, resource-efficient solutions and innovative initiatives for various needs of society.

Similar to any other new scientific development, the use of nanotechnology and nanomaterials is not to be approached without some caution. Key issues include safety-related health and environmental considerations. However, the fact that a substance is in nanoform does not automatically mean that the nanomaterial is hazardous, or that its use would involve risks. To date, nanoform has been found to

be linked to the harmfulness of substances in a few isolated cases. Carrying out research and sharing information will help understand the risks brought about by nanomaterials and develop safe products. Further information is still required on long-term effects on human health and the environment in particular. While Finnish organisations are engaged in commendable nanomaterial safety research, the reductions in government funding for sectoral research institutes made in recent years have endangered the standard of national expertise in nanotechnology. This situation will also be reflected in the work carried out by public officials if the necessary expertise is not available for national issues.

The regulatory framework for nanomaterials must keep abreast of developments and the methods of safety research must be suitable for nanomaterials. The growing range of various novel materials will make challenges even more complicated. At the same time, however, regulation should also enable new innovations. The safe- and sustainable-by-design concept could make for a suitable approach where safety questions are posed in the early stages of innovation processes while balancing safety and sustainability.

Widespread adoption of new innovation is not possible without social acceptance. Communications play a major role in addressing potential consumer concerns. Communications should be fair and evidence-based. Dialogue and openness about the advantages and disadvantages of nanomaterials should play a key role.

8 Appendices

8.1 Ongoing research projects

VTT nano research projects:

- INN-PRESSME, 1 January 2021 to 31 January 2025 (EU H2020 project no. 952972). VTT Technical Research Centre of Finland Ltd coordinates a four-year project to create a European ecosystem based on the service business. It aims to use new bio-nanomaterials (including nanocellulose) as additives in the production of packaging, energy and other consumer products (http://www.inn-pressme.eu)

- Graphene Flagship Core 2, 1 April 2018 to 31 March 2020 (H2020 project no. 785219). VTT develops graphene-based applications of printed electronics for various functional products, such as printed functionality in textiles. ((https://graphene-flagship.eu/)

- FinnCERES Flagship, 1 May 2018 to 31 December 2024 (Academy of Finland). Aalto University and VTT have teamed up to develop new sustainable bio-based materials and their use in new applications and to substitute for plastics. (https://www.finnceres.fi/)

- FireCellCoat, 1 January 2020 to 31 December 2022 (Bioeconomy in the North/Ministry of Agriculture and Forestry). The project develops sustainable, green fire-retardant coatings for wood materials. VTT is exploring the applicability of a nanocellulose-pigment coating for this end use. The aim is to improve the fire-resistant properties of nanocellulose by means of chemical modification using phosphorous compounds. (https://firecellcoat.com/)

- MIRIA, 1 June 2022 to 30 May 2026 (Horizon Europe 2021). VTT develops bio-based nanoparticles and explores the application of these and other antimicrobial nanoparticles to nonwoven textiles as coating dispersions. Demo materials produced at the large scale are tested in both laboratory and hospital settings.

Nano research projects of the Finnish Institute of Occupational Health:

- PlasticHEAL, 1 April 2021 to 31 March 2025 (EU H2020 project no. 965196). The Finnish Institute of Occupational Health is involved in studying the health effects of nanoplastics. (https://www.plasticheal.eu)

- SAbyNA, 1 March 2020 to 29 February 2024 (EU H2020 project no. 862419). The Finnish Institute of Occupational Health is involved in developing a Safe-by-Design guidance platform. (https://www.sabyna.eu)

- GrapHazard, 1 January 2021 to 30 March 2023 (Finnish Work Environment Fund/Safera project no. 200338). The research project of the Finnish Institute of Occupational Health aims to assess the hazards of graphene-based nanomaterials used in energy production and storage. (https://www.ttl.fi/en/research/projects/hazard-characterization-graphene-based-nanomaterials-energy-production-and-storage-graphazard)

- Graphene Flagship Core 3, 1 April 2020 to 30 September 2023 (EU H2020 project no. 881603). The Finnish Institute of Occupational Health explores graphene exposure in working environments and the health effects of exposure using biomonitoring studies. (https://graphene-flagship.eu/)

- NanoInformaTIX, 1 January 2019 to 28 February 2023 (EU H2020 project no. 814426). The Finnish Institute of Occupational Health participates in development of a risk management tool. (https://www.nanoinformatix.eu)

- NANORIGO, 1 January 2019 to 28 February 2023 (EU H2020 project no. 814530). The Finnish Institute of Occupational Health is involved in development of risk management and governance of nanotechnologies. (https://www.nanorigo.eu)

- PARC, 1 May 2022 to 2029 (EU Horizon Europe). The Finnish Institute of Occupational Health participates in a partnership programme for chemicals risk management, which will form an EU-wide expertise network to support public authorities addressing current, emerging and new challenges of chemicals safety. (https://www.anses.fr/en/content/european-partnership-assessment-risks-chemicals-parc)

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