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Author:

OPMCSA - Intern - Shinji Kihara

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Nanotechnology regulation in Aotearoa New Zealand: Current developments and comparison with overseas regulations

Shinji Kihara

Intern with the Office of the Prime Minister's Chief Science Advisor (*Kaitohutohu Mātanga Pūtaiao Matua ki te Pirimia*)

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This document serves as a review of the regulation framework around nanomaterial use in Aotearoa New Zealand. It aims to summarise the regulations and guidelines found in Aotearoa New Zealand and overseas (Australia, the European Union (EU), the United States (US), Canada, Japan). It assesses the extent of alignment between the Aotearoa New Zealand regulatory framework and international examples. Timelines are provided for the development of regulations, guidelines, and standards published by these international institutions, along with a detailed discussion comparing it to the European and American systems and the guidelines published by the Organisation for Economic Co-operation and Development (OECD) and International Organisation for Standardisation (ISO).

Acknowledgement

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Overview

This work approaches the regulatory question of the safe use of nanotechnology and develops its discussion upon the following:

- Nanoforms do not make materials intrinsically hazardous.
- Materials in nanoform (nanomaterials) **may** pose different risks compared to their larger analogues (bulk materials).

This work first assessed whether the current regulatory framework is able to distinguish between the nanomaterials in different types of consumer products and non-nanoform products. Furthermore, this work compares the following aspects of nanomaterial management/regulation between Aotearoa New Zealand and selected international examples (an illustrative comparison can be found in Table 1):

1. Definition – whether the regulations or guidelines provide a definition (or a working definition) for nanomaterials and related terms.
2. Nano-specific labelling – whether a mandatory labelling scheme exists to identify the presence of nanomaterials in consumer products.
3. Nano-specific notification – whether manufacturers or importers are obliged to declare the presence of nanomaterials in the product to a regulating agency.
4. Guidance on toxicity evaluation or risk assessment – whether there is guidance on obtaining relevant information prior to submission for pre-market safety assessments.

Aotearoa New Zealand's regulations for cosmetic products (managed under the HSNO Act and Cosmetic Products Group Standard) align strongly with most of the selected international examples – in particular with the EU, regarding definition, labelling scheme, and a compulsory notification system. Australia, the US, and Canada implement a similar approach, with the exception of labelling schemes. However, guidance on safety assessment is not present.

For other types of non-cosmetic products, many regulatory aspects were **not** present:

- **Drugs** – Definitions of nanomaterials or nanomedicine are unspecified. Current guidance requires products with nanomaterials (or created with 'nano-tech') to be subjected to safety assessments by the Medicine Assessment Advisory Committee. These safety assessments are required even if Medsafe concludes that the application for registration includes sufficient data to attest to the safety, quality and efficacy of the medicine, and that the benefits outweigh the risk of harm to the patient. However, there is no nano-specific risk assessment described within the guideline or in any publicly available source.
- **Biocidal products** – Nano-specific notification is not mandated for substances regulated under the HSNO Act (which also covers e.g., common/industrial chemicals, pesticides, paints, veterinary medicines). Furthermore, a nano-specific definition, labelling, and guidance are not present. However, these substances are still subject to approval from the NZEPA whether or not the products contain nanomaterials. For this assessment, the product composite information (which would include nanomaterial properties) is required. The recent amendment in safety data sheet (SDS) requirement (October 2020) incorporated 'particle characteristics' to be one of the parameters to

report (for solids) which can be an alternative pathway to recognise the presence of nanomaterials, provided that the parameters are measured reliably.

- **Food products** – The Food Standards Australia and New Zealand (FSANZ) website provides a preliminary definition of nanotechnology, while nano-related terminology is used throughout the recent risk assessment guidelines published by the FSANZ in 2014. There is no notification system implemented, unlike the EU and the US. Currently, no mandatory labelling scheme has been adopted by agencies in Aotearoa New Zealand or any of the international examples evaluated in this work.
- **Common/industrial chemicals** – Like biocidal products, these are managed under the HSNO Act. Substances containing nanomaterials are not subject to mandatory notification, although approval is still required from the NZEPA. Nano-specific definition, labelling and guidance are not present. Definition and guidance are included in the regulatory framework adopted in other places such as Australia, the EU, US, and Canada. Amendment to SDS requirement (October 2020) also applies to these products, thus the nanomaterials can be monitored with an alternative pathway with reliably measured particle characteristics.

Notably, there is a lack of nano-specific regulation on drug products internationally. However, the European Commission published a white paper in 2019, suggesting the implementation of nano-specific regulations on therapeutic products in the near-future.[1]

Recent regulatory development

Regulatory development in this field is anticipated in the coming years. In the last regulatory review conducted in Aotearoa New Zealand by Moore and Gavaghan in 2011 (hereafter referred to as Otago report (2011))[2], the main focus was to determine if the regulatory framework then was able to recognise nanomaterials as a 'new' substance compared to their bulk analogues. Recent findings from nanotoxicology increasingly support the idea that physicochemical properties (e.g. size, shape, and surface coating) play a critical role in determining the nature and severity of risks imposed by some nanomaterials, and overseas regulatory and guidance development reflects this point. A few examples include:

- **EU** – Cosmetics (Regulation (EC) No 1223/2009), biocides (Regulation (EU) No 528/2012), food (Regulation (EU) No 2015/2283), and common/industrial chemicals (Commission regulation (EU) 2018/1882 amending Regulation (EC) No 1907/2006).
- **US** – substances (including general/industrial chemicals and pesticides) which contain nanomaterials are to be reported to the USEPA for the products managed under the TSCA Act (RIN 2070-AJ54).

It is worthwhile noting that a recent piece of legislation in the EU (Regulation (EU) 2019/1857, amending Annex VI to Regulation (EC) No 1223/2009 of the European Parliament and of the Council), incorporates restrictions which differentiate the risk of nanomaterials depending on their physicochemical properties. Specifically, the measure bans the use of titanium dioxide in cosmetic products, if an application leads to inhalation exposure of the titanium dioxide nanomaterials consisting of particles with airborne diameter <30 nm or with a specific aspect ratio. Additionally, this was also covered by the risk assessment guidelines and standardised tests by the EU within the last two years (2018–2020) (Table 3).

In Aotearoa New Zealand, if the nanoform of a substance is known to have hazardous properties where the bulk form does not, then that nanoform would be considered a hazardous substance, which requires separate approval under the HSNO Act. Likewise, for different nanoforms of substances which exhibit different hazardous properties (e.g. carbon black vs. carbon nanotube), separate approval is required for these two products (i.e. the legislative framework recognises these two products distinctively).

However, currently in Aotearoa New Zealand, there is no such legislation present that mandates the reporting of physicochemical properties nor a registration system which catalogues nanomaterials according to their physicochemical properties (except for cosmetics). Implementation of a track-recording system could allow regulators to assess nanomaterials more accurately and help identify nanomaterials for re-evaluation, should there be a surge in toxicological data on a nanomaterial with specific physicochemical properties. Importantly, if new toxicological profiles are discovered for specific physicochemical properties in the future, regulators would be able to trace only the registered nanomaterials of interest (i.e. not all registered nanomaterials), allowing them to focus only on the relevant products on the market.

For characterisation of nanomaterials to the level of information required on the European market, the capability of conducting standardised testing in Aotearoa New Zealand should be analysed carefully. For guidance on characterising the nanomaterials, Aotearoa New Zealand can look to the EU (part of safety assessment guidance), OECD and ISO (Table 2 and Table 3) for resources to establish standardised protocols locally.

Occupational guidance

Occupational guidance on use and handling of nanomaterials is **not** present in Aotearoa New Zealand.

Testing standardisation

This report highlights that current development overseas by the EU, OECD, and ISO focuses on guidance around the detection of nanomaterials in the environment, food matrices (by the EFSA whose remit covers food, feed, food-contact materials, and pesticides), and workplaces (Table 2 and Table 3).

Considerations

Based on the assessment above, it may be useful to consider the following points for future regulatory development in Aotearoa New Zealand:

- The definition of nanomaterials is not present in some of the legislation and guidance, although their existence is recognised (see Table 1). It would be useful to consider definitions adopted overseas and track any developments if definitions were to be incorporated in future.
- It would be useful to distinguish between nanomaterials and bulk materials in any future regulation, so that regulators are aware of the presence of nanomaterials on the market.

- It could be useful to track nanomaterials on the market and record their physicochemical properties (similar to the way that cosmetic products are monitored). This recording of data would enable efficient re-evaluation of a nanomaterial-containing product, should there be a surge in new scientific data.
- It may be valuable to discuss standardised testing further, including Aotearoa New Zealand's capability in testing, what data might be required, and how it aligns to European guidance.
- The precautionary principle may warrant the development of occupational safety guidance where exposure to nanomaterials, particularly via inhalation, is expected.

Table 1. Regulations in selected countries and geopolitical regions, with or without a definition or working definition for nanomaterials. 'Labelling' refers to regulatory obligations to indicate the presence of nanomaterials; 'Nano-specific notification' and 'Guidance on risk assessment' indicate if mandatory notification to regulating agencies for the presence of nanomaterials and associating guidelines on risk assessment exist, respectively. Note: the abbreviations used for Aotearoa New Zealand (NZ), Australia (AU), European Union (EU), United States (US), Canada (CA), and Japan (JP). The cross sign (✗) is colour-coded with red to highlight the aspects that are not present in NZ but are present in other country or region on the table.

