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Identification of Nanotechnology skill shortages in Ireland's Agri-food sector: Towards the safe, innovative and sustainable development of nano-food technology

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Identification of Nanotechnology skill shortages in Ireland's Agri-food sector: Towards the safe, innovative and sustainable development of nano-food technology.

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Thesis submitted to the School of Physics and Clinical & Optometric Sciences in fulfilment of the requirement for the Degree of Doctor of Philosophy (PhD)

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Abstract

The purpose of this research was to assess the nanotechnology skill and capacity shortages in Irelands Agri-food sector. In 2008 the Food Safety Authority of Ireland (FSAI) published its statement on 'The Relevance for Food Safety of Applications of Nanotechnology in the Food and Feed Industries'. The importance of the food sector to the Irish economy was clearly emphasised by the FSAI's statement. The report identified the urgent need for focused research programs into the potential of nanotechnology in the agri-food sector and it highlighted the need for a multi-organisation approach between state agencies, industry and academia to ensure safe innovations of nanotechnology are applied in the sector. This concept was first proposed by the FSAI more than ten years ago, however to date no attempt has been made to quantify the precise role or contribution each organisation could play in closing knowledge gaps.

A review of Ireland's nanofood and agriculture research expenditure over the period 2008 - date revealed that almost €29 billion was invested into nano related activities. Only a fraction of that investment was directed towards nanofood i.e. < 5%. Additionally a survey of the academic community revealed that almost 50% had not actually received exchequer funding for nano-food or agriculture related activities. Despite the lack of funding 40% of academic respondents indicated that they had suitable analytical infrastructure in their home institute to fully characterise food related nanomaterials. In addition more than 60% are confident that the infrastructure was available nationally as well. In contrast the regulatory and enforcement community where not as confident that such infrastructure was accessible to them and more than half of enforcement officers indicated that they would need significant upskilling and training. Interestingly interaction between the regulatory bodies and academia also seems to be quite limited with academics indicating that collaboration with industry was more valuable i.e. 95% of academics did not consider collaboration with competent authorities as being of primary importance. This may be reflective of the fact that the competent authority for food safety does not appear to have a strong research arm nor the available resources to fund research in a similar manner to the EPA.

A brief overview of suitable tools and techniques for the determination and the characterisation of nanomaterials is presented, and an example of a collaborative approach taken by a regulatory control agency and an academic institution is given as evidence of the potential to capitalise on the skillset and analytical infrastructure which is currently available. A potential roadmap for Ireland is presented, involving further engagement between all stakeholders, from academia through to the competent risk assessment bodies, at national, and subsequently at EU level.

This research builds upon the recommendations of previous national reports and it delivers a fresh quantitative look at nanotechnology in the agrifood sector in Ireland. It presents the 'state of the art' and it establishes baseline data of the current national capacity to assist the development of safe nano-food technology, and to fully implement any potential nano-legislation arising from an informed regulatory process.

Declaration

I certify that this thesis which I now submit for examination for the degree award of Doctor of Philosophy, is entirely my own work and has not been taken from the work of others, save and to the extent that such work has been cited and acknowledged within the text of my work.

This thesis was prepared according to the regulations for graduate study by research of the Technological University Dublin and has not been submitted in whole or in part for another award in any other third level institution.

The work reported on in this thesis conforms to the principles and requirements of TU Dublin's guidelines for ethics in research.

TU Dublin has my permission to keep, lend or copy this thesis in whole or in part, on condition that any such use of the material of the thesis be duly acknowledged.

Candidate Signature: Eileen McCarron Date: 12/07/2022

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List of Figures **Page**

List of Figures **Page**

List of Tables **Page**

1.1 Background to this research

The purpose of this research is to assess the nanotechnology skill and capacity shortages in Ireland's agri-food sector. In 2008, the Food Safety Authority of Ireland (FSAI) published its statement on nanotechnology in the food and feed industries in Ireland (FSAI, 2008). The importance of the food sector to the Irish economy was clearly emphasised by the FSAI's statement. The statement essentially reviewed in a qualitative manner the available literature at the time and attempted, via an expert working group, to assess the state of the art of Nano food-technology. The report highlighted the growing concern internationally about the relatively unregulated use of nanomaterials and the apparent lack of toxicological data on some of the more commonly used nanomaterials in the food sector. The report identified the urgent need for focused research programs into the potential of nanotechnology in the agri-food sector.

In 2013 'SafeFood' commissioned Teagasc to carry out a review of the applications of nanotechnologies in the agrifood sector. A key conclusion of this report mirrors the FSAI report by highlighting the need for a multi-organisational approach between state agencies, industry and academia to ensure that safe innovations of nanotechnology are applied in the sector (Handford *et al*., 2014). The concept of a focused multi-agency research approach was first proposed by the FSAI more than ten years ago, a question to be raised at this point in time is; have any of the FSAI recommendations been addressed over the ten-year period, and if so, to what extent have they been addressed?

In light of the urgency the FSAI attributed to the focused research programmes, it is important that this current research identifies; if there has been any attempts to quantify the precise role or contributions of the relevant government departments and state agencies. The role which academia can play in closing the knowledge gap needs to be identified also. A key question to ask is what progress has been made with respect to this? The potential consequences of a lack of implementation include; a lack of regulatory controls on applications of nanotechnology, potential health and safety issues relating to applications of nanotechnology, and possible consumer concerns or rejection of this technology in the agri-food sector. From a regulatory prospective, anecdotally there appears to be infrastructure and knowledge deficits, these deficits would need to be addressed in order to support

state agencies who are responsible for regulatory control and/or for characterisation of applications of nanotechnology in the agri-food sector.

Furthermore, the national capacity to address these potential challenges does not appear to have been reviewed. The situation is further compounded with international uncertainties in basic approaches to the characterisation of nanoparticles in food matrices.

It is crucial that this thesis builds upon the currently available reports and that it delivers a fresh quantitative look at Ireland's ability to enforce any potential 'nano' regulation, and/or to identify applications of nanotechnology, nanomaterials and nanoparticles which may be used in the agrifood sector. It is imperative that this research quantitatively reviews the 'state of the art,' and that it establishes the national capacity baseline data, in order to assist the development of safe nano-food technology and to fully implement any potential nano-legislation arising from an informed regulatory process.

1.2 Overview of Nanotechnology in the Irish Economy

The most relevant published reports on nanotechnology in Ireland, from a statutory, strategic, and/or regulatory prospective were reviewed. Recommendations arising from the Irish Council for Science Technology and Innovation (ICSTI) report of 2004 (Forfás, 2004), the FSAI report published in 2008 (FSAI, 2008) and the Teagasc/SafeFood report from Handford *et al*. published in 2014 (Handford *et al*., 2014) are summarised in brief below. An overview of Ireland's nanotechnology reporting landscape over the period 2004 – 2014 is outlined in Figure 1.1

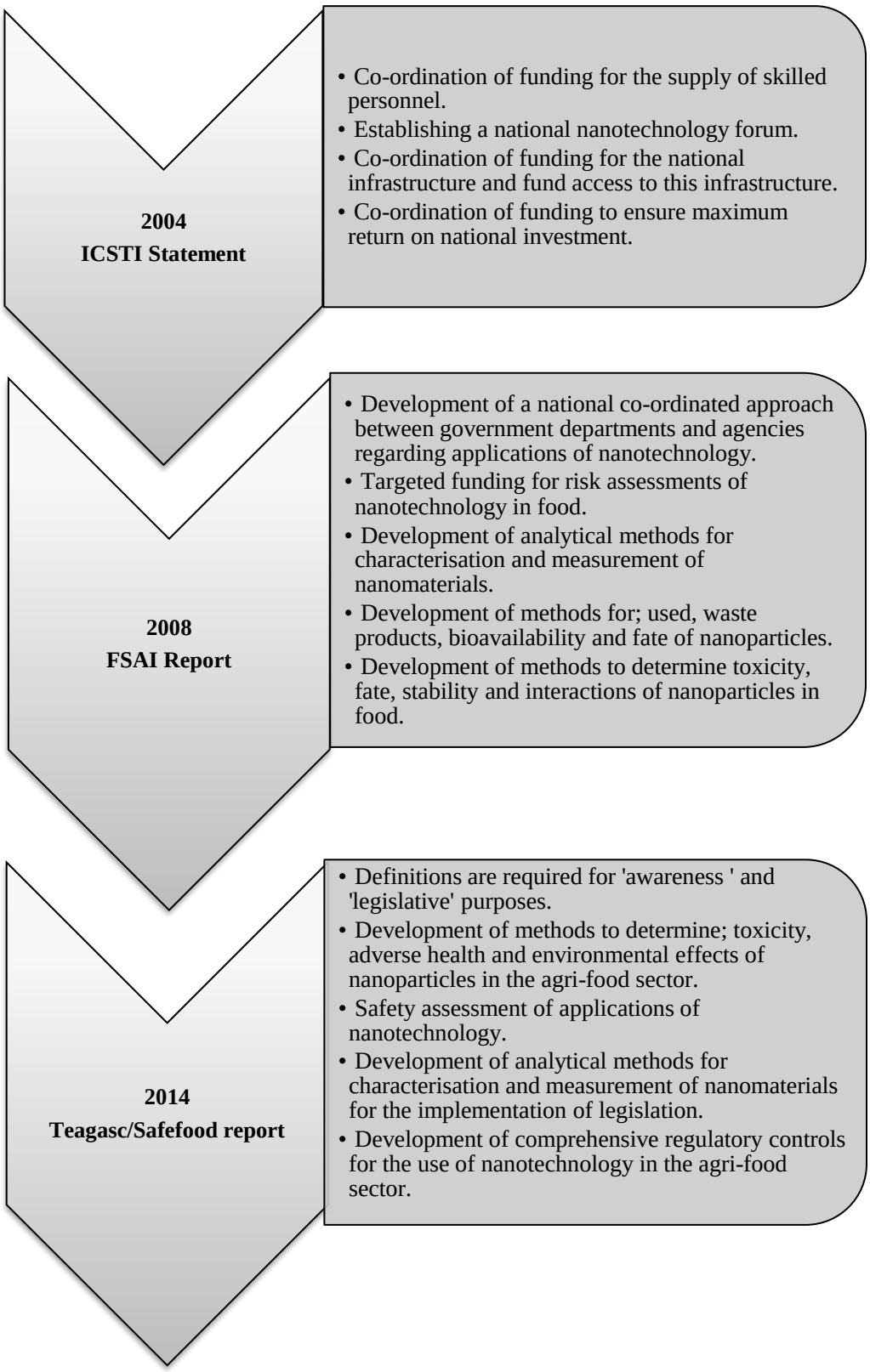

Figure 1.1: Timescale, and key recommendations from the relevant reports

1.2.1 ICSTI Statement on Nanotechnology report (2004)

In 2004 the ICSTI Nanotechnology Task Force issued a 'Statement on Nanotechnology' (Forfás, 2004), the Nanotechnology Task Force, (along with various stakeholders) conducted an analysis of 'major global trends and the needs of Ireland as a small open knowledge-economy' (Forfás, 2004, p. 4). The stakeholders included relevant government departments, their agencies, research organisations, indigenous and multinational industries, and the wider community. The Nanotechnology Task Force identified a number of objectives:

- To agree, on a national nanotechnology definition, and implementation of a national nanotechnology roadmap.
- To understand, the 'general' nature of the nanotechnology opportunity for the Irish economy, and the 'specific' nature for key sectors of the Irish economy.
- To assess the existing national nanotechnology capability.
- To develop a sustainable vision and strategy for nanotechnology in Ireland.
- To agree on recommendations to enable the key stakeholders to work together to exploit the nanotechnology opportunity for Ireland (Forfás, 2004).

Sectoral analysis was carried out in order to identify specific opportunities which could arise in key sectors of the Irish economy. In the agri-food sector overview, the ICSTI statement indicated that 'the most important requirements for the agri-food sector are to increase the functionality of food and to ensure its complete safety' (Forfás, 2004, p. 46). The report also states, 'it should be recognised that all important trends in this sector will be shaped by the relevant legislative environment' (Forfás, 2004, p. 47).

A national nanotechnology strategy was developed as a result of the task force review and the ICSTI statement on nanotechnology outlined a series of recommendations based on the agreement of stakeholders. A number of key recommendations that are of particular relevance in the context of this research are the requirement for:

- Co-ordination of funding, of fundamental and of applied nanotechnology research in third level institutions, with a view to ensuring the necessary supply

of skilled professionals, to enable key sectors to exploit specific nanotechnology opportunities.

- The establishment of a national nanotechnology forum to facilitate co-operation between academics, industry and funding agencies.
- The relevant agencies should co-ordinate funding of the national infrastructure necessary for international competitive research, and they should fund access to this infrastructure.

The relevant agencies should co-ordinate funding, with a view to ensuring maximum return on the national investment (Forfás, 2004).

1.2.2 FSAI Report (2008)

In 2007, the FSAI's Scientific Committee set up an expert working group to carry out a scientific assessment of applications of nanotechnology in food production and processing, in order to consider any potential issues relating to food safety and risks to the consumer. (FSAI, 2008). The terms of reference for the scientific advisory working group on nanotechnology were as follows:

- To provide advice on; the main applications of nanotechnology foreseen in food and animal feed, on the adequacy of current risk assessment methodology for identification, assessment and control of any potential risks arising from the use of nanotechnologies in the agrifood sector, or as a result of the presence of nanoparticles in food.
- To identify gaps in the regulatory framework and any information which is needed to carry out an assessment of the risk of nanoparticles in the food chain, and to advice on approaches which could be used to fill such gaps.
- To advice the FSAI on the development of a national position on nanotechnology in relation to food safety and risks to the Irish consumer.
- To support the FSAI in the drafting of a report to reflect these issues (FSAI, 2008).

In relation to applications of nanotechnology in the food and feed industry, the FSAI Scientific Committee issued a comprehensive list of recommendations. A number of key recommendations which are particularly relevant in the context of this research are as follows:

- The FSAI should keep under review; advances in the science of nanotechnology, risk assessment approaches and the legal framework governing the application of nanotechnology in food and feed.
- Where nanoparticles are incorporated in food or food packaging, EC labelling provisions should require that such products are labelled to provide this information.
- Legal provisions should be considered at EC level to ensure that food and feed ingredients produced via the application of nanotechnology are specifically controlled, to ensure that where the properties are changed/re-engineered to the nanoscale, they should be re-evaluated in terms of safety.
- Consideration should be given to whether additional controls are required for the disposal and/or recycling of nanoparticle-containing food contact and other materials.
- Food surveillance programs should include investigation of the potential for nanoparticles used in packaging to migrate into foods and also to be recycled in the environment and enter the food chain indirectly (FSAI 2008).

At national level the committee see the importance of developing a coordinated national approach between government departments and agencies, additionally it recommends:

- Research with application of targeted funding should be undertaken to increase the reliability of the risk assessment of nanotechnology in food.
- Development of methods for the characterization and measurement of nanoparticles.
- Development of methods for the safe and effective disposal of used, unused, or waste nanoparticles and for determining the bioavailability and fate of nanoparticles in humans and animals.
- Development of methods to investigate the potential toxicity of nanoparticles, the stability/lability/potential interactions of nanoparticles in foods (FSAI, 2008).

1.2.3 Teagasc/Safefood Report (2014)

In 2013 'Safefood' commissioned research in relation to '*Nanotechnology in the Agri-Food industry on the island of Ireland: applications, opportunities and challenges'* A report arising from the research of Handford *et al*. was published in 2014 (Handford *et al*., 2014). The research was conducted jointly by the Institute for Global Food Security at Queen's University, Belfast, and the Teagasc Ashtown Food Research Centre, Dublin. The aims of the research were:

- To investigate the agri-food industry's awareness and perception of nanotechnology.
- To undertake a review of the scientific and technical literature to ascertain the industrial ramifications of nanotechnology.
- To conduct a review of the literature concerning consumer perceptions and the factors that influence acceptance of nanotechnology (Handford *et al*., 2014)

The research involved conducting a literature review into the industrial ramifications of nanotechnology on the island of Ireland. The review was followed up by a qualitative survey, conducted through face-to-face and telephone interviews, and by an online survey also.

The report issued following the research presented a number of recommendations for consideration, those of particular relevance in the context of this research are:

- Definitions of nanotechnologies and associated terminology should be provided in relation to food/agri-food products, for 'awareness' and 'legislative' purposes.
- Toxicological assessments are needed to establish potential health and environmental effects associated with the use of nanoparticles in agriculture, animal feed, food and food-related products.
- Adequate safety assessment should be conducted where the application of nanotechnology alters existing products or processes.
- Analytical tools and methodologies should be developed, for the determination and measurement of nanoparticles in food, the environment,

for quality control, risk assessment and for the implementation of legislation.

- A clear, transparent and comprehensive regulatory framework should be implemented for the use of nanotechnology in agri-food products. The governance of nanomaterials should be globally harmonised through international bodies where possible, in addition to implementing regulations at local government and at EU level. Relevant legislation should also incorporate a risk assessment framework (Handford *et al*., 2014).

The most relevant conclusions to note from the research of Handford *et al*. were that there is uncertainty from a scientific perspective regarding the potential risks of nanotechnology, there is also uncertainty regarding the likely consumer acceptance of this technology. Handford *et al*., indicate that 'there is an important role to be played by organisations such as SafeFood … and other actors, e.g. universities/research institutions, industry, [non-government-organisations] (NGO) etc., in influencing consumer reactions' (Handford *et al*., 2014, p65), by providing them with accurate, unbiased and reliable information.

1.2.4 Conclusions from the overview of Nanotechnology in the Irish Economy (2004-2014)

In conclusion, it should be noted that the most important themes underpinning the reports reviewed is the requirement for the following:

- Development of comprehensive regulatory controls for the use of nanotechnology in the agri-food sector.
- Development of a national coordinated approach between government departments and agencies regarding applications of nanotechnology.
- Co-ordination of funding; to support the national infrastructure, for the supply of skilled personnel and providing funding allowing access to this infrastructure.
- Development of analytical methods for the characterization and measurement of nanomaterials and methods to determine; toxicity, adverse risks to health, and environmental effects resulting from the use of nanoparticles in the agri- food sector.

In recognition of the importance of supporting these national developments, it is necessary to determine how have the recommendations from the reports been disseminated to the relevant government departments and agencies. Who, (government department/agency) has national responsible for coordinating and for ensuring that the recommendations from these reports are implemented? What role/responsibilities does each of the government departments and agencies have regarding regulatory control of nanomaterials? In addition, has exchequer funding supported the national research infrastructure; with respect to targeted research, towards the development of skills and knowledge, and supporting access to the national research infrastructure?

1.3 Research Aim and Objective

The aim of this research is to identify the regulatory and monitoring challenges presented to Irish state agencies due to the evolution of nanotechnologies in the agrifood industry and to assess the national capacity to respond to such challenges. The objective of this research is to provide support to state agencies to enable them implement regulatory controls, arising from any potential 'nano' legislation within the sector.

1.4 Conceptual Framework

This research investigates a research hypothesis that; "Ireland's analytical and research infrastructure is not sufficiently future proofed to support state agencies with responsibility for the regulatory control of nanotechnology in the agri-food sector".

The hypothesis is investigated using a 'conceptual framework' comprising of four phases of research, as indicated in figure 1.2.

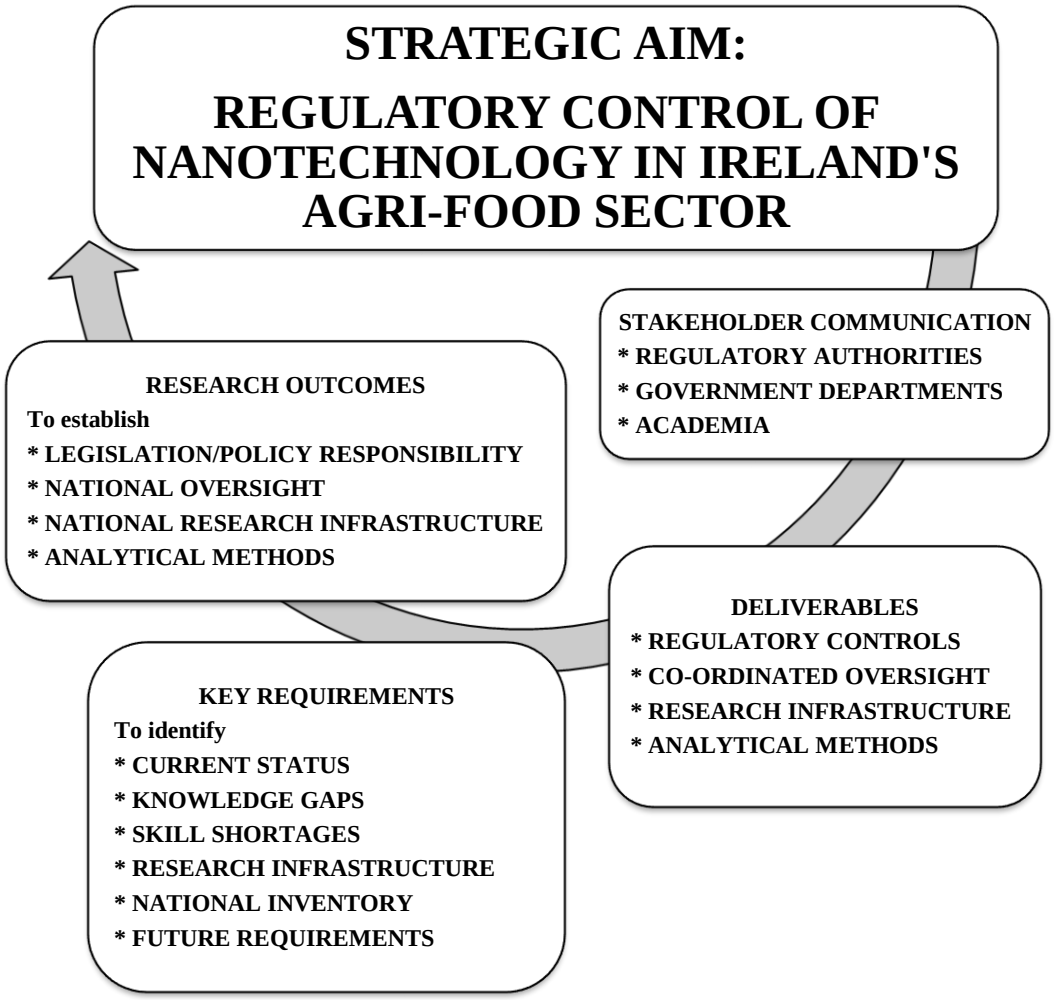

Figure 1.2: Schematic representation of the conceptual framework adopted for this research thesis

Phase 1: Communication with stakeholders to determine the 'state of the art'

A progress review was undertaken to determine what actions if any have been taken with respect to the recommendations arising from the FSAI report of 2008 and/or the Teagasc/Safefood Report of 2014. In 2016 the FSAI was the only government agency who indicated that they were directly involved in this area of work at that point in time (O'Mahony, 2016). Other government departments/agencies (e.g. Department of Agriculture, Food and the Marine (DAFM), Health Products Regulatory Authority (HPRA), Environmental Protection Agency (EPA)) appeared to have no direct involvement with respect to applications of nanotechnology.

In 2017 a survey from the Joint Research Centre (JRC) of the European Commission (EC) was sent to all member states (MS) in order to help identify and specifically address EC requirements for nanomaterial reference materials. The survey was directed to the relevant government agencies, i.e. the FSAI (competent authority), the State Laboratory (SL) and the Dublin Public Analyst's Laboratory (DPAL). The agencies agreed to take a collaborative approach with respect to this area of work, to avoid duplication of efforts and to provide for the prudent use of technical resources and equipment. The DPAL was designated as the enforcement laboratory for nanomaterials in food in Ireland. To date, there has been no requests for technical/analytical support from the competent authority, nor has there been any requirement for DPAL or for the SL to carry out any investigations/analysis with respect to nanomaterials.

In light of the fact that no enforcement activities or monitoring of controls have taken place to date, Ireland's analytical and research infrastructure in the area of nanotechnology has not been sufficiently tested to identify what support can be provided to state agencies who are responsible for the regulatory control of nanotechnology in Ireland's agri-food sector.

Phase 2: Outlining the Research Themes – Deliverables

This phase of the research comprised a comprehensive literature review and technology assessment of nanotechnology in the agri-food sector.

The review process consisted of three aspects:

- A review of literature was carried out to determine key theories and future potential, this aspect of the work presented an opportunity to examine terms and definitions that were relevant throughout this research.
- A review of international projects such as European Union (EU) programme projects and reports was conducted; this helped to identify aspects of best practice.
- A review of literature was also carried out to identify technology and methodology, which could be suitable for the characterization of nanomaterials.

Based on the review of literature, and as outlined in section 1.2.4, conclusions drawn from the relevant reports of nanotechnology in the Irish economy over the period 2004-2014 relate to four key themes or deliverables, i.e. the need for;

- Development of regulatory controls.
- Development of a coordinated approach between government departments.
- Coordination of funding to support the national research infrastructure.
- Development of analytical methods for characterization and measurement of nanomaterials.

These research themes/key deliverables formed the cornerstones of this research.

Phase 3: Identification of the key requirements

This phase involved engagement with stakeholders to determine what are their roles and responsibilities, to identify their specific requirements and to determine what initiatives could be implemented in order to future proof Ireland's analytical and research infrastructure.

The investment of exchequer funding in recent years into research has been significant, however little public information exists to represent how such investment impacts directly on areas such as the Nano food sector. An assessment was carried to identify projects, infrastructure, and facilities that were funded by the exchequer, in order to establish a base line measure of Ireland's capability in this area. This involved accessing funding agencies databases and exploring the outcomes of funded projects. A review of exchequer investment was also undertaken to determine the availability of, and the location of skilled personnel/resources and infrastructure, which could be made available to state agencies if required in order to support their regulatory function.

An overview of some of the most suitable techniques and methodology used for determination of the physio-chemical properties of nanomaterials is presented. The purpose of this is to provide a comprehensive guidance document outlining the relevant characterisation techniques/methods, with a brief overview of the application range, advantages and disadvantages, as well as the limits of application/quantification.

Phase 4: Presentation of the Research Outcomes

This is the analysis phase, assembling and integrating the data from phases 1-3 which is used to formulate and identify Ireland's skilled resources, research infrastructure, and any potential barriers to the development of nanotechnology in the agricultural sector. Recommendations from this research will be presented for consultation and consideration of the relevant stakeholders.

1.5 Research Questions

One of the first steps to be considered at the beginning of any research is to identify the research question(s) and how to go about answering the question(s). The main research question guiding this study is: **What are the gaps and deficiencies in Ireland's 'analytical and research infrastructure', in order to support state agencies who are responsible for the regulatory control of nanotechnology in Ireland's agri-food sector?**

This research will address the main research question by investigation the following key related questions

- What is the current status of nanotechnology in Ireland's agri-food sector?
- What are the knowledge gaps for state agencies in assessing the safety of potential nanotechnology innovations with respect to legislative requirements?
- Are there identifiable skill shortages within state agencies in order to facilitate closing any knowledge gaps?
- Could Irelands 'exchequer funded' research infrastructure support state agencies in closing any identified gaps and shortages?
- How can Ireland establish and promote an accessible inventory of national nanotechnology infrastructure which is suitable for the characterisation of nano-food technologies?

These questions underpin the research themes investigated within this research. The dissemination of the results could potentially have impacts beyond a purely national interest. They may be particularly relevant for the attraction of foreign direct investment in the nano-arena by demonstrating a level of awareness of

nanotechnology amongst Irish stakeholders. In addition, they could ultimately give greater confidence to the Irish food industry and to its customer base nationally and internationally in relation to Irelands approach to the development of novel nano-food products.

1.6 Relevance of the Research

An underlying theme of the reports referenced earlier has been the growing concern with regard to the relatively unregulated use of nanomaterials. Additional concerns relate to the lack of analytical tools and methodologies available for the determination and measurement of nanoparticles in food, the apparent lack of toxicological data on some commonly used nanoparticles in the food sector, and the fear that such knowledge gaps could potentially stifle nano-innovation in the sector with significant loss to the national economy. The work proposed as part of this research has been specifically designed with the relevant report recommendations in mind and it seeks to address many of the key information deficits that have been highlighted.

The importance of the food sector to the Irish economy was clearly emphasised in the FSAI's Statement and the relevant reports highlight the urgent need for focused research programs into the potential of nanotechnology in the agri-food sector.

The awareness of and the potential impact of legislation, as it applies to the competent authority and to the designated laboratories is pertinent, and the strategies used to communicate; innovations, risks, and legislative implications to all stakeholders are paramount to the success of this technology in the agri-food sector.

Additionally, is imperative that this research clearly identifies the extent and the impact of knowledge and skill transfer from academia to Irish state agencies, and that it highlights any knowledge and skill gaps which require addressing.

This research will examine ways in which state bodies can collaborate with each other in order to establish a national regulatory network, which is a strong, informed, and proactive network.

1.7 Research Design

The aim of this research is to identify the regulatory and monitoring challenges presented to Irish state agencies due to the evolution of nanotechnologies in the agrifood industry and to assess the national capacity to respond to such challenges. In order to achieve this aim and to answer the research questions, the work requirements of this research are structured as outlined below:

1) Literature review and technology assessment of nanotechnology in the agri-food sector in Ireland.
2) Determination of exchequer infrastructure investment in nanotechnology and analysis of Ireland's nano-investment and returns over a 10-year period.
3) Characterisation techniques for the determination of nanomaterials in the agri-food sector, satisfying regulatory needs.
4) Assessing Irelands capability/capacity and infrastructure needs to support construction of a searchable database of expertise and capacity, with verifiable 'nano capabilities'.
5) Identification of skill shortages and barriers to capability, with recommendations for stakeholders.

The activities pertinent to each of the phases outlined above is presented in greater detail in chapter 2, the methodology chapter.

1.8 General introduction to Nanotechnologies

As the quality and safety of our food is becoming increasingly important, producers of food are facing unprecedented challenges such as; food shortages and increasing demands globally, an increase in foodborne diseases and high levels of food spoilage and wastage (Uyttendaele, Franz and Schlüter, 2015). As a result of these challenges the food industry is actively working to develop new, more efficient, sustainable, and low cost technologies to replace and/or to supplement existing ones (Eleftheriadou, Pyrgiotakis and Demokritou, 2017). The industry is constantly looking for ways to improve the quality of food, to improve the taste, nutritional value, shelf life and the traceability of food products (Chaudhry *et al*., 2008). Over the past number of years, advances in research has led to the use of new technologies within the food sector. The most notable advances in research are

those related to applications of nanotechnology. Nanotechnology is an enabling technology that has opened up new opportunities for many industries, including the agriculture food and the feed sector (Eleftheriadou, Pyrgiotakis and Demokritou, 2017, Peters *et al*., 2016). Nanotechnology can be used to manipulate and/or to change the structure, texture, colour, taste, or quality of products. Nanomaterials may be intentionally added to food to supplement minerals and vitamins. They are often used as pigment enhancers too. One of the most commonly used pigments globally is Titanium dioxide (TiO_2) which is often used to increase the 'whiteness' and to improve the flavour of foods (Winkler *et al*, 2018).

TiO_2 is a naturally occurring element which has been used universally in the food sector for many years, and food-grade TiO_2 (E171) has been authorised as a food additive in the EU (Winkler *et al*, 2018). In recent years TiO_2 in the Nano form (TiO_2 NP's) is been used more readily due to the perceived superior properties of these materials as compared to the corresponding macro or fine particles. The smaller particle size and greater surface to volume ratio increases the reactivity of their surface area, and consequently the bioavailability of the particles, additionally TiO_2 NP's have different physiochemical properties compared to the larger particles, i.e. different size, shape, and/or surface characteristics. (Shi *et al*, 2013).

TiO_2 (E171) is used in various food products such as sweets, confectionary and milk based products. Figures provided by the food industry show highest expected concentrations of TiO_2 in various foods e.g. decorative coatings and fillings (for pastries) may contain up to 20,000mg/kg, chewing gum may contain up to 16,000mg/kg, processed nuts up to 7,000mg/kg, with salads sandwich spreads containing up to 3000mg/kg (EFSA, 2016). Sweets and chewing gums have comparatively high levels of TiO_2. In a study carried out by Chen *et al* in 2013, six different brands of chewing gum were analysed to determine the (TiO_2) physiochemical properties (e.g. composition, shape, size distribution, surface chemistry). Results from this study showed that more than 93% of the TiO_2 particles in the chewing gum samples were smaller than 200 nm and between 18–44% were smaller than 100 nm (Chen, 2013).

Many reports express health concerns about the inclusion of TiO_2 NP's in food. Researchers raise concerns about the potential for these smaller nano sized particles

to cross over cell wall barriers (Musial *et al*, 2020, Winkler *et al*, 2018, Chen, 2013). The International Agency for Research on Cancer (IARC) have classified TiO_2 as a Group 2B carcinogen (possibly carcinogenic to humans) (Shi *et al*., 2013). In light of this it is particularly concerning that children, who are the main consumers of sweets, chewing gum, and pastries are been exposed to high levels of TiO_2, and potentially for a substantial period of time during their formative years.

In 2016 EFSA conducted a 'Re-evaluation of titanium dioxide (E171) as a food additive', based on the data provided by various international sources, the panel concluded that "the toxicological data available and exposure data obtained from the reported use/analytical levels of TiO_2 (E 171), considered in this opinion would not be of concern" (EFSA, 2016). Data detailing the potential health effects of TiO_2 in humans is not widespread, however several studies demonstrate the adverse effect of TiO_2 arising from experiments which were carried out on animals (Winkler *et al*, 2018). In 2017, the French Agency for Food, Environmental and Occupational Health (ANSES) published concerns about the health implications of the use of TiO2 NP's arising from a study conducted by Bettini *et al* in 2016. This study reported exposure levels in rats which "could potentially cause precancerous colorectal lesions" (Bettini *et al*, 2017) ANSES indicated that further studies were required to fully characterise TiO_2 NP's and toxicology studies were needed to determine if there was any evidence of potential carcinogenic effects in humans.

In 2019, ANSES reviewed the most recent studies published between 2017 and 2019 on the use of TiO_2 as a food additive. ANSES carried out a scientific review of the available data and concluded that no further studies were available which demonstrate that TiO_2 NP's does not pose long-term health risks. Pending further data and full characterisation of TiO_2 NP's in food, France banned the use of E171 as a food additive, as a precautionary measure against any harmful effects on humans, due to any prolonged exposure to this material (ANSES, 2019, Musial *et al*, 2020). Following the ANSES review the EFSA Panel on Food Additive and Nutrient Sources (EFSA ANS Panel) were of the opinion that data gaps and uncertainties still existed, and they required follow-up actions. (Younes, *et al*., 2021). Therefore, the European Commission issued a call to interested business operators seeking further data and information from them, to address their concerns relating to reproductive and developmental toxicity. On review of the information

provided the Commission suggested amendments to the Food Additives Regulation to include new specifications for TiO_2 outlining proposals specifying that the 'constituent particle size' should be measured. The EFSA ANS Panel recommended that the "EU specifications for E 171 include the parameter of median, minimum external dimension by particle number > 100 nm (measured by electron microscopy), which is equivalent to less than 50% of constituent particles by number with a minimum external dimension < 100 nm" (Younes, *et al*., 2021).

The Commission recommended that specifications for the food additive titanium dioxide (E 171) be amended in Regulation (EU) 231/2012 (European Commission, 2012), and in January 2022 Regulation (EU) 2022/63 (European Commission, 2022) was issued amending Annexes to Regulation (EC) No 1333/2008 (European Parliament and Council, 2008) regarding the food additive E171.

This issue is only one of many potential issues, that are evident where a number of member states have undertaken substance evaluation reviews on other food additive materials in the Nano form which were identified as particularly concerning, e.g. Silver (nano) and Silicon Dioxide - 2015 (The Netherlands), Zinc Oxide - 2016, and MWCNT-2018 (Germany) (EUON, n.d.). As a consequence of the growing concern raised in relation to the use of materials in the Nano form, it is imperative that member states have protocols and procedures in place in order to implement control plans where it is necessary to restrict the use of unauthorised materials in the food chain.

1.9 Nanotechnology in the market place and food chain

Applications of nanotechnology in the consumer domain have been documented since 2005 when the Woodrow Wilson International Centre for Scholars and the Project on Emerging Nanotechnology (PEN) created an online searchable inventory of nanotechnology include based consumer products which were reportedly in the marketplace. The inventory of consumer products is available at the Consumer Products Inventory (CPI), Project on Emerging Nanotechnologies website (Project on Emerging Nanotechnologies, 2013). A search of the inventory showed, products classified according to categories as shown:

- Appliances (Heating, cooling and air; large kitchen appliances; laundry and clothing care)
- Automotive (Exterior; maintenance and accessories)
- Goods for Children (Basics; toys and games)
- Electronics and Computers (Audio; cameras and film; computer hardware; display; mobile devices and communications; television; video)
- Food and Beverage (Cooking; food; storage; supplements)
- Health and Fitness (Clothing; cosmetics; filtration; personal care; sporting goods; sunscreen)
- Home and Garden (Cleaning; construction materials; home furnishings; luxury; paint)
- Cross-Cutting (Coatings)

  (Project on Emerging Nanotechnologies, 2013)

Since the creation of the CPI inventory various other nanotechnology related inventories have become available online, e.g. in 2007, Japan's National Institute of Advanced Industrial Science and Technology created an inventory of 'nanotechnology-claimed consumer products'. In 2009, the European Consumers Organization (BEUC) and the European Consumer Voice in Standardization (ANEC) joined together to develop an inventory of 'consumer products with nano-claims'. In 2012, the Danish centre for Nano safety and the Environmental Protection Agency set up a nano database and product register. The register focuses on 'consumer products' which contain 'intentionally manufactured nanomaterials', which may be released during normal conditions of usage (The Danish environmental Protection Agency, 2015). Additionally, the Swedish Chemicals Agency, (KEMI), drafted a regulation requiring companies to provide information on nanomaterials in chemical products for inclusion in the Swedish products register (ChemSafetyPRO, 2016). The regulation relates to the intentional inclusion of nanomaterials within the product, regardless of the concentration of the nanomaterials, it does however exclude nanomaterials that are natural or incidental products. (Bergeson and Hutton, 2017).

1.10 Nanotechnology in the agri food and feed sector

Advances in research have led to the use of new technologies within the agriculture sector, of which nanotechnology is at the forefront. Nanotechnology is an enabling technology that has opened up new opportunities for many industries, including the agricultural sector (Eleftheriadou, Pyrgiotakis and Demokritou, 2017, Peters *et al*., 2016). Nanotechnology can be used to manipulate and/or to change the structure, texture or quality of products. It can be used in combination with other technologies to improve procedures for production, processing, storage, transportation, traceability, safety and security of food (Chaudhry *et al*., 2008). Its use in the agriculture sector is proving very successful, resulting in the development of new and innovative applications for the food and feed production industries.

In 2016 Peters *et al*., presented a review of '*Nanomaterials for products and application in agriculture, feed and food*'. The review sought to obtain information about applications of nanomaterials which were already on the market in the agriculture sector and those which were at the developmental stage (Peters *et al*., 2016). The most common applications of nanotechnology in the agriculture, food and feed sector were nano-encapsulated agrochemicals (e.g. nano-pesticides, fertilizers), food additives and supplements (nano-nutraceuticals), antimicrobials and biocides, and active and intelligent food packaging (Aschberger *et al*., 2015). Further examples of different applications in the agri/feed/food sector are outlined in table 1.1 (Peters *et al*., 2014).

Table 1.1: Applications of nanotechnology in the agri/feed/food sector

Agricultural activities	• Nanocapsules, designed for more efficient delivery of pesticides, fertilizers and other agrochemicals • Nanomaterials for detection of animal and plant pathogens • Nanomaterials for identification, preservation, tracking, and tracing
Food and feed	• Nanocapsules to improve dispersion, bioavailability and absorption of nutrients • Nanomaterials to improve colour • Nano-encapsulated to improve flavour • Nanotubes and nanoparticles as gelation and viscousifying agents • Nanoparticles for selective binding and removal of chemicals and pathogens from food
Food packaging	• Nanoparticles to detect chemicals of foodborne pathogens • Biodegradable nanosensors for temperature and moisture monitoring • Nanoclays and nanofilms as barrier materials to prevent spoilage and oxygen absorption • Nanoparticles for antimicrobial and antifungal surface coatings
Food supplements	• Nanoparticle suspensions as antimicrobials • Nano-encapsulation for targeted delivery of nutraceuticals

Adapted from EFSA supporting publication 2014: EN-621 (Peters *et al*., 2014)

1.11 Regulation of nanotechnology in the European Union (EU)

While it is recognised that applications of nanotechnology have potentially significant economic benefits, it is important to consider aspects of health and safety, environmental risks, along with controls and regulation of this technology. A review carried out by Amenta *et al* of nanotechnology regulation in the agri/feed/food sector in the EU and non-EU countries concluded that the EU and Switzerland are the only regions globally where nanotechnology/nanomaterials are included in legislation, or where legislation is being revised to include provisions for nanomaterial usage. (Amenta *et al*., 2015). Some sectors and member states have defined policy documents where nanotechnology/nanomaterials are referred to either explicitly or implicitly. Examples of some of the most relevant EU/MS policy, recommendations, or sector specific legislation is presented in Appendix 1, Table A1.

As the number of applications of nanotechnology in food and feed continues to grow it is important that the EU continues to develop legislation and regulatory policies to manage these applications. To date, there is no specific legislation in the EU which is solely dedicated to regulation of nanomaterials. Existing sector specific legislation covering materials in the macro form is generally considered to

be sufficient to cover applications of nanomaterials in current use (Amenta *et al*., 2015).

Enforcement of regulations within Europe is the responsibility of the national competent authority; therefore member states must ensure that they have official controls in place to monitor compliance. Key challenges in the enforcement of regulations is the availability of, or lack of:

1. Clearly defined and comprehensive regulatory policies.
2. An enforcement plan to monitor compliance and an action plan for policy non-compliance.

Some member states are concerned about the safety of applications of nanotechnology and consequently they have developed national policies and nanomaterial inventories as discussed in section 1.9. For example, the French government introduced the first national policy in the EU for the mandatory reporting of Nanomaterials (French Ministry of Ecology, Sustainable Development, Transport and Housing, 2012). The policy directs for mandatory reporting of all nanomaterials, companies are obliged to declare "the quantities and uses of substances at nanoscale produced, distributed or imported in France. A declaration is mandatory if the minimum quantity of 100 grams of substance has been produced, imported or distributed during the previous year" (ChemSafetyPRO, 2016). Similarly, Belgium and Sweden also have introduced processes for 'nanomaterial' registration (Bergeson and Hutton, 2014, ChemSafetyPRO, 2016).

No comparable national legislation or reporting protocols have been introduced in Ireland. In Ireland the FSAI is the competent authority with overall responsibility for enforcement of food legislation, this task is managed through the National Control Plan (NCP) as laid down in the requirements of Regulation (EC) No 2017//625 (European Parliament and Council, 2004). The primary objectives of the NCP are to:

1. To ensure compliance with food legislation and standards.
2. To implement an enforcement policy of food legislation.
3. To deliver an effective and efficient food safety control system.
4. To support EU harmonisation of food safety rules (FSAI, 2018).

The FSAI and the Department of Agriculture, Food and Marine (DAFM) have jointly prepared Ireland's enforcement plan, in consultation with the various competent authorities. The NCP presents the national sampling plan and it outlines the roles and responsibilities of the various competent authorities to ensure compliance with General Food Law, Novel Foods, Labelling, Additives and Flavourings, Food Contact Materials and a range of other food legislation.

1.12 Issues with EU Policy/Legislation – Terminology/Practical Application

In the early 2000's significant progress was made towards translating nanotechnology from the laboratory to practical applications for everyday use. Along with the rapid developments in this technology came multiple definitions of nanotechnology; however, there is still a lack of agreement on standardised terminology for nanotechnology (Boholm and Larsson, 2019). This vacuum with respect to terminology impacts directly on planning and decision-making and on establishing regulatory requirements for 'nano' applications and products. In particular, the lack of consensus in relation to nano terminology has led to difficulties in defining ingredients and products in the consumer domain (Handford *et al*., 2014). Several calls for standardised definitions and generic terminology for nanotechnology were made and are the subject of much debate. However, with no global consensus the area is generally in a state of uncertainty with respect to regulation.

1.12.1 European Commission (EC) Definition

In 2011, the EC published a "Recommendation on the definition of a nanomaterial" which is sometimes referred to as the EC Definition. The purpose of the definition was to promote consistency within member states. The definition is not legally binding; it serves as a reference which may be applied to various sector applications and it can be 'adapted' to specific product applications. The Commission recommends that "Member States, the union agencies and economic operators are invited to use the definition of the term 'nanomaterial' in the adoption and implementation of legislation, and policy and research programmes concerning products of nanotechnologies" (European Commission, 2011a).

In summary the EC definition refers to a nanomaterial as 'a natural, incidental or manufactured material,' particles of the material may be, 'in an unbound state, an aggregate or an agglomerate,' where ≥50 % of the particles in the number size distribution, for one or more external dimensions is in the size range 1-100 nm. In certain cases, specifically in relation to concerns for the environment, health, safety, or competitiveness, the number size distribution threshold of ≥50% may be replaced by a threshold of 1-50 % ((EU) No 696/2011), (European Commission, 2011a).

The definition focuses more on aspects of regulation and general risk assessments than on any scientific understanding. It uses 'size' as the main quantitative requirement, but it has relatively wide and indistinct criteria in relation to measurable indicators.

Prior to the publication of this definition, nanomaterial definitions were already being applied to some sector specific legislation, including legislation in the agri-food/feed sector. These definitions are legally binding, and in some cases they differ from the EU recommendation (Amenta *et al*., 2015). (Refer to Appendix 1, Table A2 giving details of the nanomaterial definitions which are referenced in this section of the report).

Current legislation covering nanomaterials, either implicitly or explicitly, in the area of agri-food/feed is presented in Appendix 1, Table A3.

An assessment of the practical impact and potential challenges of particular significance which can be attributed to some of the most relevant EU legislation is presented in this section of the report.

1.12.2 Legislation governing General Chemicals

The overarching REACH regulation (EC) No 1907/2006 (i.e. Registration, Evaluation, Authorisation and Restriction of Chemicals) (European Parliament and Council, 2006), with amendments detailed in Commission Regulation (EU) 2018/1881 (European Parliament and Council, 2018) and Commission Regulation (EU) 2020/878 (European Commission, 2020). Regulation (EU) 2018/1881 applies to nanomaterials as 'substances' and it outlines specific criteria for the measurement and characterisation of nanoforms and for chemical safety/risk assessment, requirements. In the case of (EU) 2020/878 the amendments apply to 'substances

that include ‘nanoforms’ and specifies the requirement to indicate the presence by using the word “Nano form”. (Refer to Appendix 1, Table A2 for further details). The REACH regulation places responsibility upon manufacturers to register chemicals with the European Chemicals Agency (ECHA). They must apply a new labelling system, provide a registration dossier detailing the properties of the chemical substances along with the safety information and they must provide safety data sheets where required (Cushen *et al*., 2012). ECHA evaluates product registrations for compliance, and member states review applications to highlight any health and safety or environmental concerns. Member states authorities can decide to ban substances if the risks are unmanageable, or they can restrict the use of potentially harmful chemicals (ECHA, n.d.).