Category	Definition						Labelling						Nano-specific notification						Guidance on risk evaluation					
	NZ	AU	EU	US	CA	JP	NZ	AU	EU	US	CA	JP	NZ	AU	EU	US	CA	JP	NZ	AU	EU	US	CA	JP
Cosmetics	✓[a]	✓[b]	✓[c]	✓[d]	✓[e]	✗	✓[a]	✗	✓[c]	✗	✗	✗	✓[a]	✓[b]	✓	✓[f]	✓[g]	✗*[3]	✗*[4]	✓[h]	✓[i]	✓[j]	✗	✗
Drugs	✗	✗	✓[k]	✓[l]	✓[e]	✗	✗	✗	✗	✗	✗	✗	✓[m]	✓[n]	✗	✓[o]	✗	✗*[3]	✓[p]	✗	✓[q]	✓[o]	✗	✗
Biocides*[1]	✗	✓[r]	✓[s]	✓[d]	✓[e]	✗	✗	✗	✓[s]	✗	✗	✗	✗[t]	✓[u]	✓[s]	✓[f]	✗	✗*[3]	✗	✓[v]	✓[w]	✓[j]	✗	✗
Food	✗*[2]	✗	✓[x]	✓[l]	✓[e]	✗	✗	✗	✗	✗	✗	✗	✗[y]	✗[y]	✓[t]	✓[m]	✗	✗*[3]	✓[u]	✓[u]	✓[z]	✓[m]	✗	✗
Common/industrial chemicals	✗[s]	✓[b]	✓[aa]	✓[d]	✓[e]	✗	✗	✗	✓[aa]	✗	✗	✗	✗	✗	✓ [aa]	✓[f]	✓[g]	✗*[3]	✗	✓[h]	✓[bb]	✓[j]	✗	✗

*[1] Biocide products are managed under the same regulatory framework as chemical pesticides, active chemicals, and paints, *etc.* under the HSNO Act.
*[2] The word 'nano' is mentioned in the guideline, though only a brief definition is provided for 'nanotechnology' on their website.
*[3] Voluntary notification system exists for a 'data collection' purpose for the Ministry of Economy, Trade, and industry (in Japanese).
*[4] Although not present, the guidance published by the SCCS (see footnote [i]) can be used as a reference.
[a] Cosmetic Products Group Standard 2017.
[b] Data requirements for notification of new industrial nanomaterials (working definition).
[c] Regulation (EC) No 1223/2009.
[d] Guidance for Industry: Safety of Nanomaterials in Cosmetic Products.
[e] Policy statement on Health Canada's working definition for nanomaterial
[f] RIN 2070-AJ54.
[g] Substances notification Regulations
[h] Guidance on testing health effects of nanomaterials.
[i] Guidance on the Safety Assessment of Nanomaterials in Cosmetics.
[j] Guidance on EPA's Section 8(a) Information Gathering Rule on Nanomaterials in Commerce.

[k] Reflection paper on nanotechnology-based medicinal products for Human Use.
[l] Drug Products, Including Biological Products, that Contain Nanomaterials Guidance for Industry (draft).
[m] Guideline on the regulation of Therapeutic Products in New Zealand - Obtaining approval for new and changed medicines and related products.
[n] Therapeutic Goods Administration (TGA) community Q&A on Nanotechnology and therapeutic products.
[o] Considering whether an FDA-Regulated Products Involves the Application of Nanotechnology.
[p] Guideline on the Regulation of Therapeutic Products in New Zealand Part 2: Obtaining approval for new and changed medicines (Medsafe)
[q] Guidelines are provided for individual nanomedicines on European Medicines Agency (EMEA) website (an example is given in the link).
[r] Nanotechnologies or pesticides and veterinary medicines: regulatory considerations (working definition).
[s] Regulation (EU) No 528/2012.
[t] HSNO Act Part 5 requires product composite information which would include nanomaterial properties, although not it is specifically mentioned.
[u] Agricultural data Guideline – special data (Part 10).
[v] Regulatory Guidelines for chemistry and manufacture.
[w] Dedicated risk assessments for nano-biocides are required, referencing a number of guidance published by European Chemicals Agency (ECHA) and OECD.
[x] Regulation (EU) No 2015/2283.
[y] Risk Analysis in Food Regulation (regulators are notified and pre-market assessment is needed if the products are "potentially unsafe", although the criteria are unclear).
[z] Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed. chain: Part 1, human and animal health.
[aa] Commission regulation (EU) 2018/1882 amending Regulation (EC) No 1907/2006 (REACH and CLP).
[bb] Assessing human health and environmental hazards of nanomaterials – best practice for REACH registrants

1. Timeline summary

Table 2. Summary of events, regulations, and guidance regarding nanomaterial safety in Aotearoa New Zealand and selected international examples.

Year	Aotearoa New Zealand	Australia	European Union	United States
2008	FSANZ amends the application handbook to ensure any application for the use of nanotechnology in food provides appropriate information for FSANZ to conduct a safety assessment.		European Commission (EC) establishes an advisory group on the regulations on nanomaterials. EC releases 'Communication on regulatory aspects of nanomaterials'.	USEPA issues a notice in the federal register that carbon nanotubes need to be considered a different substance from other carbon forms, under TSCA. (similarly, NZEPA takes the same position).
2009			The EU parliament calls for labelling of food products containing nanomaterials (the scheme was never adopted). The EU council approves an updated European Cosmetics regulation (Regulation (EC) No 1223/2009) on cosmetic products. Compulsory notification and labelling systems are implemented.	The TSCA is concluded to be flexible enough to manage nanomaterial safety during the hearings before the House of Representatives (subcommittee on Commerce, Trade, and Consumer Protection of the Committee on Energy and Commerce).
2011	'A review of the adequacy of New Zealand's regulations' published.		EC adopts official definition of nanomaterials (legally non-binding).	USEPA introduces a significant New Use Rule for multiwalled carbon nanotubes.

Year	Aotearoa New Zealand	Australia	European Union	United States
	'Regulation of nanotechnologies in food in Australia and New Zealand' published by FSANZ.			
2012	Amendment is made to Cosmetic Products Group Standard Section 7 to implement the compulsory labelling scheme (enforced on 1 July, 2015).		EC completes the second regulatory review and issues a communication.	USEPA bans the manufacture of potassium titanium oxide.
2013			EC adopts final report on the review of REACH performance on nanomaterial safety assessment.	
2014	FSANZ publishes 'Risk analysis in food regulation'.		European Chemicals Agency publishes a safety assessment (best practice guide) for nanomaterials under REACH.	FDA publishes 'Considering whether FDA-regulated products involve the application of nanotechnology'.

Year	Aotearoa New Zealand	Australia	European Union	United States
2015		APVMA publishes Regulatory Guidelines for chemistry and manufacture. Manufacturers and importers of AgVet products, which contain nanomaterials, are obliged to identify detailed properties of the nanomaterials for safety assessment.	Regulation (EU) No 2015/2283 amends Regulation (EU) 1169/2011. Food products remain exempted from the mandatory labelling scheme conferring to Delegated Regulation (EU) No 1363/2013.	FDA publishes 'Guidance for industry use of nanomaterials in food for animals'.

Year	Aotearoa New Zealand	Australia	European Union	United States
2017				USEPA publishes final rule (RIN 2070-AJ54) establishing reporting and track recording requirements for nanoscale materials under TSCA Section 8(a), and publishes a draft guidance document 'Guidance on EPA's Section 8(a) Information Gathering Rule on Nanomaterials in Commerce'. FDA publishes draft guidance 'Drug products, including biological products, that contain nanomaterials guidance for industry'.
2018			EFSA publishes 'Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health'.	

Year	Aotearoa New Zealand	Australia	European Union	United States
2019	Medsafe publishes 'Guideline on the regulation of therapeutic products in New Zealand – Obtaining approval for new and changed medicines and related products'.		SCCS publishes 'Guidance on the safety assessment of nanomaterials in cosmetics' European Commission releases white paper titled 'Anticipation of regulatory needs for nanotechnology -enabled health products' Regulation (EU) 2019/1857 on cosmetic products. Further restriction on the use of titanium dioxide and silicon dioxide.	
2020			Existing imported and manufactured products in nanoforms are no longer in compliance with REACH without registration in accordance with the annexes to the guidance documents. The EFSA publishes draft report of 'EFSA guidance on technical requirements for regulated food and feed product applications to establish he presence of small particles including nanoparticles'.	

Table 3. Summary of guidance and standards published by OECD and ISO.

Year	OECD	ISO
2010		ISO/TS 80004-3:2010 Nanotechnologies – vocabulary – Part 3: Carbon nanomaterials (Replaced ISO/TS8004-1:2010 and last reviewed in 2014).
2011		ISO/TS 80004-4:2011 Nanotechnologies – vocabulary – Part 4: Nanostructured materials (last reviewed in 2019).
2012	Guidance on sample preparation and dosimetry for the safety testing of manufactured nanomaterials	
2013	Recommendation of the Council on the safety testing and assessment of manufactured nanomaterials	
2014	Nanotechnology and tyres: Greening industry and transport	
2015	Harmonised tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces	ISO/TS 80004-2:2015 Nanotechnologies – vocabulary – Part 2: Nano-objects (last reviewed in 2018).
2016	Science-based support for regulation of manufactured materials	
2017		ISO/TS 80004-11:2017 Nanotechnologies – vocabulary – Part 11: Nanolayer, nanocoating, nanolayer, nanofilm, and related terms. ISO/TS 20787:2017 Nanotechnologies – Aquatic toxicity assessment of manufactured nanomaterials in saltwater lakes using *Artemia sp. nauplii*.

Year	OECD	ISO
2018		ISO 19007:2018 Nanotechnologies – *In vitro* TS assay for measuring he cytotoxic effect of nanoparticles.
2019	Physical-chemical decision framework to inform decisions for risk assessment of manufactured nanomaterials and Guiding principles for measurements and reporting for nanomaterials: Physical chemical parameters.	ISO/TR 21386:2019 Nanotechnologies – Considerations for the measurement of nano-objects and their aggregates and agglomerates (NOAA) in environmental matrices. ISO/TS 21361:2019 Nanotechnologies – Method to quantify air concentrations of carbon black and amorphous silica in the nanoparticle size range in a mixed dust manufacturing environment.
2020	Guidance document for the testing of dissolution and dispersion stability of nanomaterials and the use of the data for further environmental testing and assessment strategies and Guidance document on aquatic sediment toxicological testing of nanomaterials	ISO 21363:2020 Nanotechnologies – Measurements of particle size and shape distributions by transmission electron microscopy. ISO/TR 21624:2020 Nanotechnologies – Considerations for in vitro studies on airborne nano-objects and heir aggregates and agglomerates (NOAA).

2. Regulatory framework

During the late 2000s to early 2010s, there was considerable discussion concerning the adequacy of existing regulatory frameworks for managing the safety of nanotechnology-related products (see Appendix).

The current consensus recognises that the existing chemical regulatory framework (which manages hazardous substances) can sufficiently manage the safety of manufactured nanomaterials. Examples backing this consensus include a report published by the European Commission (EC) in 2008[3], a hearing before the House of Representatives in the US in 2011[4], Monash report in 2007[5], and the report written by Moore and Gavaghan in Aotearoa New Zealand in 2011 (herein referred to as the Otago report (2011)).[2] In alignment with these, the Organisation for Economic Co-operation and development (OECD) called on

> *…Adherents to apply the existing international and national chemical regulatory frameworks and use the tools listed in the Annex for testing and assessment, in conjunction with the OECD Test Guidelines that have been adapted as appropriate to take into account the specific properties of manufactured nanomaterials.*

However, in some cases existing legislative provisions have needed adaptations to encompass nanomaterials and nano-enabled products. This has led to amendments to the legal text of certain regulations (see Appendix). Prior to discussing the amendments that have been made, this section of the report summarises the general regulatory framework concerning general (industrial) chemicals and substances found in Aotearoa New Zealand and some example countries, namely Australia, the EU, US, Canada, and Japan.

2.1. Aotearoa New Zealand

Three main legislative instruments cover the safety and use of chemicals and substances in Aotearoa New Zealand: the Hazardous Substance and New Organism (HSNO) Act 1996, the Medicines Act 1981, and the Food Act 1981, along with the Australia New Zealand Food Standards Code. Within the scheme of the HSNO Act, the Cosmetic Product Group Standards apply to the substances contained in cosmetic products, overseen by the Environmental Protection Authority (NZEPA, *Te Mana Rauhī Taiao*).

As highlighted in the Otago review (2011), FSANZ is a "bi-national Government agency", whose "main responsibility is to develop and administer the Australia New Zealand Food Standards or variations to standards developed and approved by the Authority are subject to review by the Australia and New Zealand Food Regulation Ministerial Council", which consists of each health ministry and other relevant ministers nominated by the jurisdiction. However, it is important to note that the interpretation and enforcement of the Code is beyond the remit of FSANZ. In Aotearoa New Zealand, the responsibility lay with the New Zealand Food Safety Authority (NZFSA) at the time of the publication of the Otago report (2011). In 2012, the NZFSA merged into the Ministry for Primary Industry (MPI, *Manatū Ahu Matua*), which also has a regulatory role in veterinary medicines and pesticides. A summary of the regulatory framework is presented in Table 4.

Table 4. Overview of regulatory framework in Aotearoa New Zealand.

Legislative instrument	Regulatory agency	Scope of legislation
HSNO Act 1996	NZ Environmental Protection Authority (NZEPA, *Te Mana Rauhī Taiao*)	General/industrial chemicals, cosmetics, pesticides, veterinary medicines, paints, fuels, and explosives
Food Act 1981 & Australia New Zealand Food Standards Code	Food Standards Australia and New Zealand (FSANZ, *Te Mana Kounga Kai – Ahitereiria me Aotearoa*) Ministry for Primary Industries (MPI, *Manatū Ahu Matua*)	Food, food additives, and food contact materials
Medicine Act 1981	New Zealand Medicines and Medical Devices Safety Authority (Medsafe)	Medicines Medical devices
Health and Safety at Work Act 2015	Worksafe NZ (*Mahi Haumaru Aotearoa*)	Occupational health and safety

2.2. Australia

Until recently, the Industrial Chemicals Notification Assessment Scheme (NICNAS) was responsible for enforcing the Industrial Chemical (Notification and Assessment) Act 1989. In 2019, the institution was renamed Australian Industrial Chemical Introduction Scheme (AICIS) under the Industrial Chemicals Act 2019. Substances used in food-related products are managed by the trans-Tasman authority, FSANZ. The Australian Pesticides and Veterinary Medicines Authority manages pesticides and veterinary medicines. Therapeutic Goods and Administration (TGA) and Safe Work Australia are responsible for medicinal products (and medical devices) and occupational health and safety, respectively. A summary of the regulatory framework is presented in Table 5.

Table 5. Overview of regulatory framework in Australia.

Legislative instrument	Regulatory agency	Scope of legislation
Industrial Chemicals Act 2019 (formerly known to be Industrial Chemical (Notification and Assessment) Act 1989)	Australian Industrial Chemical Introduction Scheme, AICIS (formerly known to be National Industrial Chemicals Notification Assessment Scheme, NICNAS)	General/industrial chemicals, cosmetics,
Agricultural and Veterinary Chemical Code Act 1994	Australian Pesticides and Veterinary Medicines Authority	Pesticides Veterinary medicines
Food Act & Australia New Zealand Food Standards Code	Food Standards Australia and New Zealand	Food, food additives, and food contact materials
Therapeutic Goods Act 1989	Therapeutic Goods Administration (TGA)	Medicines (incl. sunscreen) Medical devices
Safe Work Australia Act 2008	Safe Work Australia	Occupational health and safety

2.3. European Union (EU)

Unlike other jurisdictions discussed in this report, the EU adopts horizontal and sector-specific legislation, which provide abiding frameworks for manufacturers, importers and users to ensure the safety of substances and products on the market (Figure 1). Product-specific regulations are in place to overview the safety of substances (e.g. Regulation (EC) No 1223/2009 looks particularly into cosmetic products while Regulation (EC) No 528/2009 considers only biocides). In contrast, in Aotearoa New Zealand (and other countries), chemicals, cosmetics, pesticides, paints, etc. are all managed under a single legislative instrument: the HSNO Act 1996.

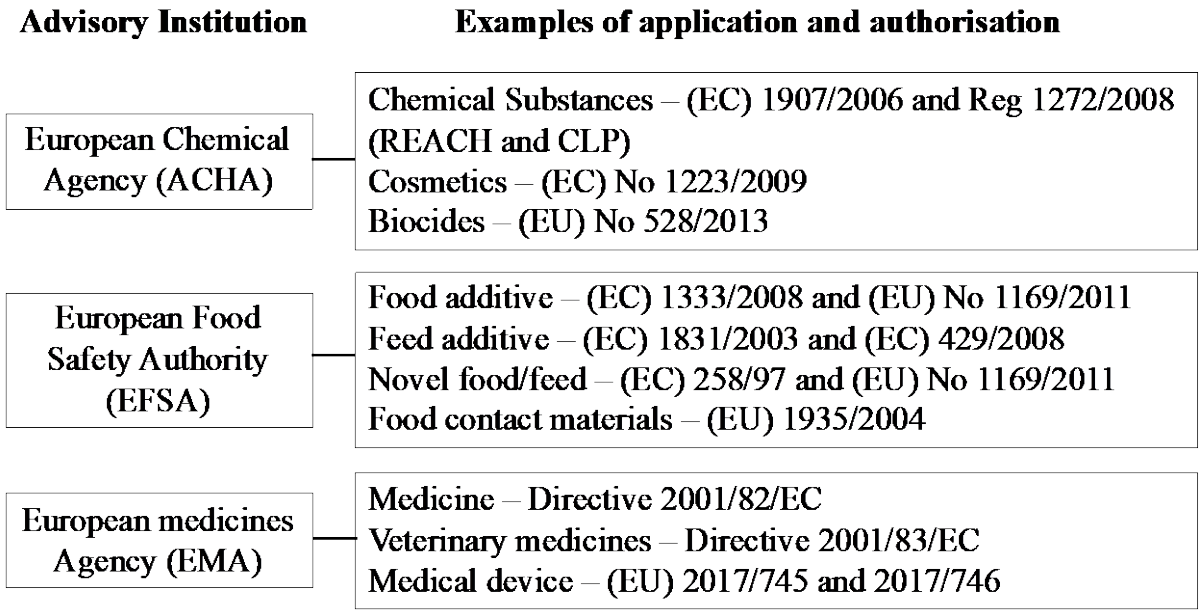

Figure 1. The EU horizontal and sector-specific legislation. Note: Pesticides and biocides are governed both by the ECHA and EFSA. The EFSA is responsible for the peer review of the EU risk assessment of pesticides under Reg 1107/2009, while the ECHA is responsible for the classification and labelling of pesticides under CLP (Reg 1272/2008).

2.4. United States (US), Canada, and Japan

Three other countries are also compared in this report, and adopt similar regulatory frameworks managed by different regulatory bodies and legislative instruments (see Table 6, Table 7, and Table 8).

Table 6. Overview of regulatory framework in the US.

Legislative instrument	Regulatory agency	Scope of legislation
Toxic Substances Control Act Federal Insecticide, Fungicide, and Rodenticide Act	US Environmental Protection Agency (USEPA)	General/industrial chemicals, pesticides, and explosives
Federal Food, Drug, and Cosmetic Act	Food and Drug Agency (FDA)	Food, food additives, and food contact materials, veterinary medicines, medicines, medical devices, and cosmetics
Occupational Safety and Health Act	Occupational Safety and Health Administration (OSHA)	Occupational health and safety

Table 7. Overview of regulatory framework in Canada.