1.12.3 Legislation governing food

Regulation (EU) 1169/2011 Food Information to Consumers (FIC) (European Parliament and Council, 2011) mandates that ingredients present in the form of engineered nanomaterials should be clearly indicated in the list of ingredients, and that the ingredient names should be followed by the word ‘nano’ in brackets.” The term ‘engineered’ means any ‘intentionally produced nanomaterial,’ however, unlike the EC definition the FIC regulation does not include naturally occurring or incidental nanomaterials. The regulation relates to nanomaterials “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” (European Parliament and Council, 2011). This definition came into force before the EC recommendation on the definition of a nanomaterial. The threshold limit of between 1-50 % outlined in the proposed EU definition is not included in the FIC regulation, in addition it allows for the inclusion of materials which may be greater than 100nm in size. For practical purposes, it would be difficult to measure these nanomaterials due to the lack of specificity.

Novel Food Regulation (EU) No 2015/2283 (European Parliament and Council, 2015), the most recent revision of the novel foods law includes a definition of nanomaterials which is the same as the FIC definition. Hence, the difficulties encountered with measurement of nanomaterials would also apply to implementation of this regulation. The regulation provides further clarification on

the previous Novel Food Regulation (EC) No 258/97 (European Parliament and Council, 1997); it stipulates rules for foods (not used prior to May 1997) where new production processes give rise to significant changes in the composition or structure of a food. Specific mention is made to food supplements, vitamins and minerals, (used in accordance with relevant legislation presented in Appendix 1, Table A3) indicating that where such foodstuffs "contain or consist of engineered nanomaterials" they should be considered as novel foods and should therefore be re-assessed in accordance with this regulation and subsequently in accordance with the relevant specific legislation (European Parliament and Council, 2015).

Regulation (EC) No 1333/2008 (European Parliament and Council, 2008) governing food additives makes reference to "a change in starting materials, or a change in particle size, including the use of nanotechnology," the European Parliament advise that food additives should be re-evaluated if necessary where there is a change of the conditions of use, or where new scientific information becomes available (European Parliament and Council, 2008).

Regulation (EU) 2022/63 (European Commission, 2022) amending Annexes to Regulation (EC) No 1333/2008 regarding the food additive titanium dioxide (E 171) issued approval for the removal of the authorisation to use titanium dioxide (E 171) as a food additive. Following a safety assessment of titanium dioxide (E171) as a food additive (Younes, *et al*., 2021) EFSA presented guidance that E171 shall be evaluated under the scope of the EFSA 'Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles' which covers materials that are not 'engineered' but which do contain a fraction of small particles (More, *et al*., 2021).

In relation to food authorisation procedures for enzymes, flavourings, and food supplements (including minerals and vitamins), which are covered by specific legislation outlined in Appendix 1, Table A3, there is no specific reference to 'nano-forms' of these substances mentioned. However, European Parliament rules relating to new production processes, change in the particle size, and new scientific information, could possibly be relevant to these substances also.

1.12.4 Legislation governing Food contact materials (FCM)

Regulation (EC) No 450/2009 (Active and Intelligent Materials and Articles) (European Commission, 2009) refers to the application of "new technologies …. for example, nanoparticles", similarly, Regulation (EC) No 10/2011 (Plastic food contact materials) (European Commission, 2011b) refers to new technologies and it also refers to "substances in Nano form", specifically mentioning "engineered substances" both legislation state that these materials should be assessed on a case by case basis regarding their potential risk to the consumer, (unless explicitly authorised and mentioned" in an annex of the regulation).

1.12.5 Legislation governing Biocides

The Biocide Product Regulation (BPR) EU 528/2012 (European Parliament and Council, 2012) closely resembles the definition proposed by the EU in 2011. There is a requirement to state the active substance on the product label and the name of all nanomaterials contained in the product, followed by the word 'nano' in brackets. Additionally, where nanomaterials are used in a product, the risk to human and animal health and the environment must be assessed separately (European Parliament and Council, 2012). Analytical tests carried out for the purpose of authorisation of a biocide product should be conducted according to the methods described in REACH guidance documents (refer to Appendix 1, Table A2). In addition, the regulation states that where "test methods are applied to nanomaterials, an explanation shall be provided of their scientific appropriateness for nanomaterials, and, where applicable, of the technical adaptations/adjustments that have been made in order to determine the specific characterisation of these materials" (European Parliament and Council, 2012).

1.12.6 Issues with EU Policy/Legislation – Summary

In general, and despite the rapidly increasing number of scientific publications dealing with nanotechnology, at the time of writing there is still no harmonised standard definition at an international level. ISO definitions have been developed for broad use across many sectors, and for industry use, whereas the EU definitions are developed mainly for regulatory purposes. From an analytical prospective applying the EU definition as part of regulatory controls could result in significant

challenges, or at least some difficulties for some member states due to the very specific measurement/characterisation requirements for some parameters e.g. Number based particle size distribution, with an indication of the number fraction of constituent particles in the size range within 1 nm – 100 nm. There is only a limited number of analytical techniques that are capable of producing a number based size distribution result, and far less techniques that can measure 1nm particles.

In 2021 EFSA's Scientific Committee published an updated guidance document detailing testing parameters, methodology and suitable technology for risk assessment of applications of nanotechnology in food and feed (EFSA, 2021). The document was drafted to reflect advances in scientific knowledge, research, and instrumentation since the first guidance document was first presented in 2011. The new guidance document outlines in a very comprehensive manner the key parameters that should be measured, with appropriate quality control criteria; it recommends the methods to be used and the most suitable analytical techniques for characterisation of nanomaterials. It recommends (for confirmatory purposes) that particle size distribution parameters must always be measured by at least two independent methods (one of which must be electron microscopy). This is likely to present difficulties for member states who do not have access to such specialised equipment.

In 2021 EFSA's Scientific Committee also published a guidance document detailing technical requirements for regulated food and feed product applications, to establish the presence of small particles including nanoparticles (More, *et al*. (2021). The technical requirements apply to conventional materials which may or may not contain a fraction of small particles, which may subsequently require assessment of particles at the nanoscale. These requirements may be applied in the case of materials which do not meet the definition of an 'engineered nanomaterial' as detailed in the Novel Food Regulation (EU) 2015/2283 (More, *et al*., 2021).

In summary EFSA's Scientific Committee recommend that 'a full assessment addressing properties at the nanoscale is required when the applicant or the risk assessor concludes that the material:

- Fulfils the definition of engineered nanomaterial according to the Novel Food Regulation (Regulation (EU) 2015/2283) (European Parliament and Council, 2015).
- Contains a nanoform as defined in the provisions under Commission Regulations (EU) 2018/1881 (European Parliament and Council, 2018) and (EU) 2020/878 (European Commission, 2020) amending Annexes of the REACH Regulation to introduce nanospecific clarifications, or
- Consists of or contains a fraction of small particles as outlined in the Guidance on Particle-TR. (More, *et al*., 2021).

1.13 Thesis 'nano' definition

In light of the fact that there is still no standard definition applicable to all applications/products/matrices, a simplified definition of a "nanomaterial", which will be used for the purpose of this report is:

> 'Any engineered material or particle (typically, but not exclusively, below 100 nanometres in one or more dimensions) that is introduced into a food (or feed) product or contact surface, which exhibits or is proposed to exhibit a functional purpose on the nanoscale (x10-9) or influence the bulk properties of the final product' (FSAI, 2008).

1.14 Chapter Summary

This chapter highlighted the growing impact nanotechnology is having on the agri-food sector and the subsequent regulatory landscape both nationally and internationally. Moreover, a brief review of EU legislation in the sector identifies that clear issues exist surrounding a common nanotechnology terminology, which crosscuts many commercial sectors and reflects the interdisciplinary nature of nanotechnology itself. From a regulatory point of view, it is crucial that terminology is exact, clear, and precise, to facilitate appropriate enforcement procedures and policies. Indeed the uncertainty in the terminology has led to many of the research questions posed in this thesis and in turn, it exposes other questions concerning knowledge gaps in methodology, and national readiness in terms of human and infrastructural capital. The research questions outlined in section 1.5 emphasis the

need to establish a baseline of the national capacity to enforce potential nano-legislation. This concept is nothing new; it has been raised by a number of national reports on nanotechnology in the agrifood sector over the last decade (FSAI, 2008, Handford *et al*., 2014). However, now more than ever, the need to genuinely assess and act upon the recommendations appears more crucial, with legislation now effective banning the use of TiO_2 as a food additive, and the potential for further EU reviews and decisions expected on the safety of a number of nano food additives. The subsequent outcome of these health and safety reviews will most likely require national control laboratories to support state agencies who are responsible for the regulatory control of nanotechnology in Ireland's agri-food sector. This thesis will of course attempt to establish the baseline capacity nationally, and ultimately recommend approaches to maintaining and developing wider links across academic, state agencies and control laboratories, to close knowledge gaps and to approach new nano-challenges in the enforcement of legislation, with a collaborative round table approach.

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2.1 Introduction

The aim of this research is to identify the regulatory and monitoring challenges presented to Irish state agencies due to the evolution of nanotechnologies in the agrifood industry, and to assess the national capacity to respond to such challenges. The key research questions to be addressed were highlighted in chapter one section 1.5. These involve considering aspects as diverse as establishing the current state of the art nationally, exploring the value for money investment of exchequer funding, as well as identifying potential shortfalls in future skill needs and human infrastructure. This current chapter presents the general methodology used and justifies the approach taken to best answer the research questions posed. Later chapters, where relevant, will expand on specific aspects of the methodology employed beyond the general methods considered here; this is particularly true where chapters have been adapted from papers submitted for publication. A key focus of this chapter will be to consider the approach taken to conduct data collection and the processes involved in analysing the data. The final section outlines the research ethics protocol and data management considerations.

The initial steps in this research involved setting out a research plan, dividing activities into selective work packages. Figure 2.1 illustrates the task breakdown of the various work-packages.

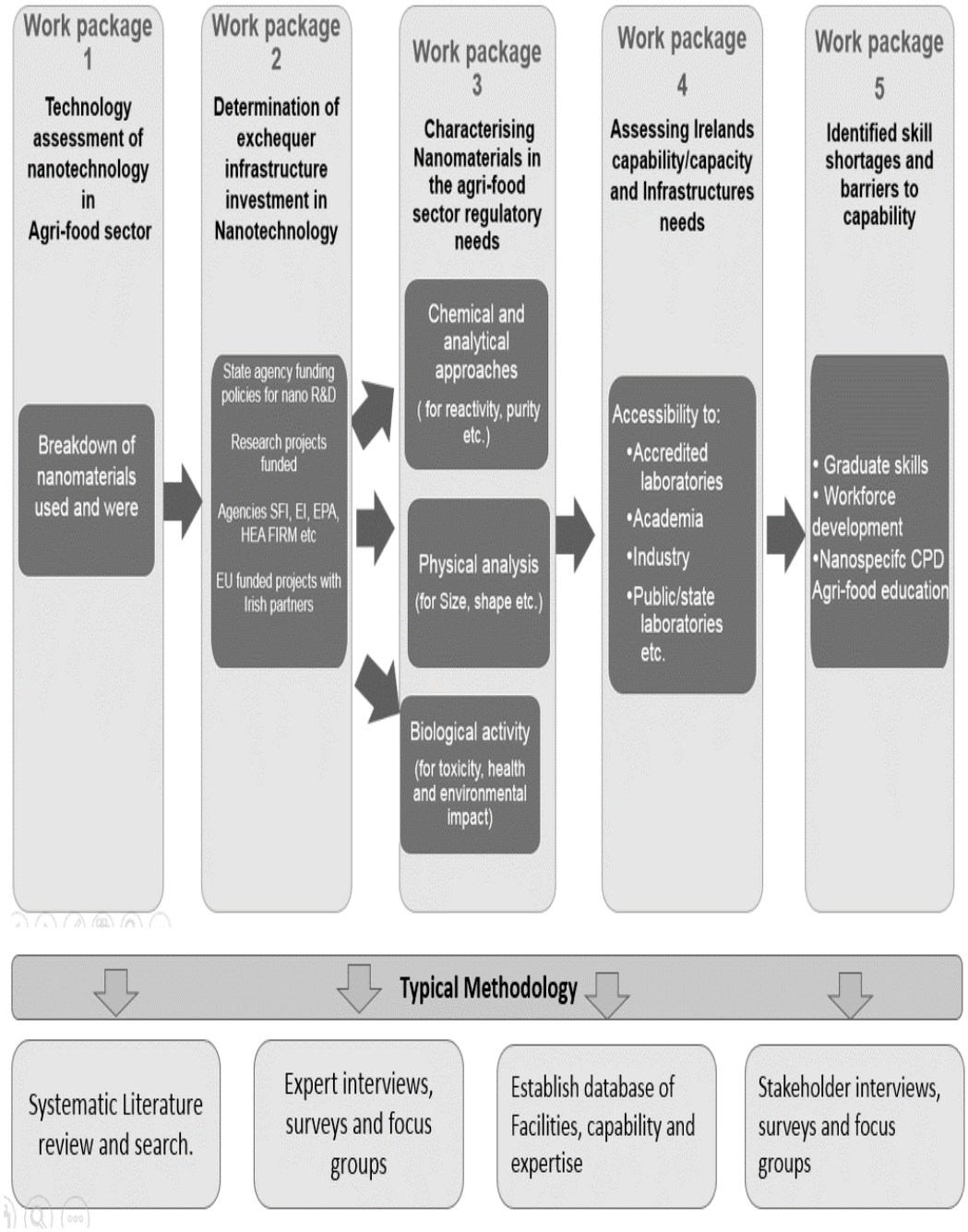

Figure 2.1: Research Work Plan – Task Breakdown

These work packages form the backbone of both the thesis and this chapter, and they will be considered throughout the chapter. Initially however, the chapter will reiterate the research hypothesis as a possible suggestion of the research outcomes.

2.2 Research Problem and Hypotheses

2.2.1 Research Problem/Question

The main research problem guiding this research is to determine 'What are the gaps and deficiencies in Ireland's 'analytical and research infrastructure', in order to support state agencies who are responsible for the regulatory control of nanotechnology in Ireland's agri-food sector?'

2.2.2 Research Hypothesis

The following hypothesis was proposed for this thesis:

Research Hypotheses: This research proposes that "Ireland's analytical and research infrastructure' is not sufficiently future proofed to support State Departments and Agencies who are responsible for the regulatory control of nanotechnology in the agri-food sector".

2.3 Research Methodology

Before deciding on the best process to follow when conducting research it is important to decide on the most appropriate methodologies which can utilised to obtain suitable data to answer the Research Problem/Question. In this research both quantitative and qualitative data collected methods have been utilised, data was analysed from surveys, focus groups and individual interviews. The conditions under which the 'hypothesis' was tested and the details of how the data was measured must be clearly defined, in order to make replication of the research easier.

Differing approaches and research strategies are implemented within the research process, and the choice of the most appropriate one(s) to use is influenced by the overarching research philosophy. It is therefore necessary to clearly state the research philosophy upon which the research is based.

2.3.1 Research Philosophy

The research philosophy describes the way we comprehend the development of knowledge (Saunders *et al*. 2009). The research philosophy best suited to this

research is ‘interpretivism’. The interpretative research philosophy is based on reflection or “constructed interpretations,” to “understand motives, actions and intentions” of research participants, to provide descriptions and to generate hypotheses (Stojanov and Dobrilovic, 2013). Having established the research philosophy the research approach adopted will influence the techniques which will be used to develop or to test the hypothesis.

2.3.2 Research Approach

The research approach applied is determined by the theory; the approach taken for this research is the ‘inductive’ approach. The Induction approach is based on collecting data, reflecting upon and interpreting the data, to derive meanings and to develop the theory (i.e. generating the hypothesis) (Thorne S, 2000). Using this approach, the researcher evaluates and reflects upon data, to become well informed about human experiences, assumptions, and values, which are relevant to the research topic and to the generation of new knowledge, or the understanding of particular concepts (Thorne S, 2000). The methods chosen for this type of research requires the researcher to gain an appreciation of the problem at hand, and to generate an in-depth evaluation of experiences as they are lived/experienced (Thorne S, 2000).

The inductive approach involves ‘building the theory’ as the research progresses and various data collection methods are used to establish different views of the experiences/events been investigated (i.e. the phenomena) (Easterby-Smith *et al*., 2002). Therefore the “study of a small sample of subjects might be more appropriate than a larger number” (Saunders *et al*., 2009, p88). The approach best suited to this research specifically was to adopt what’s called ‘Phenomenological analysis’.

2.3.2.1 Phenomenological analysis

Phenomenology is a qualitative research approach which is often used in the analysis of human interactions, to help the researcher gain an understanding of “individual’s lived experiences within the world” (Neubauer, Witkop and Varpio, 2019. p90). This approach is commonly used to discover knowledge which is common to groups of professional people, e.g. personnel in the health and educational sectors and policy makers (Stojanov and Dobrilovic, 2013). It has

proven to be beneficial where the outcomes of the analysis can be used to inform, support, or challenge policy (Lester, 1999).

Phenomenology is concerned with the study of experience from the perspective of the researcher, where the researcher is an interested party involved in the research investigation, rather than as an observer (Lester, 1999). The purpose of this approach is to identify 'phenomena' in the way which they are seen by the participants of the research investigation. This normally involves collecting 'in-depth' information, mainly through qualitative data collection methods such as by carrying out individual interviews, focused discussions and/or participant observation (Lester, 1999).

Different approaches to phenomenology analysis have been advocated by various influential scholars, and the two main approaches used within phenomenology analysis are descriptive phenomenology and interpretive phenomenology (Tuffour, 2017). Interpretive phenomenology was the approach chosen for this research. This approach is primarily involved with the analysis and interpretation of text. The researcher analyses text, sieving through the details to find meanings, and to achieve an understanding of the 'phenomena'. The premise of this approach is that the researcher's interpretations are specific to the experiences arising from the current research investigation, rather than an assumption or a generalisation of a 'phenomenon' (Kafle, 2011).

The researcher's background, knowledge and experience play a crucial role in this particular type of research, with the researcher playing an active role in the process The influence of the researcher's identity and background could contribute to bias, which cannot be discounted (Stojanov and Dobrilovic, 2013). It is important therefore to emphasise the potential difficulty of excluding the researcher's own personal opinions or bias, so the researcher needs to be very explicit about how interpretations and assigning significance to findings has been reached (Lester, 1999).

The research process involves 'intentional' selection of research participants on the basis of their role/responsibility/knowledge/expertise. The purpose of selecting specific individuals to partake in the data collection process is to obtain relevant, information rich data, to be in a position to develop theories, validate opinions and

experiences, and to derive relevant and appropriate conclusions from the research (Kafle, 2011). It is preferable not to adopt rigid procedures for data collection and evaluation procedures, as the process itself can be quite a dynamic one, and it is likely that the outcomes of the research will unfold over the course of the investigations, hence the 'phenomenon' itself can dictate how the data should be analysed (Sloan and Bowe, 2014).

2.3.3 Research Strategy

The research strategy is the general plan outlining how the research question(s) will be answered (Saunders *et al*. 2009). The research strategy used in thesis is "exploratory studies." The use of exploratory studies is appropriate as the research seeks to clarify and to understand the underlying issues relating to the research problem. The strategy is flexible, and it is adaptable to change. With this type of research, the focus can change as new data becomes available, and as new insights occur. Saunders *et al*., (2016) cites Adams and Schvaneveldt, (1991) who reinforce this point by stating that "exploratory research does not mean absence of direction to the enquiry, what it does mean is that the focus is initially broad and becomes progressively narrower as the research progresses" (Adams and Schvaneveldt, 1991, cited in Saunders *et al*., 2016, p134).

The choice of analysis methods is determined by the research objectives, practical implications, and/or by any limiting factors of the research. It is important to outline these at an early stage of the research design and planning phase, in order to ensure that the research remains focused, and to limit the scope of the research to the objectives. Various different methods, or a combination of methods (multi-method research) can be used when conducting research e.g. using a combination of in-depth interviews, focus groups, questionnaires or perhaps structured or semi-structured interviews (Esteves and Pastor, 2003). Deciding whether to choose; qualitative, quantitative, mono, mixed, or multi method research analysis is an important aspect when deciding upon the research strategy.

The research strategy selected for this research required the collection and the analysis of 'primary' research material. One of the first points to be considered when collecting primary data is to identify how best the research question(s) can be answered i.e. by using quantitative or qualitative research methods. If several

questions need to be answered, or if a broad range of information is required, then it can be useful to use both types of research methods (Brikci, 2007). In situations where knowledge is limited, or it is incomplete, or where a wide range of information is required on a research topic, it can be useful to include qualitative research methods (e.g. interviews and focus groups). It can also be a useful aid to test hypotheses, which cannot be tested by quantitative methods. For example, in this research where it is not clear what are the different issues either currently affecting, or those issues which could potentially contribute towards gaps and deficiencies in Ireland's research infrastructure. It is therefore plausible to identify the most pertinent issues at stake through the use of qualitative research methods (e.g. focus group/interview). Where some of the potential issues are known/identifiable then a quantitative approach (e.g. survey) can be used to quantify the extent these issues are affecting state agencies ability to support regulatory affairs.

This research uses a mixed method approach, where qualitative and quantitative data collection methods are both used, and they were analysed separately. The methodology used facilitates replication, it generates results; which are quantifiable for statistical analysis, and it presents qualitative results, which contribute towards gaining a deeper understanding of the challenges faced by Irish state agencies.

2.4 Data Collection Methods

Both primary and secondary data collection methods were used for the development of this thesis.

2.4.1 Secondary Data Collection

Secondary data collection, involves the use of both raw data and published articles. It includes data that has been collected by other researchers, or data that has been used for some purpose other than for the current research (Saunders *et al*. 2009). Secondary data collection was used in this research because it provides a useful source of information from which to begin to consider the research objective(s) and as a basis for establishing the research question(s) and the hypotheses. Secondary data collection for this thesis involved carrying out a systematic literature search and review.

2.4.1.1 Systematic Literature Search and Review

As outlined in chapter I, section 1.2 Overview of Nanotechnology in the Irish Economy, a literature search and review was carried out of the most relevant national reports relating to nanotechnology, from a regulatory prospective over the period 2004 to date.

These recommendations significantly overlap with the stated key objective of this research, indeed the work packages outlined as part of this research have been designed with these recommendations in mind, with the purpose of seeking to address many of the information deficits which were highlighted in the different reports.

The research plan involved conducting an in-depth literature search and review. The literature review presents an insight into the current 'state of the art' due to the evolution of nanotechnologies in the agrifood sector. The systematic literature search and review as part of work package 1 (WP1) consisted of two parts: firstly a review of the literature was conducted to determine the key theories, applications and future potential, and secondly a review of international projects and reports was carried out. This work identified the nanomaterials used, and where they are used, it informed certain aspects of the work under WP2 and WP3 as well as helping to identify aspects of best practice.

Methodology for the Review of Literature: The methodology for the review of literature consisted of three elements; the initial search for materials, the prioritization of materials, and the full review.

For the initial search for materials, literature synthesis was carried out using text mining to extract technical intelligence from the global nanotechnology, nanoscience and agrifood nanotechnology research literature. Relevant search terms and queries were applied to a variety of databases, e.g. ISI Web of Knowledge/Science Citation, Index/Social Science Citation Index (ISI/SCI/SSCI) databases. The search terms and queries were recorded for reference purposes (See Appendix 2). In addition, an extensive search covering several other electronic databases, including, Agricola, Google scholar, Wiley Interscience, World Scientific Publishing and Pubmed was carried out. Google Scholar alerts were set

up using key terms; real time alerts were reviewed as received, to determine the relevance of the material and the applicability to this research.

For the prioritization of materials, the initial searches of all materials was reviewed and the most appropriate articles were selected for further analysis. This process initially involved a review of the abstract material. Where material was deemed relevant, a more in-depth review was carried out.