Legislative instrument	Regulatory agency	Scope of legislation
Canadian Environmental Protection Act	Environment and Climate Change Canada	General/industrial chemicals
Food and Drug Act	Health Canada	Food, food additives, and food contact materials, veterinary medicines, medicines, medical devices, and cosmetics
Pest Control Act	Health Canada	Pesticides
Occupational Safety and Health Act	Canadian Centre for Occupational health and Safety	Occupational health and safety

Table 8. Overview of regulatory framework in Japan.

Regulatory agency	Legislative instrument	Scope of legislation
Ministry of Health, Labour, and Welfare	Chemical Substances Control Law	General/industrial chemicals
	Pharmaceutical Affairs Law	Drugs, quasi-drugs, drug devices, and cosmetics
	Food Sanitation Law	Food, food additives, and food contact materials
	Industrial Safety and Health Law	Occupational Health and Safety

3. Regulatory aspects considered in making comparison

3.1. Definition

In Aotearoa New Zealand, the definition of nanomaterials (or engineered nanomaterials) is provided only for cosmetic products under the Cosmetic Products Group Standard. The definition is identical to the one provided in the European equivalent (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.*

The definition has not been revised since 2009, although in 2011, the European Commission (EC) published its recommendations for the definition of nanomaterials,[6] which outlined the attributes crucial to identifying nanomaterials for scientific and regulatory purposes:

> 1. *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.*
> 2. *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%.*
> 3. *By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.*

While the recommendation is legally non-binding, the updated EU Guidance on the Safety Assessment of Biomaterials in Cosmetics (2019)[7] advised applicants to take this recommendation (and any resulting revisions of the definition) into consideration when assessing the safety of cosmetic nano-ingredients. Likewise, the definitions of nanomaterials and subclasses have emerged in recent years (ISO/TS 80004-2:2015 and ISO/TS 80004-4:2011), which provide further detail to the original definition.

Following the recommendation, the EU regulations concerning biocidal products (Regulation (EU) No 528/2012) adopted parts of the recommended definition:

'*nanomaterial' means a natural or manufactured active substance or non-active substance containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm. Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall be considered as nanomaterials.*

For the purposes of the definition of nanomaterial, 'particle', 'agglomerate' and 'aggregate' are defined as follows:

'particle' means a minute piece of matter with defined physical boundaries,

— 'agglomerate' means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components,

'aggregate' means a particle comprising strongly bound or fused particles.

And for and food products (Regulation (EU) No 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. 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.

In Australia, AICIS sets out the definition of nanomaterials as following:

…industrial materials intentionally produced, manufactured or engineered to have unique properties or specific composition at the nanoscale, that is a size range typically between 1 nm and 100 nm, and is either a nano-object (i.e. that is confined in one, two, or three dimensions at the nanoscale) or is nanostructured (i.e. having an internal or surface structure at the nanoscale)

Similarly, in the US FDA guideline[8], the term is defined as:

… a material or end product [that] is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm).

And also as:

… a material or end product [that] is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometre (1,000 nm).

While the inclusion of the size range (1–100 nm) provides a clear boundary for regulatory purposes, scientifically, this size range may not be able to fully capture the properties that are unique to the nano-scale. For example, one would not observe an abrupt change in the

extrinsic properties (e.g. interaction with biological media) between particles that are 100 nm and 101 nm in size. The size range at which nanomaterials are considered unique in comparison with their larger analogue varies for different nanomaterials. For this reason, some of the definitions used, for example by the FDA, do not restrict the size to between 1 and 100 nm. Sizes at which unique properties attributed to one or more dimensions of the materials up to 1 μm (1000 nm), are still considered within the scheme of the definition.

In an attempt to create a globally acceptable definition of nanomaterials and related terms, the International Organisation for Standardisation (ISO) took an initiative to define the core terms used within the scheme of *nanotechnology* (ISO/TC 229), which is defined as the field that concerns either, or both:

1. *Understanding and control of matter and processes at the nanoscale, typically, but not exclusively, below 100 nanometers in one or more dimensions where the onset of size-dependent phenomena usually enables novel applications;*
2. *Utilizing the properties of nanoscale materials that differ from the properties of individual atoms, molecules, and bulk matter, to create improved materials, devices, and systems that exploit these new properties.*

In the technical standard, nanomaterials are defined as "material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale". The nanoscale is defined as "length range approximately from 1 nm to 100 nm with a note: properties that are not extrapolations from larger sizes are predominantly exhibited in this length range". The most vital aspect of this definition is the size scale of the material. Nanomaterials are further categorised into nano-objects and nanostructured materials depending on whether the material exhibits the nano-scale length on extrinsic or intrinsic dimension(s) (Figure 2).

Materials that exhibit nanoscale in intrinsic dimension are classified as nanostructured materials (composition of inter-related constituent parts in which one or more of those parts is a nanoscale (2.1) region). Major classes of the nanostructured materials are presented in Figure 2. Here, the size scale of the overall structure can exceed the nanoscale, and instead, internal structure or the primary particles (the particles that constitute the overall structure) is considered. Nanolayer, nanocoating, nanofilm, and related terms were defined in 2017 (ISO/TS 80004-11: 2017).

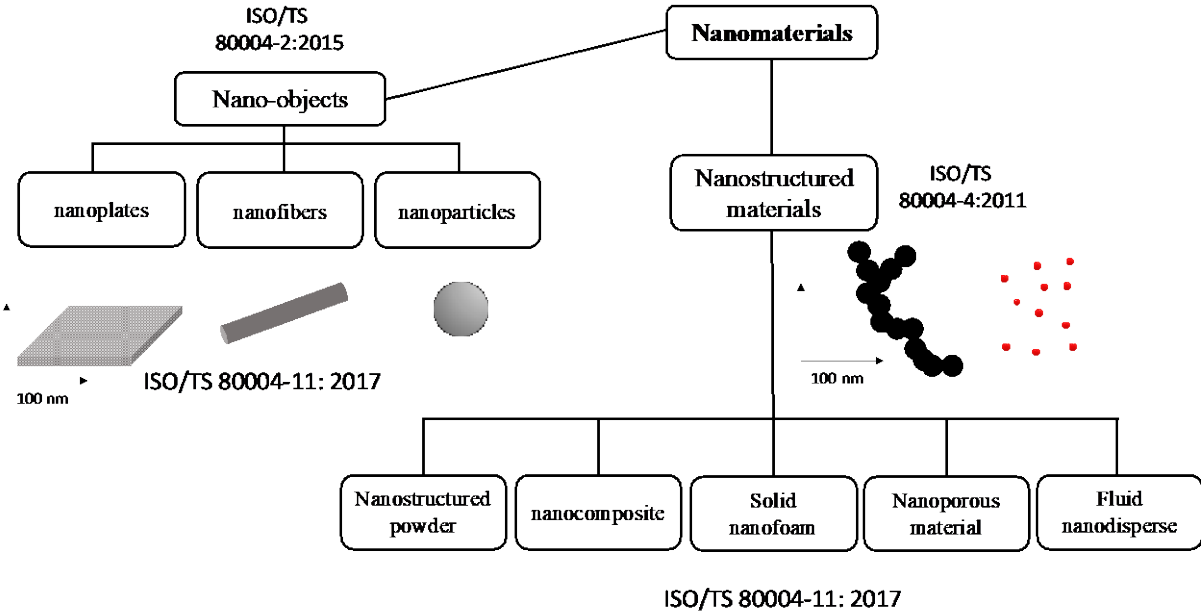

Figure 2. Categories of nanomaterials under the technical specifications published by ISO. The definitions of nanoplates and related terms are also defined and classified under both nano-objects and nanostructured materials (ISO/TS 80004-11: 2017).

3.2. Labelling

The EU initiated the nano-specific labelling schemes for cosmetic products (Regulation (EC) No 1223/2009) in 2009 and biocide products (Regulation (EU) No 528/2012) in 2012. Subsequently, the NZEPA adopted a mandatory labelling system for cosmetics. To date, such a labelling scheme has been implemented only in Aotearoa New Zealand and in the EU. In 2011, food products in the EU were subject to this labelling scheme (Regulation (EU) No 1169/2011), however, the regulation was amended in 2013 (Delegated Regulation (EU) No 1363/2013), removing the nano-specific labelling scheme, as it may cause "confusion" amongst consumers.

3.3. Nano-specific notification

In managing the safety of products that contains nanomaterials, many regulations around the world implemented a mandatory notification system (Table 1), along with the submission of safety and nanomaterial property information. The system firstly allows regulators to distinguish between non-nano conventional products and nano-related products, and secondly, allows regulators to conduct a case-by-case risk assessment based on the physicochemical properties of the nanomaterials of interest. Although this is a commonly adopted approach, there are variations in the extent to which this information is required under different regulations and guidelines.

Currently in Aotearoa New Zealand, substances and products (cosmetics, biocides, general/industrial chemicals) managed under the HSNO Act are **not** subject to mandatory notification to the NZEPA, and likewise, for food and drug products according to the guidelines published by FSANZ[9] and Medsafe,[10] respectively.

Any person intending to import into, or manufacture in, Aotearoa New Zealand a cosmetic product containing nanomaterials, must at the time they first import or manufacture the substance, notify the Authority in writing of — (1) the name of the substance; and (2) the HSNO approval number and/or title of the group standard under which the substance has a deemed approval; and (3) the nature of the nanomaterials the substance contains.

3.3.1. Guidance on toxicity evaluation or risk assessment

As mentioned, the submission of safety data and/or the physicochemical properties of nanomaterials are required along with the declaration of the presence of nanomaterials. There has been a recent surge in the development of nano-specific guidance on toxicity evaluation or risk assessment overseas, particularly the EU, and by the Organisation for Economic Co-operation and Development (OECD), and definitions and standardised testing protocols by the ISO. As early as 2014, the FDA initiated a draft report detailing the relevant physicochemical properties of nanomaterials at the time of registration of new drug products containing nanomaterials. However, at the time there was a limited number of testing methods for determining these properties, which were not standardised. The OECD has been actively involved in the developing standards for the detection, characterisation of health effects, and environmental impacts of nanomaterials.[11] In 2019, the OECD published reports concerning the safety decision-making framework[12] and guidance on the reporting and measuring of physicochemical properties of nanomaterials.[13] Following this advice, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS, Australia) adopted a safety assessment guideline – its remit is limited for cosmetics amongst the product categories highlighted in this report.[14]

In parallel, the ISO has been documenting the definitions of nano-related terms (see 3.2) and standardised toxicity testing protocols including inhalation toxicity,[15] aquatic toxicity,[16] cytotoxicity,[17] and general toxicity using zebrafish embryos, many of which emerged in the last three years. The ISO has investigated the characterisation of nanomaterials on the basis of several standardised attributes; i.e., how to specify the nano-objects,[18] quantifying the air

concentration,[19] measurements of nanomaterials in environmental matrices,[20] and particle size and shape analysis using transmission electron microscopy.[21]

In Aotearoa New Zealand, a brief guidance is provided for therapeutic[10] and food products.[9] However, nano-specific data requirements were not specified in either document. Instead, therapeutic products containing nanomaterials are subject to safety assessments by the Medicine Assessment Advisory Committee, regardless of whether Medsafe has concluded that the application includes sufficient data to attest to the safety, quality and efficacy of the medicine and that the benefits outweigh the risk of harm to the patient. For food products, the guidance states that "Food substances… which involve the use of nanotechnology, will also require pre-market approval if potentially unsafe".[9] However, the criteria under which this regulatory action is triggered is uncertain.

3.4. Conventional risk assessment vs. nano-specific risk assessment

In this section, a parallel comparison between conventional and nano-specific risk assessment is made. The scope of this exercise includes:

- Clarifying the aspects which have already been considered in characterising the risks associated with the materials or substances (in nano-form or not).
- Identifying the additional considerations in characterising and managing the risks associated with the use of nanomaterials.

There are some examples of nano-specific guidance published outside Aotearoa New Zealand, particularly by the OECD and the EU, which are used as case studies. It is critical to point out that the nano-specific risk assessment considers safety aspects associated with nanomaterials, in addition to the conventional risk assessment procedures.

Generally speaking, the basic principles of risk assessment do not differ significantly product-to-product (e.g. substances incorporated in food vs. cosmetics), with an exception of drug products where rigorous clinical trials are required to prove the benefit and risks (which will not be discussed in this report). This section does not cover an exhaustive list of methodologies employed to conduct the risk assessment, instead it aims to highlight the additional considerations taken for evaluating the safety of nanomaterials. A few examples of risk assessment guidance (non-nano specific) published by the Aotearoa New Zealand regulatory bodies, the FSANZ and NZEPA are found elsewhere.[9, 22]
Risk assessments are typically conducted with following considerations:

- Hazard identification,
- Hazard characterisation,
- Exposure assessment, and
- Risk evaluation.

The hazard identification process describes the potential adverse health effects as a result of use and exposure to the substances of the interest. This procedure involves examining the toxicological and other relevant data. One of the methods to identify the potential risk is to classify in accordance with the Globally Harmonised System (GHS) hazard classification.

Hazard characterisation involves the investigation of dose-dependent response (metabolism, toxicological profiles, dermal absorption, etc.). In addition, the environmental toxicity (ecotoxicity) needs to be considered in Aotearoa New Zealand under the HSNO Act to account for potential environmental impacts from storage, use and disposal of hazardous substances. Types and levels of required data vary depending on the purpose of the application (e.g. dermal absorption may play an important role for assessing the potential risks of applying cosmetic products on skin while metabolism data becomes essential when evaluating food products).

Anticipated exposure scenarios from the proposed uses also need to be outlined as this is relevant to the identified potential health risks. Depending on the application of the product, systematic exposure is foreseeable. In these cases, a combination of exposure studies (accumulation and translocation) and modelling tools are commonly used to predict the exposure to up-taken materials (e.g. probabilistic model for food consumption[9]). Crucially, the exposure assessment contributes to decisions on the extent of the hazard characterisation. Finally, the risk is evaluated by integrating the synthesised data – the level of exposure and the estimated hazard. While the combination of these principles are the major factors in deciding whether the products are safe to be introduced to the market, typically the functional benefit of introducing the particular material or combination of some, is compared against the estimated risk.[22]

One addition to the decision-making scheme which should be mentioned is the uncertainty (e.g. data gap in reliable toxicological data, uncertainty around whether a nanomaterial translocates from the targets considered in exposure scenario, etc.). Whether the assessed material or substance is in nano-form or not, uncertainty is commonly dealt with in a risk assessment by making precautionary assumptions in both the hazard and exposure assessments, as highlighted in the guidance published by the FSANZ.[9] Recognition of uncertainty is crucial particularly in the context of nanomaterials safety. At post-decision-making stage, there may be a surge in the scientific data which can fill in the knowledge gap. In this case, the assessors may re-evaluate the risk assessment with the newly gained data.
There are several additional aspects in conducting risk assessment on nanomaterials. Here, discussions are formulated based on the specific points raised in nano-specific safety assessment guidelines on cosmetics and food products published by the Scientific Committee on Consumer Safety (SCCS, EU)[7] and EFSA[23], respectively. Both guidelines pay particular attention to distinctive material characteristics at the nano-scale.

Nanomaterials may exhibit certain physicochemical properties, biokinetic behaviour, biological interactions, and/or toxicological effects that are different from conventional or bulk form of the same ingredients. For these reasons, the guidelines recommend methodologies to determine nanomaterial characteristics. Some of the examples from *Guidance on the safety assessment of nanomaterials in cosmetics*[7] are outlined in Table 9.

The main exercise of the nano-specific risk assessment is to identify different hazards that may not be present for non-nano forms. For example, aerodynamic particle size is known to determine inhalation exposure – only particles and droplets smaller than 10 µm can enter the lung via inhalation.[7] Furthermore, particle deposition in the lung depends on particle size, density, and hygroscopicity, all of which can be modified and may create additional hazards

that need to be identified, depending on the specific values of these parameters. Alongside the exposure scenario considering inhalation, the extent and nature of systemic exposure may differ as nanomaterials could cross dermal, respiratory, or gastrointestinal barriers, and translocate to the other parts of the body.

It is also important to note that some of the methodologies used to determine toxicokinetics may not suitable for nanomaterials due to their non-soluble particulate nature. A specific example includes a TG417 (OECD)[24] used to anticipate the diffusion/perfusion and metabolic processes (which is an important component of toxicological study). This issue is recognised by an OECD workshop report in 2017 and the SCCS cosmetic guidance.[7, 25] Similarly, FSANZ acknowledges the limitation of the traditional model in this regard in their risk analysis guidance.[9]

It is worthwhile pointing out that the manufacturing process is also important for characterising nanomaterials. A change in the process may lead to significant modification to the physicochemical and morphological characteristics of different batches of the same nanomaterial. They may also introduce different impurities and other residual materials in nano-form which also may become contributing factor(s) in changing the hazard profile.

Table 9. Some of the important nanomaterial characteristics highlighted in the *Guidance on the safety assessment of nanomaterials in cosmetics*[7] and the recommended methodologies to determine them.

Parameter	Description	Examples of methods
Production process	The entire processes used for production/ modification of the nanomaterial.	
Particle size and size distribution including presence of agglomeration or aggregation state	Information on primary and secondary particle size (mean and median size in nm and graphical diagrams of size distribution) as well as for agglomerates and aggregates particle size. Particle number size distribution and particle mass size distribution. Material specifications and any batch to batch variation during manufacturing. Information on the characterisation techniques used.	High-Performance Liquid Chromatography (HPLC), analytical ultracentrifugation, disc centrifugation, Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM), Dynamic Light Scattering (DLS), etc.
Morphology/shape	The physical form, shape, and aggregation/agglomeration state. Information on the nanomaterial preparation (powder, solution, suspension or dispersion).	AFM, TEM, SEM, Nuclear Magnetic Resonance (NMR) spectroscopy, X-Ray Diffraction (XRD)
Structure	Description of the structure, including 1D, 2D and or 3D spatial distribution of the components (e.g. homogeneous mixture, core-shell, surface coating) (EFSA, 2018). High quality electron microscopy images of non-homogeneous particles.	TEM, SEM, AFM
Crystallographic structure	Description of crystalline form (amorphous, polycrystalline, crystalline including specification of phase and volumetric fraction as well as spatial distribution).	XRD, TEM
Surface area	Information on Brunauer-Emmett-Teller (BET) specific surface area, and volume specific surface area (VSSA).	BET
Surface characteristics	Information on nanomaterial surface, presence of any functional groups. Information on surface charge (zeta potential), morphology, as well as information on any surface contamination.	X-ray photoluminescence spectroscopy, mass spectrometry, Fourier-Transform Infrared (FTIR) spectroscopy, NMR, DLS *etc*.
Catalytic activity	Information on the chemical reactivity of the core material or surface coating. Information on photocatalytic activity and radical formation potential of relevant materials.	Kinetic measurements of chemical biochemical and/or catalysed reactions

3.4.1. Differentiating nanomaterials from other nanomaterials and bulk materials (data requirement on physicochemical property)

As emphasised in the nano-specific risk assessment scheme, nanomaterial characteristics are essential parameters used in analysing the associated risks. This is an important issue to recognise as there are variants of nanomaterials that impose particular risk while the nanomaterial with the same identity but different shape, for instance, does not. If the regulatory framework does not differentiate between the two, it is possible that assessors reach a flawed conclusion.