The full review focused on policy documents and reports produced by Government agencies, NGO's and international projects such as EU framework programmes. The selection of relevant materials for further analysis was based on;

- The source of the material e.g. peer review journal publication, Government/EU policy documentation, reports or recommendations.
- The quality of the sources i.e. peer reviewed journals, Government/Agency/EU publications, reports from recognized research institutions or international bodies.
- The approach and the methodology used in the reference/literature material, and its relevance to the research topic.
- The terms of references of the reference/literature material, and the level to which the key points such as the research issues, stakeholder concerns, and analytical methodology were discussed.

The literature search and review extends over the full duration of the research in order to ensure that up to date literature is included in the final thesis. The bulk of the work however was carried out as part of this thesis.

The systematic literature search and review in relation to WP3 (Characterisation techniques for the determination of nanomaterials in the agri-food sector, satisfying regulatory needs) employed a similar approach to that used for WP1 (outlined above). This work involved carrying out a review of some of the most suitable tools and techniques for determination of the physio-chemical properties of nanomaterials. The aim was to provide a comprehensive guidance document outlining the relevant characterisation techniques, with a brief overview of their; application range, advantages and disadvantages, as well as the limits of application/quantification. This work assignment was significantly informed by

work packages one and two, and will be expanded upon via a combination of methods such as surveys, expert interviews and focus groups as this information becomes available. The process will involve contributions from the key stakeholders involved i.e. academia, and regulators.

2.4.2 Primary Data Collection

Primary data, is data that has been collected by the researcher, specifically for the purpose of the current research. The purpose of primary research is to learn something new, to solve a research question/problem, to test and/or to confirm or refute a hypothesis. It involves the researcher collecting data using various methods as appropriate e.g. surveys, interviews and/or focus groups. It is important to ensure that the data collected can potentially be reproduced by others if necessary. Potential researcher bias should be acknowledged where applicable, indeed it should be reduced or eliminated where possible (Driscoll, 2011). Primary data collection was used in this research because it provides results which; are original, current, apply directly to the research question in hand, and the results are reliable because they are collected first hand by the researcher.

Research population and sample size: The research strategy used in thesis is "exploratory studies" for this reason it was not practical to collect, and to analyse data from the entire target population, so a selected "sample" (i.e. 'a subgroup of the target population') was taken. This model is appropriate for both qualitative and quantitative research, and it allows for a reduction of the amount of data required, by considering only data from a small subgroup rather than from the larger population group. (Saunders *et al*., 2009). The most practical sampling technique for completion of this research thesis was 'non-probability sampling'.

Non-probability sampling was selected for this research, as it allows for the use of a range of sampling techniques that are suited to research where 'exploratory' analysis is the main feature of the investigation. While 'probability sampling' is preferable for statistical analysis of results, it is still possible to carry out generalised statistical analysis using non-probability sampling, in order to test the hypothesis. Non-probability sampling is useful where the researcher needs to be selective in the identification of research participants, to ensure that information rich data can be

generated to explore a particular phenomenon. One of the major limitations of this type of sampling is that generalisations cannot be made on the basis of the research findings. It must be stressed that findings obtained through this method apply only to the group studied, and they are specific to the experiences arising from the current research investigation (Showkat and Parveen, 2017).

For the sampling techniques selected, the sample size is ambiguous. There is no target quota to be reached, any and all of the methods selected are acceptable as long as they provide enough data to answer the research questions, and that they fulfil the objectives of the research. The validity of the data and the research conclusions will depend more on the analysis of results, than it will on the sampling technique used.

Primary data collection for this research involved using the multi-method strategy, carrying out online surveys, focus group meetings and in-depth individual interviews. An overview of the strategy and the approach used for the online surveys, the focus group meetings and the in-depth individual interviews is outlined below.

2.4.2.1 The survey strategy

The primary quantitative sampling method selected for this research was the survey strategy, using questionnaires. This strategy was used because it is an efficient way to collect standardised data from a relatively large sample group. The questionnaires were administered on-line using the cloud-based Survey Monkey software (www.surveymonkey.com) (Surveymonkey, 2018) and Google Forms (Google Forms, 2018). Questionnaires were used due to the ease of administration, the diversity of questions which could be asked, the flexibility of data collection, and because it allowed for the retention of anonymity of respondents. Google Forms and Survey Monkey software applications were selected as the most appropriate survey tools because these applications are simple to use, they are familiar software applications for many individuals, and both applications include a quantitative statistical function to aid with the evaluation of results. The purpose of the survey was to obtain information relevant to specific populations, (i.e. regulators and academics), where the results were quantifiable and they could be used to produce numerical outputs, which was subsequently evaluated using statistical analysis.

Three surveys were administered through survey monkey; separate surveys were developed for individuals from academia, and for those employed by state agencies/regulatory authorities. The question design of each survey was informed by the systematic literature review and by the objectives of the study. The individual surveys were formulated with questions specific to the relevant area of involvement, in order to elicit information from experts who are involved in nanotechnology education, or those who are involved in regulatory control of nanomaterials. An important consideration in the design of the questionnaire was to ensure that all of the relevant objectives were captured in the questions, because once administered it is not practical to re-test the same participants for any missing information, once the survey has been completed. In addition the surveys were devised via a systematic approach of testing and revision, in a series of pre-tests and revisions before the main surveys were conducted on-line. The surveys were continuously refined throughout the research process based on feedback received from participants.

Questionnaire Design: An explanatory preamble was included in the email introduction to the survey. This preamble presented an introduction to the requirements for participation and a brief overview of the research objectives. The questionnaire was designed to keep it practical, and as short as possible. The aim was to ensure that the questions were not too long, nor too complex. Survey participants were asked a variety of questions, where most of the questions were based on a 'fixed-response' from a range of alternative answers. The optional answers were structured in such a way as to control the data collection process. The quantifiable data included 'structured' questions based on ranking and likert scales, while the qualitative data involved the use of and 'semi-structured' questions to obtain opinions on key issues of relevance to this research.

The surveys, informed by the systematic literature review, and by the objectives of the study were conducted through direct and indirect contact with selected academics and personnel employed by state agencies/regulatory authorities. The questions were designed to get information relating to the participants expertise/knowledge and their opinions about the various issues affecting the development of knowledge, skills and research infrastructure, to support Ireland's

regulatory control of nanotechnology in the agrifood sector. Participants were given the option of adding additional comments throughout the survey where applicable.

(Refer to Appendix 3 for the survey design, and the questions asked).

Sample and sample size:

Regulatory Authority survey: The target sample for the regulatory control focused survey were professionals working either directly or indirectly in the area of nano-regulation. This included those in accredited control laboratories, in the Food Safety Authority of Ireland and personnel actively involved in the Environmental Health Service (EHS) or Environmental Health Officers (EHO). This greatly limited the potential sample size, but it ensured a true reflection of those most likely to be involved in the regulatory control of nanotechnology in in Ireland's agri-food sector.

In total 138 survey responses were received from EHO's, 122 responses were received as part of a preliminary review of the knowledge, skills and expertise of this professional group (2017-2019 survey), 16 responses were received as part of a focused survey which was distributed through emails and was available through various 'social media' platforms (2021-2022 survey). There were 14 responses received from 'targeted professionals' in regulatory control agencies.

Academic Survey: The academic survey presented a better opportunity to achieve a larger sample size; however, it was imperative that the target academic population was drawn from those academics or researchers who identify themselves as 'nano active researchers'. This was again deemed important to ensure that responses were informed, and that they reveal a true reflection of the opinion from the national academic 'nano' community.

In total 59 survey responses were returned from individuals identified as 'nano active researchers' across a range of academic institutions in Ireland.

Data Analysis: Data collection and storage is automatic with both software applications. Responses are uploaded to the relevant survey account when participants complete the questionnaire. Once the data has been collected and entered into the database it is encoded and statistical analysis can be performed.

The ‘analyze’ function of ‘SurveyMonkey’ was used to perform some very basic statistical analysis. This function was used to display basic tables and charts. Responses in Google Forms are depicted as pie-charts, bar graphs and histograms, as well as in narrative form where applicable. Filters were applied to questions based on the responses, analysis of trends and more complex statistical evaluations was also possible using this software. The data was also extracted and it was analysed using alternative independent statistical packages, allowing the survey results to be cross tabulated and common trends to be extracted.

Most of the data analysis focused on descriptive statistics, including; univariate frequency distributions, estimated totals, averages and proportions, for all the variables generated directly from each survey, or derived from each survey during processing.

The estimates are accompanied by an estimated standard error, where appropriate cross-tabulations between questions and stakeholder survey categories is presented. Some of these cross-tabulations were pre-planned to assess cross cutting issues regarding, for example, communication between the stakeholders, which has been evident in other international studies. Other cross-tabulations were developed as a result of the preliminary data analysis identifying a specific trend in responses.

2.4.2.2 The online focus group strategy

Focus Group discussions (FGD) are a valuable data collection strategy that can be used as part of exploratory research, in order to collect qualitative data that may be difficult to gather using quantitative surveys and/or questionnaires. (Woodyatt, Finneran and Stephenson, 2016). Traditionally focus groups are considered as a qualitative study, however Rabiee, (2004) and Schmidt, (2015), indicate that focus group transcripts can be analysed and undergo quantitative statistical analyses, basically frequency analyses to estimate the keywords and trend of the discussions (Rabiee, 2004, Schmidt, 2015). Schmidt (2015) in particular, demonstrated a number of approaches to the analysis of qualitative data in a quantitative manner. Further details of the methods chosen for this research are presented in chapter 5 section 5.1.

An online FGD strategy was selected for this research because it was considered to be suitable for adapting to the more traditional in-person focus group discussions that are commonly used in various disciplines. The online environment was used to recruit hard-to-reach participants due to restrictions imposed by a global pandemic.

Five FGDs, comprising of 20 people in total, were held online using the real-time web-based meeting platform Cisco Webex Meetings desktop app. This software was selected as it is widely used by professional organizations, it is reliable and it allows for real-time audio and visual communications in a secure manner online. Cisco also has the facility to record both audio and visual aspects of the discussions. This platform did not require participants to download software, an invitation was sent to them containing a link that could be accessed through the web browser. Usability of the software was evaluated by three people from the university as part of a pilot trial of the software.

Participants were selectively recruited based on their knowledge and expertise, and on occupation of relevance to the research (i.e. regulators and academics). A participant information sheet was sent by email to all individuals prior to the FGD. The information sheet provided details of the purpose of the study, what was required from participant's involvement, it provided a guarantee of confidentiality, and it outlined how ethical considerations had been addressed. The email also contained the weblink to join the online FGD at the designated time.

FGD Methodology: An experienced moderator led the FGD. As participants joined the FGD they were asked to indicate their informed consent to participate, prior to the start of the discussions. They were informed that they had the option to leave the discussions at any time if they wished to do so. The FDGs each lasted for an average of 90 mins, this included time for introductions and a short PowerPoint presentation outlining the background to the research. Each FGD consisted of four to five participants. The semi-structured discussions led by the moderator included questions concerning the participant's personal views, their knowledge of; nanotechnology in general, legislation, and methodology for characterisation. The FGD's were recorded and they were automatically downloaded to a readable file, this file was accessible to the lead researcher only. The FGD's were transcribed verbatim. All participants were provided with a transcript of the discussions, they

were encouraged to provide feedback or to correct aspects of the transcript if required.

(Refer to Appendix 4 for a list of the questions/reflections posed by the moderator).

Data Analysis:

Data analysis and interpretation was conducted using a 'deductive coding' approach (Skjott, Linneberg and Korsgaard, 2019). Deductive coding was used in this research, to test the research hypothesis. This approach was deemed appropriate as this is exploratory research and there were no theoretical frameworks/concepts deemed to be suitable for use, or adaptation. Coding of data involved examining the focus group transcripts, word-for-word and labelling specific portions of text with a word or 'theme' that encapsulates the content and the essence of the data. A list of codes/themes was generated based on, issues that are identified to be important as a result of carrying out the literature review, and as evolved from the focus group discussions.

2.4.2.3 The Expert in-depth interview strategy

Semi-structured, in-depth, focused interviews were conducted as part of the research process to build upon the 'themes' identified in the earlier research, and to bring out more refined interpretation(s), based on the 'lived experiences' of experts in the field of interest. The Phenomenological approach as detailed in section 2.3.2.1 was applied through purposeful selection of samples (interview participants), using a closely defined group of participants for whom the research question is particularly relevant. The intention of the in-depth interviews is to discover details about the opinions/experiences/perceptions/understandings of this particular group, rather than to make assumptions and apply them to more general or similar situations (Smith and Osborn, 2003).

Sample Population

Selection of research participants was based on 'purposeful sampling' which is an approach commonly used in qualitative methods. As described by Patton (1990), "the logic and power of purposeful sampling lies in selecting information-rich cases for study in depth. Information-rich cases are those from which one can learn a great deal about issues of central importance to the purpose of the research, information-rich cases whose study will illuminate the questions under study." (Patton, 1990,

p169). Sampling of participants was an ongoing process, as data was collected and analysed. Individual 'specialists' were intentionally chosen to take part in the in-depth interviews, following a similar process of selection to that of the focus group discussions. The intention was that these people would have relevant expertise and would as such be able to provide follow up on some of the themes identified, and/or to clarify or elaborate on points raised by the focus group participants.

Data generation

Data was collected and analysed from five interviews, and one written responses to a set of 'proposed' interview questions. The focus of the interview questions influences the processes of data gathering and the subsequent analysis of the research problem. Interviewees were provided with a list of 'potential' questions in advance of the interview to familiarise themselves with the possible areas of questioning, and the questioning on the day was 'unstructured' to allow the interview to flow and the interviewee to expand upon certain areas if they choose to do so. This allowed the interviewee to give his/her own views before the questions were specifically focused to explore areas which were relevant to the topic of interest. This approach involved asking broad questions initially and the questions are modified in the light of the participants' responses.

Transcript Analysis

Data generation involved analysing written transcripts arising from interviews with specialists in the area of interest. Data analysis involved sequential steps of reading, reflection and interpretation of the transcripts to transform the text into research data and research findings. The research data consisted of selected phrases and/or statements that were interpreted to represent the experience/understanding of the interview participant. The research data arising from the review process was arranged into "themes" which can be viewed as being representative of 'phenomenon' of interest or of the lived experience As outlined by van Manen (1997), with phenomenology methodology there a requirement to examine the text, to discover something 'meaningful,' 'significant,' or 'insightful' to "focus on the substantive, conceptual, analytic or thematic that the text may offer the reader. The focus on the thematic aspect of the text is primarily concerned with what the text says, it's semantic, linguistic meaning and significance" (van Manen 1997, p346). Having isolated the themes, they were then broken down into subthemes,

connections were made between themes where applicable and/or themes are arranged according to categories.

The aim of the transcript review process was to detect and to acknowledge similarities and differences within the data from the different interviews. It was to challenge assumptions, trying to understand 'phenomenon' from the viewpoint of individual research participants, adding interpretations or discovering new concepts (Lester, 1999). Phenomenological analysis methodology was considered to be appropriate for use in this research, enabling the findings to be used to inform, support or challenge policy, and to potentially entice actions to be taken.

2.5 Ethical Issues and Procedures

This research study was approved by Technological University Dublin's Ethics Committee. Approval was sought by the project supervisor using the TU Dublin online ethics portal. The project method was risk assessed, approved and it was allowed to proceed.

At the beginning of the research process participants were provided with a study outline and a consent form, and they were assured that their identity would not be disclosed in any way in order to protect their privacy. They were assured of strict adherence to ethical standards and confidentiality throughout the research process and that the research findings would be shared with them on completion of the study, if they wished to avail of this opportunity.

With social research, when applying phenomenological methodology, the emphasis of the research is to understand 'lived experiences' through the eyes of the participants. Ethical considerations were therefore particularly important where the participants have provided information, opinions or advice. In this case it was imperative that accurate interpretations of the findings have been presented in order to adequately answer the research question(s). Principles of integrity and good professional judgement were strictly observed throughout the research process to ensure that the data and the findings were not misrepresented, distorted or unnecessarily deleted. As illustrated by Clark and Sharf (2007) "we learn things through our inquiries, and there are times when what we learn can have consequences for our informants. Is the truth always beneficial? No. Can it be

harmful? Yes' (Clark and Sharf, 2007, cited in Williams, 2009, p134). In other words it is important to ensure that information is presented in such a way that it does not cause harm or unintended consequences for those who participated in the research process in good faith.

2.6 Data management

The project complied with all applicable Data Protection, privacy and security laws and regulations as specified under GDPR and data protection policies in place in TU Dublin. A data management plan was implemented from the start of the project and it was strictly adhered to.

At the beginning of the research all participants (survey, focus group and interviewees) were forwarded a letter explaining; the purpose of the research and guaranteeing the confidential nature of their involvement. Research participants were provided with consent forms, requesting agreement to become involved in the research, and they were given the opportunity to opt out at any stage of the process if they choose to do so. Participants were asked to confirm agreement for the use of recording (visual and audio) where applicable, to aid the transcription process. Interviewees were forwarded the list of draft interview questions in advance of the interview process. Recordings of the interviews and the focus group discussions were deleted once the transcripts were written up. Research participants were provided with the draft transcript once completed, to enable them to make corrections, redact information or add additional information if they choose to do so.

Participants consent was requested to allow the results of the research to be published or presented at professional meetings, or to be shared and/or reused in summary or in statistical form.

All research data has been completely anonymized, it will be stored in a secure location within the TU Dublin the Data Portal with the data being regularly backed-up guaranteeing recovery and conservation. Post research the data will be stored for the appropriate period and subsequently disposed of in accordance with the Universities policy.

2.7 Secondary Data Collection results - Statistical Evaluations

Statistical calculations involving quantitative data were evaluated using the Social Science Statistics website (Social Science Statistics, 2022). The website offers a set of freely available statistical calculator tools, which are suitable for carrying out evaluations in the social sciences disciplines, the software is interactive and it is easy to use. The statistical calculators used were for chi-square test, hypothesis testing *p*-value calculators, Pearson correlation coefficient and chi-square goodness of fit test. The statistical calculation description, equation and location where used in this report is presented in table 2.1.

Table 2.1: Statistical calculation descriptions and equations used for data evaluation

Statistical Calculation and Equations **(Social Science Statistics, 2022)**	**Section of report**
Chi Square Calculator 2x2 contingency test (of independence) The chi-square calculator tests for association between two categorical variables. The rows represent two classifications of one variable and the columns represent two classifications of another variable. The classifications must be independent. $$X^2 = \sum_{i=1}^{r}\sum_{j=1}^{c} \frac{(O_{i,j} - E_{i,j})^2}{E_{i,j}}.$$ **Where for** r (rows) c (columns) (n) observations, (O) observed frequency (E) Estimated expected frequency. The expected frequency for any cell is estimated as the row total times the column total then divided by the grand total (n).	**4.4.1** **5.3.2**

Statistical Calculation and Equations **(Social Science Statistics, 2022)**	**Section of report**
Binomial Test Calculator This binomial test calculator determines the probability of a particular outcome (K) across a certain number of trials (n), where there are two possible outcomes. **Binomial Distribution Formula** $P(x) = \binom{n}{x} p^x q^{n-x} = \frac{n!}{(n-x)!\,x!} p^x q^{n-x}$ where n = the number of trials (or the number being sampled) x = the number of successes desired p = probability of getting a success in one trial $q = 1 - p$ = the probability of getting a failure in one trial	**5.3.2** **5.5.3**
Pearson correlation coefficient The Pearson correlation coefficient is used to measure the strength of a linear association between two variables, where the value r = 1 means a perfect positive correlation and the value r = -1 means a perfect negataive correlation. $r = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}}$ Where: r = correlation coefficient x_i = values of the x-variable in a sample $\bar{x}$ = mean of the values of the x-variable y_i = values of the y-variable in a sample $\bar{y}$ = mean of the values of the y-variable	**5.3.2** **5.4.2**

Statistical Calculation and Equations **(Social Science Statistics, 2022)**	**Section of report**
Chi-Square goodness of fit test The chi-square goodness of fit testis used to compare the observed sample distribution with the expected probability distribution. Chi-square goodness of fit test determines how well theoretical distribution (such as normal, binomial, or poisson) fits the empirical distribution. **Chi Square Test for Goodness of Fit** $chi\ square = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$ where, Oi is the observed frequency Ei is the expected frequency $Ei = N * p_i$ degrees of freedom, $df = (r-1) * (c-1)$ where r = number of rows c = number of columns	**5.4.2**

2.8 Proficiency Testing (PT) scheme results - Statistical Evaluations

Laboratories carrying out control testing within member states must comply with accreditation requirement as specified by standards such as ISO/IEC 17025. (ISO/IEC, 2005). A part of this research involved participation in an EU wide PT scheme, and organisation of a national PT scheme.

Evaluation of the EU and the national PT scheme results were carried out according to procedures recommended by the International Organization for Standardization (ISO), the International Union of Pure and Applied Chemistry (IUPAC) and the Analytical Methods Committee (ISO, 2015, Thompson, Ellison, and Wood, 2006, The Analyst, 1989) using appropriate statistical methods for standardising and evaluating proficiency test results from inter-laboratory comparisons.

The following statistical evaluations were relevant in the context of the PT review;

- Stability
- consensus value (X),
- uncertainty of the consensus value (u)
- Z-score.

Stability is the "capability of a sample material to retain the initial property of a measured constituent for a period of time within specified limits, when the sample is stored under defined conditions" (ISO, 1992). Stability testing for the purpose of the national PT scheme involved analysing sample replicates at the beginning (Day 0) and at the end (Day 40) of the study, to determine if 'consequential instability' is evident (ISO, 2015). Consequential instability is evident when the difference between the average of the results measured at the end of the study (day 40) is less than 0.3 σp the average of the results measured at the beginning of the study (day 0). If the difference in results between Day 40 and Day 0 is less than 0.3σp then the instability has an influence on the calculated Z score, and this factor must be taken into account when calculating the Z score (Elbers and Peters, 2018). The measurement of 'consequential instability' is calculated as follows:

$$0.3\ (\sigma * p)$$

Where: σ = estimate of the standard deviation of the replicates

p = 0.1 (i.e. 10%, the specified limits for the study)

Consensus value (X): Where there is the potential for some variation of results, as is often the case with chemical analysis PT schemes, where the results are not necessarily normally distributed, then it is preferable to evaluate the consensus value as the 'median' value. The median value is the middle number in a list of numbers, which is sorted either in in ascending or descending order. Consensus values were determined using robust statistics, where all participant result values were taken into account including 'outlier' results. The 'outliers' were however given less weighting than the standard values.

Uncertainty of the consensus value (u): is calculated to determine the influence of uncertainty on the evaluation of the results (Elbers and Peters, 2018). The uncertainty of the consensus value is calculated as follows;

$$u = 1.25*(\sigma/\sqrt{n})$$

Where: u = uncertainty of the consensus value,

n = number of values (results) used to calculate the consensus value,

σ = estimate of the standard deviation of the consensus value.

Where $u \leq 0.3$, the Z score is calculated without adjustment, where $u \geq 0.3$, then the uncertainty of the consensus value (u) must be taken into consideration (Elbers and Peters, 2018).

Z score: The accuracy of the results of laboratories who are participating in PT schemes is determined by the calculation of a Z-score. The Z score is a measure of how many standard deviations below or above the mean an individual result is.

The Z_a score is calculated (where $u \leq 0.3$) as follows;

$$\mathbf{Z_a = (\ddot{X} - X) / \sigma_p}$$

Where: Z_a = accuracy Z-score

$\ddot{X}$ = the individual laboratory result,

X = consensus value,

σ_p = standard deviation for proficiency testing

(Elbers and Peters, 2018).

The Z'_a score is calculated (where $u \geq 0.3$) as follows;

$$\mathbf{Z'_a = (\ddot{X} - X) / \sqrt{(\sigma_p\text{^}2 + u\text{^}2)}}$$

Where: Z'_a = accuracy Z-score taking into account the uncertainty of the consensus value,

$\ddot{X}$ = the individual laboratory result,

X = the consensus value,

σ_p = standard deviation for proficiency testing

u = the uncertainty of the consensus value.