This issue could potentially become more prominent when patents protecting some of the first marketed nanomaterials have expired or are close to expiry, or follow-on nanomaterials (or nano-similar[1]) emerge. To date, internationally, there is no specific regulatory pathway designed for nanosimilars and a level of comparability with the already-registered product has to be met in order to avoid the rigorous premarket authorisation process. This issue is in no way unique to nanomaterials, and typically substances at the time of market registration require appropriate justification to prove similarity with already-registered products in Aotearoa New Zealand (under HSNO Act, Food Act & Australia New Zealand Food Standards Code, and Medicine Act). The common approach (for nanomaterials) taken by the EU and US regulatory bodies is to mandate submission of the aforementioned datasets (although the level varies) and track records of existing nanomaterials with their corresponding physicochemical properties. Examples include the Regulation (EC) No 1223/2009 (EU) for cosmetics, Regulation (EU) No 2015/2283 for novel food, and , and RIN 2070-AJ54 (the US) for products managed under the TSCA Act (see Table 9 for examples of physicochemical properties).

For non-food and non-medicine hazardous substances in Aotearoa New Zealand, the data requirement is managed under the Part 5 of the HSNO Act, and the presence of engineered nanomaterials must be declared at the time of market registration. For chemical pesticides and active ingredients (including new veterinary medicines, pure chemicals, and biological pesticides) data requirements indeed include particle size distribution, allowing the tracking of nanomaterials with relevant information.[26] However, for other kinds of substances and products managed under the HSNO Act, the submission of size information or other relevant information such as surface coating and particle shape is not mandated.

Recently the NZEPA has updated schedule 1, section 9, of the Hazardous Substances (Safety Data Sheets) Notice 2017 (amended in October 2020 and enforced on 30 April 2021), which improves the clarity of the physicochemical properties of nanomaterials. This measure clarifies the datasets that need to be included in the safety data sheet (SDS), which manufacturers/importers are obliged to generate. Specifically, 'particle characteristics' in accordance with the GHS (Annex 4 Guidance on the preparation of SDS, A4.3.9.1) has been added to the list as one of the physicochemical properties, so that nanomaterials can be described and identified when submitted to the assessors. It could be argued that better monitoring of the nanomaterials can be achieved via submission of SDS without the nano-specific notification system, provided that the reported parameters are reliably measured.

4. Occupational exposure and guidance

Contrary to some of the international examples presented here (e.g. Australia, US, EU, and Canada), Aotearoa New Zealand lacks published safety guidance for occupational settings (Table 10). The adequacy of the Aotearoa New Zealand regulatory framework in managing occupational health and safety was previously discussed in the Otago report (2011). As emphasised then, the level of nanomaterial exposure for Aotearoa New Zealand workers is uncertain due to the absence of globally harmonised methods to detect nanomaterials. Furthermore, there is inadequate toxicological data for certain nanomaterials (with certain physicochemical properties), and the level of evidence required to trigger a regulatory action is unclear. The guidance found overseas aims to address this knowledge gap by adopting a precautionary approach to minimise the risk in workplaces where exposure to nanomaterials is expected (particularly for inhalation exposure).

Table 10. Summary table of safety guidance and/or safety guidance for occupation settings from different countries and geopolitical regions.

Country/area/organisation	Safety guidance and/or safety assessment for occupational settings
Aotearoa New Zealand	✗*
Australia	✓[a]
EU	✓[b]
US	✓[c]
Canada	✓[d]
Japan	✗
OECD	✓[e]

There has been international effort in standardising nanomaterial detection methodologies and improving the occupational handlings of nanomaterials, exemplified in the reports found in Table 10 and the number of standards published by the ISO which include:

- ISO/TR 2885:2018 Nanotechnologies– health and safety practices in occupational settings

* A specific safety guidance on accelerated silicosis (caused by exposure to crystalline silica with particle size < 10 μm, which also may include the crystalline nanoform silica) is found in the websites published by Worksafe NZ and Ministry of Health.

[a] Nanotechnology in the workplace (Queensland government).

[b] Managing nanomaterials in the workplace by European Agency for Health at Work.

[c] A list of guidance and publications on managing the risk of nanomaterials is found on the NIOSH's website.

[d] A free course on the health and safety in work settings is offered by the Canadian Centre for Occupational health and Safety (CCOHS).

[e] Guidance on air-borne nanomaterials at workplaces.

- ISO/TR 21386:2019 Nanotechnologies – Considerations for the measurement of nano-objects and their aggregates and agglomerates (NOAA) in environmental matrices.
- ISO/TS 21361:2019 Nanotechnologies – Method to quantify air concentrations of carbon black and amorphous silica in the nanoparticle size range in a mixed dust manufacturing environment.

A few workplaces are thought to have close contact with engineered and unintentionally produced nanomaterials in Aotearoa New Zealand. Plausibly, these places are involved with (ultra)fine dust and particles, which subject the workers to systematic exposure to airborne nanomaterials. One of the examples that is frequently discussed is silica dust, as highlighted by Worksafe NZ on their website. The persistent exposure to crystalline silica dust (which may not necessarily be in nanoform) may lead to accelerated silicosis, a major occupational disease. Although the prevalence of silicosis is unknown in Aotearoa New Zealand, a number of precautionary practices are recommended in the guidance. Such precautionary practices could also be used to mitigate the hazard of nano-sized dust.

Another example includes tyre production factories. As outlined in the 2016 OECD report on nanotechnology and tyres,[27] black carbon and highly dispersible (HD) silica nanoparticles are commonly used to improve tyre performance. The report also highlighted other types of nanomaterials that are in market entry and market-entry stage, namely silica carbide, core-shell polymer nanoparticles, and poly(alkylbenzene)-poly(diene) block copolymer nanoparticles. If these proceed to market, they may increase the chances of workers being exposed to multiple types of nanomaterials in work settings.

Evaluating the adequacy of existing practices in dealing with above mentioned examples is outside the scope of this report. Future studies are likely needed to address this gap and assess the suitability of occupational risk assessment in managing emerging nanomaterials in workplaces.

5. Case studies

Although there are differences in the approaches taken by different regulators, safety regulations are typically specific to the physicochemical properties of nanomaterials. The recent surge of scientific knowledge on nanomaterial toxicity has allowed regulatory bodies, particularly in EU and US, to publish guidance and restrictions on the use of nanomaterials with specific physicochemical properties – or in the strictest sense, not approve their use.

Examples below introduce frequently used nanomaterials in consumer products, and compares approaches taken by Aotearoa New Zealand regulators and overseas institutions based on the publicly accessible information. Due to the limited information found on therapeutic and biocide products containing nanomaterials in Aotearoa New Zealand, the discussion of these case studies primarily focuses on cosmetic and food products.[9]

5.1. Nano-silica

Silicon dioxide, or silica, is widely used in food and cosmetic products. Here the discussion is limited to amorphous silica as crystalline silica is not approved for these applications. Amorphous silica can be classified into two types: fumed silica (used for thickening and anticaking food agents) and hydrated silica (silica gels and precipitated silica). Among the hydrated silica, colloidal silica is approved for cosmetic products, but not in food products. Broadly the amorphous silica types that are approved in food products are referred to as E551.

In Aotearoa New Zealand, nanoform silica constitutes the majority of registered cosmetics products containing nanomaterials, and new products with nano-silica are subject to mandatory notification to the NZEPA for pre-market safety assessment.[28] In food items, although there is no nano-specific notification system, the safety assessment is conducted if the products with nanomaterials are "potentially unsafe".[9]

The Scientific Committee on Consumer Safety (SCCS) published a final opinion on the safety of nano-silica in cosmetic products.[29] The SCCS adopted a case-by-case approach to assess each silica material against the physicochemical and toxicological safety data provided for that particular silica type. A detailed evaluation by the SCCS concluded that:

> *the evidence, both provided in the submission and that available in scientific literature, is inadequate and insufficient to allow drawing any firm conclusion either for or against the safety of any of the individual SAS* [synthetic amorphous silica] *material, or any of the SAS categories, that are intended for use in cosmetic products*.

Further studies are also needed to exclude the possibility of dermal penetration of SAS materials, especially the surface modified hydrophobic types, in the media/formulations that are relevant to the final product.

In 2016, FSANZ commissioned an external group to assess the safety of silica (bulk and nano) in a part of the report "Potential health risks associated with nanotechnologies in existing food additives", citing the EFSA's safety opinion on silica in food products.[30]

In light of the recent surge of scientific data, the EFSA re-evaluated the safety of silica in food products in 2018.[31] The EFSA panel considers that E551 and its nanoform display no indication of adverse effects based on the available *in vivo* data under the permitted dose. However, the panel acknowledged that current EU specifications for E551 are insufficient to adequately characterise silica, and recommended the inclusion of particle size distribution in the specification, especially in the absence of long-term studies for nano-silica.

5.2. Titanium dioxide nanoparticles (consumer products and occupational exposure)

Titanium dioxide nanoparticles have been used in cosmetics, food, and therapeutic products since the early stages of nanotechnology. The ingredients in nanoform are regulated specifically under the Cosmetic Products Standard Group 2017 in Aotearoa New Zealand. Whether it is bulk or nanoforms, titanium dioxide has been an approved food additive internationally for decades. However, the current regulatory framework may not be suitable to allow the regulator to distinguish between bulk and nanoforms in food products.

The recent surge of data relating to potential nano-specific toxicity of titanium dioxide urged some overseas regulators (particularly in Europe) to re-evaluate the regulatory approach. For instance in France, the use of the titanium dioxide (both bulk and nano) in food products is banned by the French government until its safety is proven (the decree in 17 April 2019).[32] The decision was made based on a recommendation from the French Food Safety Agency (ANSES) concluding that there is not enough evidence to prove the absence of adverse health effects, particularly for nanoforms.[33] The order from the French government applies both to domestic (French) manufacturers and imported goods.