(Elbers and Peters, 2018).

The Z_{ai} score is calculated (where 'consequential instability' is evident) as follows;

$$\mathbf{Z_{ai} = (\ddot{X} - X) / \sqrt{(\sigma_p\text{^}2 + \Delta\text{^}2)}}$$

Where: Z_{ai} = accuracy Z-score taking into account the uncertainty of the consensus value,

$\ddot{X}$ = the individual laboratory result,

X = the consensus value,

σ_p = standard deviation for proficiency testing

Δ = difference between the test result at the beginning and at the end of the PT scheme.

(Elbers and Peters, 2018).

In cases where the uncertainty of the consensus value (u) does not comply with the criterion and 'consequential instability' is evident then the Z'_{ai} score is calculated as follows;

$$\mathbf{Z'_{ai} = (\ddot{X} - X) / \sqrt{(\sigma_p\text{^}2 + \Delta\text{^}2 + u\text{^}2)}}$$

Where: Z'_{ai} = accuracy Z-score taking into account the uncertainty and the instability of the consensus value,

$\ddot{X}$ = the individual laboratory result,

X = the consensus value,

σ_p = standard deviation for proficiency testing

Δ = difference between the test result at the beginning and at the end of the PT scheme.

u = the uncertainty of the consensus value.

(Elbers and Peters, 2018).

A measure of the accuracy of results (Z scores) (ISO, 2015) has been classified as follows;

$Z \leq 2$ is Satisfactory	$2 < Z \leq 3$ is Questionable	$Z \geq 3$ is Unsatisfactory

The Proficiency Testing (PT) scheme statistical evaluations outlined above have been practically applied to the calculation of results arising from the EU PT scheme and the national PT scheme as illustrated in chapter 7 section 7.4, Proficiency testing.

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3.1 Introduction

This chapter is presented in it is entirety as it was presented in the paper which has been accepted by the Journal of Physics.

Increasing demands for food globally over the next 20-40 years will require the agri-food sector to adapt to changing circumstances, especially in relation to demand, production and distribution of food (Foresight, 2011). Food Processing companies are constantly looking for innovative ways to improve production efficiencies, the quality of our food and to meet the demands of consumers, while still remaining competitive. In light of this, industries have invested significantly in research into novel food technologies (NFT). "NFT's are described as scientific and technological developments that alter the way food is produced and processes which may or may not result in differentiated products for consumers" (Henchion *et al*., 2014). One of the latest novel food technologies which has seen rapid development over the past number of years is foods produced using nanotechnology. Nanotechnology has the potential to influence the entire food system. While it is recognised that applications of nanotechnology in the agricultural sector may offer potential benefits, there is also concern that some nanomaterials may present unidentified hazards. A number of expert groups at National, European and International level have issued opinions on applications of nanotechnology, and they have identified some potential safety concerns (FSAI 2008, European Commission, 2008, ESFA, 2009). The general concern was that not enough was known about the toxicological, physiological and environmental effects of nanomaterials. In addition, it was noted that the risk assessments and available methodology at the time may not have been adequate to identify the potential risks of nanomaterials (FSAI, 2008).

The European Food Safety Authority (EFSA) is responsible for establishing criteria for the risk assessment of nanomaterials in food, feed and food contact materials prior to authorisation by European member states. As a consequence of this EFSA have published scientific guidance documents for those who are responsible for performing risk assessment of applications of nanotechnology in the food chain (Hardy *et al*., 2018). The European Union (EU) has also funded numerous research projects to support the risk assessment of nanomaterials. An example of one such

project is the NanoDefine guidance framework which provides standardised analytical methodology and measurement criteria for nanomaterials. This NanoDefine project was developed to support industry, risk assessors and policy/enforcement bodies to allow them to enforce legislation and to facilitate the safe innovation of nanotechnology in consumer food and in food production, based on the European Commission (EC) definition of nanomaterials (Mech *et al.*, 2020).

Various EU regulations govern the authorisation and regulation of nanomaterials within different sectors. In the agri/food/feed sector some regulations refer specifically to nanomaterials, providing details regarding approval procedures, safety assessment, labelling requirements and in some cases a definition of nanomaterials e.g. the Novel food regulation 2015/2283 (European Parliament and Council, 2015), the Plastic food contact materials regulation 10/2011 (European Commission, 2011), the Food Information to Consumers Regulation 1169/2011 (European Parliament and Council, 2011), and the Food Additives Regulation 1333/2008 (European Parliament and Council, 2008). The overarching regulation covering registration, evaluation, authorisation and restriction of chemicals is (REACH) 1907/2006 (European Parliament and Council, 2006). While REACH is not directly related to food/feed, nanomaterials fall within the heading 'substances' as defined in article 3(1) of the 2006 regulation. In 2018, changes to the REACH regulation were enforced by the EC to address nanoforms of substances; the changes came into effect in January 2020. The regulation has been met by legal appeals on compliance checks and on substance evaluation decisions, many of which stem from a lack of guidance on the EU definition of nanomaterials which was used to underpin the REACH regulation. Indeed, a number of EU Member States have undertaken substance evaluation reviews on nanomaterials of particular concern, e.g. Silver (nano) and Silicon Dioxide - 2015 (The Netherlands), Zinc Oxide-2016, MWCNT-2018 (Germany) and Titanium Dioxide (171) - 2015/19 (France) (European Union Observatory for Nanomaterials (EUON, n.d.). The European Commission have suggested amendments to the Food Additives Regulation to include new specifications for Titanium Dioxide. The draft amendment has not been approved by the European Parliament yet, however stricter requirements will be required for characterisation of Titanium Dioxide, or alternatively there could be an outright ban on its use as a food additive (Morrison

O., 2020). In addition, EFSA have recently carried out a data assessment of Titanium Dioxide (171) and have recommended measurement of the 'Constituent particle size' using electron microscopy (Younes *et al.,* 2019).

In Ireland, the competent authority with overall responsibility for the enforcement of food legislation is the Food Safety Authority of Ireland (FSAI). In 2008, the FSAI carried out an assessment of the potential risks associated with nanotechnologies in the food and feed industries of Ireland. A report was issued with a number of recommendations, including the need for coordinated allocation of funding across government departments and agencies, to support the national infrastructure for the supply of skilled personnel and for the development of methodology for regulatory control of nanomaterials. The report also identified the important role that academia could potentially play in supporting the development of expertise and skills within the state. A concern was raised at that time in relation to the apparent lack of preparedness and the inadequate regulatory control infrastructure within the state (FSAI, 2008). In 2013 Safefood' commissioned a follow-up study to identify applications, opportunities and challenges to the implementation of nanotechnology on the Irish market (Handford *et al.,* 2014). The FSAI report was published more than a decade ago, this aspect of the thesis seeks to determine what has been achieved nationally since the publication of the report. The focus of this part of the overall review is to examine both qualitatively and quantitatively how the Irish nano food safety strategy has evolved in the 10 years since the first national report. This work will identify knowledge gaps and legislative dissemination issues associated with nanosafety in consumer food. It will examine exchequer investment in developing the infrastructure, in terms of both the physical infrastructure and the human capital. Furthermore, it will assess the knowledge gaps that remain in the strategic approach to nano-food safety in Ireland. Comparisons to other national strategies will also be drawn.

This chapter presents the results of the review which was carried out to identify and to evaluate nanotechnology skill and capacity shortages in Ireland's agrifood sector. Various collection methods were used, a brief overview of these methods is presented in section 3.2.

3.2 Methodology

This aspect of the work involved reviewing the status of projects, infrastructure and facilities which were funded by the exchequer across multiple agencies. Data mining was used to carry out qualitative analysis of policy documents, reports, and funding databases pertaining to exchequer investment in nano-specific projects capable of supporting the enforcement of nano-specific legislation. Interviews, surveys and focus groups have been used to varying degrees to establish the investment potential, dissemination issues and future concerns for nano food safety from a regulatory perspective.

Data collection consisted of three processes: review of exchequer policy documents and reports, direct communication with relevant government department and agency officials and an in-depth review of the exchequer funding databases to determine how much money was allocated towards research projects, equipment and associated facilities, training, and other related activities.

3.2.1 Review of exchequer policy documents and reports

The initial collection of data was mainly desk-based research, focusing on obtaining information from policy documents and reports produced by government departments and agencies. Assessment at department/agency level is generally available on government/agency websites, Annual Accounts, and/or Annual Output Statements and these reports were accessed to get an indication of the overall amount of exchequer funding which was directed towards research. This information, which is freely available on government websites was prioritised based on the content and on the relevance to this investigation. Relevant documents and reports were selected for comprehensive review, and any pertinent data was included in the overall estimation of funding. Internet search of relevant government department and agencies websites was conducted, e.g. DAFM, DBEI, EPS.

3.2.2 Communication with government departments, agency officials and academics

This aspect of the project involved making direct contact with individuals with responsibility for administering funding/supporting policy and regulation, seeking

information which was either not readily available, or it was difficult to locate. Interviews and surveys were conducted with these individuals as well as with members of academia. The interviews focused on discussions around funding calls in the period 2008-2018. Extensive discussions with these people provided additional qualitative and/or quantitative information, which complemented and enriched the data already retrieved. The surveys and interviews were encoded and statistical analysis was performed using Microsoft Excel.

3.2.3 Review of the Exchequer funding databases

The review of Exchequer funding which was allocated towards research projects, equipment, facilities, and/or training involved the process of accessing funding agency databases and exploring the outcomes of funded; projects, research, infrastructure, facilities, and/or training courses. This involved identifying who/where (academic institution/state body location) received exchequer funding in the period 2008-2018. What was the purpose of the funding? (e.g. equipment, facilities, research infrastructure/grants, training). The analysis involved identifying; which funding was specifically directed towards establishing research infrastructure? What funding was directed towards the agri-food sector, and how much of this funding was 'nano' related? This facilitated identification of key documents for in-depth review and for qualitative analysis of relevant documents pertaining to exchequer investment in nano-specific projects, capable of supporting regulatory enforcement.

Various research projects were selected for further review. The material was prioritised and the most appropriate projects were selected for in-depth analysis. Literature synthesis was carried out based on a stepwise approach to data mining involving keywords searches and cross-referencing (Gibson *et al.,* 2007). Relevant search terms and queries were applied to a variety of websites and databases. Combinations of different search terms were used to determine 'nanospecific' funding. The search terms and queries were recorded for reference purposes. A representative list of keywords used is illustrated in table 3.1.

Table 3.1: Representative list examples of keywords used for data mining.

Nanotechnology	Nanoscale	Food/foodstuff	Food packaging	Nanodevice
Nanoscale properties/phenomena	Manufactured nano	Nanospecific method	Nano manipulation	Size determination
Nano-scale measurement techniques	Nano-encapsulation	Food production	Engineered material	Food contact material

3.3 Results

A review of Ireland's Gross Expenditure on Research and Development (GERD) indicates that approx. €29 billion was directed towards research and development (R&D) over the period 2008-2017 (DBEI, 2018b). GERD is the sum of R&D expenditure in the business, higher education and government sectors. The main source of funding comes from; business enterprises, the government sector, sources from abroad (e.g. the European Commission, international organisations) and private not for profit organisations. An overview of those contributing towards Ireland's expenditure on R&D funding (2008-2016) is illustrated in Figure 3.1

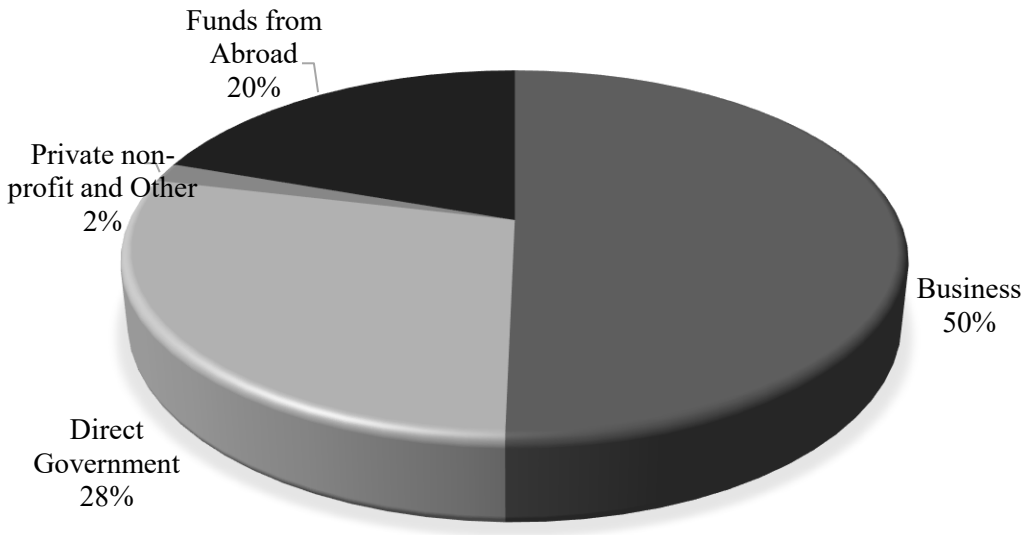

Figure 3.1: Expenditure on R&D, Source of Funding 2008-2016, % breakdown by sector.

3.3.1 Business Sector R&D Funding

Data relating to the outcome of Business Sector Expenditure on Research and Development (BERD) is available from the Central Statistics Office (CSO) biannual survey results, which are accessible on the CSO 'Statbank' database. The CSO survey involves all enterprises who are thought to be engaged in research and development activities across all sectors of the economy. A search of the database records from 2009 to current records (obtained in 2019) indicated that the vast majority of the business sector funding comes from self-funding (CSO, 2019a). While Ireland's R&D is predominately funded via the corporate sector, significant interaction and collaboration occurs between the corporate and public sector to take advantage of economic efficiencies. Researchers can avail of the national research and business knowledge transfer system i.e. Knowledge Transfer Ireland (KTI). Since 2007 the Irish Government have invested €86.5 million in KTI supporting industry-academia research collaborations (KTI, 2019). In addition, exchequer funding for business sector R&D is also allocated through various government departments and agencies.

3.3.2 Direct Government R&D Funding

The international indicator of 'state funded performance in R&D' is measured by the 'Government Budget Allocations for R&D' (GBARD) indicator. GBARD includes 'direct government' funding allocations which is distributed by various government departments and agencies for the purpose of R&D in the Higher Education Institutions (HEI), the corporate sector, the public sector, and any contributions made by the Government towards international programmes involving R&D (CSO, 2019b). This funding can be prioritised by government departments and Agencies for the purpose of R&D to build capacity and infrastructure of importance. This public or exchequer funding is normally made available through research funding bodies from open research calls aligned to national priorities (DBEI, 2018a). Exchequer funding which was allocated towards R&D in the business, higher education and Government sectors for the period 2008-2018 amounted to more than €12.9 billion. Figure 3.2 represents the main public research funding agencies and departments who are responsibility for the distribution of these funds. A breakdown of % of overall budget allocations by

government department or agency is shown (figures were taken from 2008-2018 annual reports, Exchequer documents and websites).

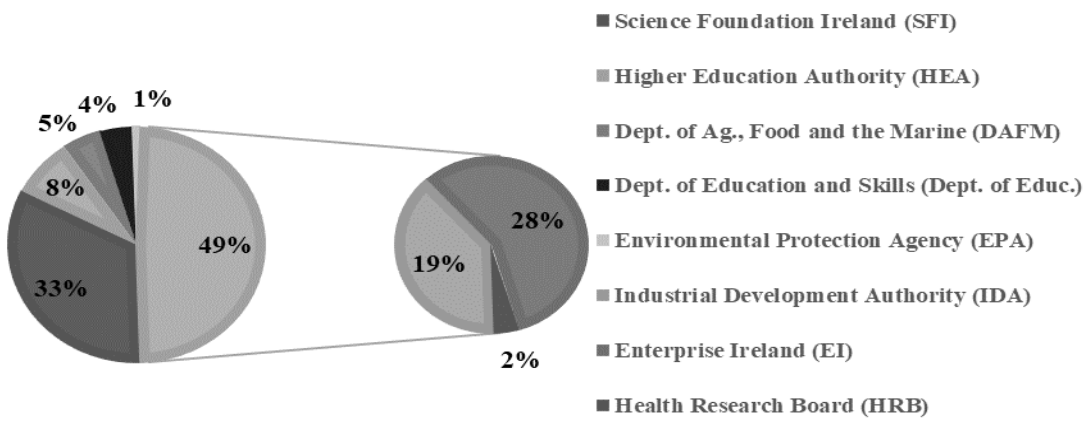

Figure 3.2: Exchequer investment 2008-2018, % breakdown by government department/agency.

A significant amount of exchequer funding (49%) was dedicated to building the infrastructure for innovation and product development i.e. funding from the EI, IDA, and the HRB. EI is responsible for supporting Irish businesses with strong R&D remits, helping them at start up, to expand, and to enter global markets. The agency provides Exchequer funding to support infrastructural development and promotes collaboration between industry and research institutions. The role of the IDA is to promote foreign direct investment to Ireland, which mainly involves sectors such as financial services, software, engineering, medical technology and bio-pharmaceuticals. The agency is strongly involved in supporting collaboration between industry, academia, state departments/agencies and regulatory authorities. The Health Research Board is the main funding agency for medical/pharmaceutical research in Ireland.

Nanotechnology was identified as one of a number of 'key enabling technologies' in the Irish Government's 'Innovation 2020' strategy for research and development in science and technology (DBEI, 2015). The Government identified the need for 'Research Prioritisation' and investment to build capacity and to maximise on investments which have been already financed by the Exchequer (DBEI, 2015). Exchequer funding committed to building Ireland's research infrastructure and

resource capacity within the 'public/state' sector (approx. 51% of exchequer funding) is distributed through Science Foundation Ireland (SFI), Department of Agriculture, Food and the Marine (DAFM), the Department of Education and the Higher Education Authority (HEA). This investment is dedicated to funding R&D in Higher Education Institutions (HEI's) providing facilities, equipment, resources and services, and to maintaining research centres. SFI, the largest exchequer funding agency's role is to promote study and engagement in the areas of science, technology engineering and maths (STEM). The Agency is involved in supporting the establishment and operation of Research Centres (SFI, 2017). These Research Centres are focused on areas of strategic importance to Ireland, one of which is Nanotechnology/Materials. SFI Research Centres of significance with respect to nanotechnology include, but are not limited to:

- AMBER: research centre for Advanced Materials and BioEngineering Research, with facilities to include advanced microscopy and Metrology/spectroscopy.
- CÚRAM: research centre for Medical Devices, with facilities for biological and physiochemical analysis.
- VistaMilk: research centre for Digitalising Dairy Production and Processing, with enhanced Chemistry laboratory 'nano' facilities.

Exchequer funding directed towards SFI activities from 2008-2018 amounted to €4.2 billion. This makes SFI the largest funder of nanotechnology led research in the State. A review of the breakdown of funding over that period shows that approx. €95 million (2.2%) of the total SFI funding was referenced as 'Nanoscience/Nanotechnology' – comprising: Approx. 90% Information and Communications Technology (ICT) and 10% biotech, medical, and pharmacy, which were specifically referenced as 'nano' related. A large amount of the SFI funding (approx. 44%) was allocated to establishing and maintaining Strategic Research Centres; significant expenditure (approx. 35%) was additionally used to support R&D Investigator /Research Programmes within the Higher Education Sector.

In contrast, food based research and infrastructural supports for the agrifood research sector are predominantly funded by DAFM, which accounts for

approximately 5% of the total exchequer research funding. It should be noted that the other agencies do fund overlapping disciplines and support transferable infrastructure, however it is not their primary focus. Research funding from exchequer sources in areas related to agricultural science is significantly lower than for any other fields of science. Data from the Central Statistics Office (CSO) indicates consistently low level of funding for this research area at approx. €20 million/pa, or 3% of total research funding since 2006 (CSO, 2019b). This is surprising since the agri-food sector in Ireland generates an average of 7% of the country's gross value added per annum.

3.3.3 Higher Education Sector R&D (HERD).

HERD involves direct funding which comes from various government departments and state agencies, e.g. SFI, Irish Research Council (IRC) the HEA and others. Direct Government funding involves supporting the national research capacity, the research infrastructure, and facilitating research programmes e.g. the Programme for Research in third Level Institutions (PTRLI). Indirect funding from the Government comes from the Higher Education Authority (HEA), supporting research in Universities and Institutes of Education, and includes funding for general operational activities. Funding directed towards R&D in the higher education sector amounted to more than €4.2 billion from 2006-2017. The Government contributed over €3.4 billion (81%) to this funding in 2017.

Latest figures for 2016 show that there were 26,293 full time equivalent researchers working across the business, education and public sector in Ireland. The higher education sector employed the greatest number of researchers, (56% of total), followed by the business sector which employed 42% of the total researchers, with a small number of researchers employed in the government sector (2% of total) (DBEI, 2019). Most research carried out in higher education institutions is basic research in the social and natural sciences areas, along with research in humanities. Applied research comprises about one third of all research activity, i.e. in the medical/health or engineering/technology areas of interest. Practical/experimental research accounts for a very small amount of the overall research activities in the higher education sector (DBEI, 2019). Figure 3.3 presents a typical breakdown of research activity by field of science.

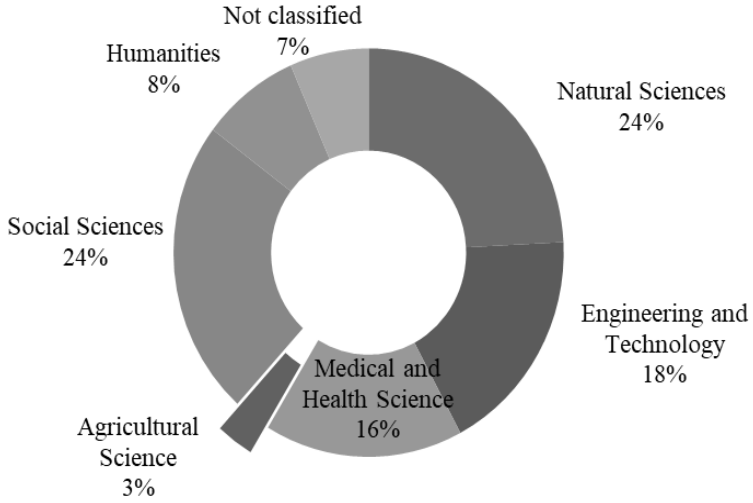

Figure 3.3. Breakdown of research activity by field of science (2016 Headcount figures)

As illustrated in Figure 3.3 research in areas related to Agricultural Science is significantly lower than for any other fields of science, this is also reflected in the consistently low level of funding for this research activity i.e. approx. €20 million/pa (3% of total research funding) since 2006 (DBEI, 2019).

A review of an Irish institutional repository of research activities (i.e. rian.ie) was carried out to obtain information relating to research activities that were specifically referenced as ‘nano’. The rian.ie website provides information in relation to research bodies/institutions and funders the information is freely accessible by open access. A search of this website using relevant search criteria and terms provided information in relation to the research activities by funder and by institution, for those which are specifically referenced as ‘nano’. The search period criteria extended from 2008-date. Figure 3.4 represents the main research activity focus relative to search terms for ‘nano’ related activity.

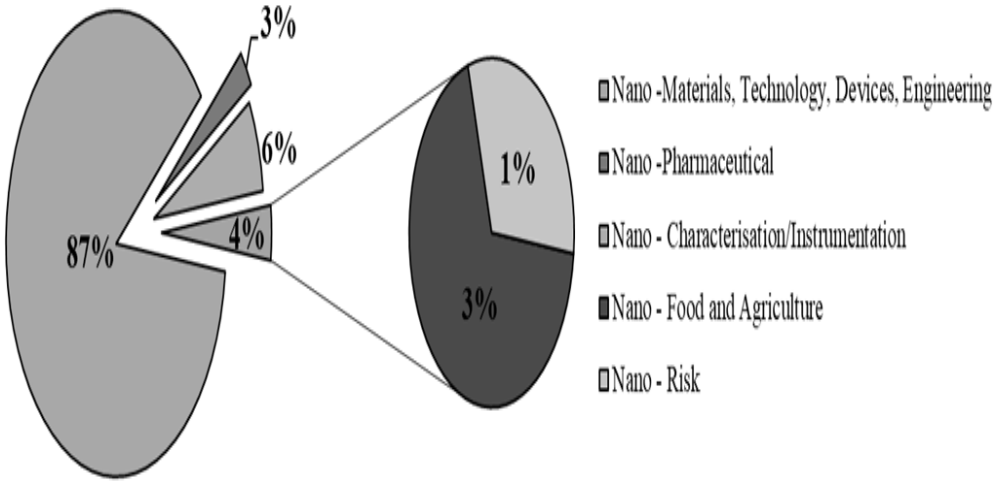

Figure 3.4: Research activities specifically referenced as 'nano' by research focus

This figure illustrates a broad overview of 'nano' research activities across all institutions and clearly shows that nano-agriculture/food, risk and characterisation/instrumentation comprises only approximately 10% of all 'nano' related research in the Higher Education Sector. A breakdown of institute activities based on repository data also reflects the trend in figure 3.4 as displayed in figure 3.5.

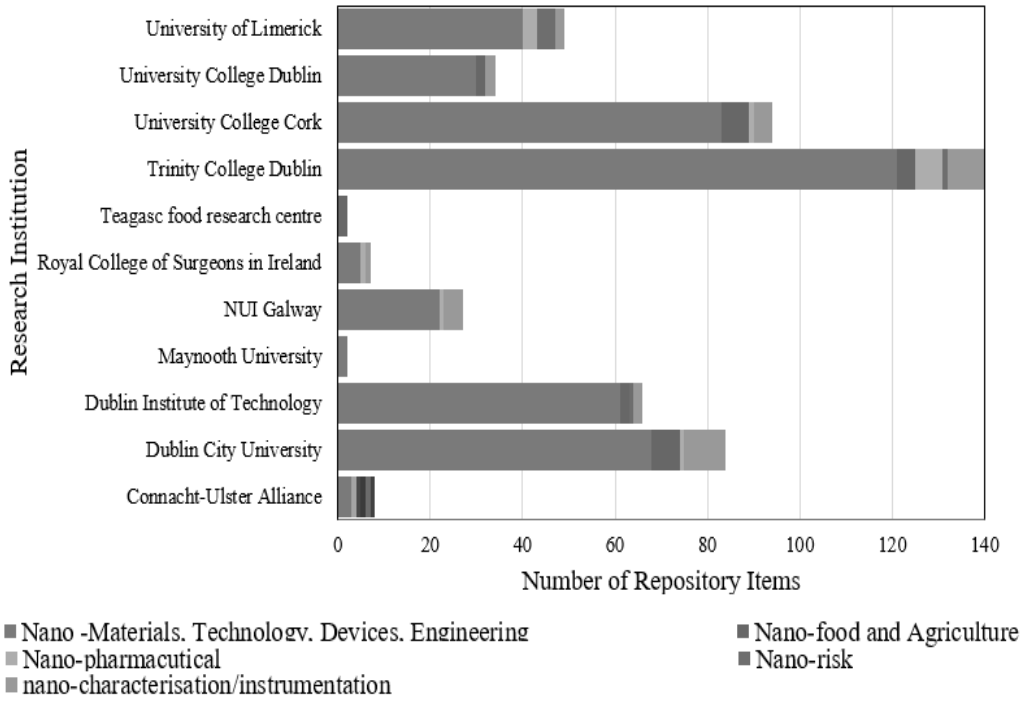

Figure 3.5: Nano Research activities: Research Institute and research focus by discipline

Figure 3.5 clearly illustrates a significant deficiency of 'nanofood/risk based research' which could potentially support method development for legislative purposes, and/or deliver the infrastructure to underpin enforcement in the nano-food area. This is not surprising since all but one of the listed organisations are Higher Education Institutions (HEI's) with broad remits of research, and they have minimum engagement with competent authorities for state risk assessment. Outside of HEI's Teagasc the Agriculture and Food Development Authority is the leading performer of R&D in the agrifood sector. Teagasc is a government sector organisation providing integrated research, advisory and training services to the agriculture and food industry and rural communities in Ireland, the agency is primarily funded by the Department of Agriculture Food and the Marine (DAFM). As a result, it has the potential to support the infrastructural and expertise needs of state laboratories and agencies engaged in regulatory enforcement of nano-food. It should also be noted however, that there is significant overlap in skillsets between the categories listed in figure 3.5, and so the potential for knowledge transfer from academia to national risk assessors is also present, which will be investigated further in chapter 4.

Indeed, in chapter 4, the role that academia could potentially play in supporting the development of expertise and skills within the state regulatory infrastructure will be explored. As data from the level of exchequer funded projects would anecdotally suggest that academia has the available technology and the skilled personnel. However, the regulatory requirements for official controls involve the use of accredited test procedures, facilities and authorised analysts. This is not the norm for academic institutions and it would potentially take a lot of laboratory resources, funding, and personnel to get the existing infrastructural capacity to that level. This would involve method validation, participation in proficiency testing schemes, and competency reviews with assessment by an accreditation body, which would be a very significant undertaking for academic institutions.

2.3.4 Government Sector R&D (GOVERD)

GOVERD is expenditure which is allocated to Government Departments, State Agencies and Government funded hospitals for the purposes of R&D. Exchequer funding which was directed towards Government Sector R&D for the period 2008-2018 amounted to approx. €1 billion. This figure represents less than 4% of Ireland's Gross Expenditure on R&D. Figure 3.6 shows a typical breakdown of Government Sector R&D performers. Figures were taken from 2017 statistics (DBEI, 2018b).

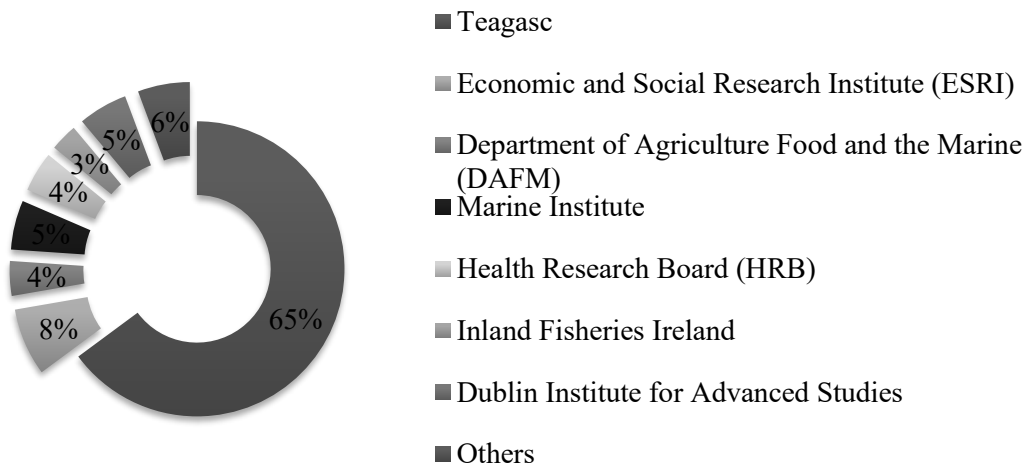

Figure 3.6: Government Sector R&D Performers - 2017, % of total R&D Performers

Government figures made available for OECD reporting (available for 2017 only) estimate that approx. €47 million of Exchequer funding referenced as 'nanotechnology' related, was made available to the higher education sector and €1.6 million was made available to government sector R&D (this equates to approx. 4.8% of all government funding which was allocated to higher education and public sector R&D for 2017).

As illustrated above Teagasc is the leading performer of R&D in the government sector. Food research conducted by Teagasc, of particular relevance to applications of nanotechnology mainly involves food formulation, protein/carbohydrate manipulation and nano-engineered food ingredients. Research relating to the development of nanosensors for crop spoilage also features.

DAFM conduct their own in-house research also and the Marine Institute (an agency under the remit of DAFM) are responsible for supporting marine based research. Inland Fisheries Ireland are responsible for development and improvement of inland waterways and sea angling. DAFM "nano' funded research projects for the period 2007-2017 amounted to approx. €7.7 million (5%) of total DAFM research funding. Research projects funded by DAFM to Irish Universities and Institutes of Technology range from 'smart' nano impregnated packaging, 'nano' pharmaceutical delivery, and nutraceutical formulations. Nano related research and development at departmental level in DAFM laboratories was not evident in the review of DAFM research activities.

Information obtained from the EPA relating to a query of funded research projects for the period 2007-2017 showed that approx. €3.4 million (4%) of total EPA research funding was referenced as 'Nanoscience/Nanotechnology'. For the most part, the EPA funded research activities in Irish Universities, involved supporting water purification/decontamination and waste treatment/management, using 'nano' enabled structures, devices or nanoparticles. The EPA also part funded research relating to an evaluation of the applicability of existing REACH procedures for chemical safety assessment of nanomaterials. Research relating to detection, toxicology and risk assessment of nanomaterials in the aquatic environment also featured, as did an assessment of the applicability of existing regulation to nano-enabled green technologies. It can be assumed that the analytical capacity/instrumentation is available for the characterisation and measurement of these applications of nanotechnology as a requisite of the final research output.

3.4 Discussion

The main focus of this chapter was to explore the recommendations made by the various national reports to prioritise research funding for the development of nano-risk assessment methodologies, to underpin the regulatory process. This was a specific recommendation made by the FSAI report more than a decade ago. In the intermitted time period more than €29 billion was directed towards research and development in Ireland (DBEI, 2018b), of which almost one third was from direct exchequer funding sources. In the same period, Irish agri-food sector exports have

increased by 73% from €7.8 billion in 2009 to €13.7 billion in 2018 (DBEI, 2015). The agri-food sector is Ireland's most important indigenous industry playing a vital role in Ireland's economy. In terms of exports the agrifood sector is second only to the pharmaceutical sector and is constantly placed ahead of other manufacturing sectors such as the ICT sector. As indicated in the results outlined in 3.3, research funding from exchequer finances in areas related to agricultural science is significantly lower than for any other field of science.

The consistently low level of funding for this research area i.e. approx. €20 million/pa undoubtedly reduces the dedicated infrastructural capacity and support expertise available to regulatory bodies and national risk assessors for emerging areas of concern such as nanotechnology. Much of the shortfall in funding for applied research in the agrifood sector is made up by corporate or business sector funding which often comes from corporations self-funding research, or engagement in collaborative 'matched' funding schemes with public sector bodies such as Teagasc the Agriculture and Food Development Authority. As outlined previously the Irish government have invested €86.5Million in such schemes through the KTI initiative, which supports industry-academia research collaborations (KTI, 2019). The focus of such programmes often is on the aims and objectives of the industry partner as opposed to any national risk assessment agenda. Significantly, such schemes do provide an avenue for the development of important research expertise and trained personnel, which could play a role in supporting the development of new methods for risk assessment.

Irish Government expenditure that was allocated to the 'State sector' for the purposes of R&D was less than 4% of the Exchequer's Gross Expenditure on R&D for the period 2008-2018. When Ireland's performance is measured against international standards, (expressed as GOVERD % of GDP) the figure of 0.06% compares very unfavourably against the EU28 average figure of 0.23% and the OECD average figure of 0.26% (DBEI, 2018b). While it appears to be the case that the HEI's have sufficient knowledge/expertise and availability of equipment, this is not the case for the 'state sector'. Anecdotally state sector personnel report the unavailability of equipment e.g. Electron Microscopy (EM), Dynamic Light scattering (DLS) and other highly specialised equipment that could potentially be required for characterisation and regulatory control purposes. In addition, it appears

that the skillset is not available either as evidenced from the 2018 meeting of the EFSA Scientific Advisory Network for the risk assessment of nanotechnologies in Food and Feed, where MS were asked to give a brief overview of their experiences and expected implementation of the EFSA Guidance of technical evaluation of nanomaterials. The Irish response was that there are no case studies to be presented as the laboratories contacted have reported that they have not yet done enough work in this area for implementation of the Guidance (EFSA, 2018).

3.5 Conclusion

This chapter presents an overview of the Irish research funding landscape and how it was utilised to help develop national capacity and infrastructure, to underpin nano-risk assessment, in response to recommendations from the Food Safety Authority of Ireland and other international reports. It is clear that the recommendations were not central to the decision making processes for national funding calls, with the agrifood sector accounting for only 4% of the reach activity ascribed to Exchequer funding. Nevertheless, funding to the wider nanotechnology area has developed a significant level of expertise and infrastructure capable of upskilling and adaption to help service the agrifood sector and underpin nano-risk assessment activities on the island of Ireland.

The nanospecific infrastructure capacity in Ireland, based on the exchequer funding models employed, has largely been established in the University sector, through Exchequer funding. The predominant nano-research areas funded nationally include nanomaterials and characterisation, devices and technology. This reflects much of Ireland's multinational landscape, with large ICT, medical device and pharmaceutical corporations based on the island. This has therefore evolved a competent academic community of researchers and infrastructure, suggesting that the skillset is available to help national risk assessors who are engaged in the enforcement of nano-specific legislation. It is acknowledged that some degree of up skilling would be required to adjust the expertise to meet the needs of the nano-agrifood sector. A significant disadvantage however with respect to the infrastructure, is the need for accredited laboratories facilities. Many of the academic laboratories funded by the Exchequer are research laboratories or

research centres and are not accredited facilities. This will be examined at interview, and survey responses in chapter 4, in which regulators queried the infrastructure capacity. It is evident from the results of the funding assessment that the infrastructural needs and expertise required to enforce nanosafety legislation in consumer food has been invested in, and that the national funding strategy over the last decade has created the required infrastructure. However, issues of accessibility and an awareness of the 'risk assessment community's' need for accredited facilities as the norm for regulatory agencies remains. It is imperative moving forward that greater communication and co-ordination is developed between the various risk assessment organisations and the wider scientific community, in order to take advantage of the infrastructure and expertise that have been put in place by a decade of research funding.

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4.1 Background to this research

Chapter 3 clearly established that the Irish exchequer has invested heavily in nanotechnology, with a particular focus on the Information and Communications Technology sector. Indeed the Information and Communications Technology sector contributes almost €50 billion per annum to the gross domestic product (GDP) and employs 74K people. In contrast, the Agrifood sector (labelled food and beverage) as shown in figure 4.1 has a higher Nano-product to market ratio then the Information and Communications Technology sector and is expected to grow in the coming years. Currently the sector contributes just under €15 billion to the GDP however; it is significant that the Agrifood sector employs 165K people.

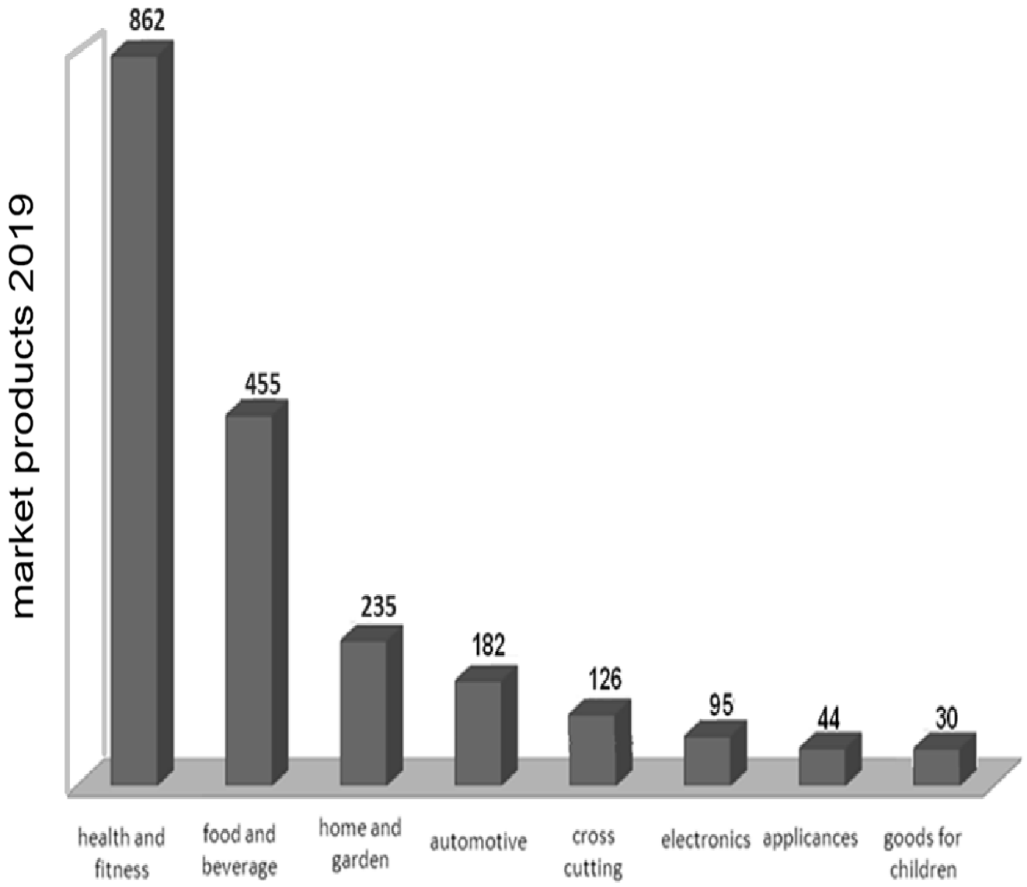

Figure 4.1: Nano-product to market per sector [original image assembled from Campos 2021] **(Jogaiah, Singh, Fraceto and Lima, 2021)**

Nevertheless, despite the development of the research infrastructure via exchequer funding for the Information and Communications Technology sector, the nano-agrifood sector can benefit also, with much of the infrastructure fully transferable

and adaptable to many nano related areas. Moreover, the development of a skilled and trained 'nano' workforce from the ICT sector would also potentially help service the anecdotal skill shortages in nanotechnology for the agrifood sector. Indeed, identifying the potential shortages in the necessary nano-skill set was explicitly highlighted in the FSAI report, and this forms a key question to be answered in this chapter. An additional question to be addressed is whether or not the exchequer funded nano infrastructure is accessible to the national risk agencies and competent authorities in Ireland. Anecdotal evidence would suggest that that there is a lack of awareness in these agencies, as to where such infrastructure would be located, and how it could be accessed. Furthermore, concerns exist as to whether such facilities would meet the requirements for regulatory enforcement. The 2013 Safefood report into nanotechnology and food actively encourages a dialogue between academia and regulatory bodies, to promote a greater level of food safety at the innovation stage of novel technologies such as nanotechnology (Handford *et al*., 2014). However, again no evidence of such dialogue or communication forum is apparent. This chapter thus will also consider the level of engagement between the sectors, and the prioritisation of such a dialogue, with a focus on nano-safety and policy enforcement. This chapter will explore these questions via a series of surveys.

It is acknowledged that enforcement of regulation policy requires an integrated approach, combining the strengths of the competent authority, available test facilities in control laboratories and the enforcement officers on the ground. In addition, the process should be underpinned by the core academic disciplines and state of the art research. This is an approach widely used across the EU, with a typical interdependent model of stakeholders as shown in figure 4. 2

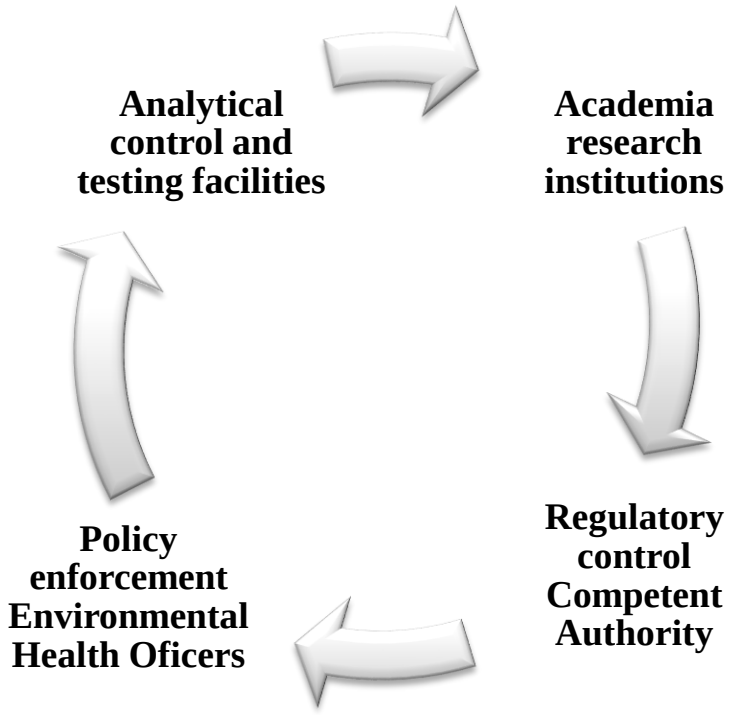

Figure 4.2: Multi-organisational stakeholders potentially involved in the safe management of nanotechnology

The key stakeholders as identified in figure 4.2 have been surveyed in this chapter. The regulatory competent authority invited to participate in the survey was the FSAI, who are the competent authority with overall responsibility for the enforcement of food legislation in Ireland. They are the experts with extensive knowledge of food legislation and it is their responsibility to organise official controls to ensure that food legislation is applied at all stages of food production and distribution for public supply. The policy enforcement officials, the Environmental Health Officers (EHO's) are the enforcers of legislation, the on-the-ground officials who carry out testing, compliance checks and monitoring of risks. They are principally aligned to the FSAI, working with the competent authority to support industry and the interests of the consumer. The analytical control and testing facilities invited to participate in the survey were the competent control laboratory (Dublin Public Analyst Laboratory) and the State Laboratory (provides service contract support to the FSAI). These establishments while not working directly on aspects of nanotechnology could be asked to facilitate this testing if required by the competent authority.

Academia has been recognized as a potential contributor towards the safe development of nanotechnology, by targeting research applications of relevance to regulatory authorities, and by communicating risks, benefits and knowledge/skills to support analytical testing activities. Traditionally academia would be seen as primarily university/higher educational institutions, however publically funded research agencies such as Teagasc the national agriculture and food development authority would be considered to be an 'academic' research institution, with the potential capacity to provide public research, advisory, analytical testing and/or training services if required to do so.

The key stakeholders could potentially work towards recognition of mutual benefits, developing applications, analytical capability and sharing expertise relating to regulatory policies and testing requirements. These stakeholders were presented with a series of questions via an online survey seeking to quantify the state of the art, to obtain stakeholders opinions, their future projections and to identify any infrastructural or skill/knowledge deficits that may exist to facilitate future testing of nanomaterials.

4.2 Research Objective

The objective of this research is to provide support to state agencies to enable them implement regulatory controls, arising from any potential 'nano' legislation within the agrifood sector.

Having identified the key stakeholders who would potentially be involved in providing this support to state agencies a series of questionnaire were developed to establish the state of the art, to examine their levels of awareness and perceptions and to identify any potential future shortfalls.

Survey questionnaires were designed to obtain information relating to the following key requirements;

- What is the current status of nanotechnology regulatory affairs/research?
- What are the potential knowledge gaps in assessing the safety of potential applications of nanotechnology?

- Are there identifiable skill shortages, in order to facilitate closing any knowledge gaps?
- What is Ireland's skill needs going forward with respect to nano-food technology?