Although the remit of this food-related legislation is limited to France, the EU, as a whole, has taken a more careful step in its governance. The current opinion of the EFSA allows the incorporation of titanium dioxide in food products, and the most recent safety review (in 2018) concludes there that there is insufficient evidence to reopen their stance. Nonetheless, they acknowledged that toxicity studies of titanium dioxide nanoparticles in a food matrix need to be conducted in order to understand their health effects.[34]

In contrast, for cosmetic products, the EU initiated regulatory restrictions on the use of titanium dioxide nanoparticles. The EU issued Regulation (EU) 2019/1857 which amends Annex VI to Regulation (EC) No 1223/2009, restricting the upper concentration of titanium dioxide and its nanoforms to 25 weight % in UV-filter. Noting that the toxicity of titanium dioxide for the most part occurs via oral ingestion, products with uses that lead to this exposure pathway (such as lipsticks) are only approved after careful risk assessment, taking into account the oral toxicity. Importantly, the regulation states what physicochemical properties titanium dioxide nanoparticles are allowed in order for the products to obtain pre-market approval.

More recently, the Commission Delegated Regulation (EU) 2020/217 was established, issuing a final opinion on the safety classification of titanium dioxide (not specific to nanoforms). The new legislation classifies titanium dioxide as a category 2 suspected carcinogen by inhalation. For substances or powder mixtures containing 1% with aerodynamic diameter of 10 μm or

less, a cancer warning label is required. The new scheme aims to inform users of precautionary measures.

5.3. Nano-silver

Although not registered in cosmetic products in Aotearoa New Zealand, nano-silver is commonly used in a wide range of consumer products overseas, including food (packaging), cosmetics, and therapeutics. Nano-silver is used in consumer products for its antimicrobial activity, colouring, and UV-filtering.

Under the Aotearoa New Zealand regulatory framework, if nano-silver-containing cosmetic products were to be introduced to the market, the importer or the manufacturer would be obliged to notify the NZEPA. Keeping record of these notifications may allow the NZEPA to identify and re-evaluate the risks when new toxicological data emerges. Similarly for therapeutic products, a notification needs to be made with regard to the presence of nano-silver. However, there is no such obligatory notification present for food (i.e. FSANZ may not be able to distinguish bulk silver or silver ions from nano-silver in products).

An EU final opinion and a USEPA report both acknowledge the limited data to understand health effects related to nano-silver exposure.[35,36] The National Institute of Occupational Safety and Health recommends occupational exposure limits and safety protocols to reduce exposure. The USEPA plans to issue a final decision on nano-silver in May 2022.[36] A serious knowledge-gap exists regarding antimicrobial resistance following the use of silver nanoparticles and may warrant continued monitoring.[36]

5.4. Industrial chemicals

Industrial chemicals are managed under the HSNO Act (see Section 3.4) in Aotearoa New Zealand. The presence of nanomaterials also needs to be indicated by the applicant at the time of market approval application, although specific physicochemical properties may not be reported under the current scheme (unless the chemical is recognised as an 'active ingredient' (see 3.4.1) or for solid materials, where the particle size distribution needs to be reported).

In the EU, a new measure was enforced under the REACH (and CLP) programme in January 2020 (Commission regulation (EU) 2018/1882 amending Regulation (EC) No 1907/2006), requiring existing registrants to update their dossiers with nano-specific information. Likewise, future registrants must meet this new criteria. In the US, similarly measures have been required for substances managed under the TSCA Act (which includes industrial chemicals) since 2017 (RIN 2070-AJ54). Nano-specific information must be reported and tracked for each registered substance.

5.5. Future nanomaterials

One of the major focuses in the nanotechnology field is to develop multifunctional nanomaterials for the pharmaceutical and medicinal fields, which could serve as therapeutics, delivery platforms, and/or diagnostics.[1] While such development will bring benefit to the field,

such a hybrid nature would impose regulatory challenges in Aotearoa New Zealand. The current regulatory framework does not specify the pathway that the products need to comply with (e.g. drug vs. medical device). This issue is not unique to Aotearoa New Zealand (as also raised by the Otago report (2011))– a recent regulatory review by the EMA (EU) also recognises this as a regulatory gap.[1]

While early nanotechnology efforts focused on electronics engineering, its applications increasingly encompass use in food technology. To avoid confusion with naturally occurring nano-sized biological molecules, we solely focus on deliberately introduced nanomaterials and also naturally occurring biological molecules whose properties are modified with the use of nanotechnology. Taking functionalised protein as an example (which is in development stage), there are concerns about modifying the nano-scale properties of proteins (such as nanostructure). Proteins have several biological roles and can naturally exist in nanostructures. The biological relevance of functionalised proteins can only be determined on a case-by-case basis, where the physicochemical properties are important to consider e.g. type of protein, state of proteins (monomer, oligomer, aggregate), shape, etc. Therefore, an appropriate risk assessment can only be conducted when there is sufficient information about these properties and relevant toxicological data, alongside evidence correlating the benefit of introducing such proteins to the modified characteristics of proteins.

6. Future considerations for Aotearoa New Zealand

- A definition of nanomaterials is not included in some of Aotearoa New Zealand's relevant legislation and guidance, although their existence is recognised. This lack of definition may create uncertainty, especially if further regulations and guidance are made to manage the safety of the nanomaterials. Any definition incorporated in the future should carefully consider the definitions adopted overseas and take note of any changes.
- In future regulation, it may be useful to distinguish between nanomaterials and bulk materials, so that regulators are aware of their presence on the market.
- It may be useful to track nanomaterials on the market and record their physicochemical properties, so that re-evaluation is possible if there is a surge in new scientific data concerning specific physicochemical properties.
- It may be valuable to discuss standardised testing further, including Aotearoa New Zealand's capability in testing, what data might be required, and how it aligns to European guidance.
- The precautionary principle may warrant the development of occupational safety guidance where exposure to nanomaterials, particularly via inhalation, is expected

7. Appendix

7.1. Timeline of nanomaterial regulations and guidelines:

7.1.1. Aotearoa New Zealand

2008 –Food Standards Australia and New Zealand (FSANZ) amends the application handbook to ensure any application to approve the use of nanotechnology in food provides appropriate information for FSANZ to conduct a thorough risk assessment. These changes are promoted to industry.

2011 – 'A review of the adequacy of New Zealand's regulatory systems to manage the possible impacts of manufactured nano-materials: Final report' by Colin Gavaghan and Jennifer Moore is published.

2011 **– '**Regulation of nanotechnologies in food in Australia and New Zealand' is published to review the suitability of regulation (Food Standards Code) to manage products that contain nanomaterials.

2011 – FSANZ regulatory framework on nanomaterial safety is reviewed (Nick Fletcher and Andrew Bartholomaeus).

2012 **–** Amendment was made to Cosmetic Products Group Standard, to implement a compulsory labelling scheme and track-recording system for products that contain nanomaterials (enforced in 1 July 2015).

2013 – Manufacturer/importers are obliged to declare the presence of substances managed under the HSNO Act that contain or consist of nanomaterials to the NZEPA at the time of application for approval.

2014 – FSANZ publishes 'Risk analysis in food regulation' which requires food products with nanomaterials to undergo a pre-market safety assessment if potentially unsafe.

2019 – Medsafe publishes 'Guideline on the regulation of therapeutic products in New Zealand – Obtaining approval for new and changed medicines and related products'. Products developed with nano-tech will:

> *typically be referred to the MAAC [Medicines Assessment Advisory Committee] irrespective of whether Medsafe has concluded that the application includes sufficient data to attest to the safety, quality and efficacy of the medicine and that the benefits outweigh the risk of harm to the patient.*

Note: FSANZ established the Scientific Nanotechnology Advisory Group (SNAP), who have an advisory role in the development of guidelines for a range of stakeholders, future uses of nanotechnology in food and food packaging and national/international legislation and policy. However, the year of the group's establishment is not specified.

7.1.2. Australia

2007 – Monash University publishes 'Communication on regulatory aspects of nanomaterials'. The report concludes that there has so far been no demonstrated need for a specific regulatory system for engineered nanomaterials.

2008 – TGA guideline on the therapeutic products that contains nanomaterials: "Any change to the composition or form of that product that influences the safety of the product creates a new product and/or requires reassessment".

2011 – National Industrial Chemicals Notification Assessment Scheme (NICNAS) publishes 'Data requirements for notification of new industrial nanomaterials' which applies to paints, dyes, inks, plastics, cosmetics, consumer goods and surface coatings. Under this scheme, the products that contains nanomaterials (whose properties align with the working definition developed by NICNAS), are considered new products if the nanoscale properties differ from the conventional products and require pre-market evaluation. Submission on health and environmental effects is required along with the guidelines aligned with OECD's advice.

2014 – Amendment on Agricultural and Veterinary Chemical (AgVet) Code Act 1994. The provision restates the importance of the human and environmental effects of the chemical of interest. Broadly, the safety criteria are tightened and human health and environmental aspects are also considered for products that contain nanomaterials.

2014 – Australian Pesticides and Veterinary Medicines Authority (APVMA) publishes Regulatory Guidelines for chemistry and manufacture. Manufacturers and importers of AgVet products which contains nanomaterials are obliged to identify the detailed properties of the nanomaterials for safety assessment.

2015 – APVMA publishes 'Nanotechnologies or pesticides and veterinary medicines: Regulatory considerations'. The report describes the regulatory framework applied for AgVet products and risk assessment considerations for health and environmental effects.

2019 – Industrial Chemicals Act 2019 replaces ICNA Act 1989, which allows the Australian Industrial Chemical Introduction Scheme (AICIS) to take over NICNAS (enforced from July 2020).