These questions which underpin the research themes are investigated throughout this research. The methods used for identification and targeting of relevant participants and the questionnaire design have been presented in detail in chapter 2 (2.4.2.1)

4.3 Summary of the survey data

Prior to issuing the surveys online questionnaires were piloted by colleagues or fellow students to identify any discrepancies, lack of clarity, or ambiguities. The surveys were started in 2017 and are they were completed in April. 2022. Respondents to the regulator survey involved personnel from the FSAI and the State Laboratory. Respondents to the EHO survey involved nationwide practicing EHOs. Respondents to the survey for academics involved personnel from the following third level institutions; TU Dublin, NUIG, DCU, UCD, WIT, UCC, NUIM, TCD, Sligo and Letterkenny IT.

The survey of the non-academic stakeholders focused on three distinct groups,

1. Regulator Competent Authority (The Food Safety Authority of Ireland). The Food Safety Authority of Ireland (FSAI) was established under the Food Safety Authority of Ireland Act, 1998. The Food Safety Authority of Ireland is a statutory, independent and science-based body, under the aegis of the Minister for Health. The organization as a whole is relatively small, and the personnel involved in overseeing policy and legislation in the nanotechnology area is limited, as a result, the participation, and the response to the survey involves a small number of people.
2. Analytical control and Testing Facility (Public Analyst Laboratory and State Laboratory). These bodies provide comprehensive analytical and advisory services to Government departments and offices, thereby enabling them to implement and formulate the technical aspects of national and EU legislation. The State Laboratory undertakes chemical analyses for a variety of different

purposes, which include monitoring the quality and safety of Irish food. The Dublin based Public Analyst's Laboratory (DPAL) is an Official Food Control Laboratory within the Health Service Executive (HSE) and the national competent laboratory for nano-food analysis. Both organizations would typically perform analysis for the Regulatory Competent Authority, however only the State Laboratory agreed to contribute towards this survey, when the DPAL were invited to participate they declined the invitation.

3. Policy Enforcement - Environmental Health Officers (EHO's). Environmental Health Officers (EHOs) work involves enforcing regulation in a variety of areas including food safety. The bulk of this survey focused on EHO's operating as part of the Health and Safety Executive, with respect to food safety, but EHO's are also employed by the Health and Safety Authority in terms of enforcing REACH legislation. This group were surveyed on two occasions, i.e. 2017-2019 again in 2021-2022 (post TiO_2 EFSA opinion). A large group of practicing EHO's (122) were surveyed in 2017 and the results from that survey will be used where possible as an indicator of skill/knowledge/policy development advancement or otherwise since that period.

4.4 Research Key Requirements

4.4.1 Key Requirement 1: Status of nanotechnology

Nanotechnology research has been pioneered by many research institutions nationally and internationally for at least the past 15 years. Many reports acknowledge the contributions which academia could make towards the safe development of applications of nanotechnology, through collaboration with regulators, and facilitating access to their research infrastructure. In order to determine the relevance of the research undertaken, and the extent to which the research infrastructure could be utilised by state agencies, members of academia were asked a series of questions.

Of the members of academia surveyed, the vast majority (71%) of them have been involved in nanotechnology research for at least five years, indeed most (approx. 53%) of them have been working in this area for more than ten years, either

supervising research, faculty teaching, or they were involved as a student/researcher. While details about the area of research focus was not asked in specific terms, many respondents (42%) did however indicate that their area of focus/expertise could be classed as "related to aspects of nano-food or nano-agriculture", thereby indicating a good level of relevant expertise amongst the interview cohort.

Academic research is funded predominately through research grants obtained from various EU framework programmes, in addition to Irish Exchequer grants and funding calls. Figure 4.3 presents an overview of the main Irish exchequer funding agencies and the level of engagement which academics have with these agencies, specifically with respect to nano food/agriculture funding.

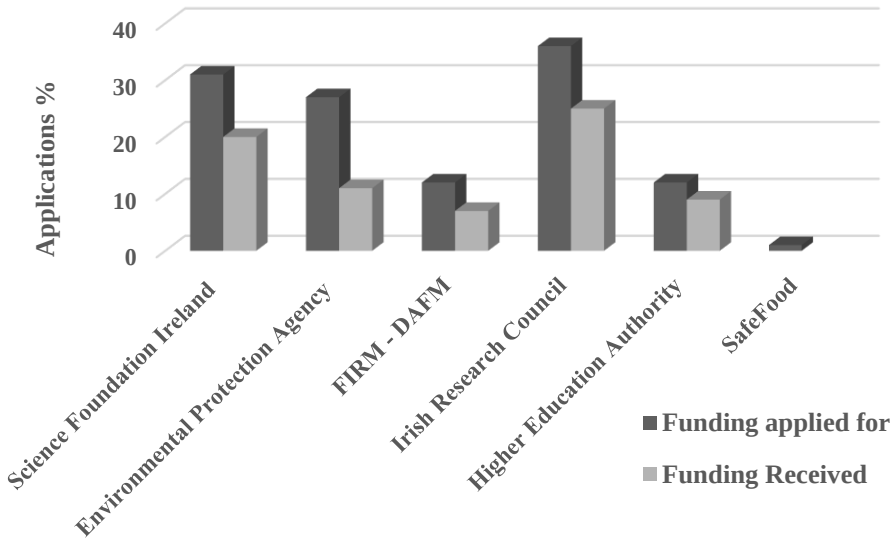

Figure 4.3: Exchequer funding applications by Exchequer Funder

As illustrated in Figure 4.3 the most significant funders of research activities are the Irish Research Council and Science Foundation Ireland, interestingly the Dept. of Agriculture (FIRM) (potential food related) funding applied for, accounted for only about 12% of the total research funding applications. Of those academics who applied for 'exchequer' research funding approx. 22% or 1 in 5 of them were unsuccessful in their application. Additionally, it is noteworthy that less than half of those who applied for Dept. of Agriculture funding where successful in their application for funding. This is similar in the case of the EPA, and is less apparent in the case of the other exchequer funders.

When presented with a range of national collaborations which could potentially be utilised by them, academics indicated that the most highly rated collaborations were those with industry e.g. internship/job funded research/short term contract, followed by collaborations with another HEI. The least preferred options for collaboration were 'collaboration with relevant government department' and 'with a state or semi-state body (State Lab, PAL)' with all but three participants (5%) ranking this form of collaboration as their $4^{th}/5^{th}$ preference. Analysis was conducted to determine if any relationship exists between academics receipt of funding from a 'state' institution, and their stated preference for collaboration with Government departments and/or state institutions or agencies. A chi square test of independence showed that no significant relationship exists between whether academics who received state funding or not consequently expressed a high preference for collaboration with 'state' institutions, as opposed to collaboration with industry/HEI collaborations, $X2\ (2, N = 52) = 0.8$, $p = .370426$.

The vast majority (80%) of academics indicate that they have not participated in any national or international programmes/projects relating to the development of nano standards, or method development for regulatory or traceability purposes. Consequently, it is not surprising to see that academics rate engagement with a regulatory body e.g. FSAI/EPA and collaboration with the relevant government department of lesser importance than collaboration with industry. However, this could also be reflective of the fact that perhaps engagement between regulators and academics does not feature much when participation/opinion is sought with regard to development of national/international standards or regulatory policies. It is interesting to note that, of those who did participate in some form of method standardisation protocols, some were involved in national standardisation procedures e.g. SFI programmes, one participant referred to participation of particular relevance to this research i.e. involvement with EFSA and JRC panels, QNANO, NANOIMPACTNET, EUFP7 and IMPART FP6. Otherwise most were involved in European Projects e.g. JRC, EU Framework programmes.

While more than 40% of those surveyed would classify their research as "related to aspects of nano-food or nano-agriculture", respondents appeared to be somewhat unsure whether they had suitable analytical infrastructure available to them within their institution to fully characterize nanoparticle applications in the agri-food

sector. Just over 40% of respondents indicated that they believed that they had suitable analytical infrastructure, while 57% said they did not, or that they did not know if they had suitable instrumentation or not. A closer look at the individual results in relation to opinions expressed relative to receipt of funding, compared with perceived access to facilities was carried out using a chi-square test of independence. The results showed that there was no significant association between academics who received state funding, or not, and whether they perceived they had sufficient access to facilities, X2 (2, N = 39) = 0.6, p = is .428987.

A low percentage of respondents (32%) confirmed that they believed they have suitable analytical infrastructure available to them in terms of 'supporting teaching and training of undergraduates' on techniques for the characterization of nanoparticles. The majority (64%) of people however indicated that they thought that the equipment (physical) infrastructure was available through access programmes in organisations outside of their university, college or research centre. This is a good reflection of implementation of the national access programme which is available to third level institutions, and it demonstrates the successful output from the exchequer funding initiatives over the past decade or more. While it is good to see that researchers are confident that they have suitable access to equipment, survey respondents appeared to be less confident that they would have access to the appropriate training programmes (skill development) nationally, with 63% of people indicating that they believed the appropriate training and skill development was not available to them outside of their organisation.

Personnel from a number of state agencies and from the national regulatory enforcement facility i.e. Environmental Health Officers, (EHO's) were asked a series of questions to determine their roles/responsibilities, current involvement with nanotechnology controls and their potential capacity to manage the safe development of applications of nanotechnology.

The regulatory authorities involved in the survey were predominately involved in carrying out their regulatory/legislative function (competent authority), or they were involved in supporting the competent authority in an advisory/analytical capacity. Their key stakeholders are; the European Union and/or relevant government department/agency, where the regulators surveyed were involved in

activities such as policy development, regulatory control functions and developing expertise (43%). The agencies surveyed indicated that they are mainly involved in following developments in nanotechnology (70%), as opposed to active participation in this area. While it is acknowledged by many regulators that developing the national nanotechnology testing capability is not a pressing priority at this point in time, the majority (80%) feel that this will become a priority in less than 5 yrs. time.

The EHO's role involves providing support to consumers and industry, working with the competent authority they are the practical 'enforcers' of food policy and legislation in Ireland. Most EHO's (>60%) are 'aware of the term nanotechnology but that is all' and some respondents (31%) indicated that they were 'aware of a very limited number of products and/or applications of nanotechnology'. When asked if they were aware of any food or beverage products currently on the market that contain nanomaterials or nanotechnology, more than 80% of survey respondents indicated that were not aware of any such products. This response would imply that monitoring of applications of nanotechnology is not seen to be relevant at this point in time for the sampling enforcement officials, which is similar to the fact that it is also not a high priority focus area for the regulatory authorities either.

The potential lack of awareness of consumer products which could be on the market was explored in the survey by presenting participants with a range of fictitious items along with the product description. Participants were asked to indicate if in their professional opinion the items would be classed as nano or not? The answers given by respondents were correct in 58% of the time, in the one case where a material would indeed be classified as nano, and where the particle size range was provided, one in five respondents gave an incorrect answer. The overall success rate for all questions was <10%. Analysis was conducted to determine if a relationship exists between EHOs self-confessed 'awareness' of nanotechnology versus their actual ability to correctly determine 'nano' products as described. A chi-square test showed that there is a significant relationship between the two variables. Surprisingly it appeared that EHO ability to correctly determine 'nano' products is significantly greater amongst those who are 'aware of the term nanotechnology, but that is all' as opposed to those who indicate their 'awareness of nanotechnology

products., X2 (2, N = 96) = 4.0, p < .005. It may well be however that correct selection of 'nano' products was random amongst the entire group.

When EHOs were asked did they think that nanotechnology might represent an emerging public health or an environmental health risk in the future, most respondents (69%) answered that they did not have sufficient information at this point in time to determine any emerging risks that might arise. One in four respondents indicated that they do believe applications of nanotechnology may represent an emerging public health and/or an environmental health risk. When presented with a range of options, querying which they would potentially use to gain access to information to enable them keep up to date with emerging public health or environmental risks, the most popular options selected by the EHO's was that they would rely on Government dept./government agency reports, EU reports and/or Peer review Journals. An interesting point of note is that some of these professions would also rely on news /media reports, and they would use web browsers to access this information. A breakdown of the resources used is illustrated in Figure 4.4.

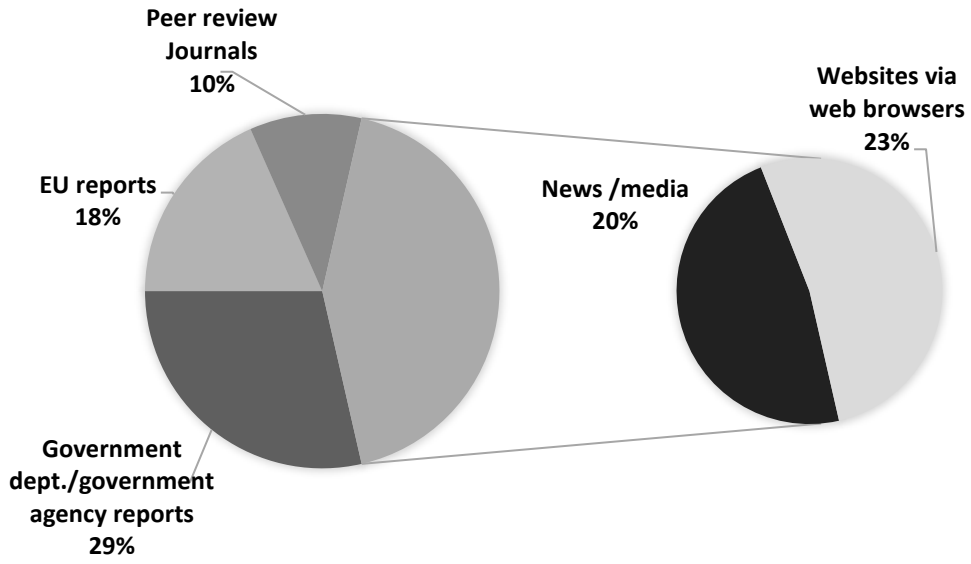

Figure 4.4: Information resources used by EHOs to keep up to date with emerging public health or environmental risks

Examples of sources used include the following: Food Safety Authority of Ireland, HSE, ESFA, europa.eu, and/or EPA websites. Tobacco control, ESFA and/or WHO Journals, The operational units within the Environmental Health Service which

specialise in different topics e.g. sunbed, food safety and tobacco. Internal HSE staff emails, staff training in new/ updated legislation, FSAI food alerts.

Results from data collected in the period 2021-2022 involving practicing EHO's are presented in figure 4.5 below. When participants were asked if they had a query regarding a particular nanotechnology application where/who would they contact for advice, most respondents first or second preference would be to refer to the relevant government agency e.g. FSAI, HSE, EPS, HSA. Additionally many would seek information from a 'non-government agency' (e.g. SafeFood, WHO, IBEC) and likewise they might not seek advice from anybody, they would "read-up myself using websites, library resources etc." Seeking advice from academia features quite well, with many respondents ranking this engagement as their 2nd/3rd preference. It would also appear from the charted results that practicing EHOs would preferentially avail of all of the information sources presented to them, possibly to compare and contrast, or to validate the information gained from many sources.

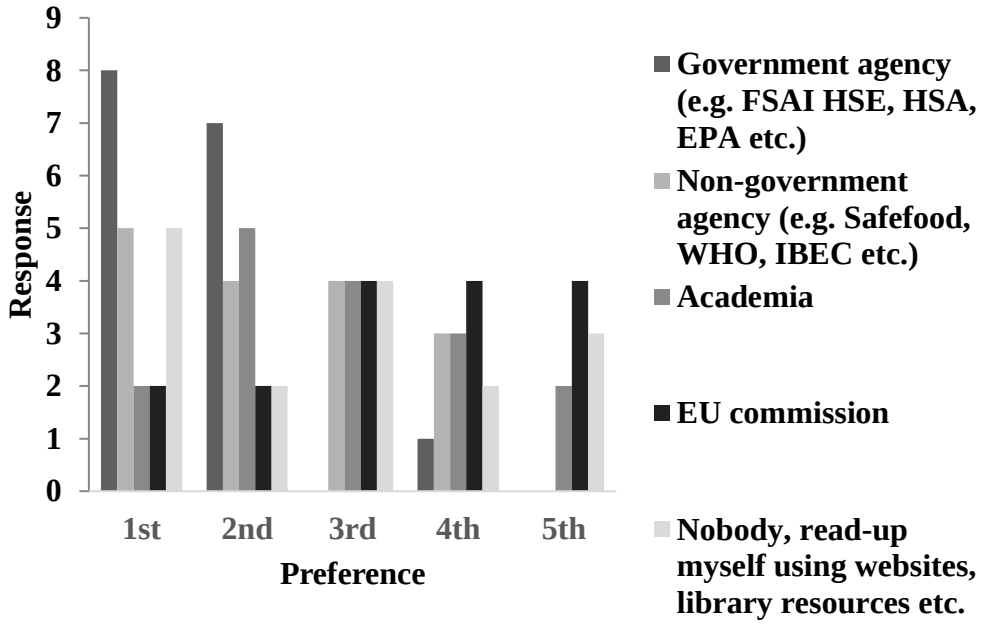

Figure 4.5: Information source preferential expressed by EHOs relating to a potential nanotechnology query - Results from data collected in the period 2021-2022

Results from the 2017-2019 survey are illustrated in Figure 4.6 for comparative purposes.

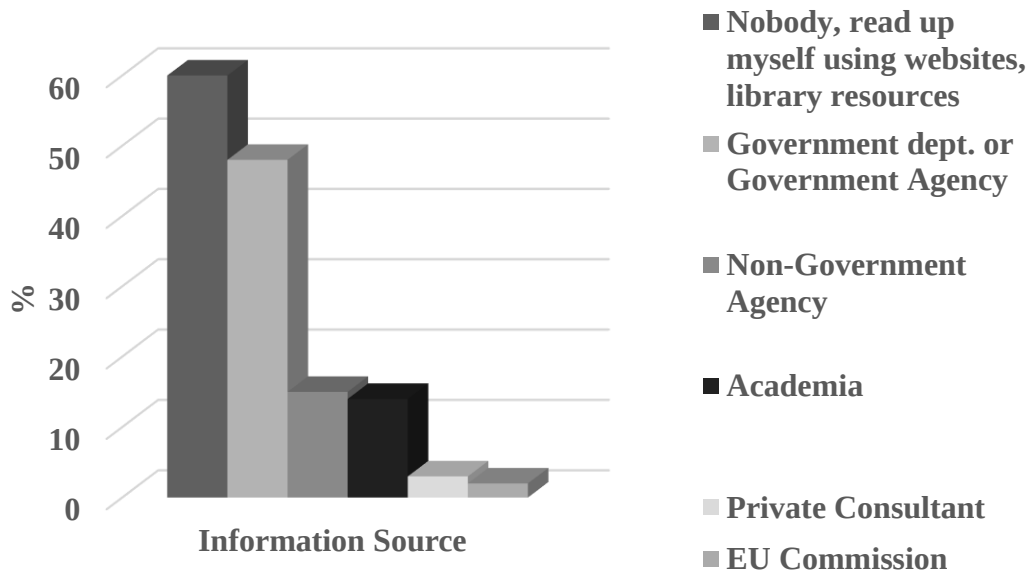

Figure 4.6: Information source preferential expressed by EHOs relating to a potential nanotechnology query - Results from data collected in the period 2017-2019

It is interesting to note, when comparing results from the survey conducted in 2017-2019 that the most highly rated response at that time was not to seek advice from anybody, i.e. they would "read-up myself using websites, library resources etc.". It is encouraging to see that engagement with government agencies and/or non-government agencies has improved over the past few years, and that practicing EHO's do view these support networks as valuable sources of information.

4.4.2 Key Requirement 2: Potential Knowledge gaps

Given a choice of the analytical technology listed below, academic researchers were asked to indicate the most appropriate techniques, which could be used to obtain routine high throughput and reliable data for a broad range of nanomaterials, in terms of analysing particulates, nanoparticles, or ingredient size distributions in complex systems e.g. chemical mixtures or food products, i.e.

- Dynamic Light Scattering (DLS)
- Atomic Force Microscopy (AFM)
- Field Flow Fractionation (FFF)
- Inductively Coupled Plasma Mass Spectroscopy (ICP-MS)

- Scanning Electron Microscopies (SEM)
- X-ray Diffraction and Elemental Analysis (XRD)
- Electronic Spectroscopy (Atomic Emission or Absorption (AAS or AES)

Regulators were asked to indicate their awareness of these techniques, which could be used for regulatory control/monitoring plans/testing procedures for applications of nanotechnology, the respondents level of awareness is shown in table 4.1.

Table 4.1: Analytical techniques used for regulatory control/monitoring plans/testing procedures for applications of nanotechnology

Analytical Technique	**Knowledge of (%)**	**No Knowledge of (%)**
Dynamic light scattering (DLS)	43	57
Atomic Force Microscopy (AFM)	43	57
Field flow fractionation (FFF)	50	50
Inductively coupled plasma mass spectroscopy (ICP-MS)	64	36
Scanning Electron microscopies (SEM)	64	36
X-ray Diffraction and Elemental Analysis (XRD)	79	21
Electronic spectroscopy:- atomic emission or absorption (AAS or AES)	79	21

While regulators have a good level of knowledge about the commonly used technology e.g. AAS/AES, ICP-MS, XRD, and SEM, the majority of survey participants have limited or no knowledge of techniques such as DLS, AFM. This is not surprising since the competent authority has no direct involvement with analytical activities/instrumentation and the regulatory laboratories surveyed have a very limited range of instruments at their disposal, they do not have access to the sophisticated range of instruments highlighted in table 4.1. Indeed, the only instruments available to the control laboratories surveyed were ICP-MS and AAS. In contrast, with the exception of ICP-MS and XRD at least 80% of all researchers surveyed indicated that they do have access to the requisite technology.

Academics, when given a range of options were asked to give their opinion on what are the most important considerations in relation to gaining an understanding of any potential health risks associated with particulates/nanoparticle applications in the agri-food sector. More than half of the participants indicated that determination of the particle size distribution in the initial food formulation (or migrated into the food) was the most important consideration. Factors such as; how the nanoparticles interact with bio-molecules and cellular structures e.g. membranes, determination of the bioavailability and fate of particulates/nanoparticles within the human body, whether they are degradable or not, and how will their properties change during degradation were also considered to be important factors when evaluating potential health risks associated with particulates/nanoparticle applications in the agri-food sector.

The competent authority (FSAI) has responsibility for co-ordinating the enforcement of food safety legislation in Ireland and for managing emerging risks in the food chain. As the stakeholders with expertise in policy enforcement it is their role to provide information and advice, supporting industry and consumers to comply with food safety standards in Ireland. It is the responsibility of the FSAI to provide guidance and assistance to the agencies with responsibility for enforcement and analytical control on any technical or policy aspects of implementing official food controls. The competent authority will have specialist knowledge in food related legislation. When questioned about their knowledge of legislation, specifically relating to nanotechnology, approximately half of the respondents were aware of regulatory controls already in place, and they were aware of risk assessments which have been carried out relating to applications of nanotechnology in the agri-food sector. This response is consistent with the answers from those who have been assigned specific responsibility for regulatory controls, monitoring and surveillance (57% of respondents). Those respondents who are involved in analytical control activities would not necessarily be aware of nanotechnology legislation/regulation unless they were directly involved in this area of work, hence a good level of awareness of 'nano' legislation is not relevant in the context of their current role. When regulatory control authorities were asked "do you think that the existing legislation and the regulatory frameworks are sufficiently evolved in

order to support nanotechnology testing procedures" only 7% of respondents indicated that they believed that it was not sufficient to meet those needs.

Practicing EHO were asked about their awareness of specific activities which might apply to applications of nanotechnology in the agri-food sector. More than half of all respondents (56%) indicated that they were aware of a number of activities listed. As illustrated in figure 4.7 most of those who responded indicated that they were aware of 'monitoring/surveillance plans' in place.