7.1.3. European Union

2004 – European Commission releases 'Towards a European Strategy for Nanotechnology'. The report proposes strategic directions to encourage the development of nanotechnology while ensuring its proper regulation.

2006 – Establishes Regulation (EC) No 1907/2006, Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH). The legislation broadly manages the production, use of chemical substances, and their potential impacts on environments and human health. The chemicals produced in the EU or imported into that exceeds one tonne per year criteria are subject to the REACH programme.

2008 – Establishes Regulation (EC) No 1272/2008, Classification, Labelling, and Packaging (CLP) which concerns dangerous substances and mixtures.

2008 – European Commission establishes an advisory group on the regulation of nanomaterials. It is an advisory body that assists the European Commission in the implementation of EU REACH and CLP guidelines that govern environmental health and safety aspects and product labelling with respect to nanomaterials.

2008 – European Commission issues a report 'Communication on regulatory aspects of nanomaterials'. The Commission concludes that, "…risks related to nanotechnology can be dealt with under the current legislative framework, but that certain modifications may be required in light of new information becoming available."

2008 – Establishes Regulation (EC) No 1333/2008 on food additives. The regulation states that if there is a significant change in production methods or in the starting materials used, or there is a change in particle size (for example through nanotechnology) then the food additive prepared by those new methods or materials is considered a different additive and is subject to pre-market safety evaluation by EFSA.

2009 – The EU council approves an updated European cosmetics regulation (Regulation (EC) No 1223/2009). Manufacturers of new cosmetic products that contain nanomaterials are required to notify the EC and provide information six months prior to the product release on the European market. Also, a catalogue is made available of all nanomaterials used in cosmetic products. The regulation also enforces a compulsory labelling scheme for cosmetic products that contain nanomaterials.

2009 – The European Parliament calls for labelling on food products that contain nanomaterials.

2011 – Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. Substances in nanoform require pre-market safety assessment from EFSA.

2011 – The European Commission adopts the Recommendation on the definition of a nanomaterial.

2011 – Regulation (EU) No 1169/2011 on the provision of food information to consumers, which adopts the recommended definition (2011) of engineered nanomaterials, and introduces a compulsory labelling scheme for food products that intentionally incorporate or produce nanomaterials.

2012 – Establishes Regulation (EU) No 528/2012 on making available on the market and use of biocidal products. The legislation provides the standard definition for nanomaterials and related terminologies and requires products that contain nanomaterials to undergo separate risk assessment (on animal and human health, and the impact on the environment) from the non-nano products. It also introduces a compulsory labelling scheme.

2013 – Delegated Regulation (EU) No 1363/2013, amending Regulation (EU) No 1169/2011 on the provision of food information. The major change includes the removal of nano-specific labelling scheme, as it may cause confusion among consumers.

2014 - European Chemicals Agency (ECHA) publishes a safety assessment (best practice guide) for nanomaterials under REACH.

2015 –Regulation (EU) No 2015/2283 amends Regulation (EU) 1169/2011. The food products remain exempted from the mandatory labelling scheme as per Delegated Regulation (EU) No 1363/2013.

2018 – European Food Safety Authority (EFSA) publishes 'Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health'.

2019 – European Commission releases white paper titled 'Anticipation of regulatory needs for nanotechnology -enabled health products'.

2019 – Scientific Committee on Consumer Safety (SCCS) publishes 'Guidance on the safety assessment of nanomaterials in cosmetics'.

2019 – Regulation (EU) 2019/1857 on cosmetic products. Further restriction on the use of titanium dioxide and silicon dioxide, detailing the allowed physicochemical properties if the ingredients contain nanomaterials.

2020 – The existing imported and manufactured products in nanoforms are no longer in compliance with REACH without registration in accordance with the annexes to the guidance documents. The new registration requirement includes detailed information on the characteristics of nanoforms (particle dimensions, shape, surface functionalisation, and surface area), chemical safety assessment, registration information requirements, and downstream user obligation.

2020 – establishes Commission Delegated regulation (EU) 2020/217, issuing a final opinion on the safety classification of titanium dioxide in powder form.

2020 – EFSA publishes draft report 'EFSA guidance on technical requirements for regulated food and feed product applications to establish he presence of small particles including nanoparticles'. The report is undergoing the public consultation (deadline September 2020) at the time of writing.

7.1.4. United States (US)

2006 – The US Environmental Protection Agency (USEPA) establishes the Nanotechnology Task Force whose responsibility is to oversee regulatory approaches that would allow the continued development of nanotechnology while ensuring the safety of FDA-regulated products.

2009 - The Toxic Substance Control Act (TSCA) is concluded to be flexible enough to manage nanomaterial safety during the hearings before the House of Representatives (subcommittee on Commerce, Trade, and Consumer Protection of the Committee on Energy and Commerce).

2011 – USEPA introduces a significant New Use Rule for multiwalled carbon nanotubes. The rule requires 90 day advance notice prior to the importation, manufacturing, or processing of multiwalled carbon nanotube.

2012 - USEPA bans the manufacture of potassium titanium dioxide. The US EPA introduces a new Significant New Use Rule which bans the manufacture of potassium titanium dioxide nanoparticles due to their health risk.

2014 – the Food and Drug Administration (FDA) publishes 'Guidance for industry: Safety of nanomaterials in cosmetic products' and 'Considering whether an FDA-regulated product involves the application of nanotechnology'.

2015 – FDA publishes 'Guidance for industry use of nanomaterials in food for animals'.

2017 – USEPA publishes final rule (RIN 2070-AJ54) establishing reporting and track recording requirements for nanoscale materials under TSCA Section 8(a). Subsequently, USEPA publishes a draft guidance document 'Guidance on EPA's Section 8(a) information gathering rule on nanomaterials in commerce'.

2017 – FDA publishes draft guidance 'Drug products, including biological products, that contain nanomaterials guidance for industry'.

7.1.5. Organisation for Economic Co-operation and Development (OECD)

2005 – Releases a report 'Opportunities and risks of nanotechnologies'. The report highlights that future manufactured nanoparticles will be released gradually and accidentally into the environment. Importantly, the report noted that special properties of nanoparticles with respect to health and safety have not yet been taken into account by regulators. A review of current legislation and continuous monitoring by the authorities is needed.

2006 - The Working Party on Manufactured Nanomaterials (WPMN) is established by the OECD Chemicals Committee.

2012 – 'Guidance on sample preparation and dosimetry for the safety testing of manufactured nanomaterials'. The report lists OECD recommendations for methodologies to assess safety of nanomaterials.

2013 – 'Recommendation of the Council on the safety testing and assessment of manufactured nanomaterials'. The report recommends that member countries apply international and national chemical regulatory frameworks to manage the safety of manufactured nanomaterials.

2014 – 'Nanotechnology and tyres: Greening industry and transport'. This report discusses the emerging use of nanomaterials in tyre products and their technological benefits, while

also highlighting uncertainty in both occupational exposure and the environmental impacts of released nanomaterials.

2015 – 'Harmonised tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces'.

2016 – Conference report 'Science-based support for regulation of manufactured materials'. Discusses and summarises the recent progress in standardisation of detection, characterisation, health effects, and environmental impacts of nanomaterials.

2019 – 'Physical-chemical decision framework to inform decisions for risk assessment of manufactured nanomaterials'.

2019 – 'Guiding principles for measurements and reporting for nanomaterials: Physical chemical parameters'.

2020 – 'Guidance document for the testing of dissolution and dispersion stability of nanomaterials and the use of the data for further environmental testing and assessment strategies' and 'Guidance document on aquatic sediment toxicological testing of nanomaterials'

7.1.6. International Organisation for Standardisation (ISO)

2005 – Establishes a technical committee to consider various matters in nanotechnology (ISO/TC229), which include terminology, nomenclature, measurement, and characterisation, health, safety, and environment.

2010 – ISO/TS 80004-3:2010 Nanotechnologies – vocabulary – Part 3: Carbon nanomaterials (Replaced ISO/TS8004-1:2010 and last reviewed in 2014).

2010 – ISO 10808:2010 Nanotechnologies - Characterization of nanoparticles in inhalation exposure chambers for inhalation toxicity testing.

2011 – ISO/TS 80004-4:2011 Nanotechnologies – vocabulary – Part 4: Nanostructured materials (last reviewed in 2019).

2011 – ISO/TS 12805:2011 Nanotechnologies – Materials specification – Guidance on specifying nano-objects (last reviewed in 2018).

2015 – ISO/TS 80004-1:2015 Nanotechnologies – vocabulary – Part 1: Core terms (last reviewed in 2019).

2015 – ISO/TS 80004-2:2015 Nanotechnologies – vocabulary – Part 2: Nano-objects (last reviewed in 2018).

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2017 – ISO/TS 20787:2017 Nanotechnologies – Aquatic toxicity assessment of manufactured nanomaterials in saltwater lakes using *Artemia sp. Nauplii*.

2018 – ISO 19007:2018 Nanotechnologies – *In vitro* TS assay for measuring the cytotoxic effect of nanoparticles.

2018 – ISO/TR 2885:2018 Nanotechnologies – Health and safety practices in occupational settings.

2019 – ISO/TR 21386:2019 Nanotechnologies – Considerations for the measurement of nano-objects and their aggregates and agglomerates (NOAA) in environmental matrices.

2019 – ISO/TS 21361:2019 Nanotechnologies – Method to quantify air concentrations of carbon black and amorphous silica in the nanoparticle size range in a mixed dust manufacturing environment.

2020 – ISO 21363:2020 Nanotechnologies – Measurements of particle size and shape distributions by transmission electron microscopy.

2020 – ISO/TS 22082:2020 Nanotechnologies – Assessment of nanomaterials toxicity using dechorionated zebrafish embryo.

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