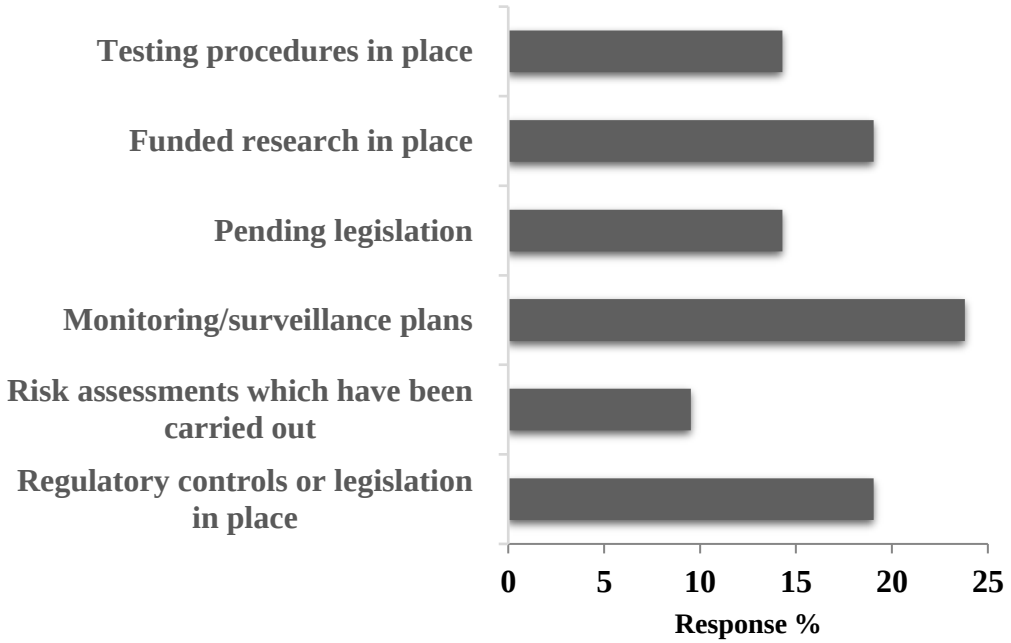

Figure 4.7: EHO Awareness of applicable nanotechnology activities in the agri-food sector.

When EHOs were asked "do you think that the existing legislation and the regulatory control frameworks are sufficiently evolved in order to support nanotechnology testing procedures" only 6% of respondents indicated that they believed that it was sufficient to meet those needs, more than half of the respondents (56%) indicated that it was not, otherwise the responses were "I do not know" or "This is not our responsibility".

In the 2017-19 survey EHO's were asked about their knowledge of government agencies official statements or reports on nanotechnology. The response given is illustrated in figure 4.8.

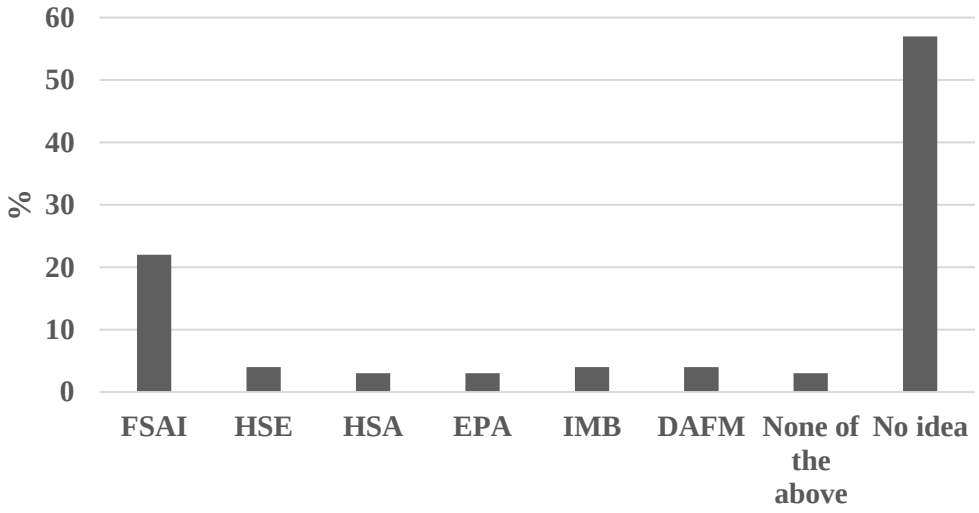

Figure 4.8: Knowledge of Irish government department or agencies statements or reports on nanotechnology

At that time the majority (57%) of EHO's surveyed had no idea about any government statements and/or reports on nanotechnology, only 22% of respondents were aware of the FSAI statement on 'The Relevance for Food Safety of Applications of Nanotechnology in the Food and Feed Industries' which was published in 2008. Perhaps this relates to the fact that this statement might be considered somewhat dated now after more than a decade since it was published, as such practicing EHO's might see this statement as no longer relevant. It appears to be the case that EHO's would preferentially refer to sources of information which they might consider to be 'current and easily accessible', as evidenced by the fact that they would rely on news/media reports and general web-browser searches, when seeking information about emerging issues, or if presented with a nanotechnology related query. In saying this, it has been acknowledged previously that EHOs said they would refer to the relevant government agency e.g. FSAI, HSE, EPS, HSA, additionally many would seek information from a 'non-government agency' (e.g. SafeFood, WHO, IBEC)

4.4.3 Key Requirement 3: Skill shortages identified

Skills gaps arise when an employer cannot recruit suitably skilled and qualified personnel to meet the requirements of their job functions. Academics were asked 'to what extent do you expect developments in nanotechnology to lead to such gaps,

and potential recruitment problems in the future?' Over two-thirds (67%) of the academics surveyed indicated that they were confident that there would be only limited, or no future skills gaps, potentially impacting an employer due to developments in nanotechnology.46% of the respondents were 'somewhat' confident that the current higher education system in Ireland is able to fulfill the skills and the technical knowledge needs related to present, and to future developments in nanotechnology. This is an interesting finding, which will be explored in greater depth at the focus group and interview stages of this research.

Most regulators surveyed (57%) indicated that they were unsure whether or not they had the available resources, in terms of analytical capacity/skilled personnel to support nanotechnology testing procedures, in the event that they may be required to do so. Their response could imply that they are unsure what skill set/competency is actually required in terms of providing analytical support for nanotechnology testing. A considerable number of participants (43%) indicated that they currently did not have the analytical capacity available for nano related testing. By extension of the fact that the regulatory laboratories do not have the requisite equipment at their disposal, it is clearly evident why a considerable number of participants have also identified the potential for skill shortages in this area. Many participants (36%) indicated that they feel there will limited, or indeed substantial future recruitment problems with the regulatory control sector. It is somewhat concerning to note, that state agencies, having identified skill deficiencies that they do not appear to have a plan to alleviate the potentially negative impact of knowledge and skill gaps arising from developments in nanotechnology into the future. Where the majority of survey respondents (57%) answered that they did not know what future recruitment problems they were likely to encounter, this could possibly be explained by the fact that generally state agencies do not see nanotechnology testing as a priority or as an immediate testing requirement, to them, it's possibly something which will be a required in a number of years' time, possibly even up to 5yrs time. When asked 'Do you think that the higher education system in Ireland is able to fulfill the skills and the technical knowledge needs, related to present and to future developments in nanotechnology?' most (86%) of the survey respondents did not appear to be confident that the current higher education system in Ireland would be able to do so, having indicated that they 'do not know' or that they felt 'somewhat' confident

in their ability to close the skills and the technical knowledge gaps.

The EHO's surveyed were asked did they believe that their training was sufficient to enable them to deal with emerging issues such as nanotechnology. Results from the 2017-19 survey indicated that almost half of respondents said that they did not have sufficient information to determine if they have had sufficient training or not, one in three respondents replied that their training was not sufficient, and one in five indicated that their training was sufficient. When surveyed again in 2022, post EFSA TiO_2 opinion, and with pending testing requirements, answers to a similar question, i.e. 'do you think that training in emerging issues such as nanotechnology for practicing EHOs is sufficient?' changed quite dramatically. Results from the post the EFSA TiO_2 opinion show that the vast majority of respondents (88%) feel that their training is not sufficient, with only approx. 6% indicating that they felt their training was sufficient to support their emerging needs. Cross tabulation was carried out on; sufficiency of EHO training in emerging issues, along with EHOs expectation regarding future developments in nanotechnology, and the relative potential of such developments leading to knowledge gaps, and potential problems for EHOs when implementing relevant policies. While it is apparent that some participants believed that their training is sufficient, and they were also of the opinion that there will be only 'limited problems', the majority of respondents believed that their training on emerging issues is not sufficient and they also believed that this would cause 'substantial problems'. Figure 4.9 shows the EHO response.

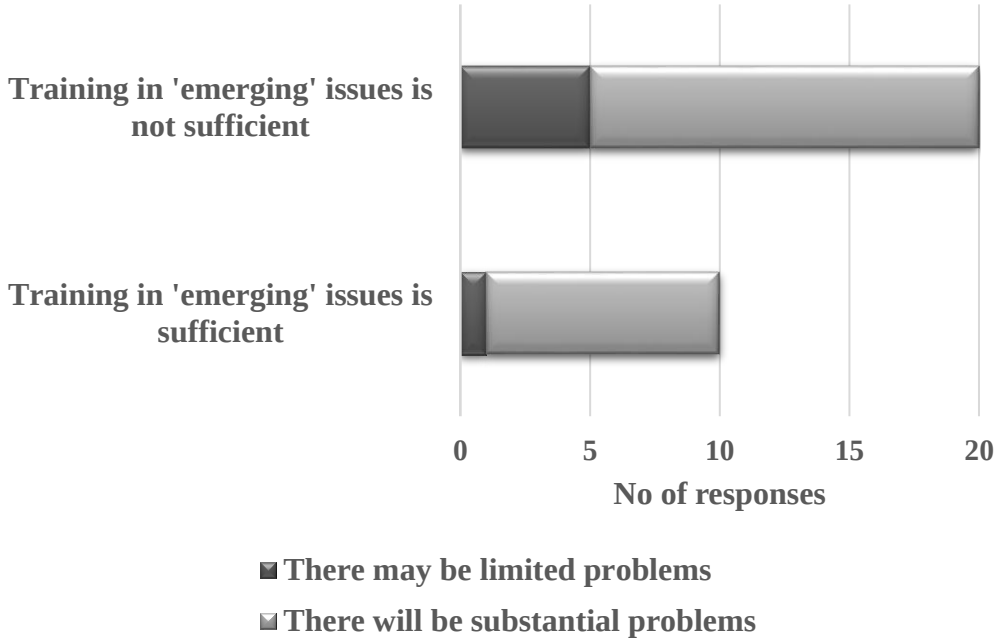

Figure 4.9: Sufficiency of training in emerging issues and awareness of legislation.

As evidenced through the surveys with members of academia, there appears to be a good level of nanotechnology expertise within academia, i.e. the vast majority of them have been involved in nanotechnology research for at least five years and many of them have been working in this area for more than ten years, additionally the regulatory control authorities indicate that they are involved in following developments in nanotechnology, however it would appear from the issues highlighted by the EHO's that this tacit knowledge is potentially not being communicated to the EHO's, the enforcement officers who will be dealing with the application of, or breach of policy/legislation, including applications of nanotechnology at the consumer/industry level.

4.4.4 Key Requirement 4: Ireland's future skill needs

Having established the 'state of the art', examined the potential skills and knowledge gaps, and highlighted the concerns of stakeholders in relation to skill shortages affecting the successfully implement of nano policy decisions, this section aims to set out Irelands future skill needs. With this in mind survey participants were asked to consider what are the most important 'technical' and 'employability' skills that they anticipate would be needed in the future. The most

important ‘technical’ skills identified by respondents are shown in table 4.2 and the most important ‘employability’ skills are shown in table 4.3.

Table 4.2: ‘Technical’ skill needs identification and order of priority

Technical Skills	**Reg* priority**	**Aca** priority**
Knowledge of nanoscale characterization techniques and methods	1st	4th
Specialised equipment expertise e.g. Imagery, Microscopy, Spectroscopy	2nd	3rd
Nano - biology specialist expertise	4th	5th
General Laboratory analytical and instrumentation skills	3rd	2nd
General Science – chemistry, physics, biology technical knowledge	5th	1st

*** Reg – Regulator, **Aca – Academics**

Table 4.3: ‘Employability skills’ and competency required and order of priority

Employability Skills	**Reg* priority**	**Aca** priority**
Specialist Knowledge (e.g. regulations, product development, applications, health and safety)	1st	3rd
Problem solving, critical thinking skills	2nd	1st
Research Experience	3rd	2nd
Quality/Accreditation experience	4th	4th

*** Reg – Regulator, **Aca – Academics**

It is interesting to note the differing priorities identified by ‘educators’ and the ‘employers’. For the regulatory control authorities the most highly ranked ‘technical skills’ related to; knowledge of nanoscale techniques/methodology and skills relating to the use of specialized equipment. In contrast, the two most important ‘technical skills’ needed to support skill development identified by academics relate to; general science: - chemistry/physics/biology technical knowledge, and general laboratory analytical and instrumentation skills. These are

skills which are ranked of lower importance by the regulatory authorities. The perception of the regulators could be that 'specialised' knowledge and expertise relating to analytical determinations at the nanoscale is lacking in the regulatory control laboratory setting, and that 'nano' expertise is potentially more difficult to attain than for the more regular routine analytical determinations. In contrast, it may also be the case that academics view this skillset, knowledge and expertise as easily achieved, once analysts have a good knowledge of general science and a good understanding or working knowledge of the general Laboratory analytical and instrumentation skills, which can be easily be transferable in the case of 'nano' determinations.

The most important 'employability skills' and competencies ranked by the regulatory authorities were similarly of a specialist nature, i.e. specialist knowledge relating to regulations, policy and specific applications. Problem solving, critical thinking skills were also identified as important skills by potential employers. Likewise, the academics surveyed rated this as one of the most important skills for future employment. The academics however ranked research experience as more important than specialist skills, interestingly the future employer (Regulatory Authorities) deem specialist skills as their greatest priority, with research experience as a lower order of priority. This could suggest a possible disconnect, or lack of engagement between the academic community and the potential employers of graduates, if the academic community is focusing on equipping graduates with technical skills and competencies which are not the priority needs of the employer.

When presented with a range of options which could potentially be utilised to address any potential skill shortages and knowledge gaps arising from developments in nanotechnology, regulators were most interested in the following initiatives;

- 1st preference - facilitating the development of a broader knowledge of nanotechnology topics and applications in academia.
- 2nd preference - encouraging stronger cooperation between Government departments and agencies with research institutions.
- 3rd preference – encouraging more collaboration with industry and with academia.

The response from regulators indicates yet again the importance they place upon nano specific knowledge and technical expertise, and it shows their willingness to engage with other stakeholders including academia, industry and research institutions in order to facilitate closing any knowledge gaps which may arise due to future developments of nanotechnology.

The top three priorities of the researchers, the educators of the future workforce were;

- 1st preference - develop stronger cooperation with potential employers.
- 2nd preference - improve the theoretical level of education programs at Bachelor or Master level, and more possibilities for part-time PhD programs.
- 3rd preference - provide greater focus on technical developments within the curriculum.

When EHOs were asked for suggestions or strategies to address any potential knowledge gaps as a result of developments in nanotechnology, ideas presented included the following;

- Recruiting nano specific researchers/trained personnel.
- Participation by employees in external training or education programs e.g. academic modules or lectures, Safefood or FSAI facilitated training.
- Improvements in legislation.
- Greater collaboration with industry and with academia.
- Facilitating development of a broader knowledge of nanotechnology topics and applications in academia.
- Encouraging stronger cooperation between Government departments, agencies and sampling officers with research institutions.

When asked what they think could be added to the curriculum in order to support the regulation, health and safety, monitoring and control of nanotechnology, ideas presented included the following;

- Inclusion of elements of nanomaterial safety into existing food safety modules.
- Specific modules relating to regulation of nanomaterials in consumer

products.

- Continuous professional development programmes supported by industry/producers.
- New nano specific modules included in the curriculum.
- Seminar on emerging health risks in the final stage Environmental Health Officer degree programme.
- Specialised degree options focusing on emerging consumer products innovations and potential health and safety risks.
- Postgraduate certificate/diploma in nanotechnology.

Individual suggestions given by academics and regulators, for the attention of policy makers, to specifically help fulfill any skill needs related to the present, and for the future development of nanotechnology and agrifood nanotechnology development, are presented in Appendix 5.

4.5 Discussion

The results of the surveys in this chapter were obtained from an academic survey of sample size of 59 self-declared Irish nano scientists, which represented an estimated response rate of 10% uptake of the survey. Enforcement /regulatory participant results were obtained from 138 EHO's, and 14 responses were received from Regulatory Agencies. The survey numbers were significantly impacted by the ongoing COVID pandemic, with direct face-to-face contact with participants at events and workshops greatly reduced, forcing an entirely online survey approach. The key aspect being investigated as part of this thesis was the understanding of the national capacity and available infrastructure to enforce any potential nano-legislation. An underlying theme which emerged however, was a perceived lack of collaboration, and significant disjoins between the multi-stakeholder organisations involved, including academia. In the latter case, 80% of academic responses indicated that they have had no involvement, or requests to participate in the development of national nanomaterial standards or method development. This is despite many respondents working on basic and applied nano research for at least a decade. Furthermore, 40% of those surveyed classified their work as nano-food orientated, indicating a significant knowledge base and potential resource. In

comparison, 50% of those surveyed from organisations with regulatory or enforcement backgrounds indicated that they had insufficient analytical infrastructure, and/or the knowledge base to support nanotechnology testing procedures. This was also underpinned by the response from enforcement officers, who strongly indicated that they would require additional training to enforce any potential new legislation in the area of nanotechnology. Indeed, many enforcement officers expressed a lack of awareness of where they can receive support and advice with respect to nanotechnology as highlighted by Figures 4.6, 4.7 and 4.8. These responses all indicate a breakdown in communication between each stakeholder category, and a poor use of the potential academic nano-community to horizon scan and explore novel emerging risks.

Further analysis of the primary funding sources, as discussed in chapter 3 reveals a possible explanation for the poor integration of the scientific academic community into the regulatory process. Many of the funding calls explicitly emphasis a requirement for, or at least a bias towards industrial collaboration, as opposed to regulatory bodies or competent authorities. This undoubtedly has influenced the academic communities' priorities for research collaborators, and is clearly evidenced by 93% of academics ranking engagement with industry or another HEI as their first preference. Two exceptions to this tend to be the EPA, who often have an active participation in their funded research programmes, and the Department of Agriculture Food and Marine (DAFM), who encouraged regularity engagement in the 2021 call. The ranking of engagement with regulatory bodies, i.e. the academics least important collaborative perspective in the nano-food sector, may also be influenced by the fact that the regulatory body FSAI does not have the necessary resources available to undertake an independent research agenda. The FSAI acknowledge that research is essential to address gaps in knowledge. However, it is not a funding body; it can only advise national funding bodies on potential research priorities. In addition, much of the work of the FSAI as a regulator is desk based, and the organisation is dependent on contracts with third parties for analytical determinations e.g. State Laboratory and Public Analysts Laboratories.

This is in contrast to many other EU Member States (MS). For example, Germany and the Netherlands. Germany has a highly developed chemical industry and the Government works with public and private stakeholders to establish regulatory

policies, in order to categorize and to manage potentially harmful substances. Regulatory policies are developed to meet environmental, health, and consumer safety standards, which are then implemented in a highly regulated and consistent manner across all industrial sectors in Germany (McManus and Eijmberts, 2016).

In 2005, a number of policy decision makers including the German Federal Ministry for the Environment (BMU), the Federal Institute for Occupational Health and Safety (BAuA) and the Association of the Chemical Industry (VCI) carried out a stakeholder survey involving all firms throughout the country. The results of the survey provided an overview of the production, protective measures, and handling of nanomaterials throughout the German economy. This process was conducted to establish national regulations, which would be applicable across all industries (BAuA, 2008). This highlights the inclusive nature of German regulatory policies, which regularly include representatives, from industry, scientific experts, and environmental representatives along with policy/regulators.

In 2013, the German federal authorities presented a Background Paper on the Position of the German Competent Authorities with regard to the regulation of nanomaterials under REACH. The opinions were prepared to influence EU decisions with respect to regulation of nanomaterials under REACH, to explain, and to justify the position of the German competent authorities. The EU is currently in the process of reviewing and amending the REACH legislation (BfR, 2013).

The Dutch are also actively involved in supporting R&D and in shaping nanotechnology regulations within the EU. The Government aims to ensure that they promote responsible development of nanotechnology in the Netherlands, which is based on:

1. Strategic plans to support research and business opportunities.
2. Consultation with stakeholders to address any ethical, social, or legal issues relating to nanotechnology.
3. A mechanism to allow public engagement.
4. Regulation relating to the risks and uncertainty associated with nanomaterials.

An example of a State funded network involving public–private stakeholders is the NanoNextNL consortium, which includes universities, research institutes and

companies who have been involved in developing various research activities relation to nanotechnology (McManus and Eijmberts, 2016).

The Netherlands, like Germany adopted REACH regulations relating to the use of materials and chemicals, which included the use of manufactured nanomaterials. In 2008, the EC set up the Competent Authorities Sub-Group on Nanomaterials (CASG Nano) in order to address concerns relating to regulation of materials at the nano-scale. Through their participation in this group, the Dutch Government encouraged EU and MS collaboration towards the development of a common strategy for the risk assessment of manufactured nanomaterials (McManus and Eijmberts, 2016).

In 2012, the Dutch Cabinet proposed the NANoREG project to the EU. The project, which is coordinated by the Dutch National Institute for Public Health and the Environment (RIVM) supports stakeholders with risk-related research for regulation of nanomaterials. NANoREG involves collaboration from various stakeholders who are involved in industry, academia, policy and regulation, the project presents a multidisciplinary approach to nanotechnology, to support innovation and to allow for a common EU approach, supporting the safe development of nanotechnology (RIVM, 2013).

The activities of these MS illustrate how national governments and state agencies can potentially influence and determine EU rules and regulations. By collaborating with EU institutions, Non-Government Organisations (NGO's), academia, and other stakeholders, they are able to highlight issues, identify best practices, provide guidelines, and influence standards for the responsible development of nanotechnology which reflect their own national priorities

It is clear therefore, that cross collaboration with research bodies and regulatory authorities facilitate horizon scanning, and independent method development, which is crucial as part of a national risk assessment strategy. It enhances the capacity to develop responses to crisis, and to plan appropriately future expenditure. However, it forms merely one part of the communication chain. Dissemination of data represents just as much of a challenge to policy and regulatory enforcement. When surveyed, enforcement officers exhibited an over dependence on news and media, and non-specific websites, to keep abreast of developments in the area.

Professionally, the enforcement officers supported their knowledge via government sources, but few followed academic peer reviewed literature. Surprisingly however, 59% were not aware of any government reports on nanotechnology e.g. FSAI report from 2008.

A similar lack of awareness for available infrastructure is also evident from all sectors surveyed, exposing another potential flaw in the national approach. This may be further accentuated due to the aforementioned lack of collaboration between the academic and regulatory bodies. In contrast, the understanding of key parameters, and methods for the characterisation of nanomaterials is high amongst all stakeholders. Although it is acknowledged by the enforcement and regulatory bodies that skill shortages exist, and continuous professional development (CPD) training would be required to meet potential demands. This again reverts to the role the HEIs and academia can play in the system, by providing the necessary CPD training for emerging areas such as nanotechnology. The majority of academics surveyed (70%) were confident that any perceived skill shortage in knowledge could be readily addressed by the education system. However, counter to this, clear uncertainty with regard to analytical capacity for training purposes is evident, with 43% of academics indicating limited access in their home institutions.

Further discrepancies in the expectations of the skill set and training needs between stakeholders can be observed. Academic priorities focus more on the provision of general knowledge and skills, particularly at undergraduate level. The focus at postgraduate level tends to be more specialisation in instrumentation and technical skills, with a strong academically valued research theme. The other stakeholders valued specific skillsets and knowledge of nano components more so than the academic community. The prioritization of specific skill sets is typically encountered by recruiters in part, in response to fears of uncertainties with respect to the rapidly changing environments faced by employers. Some degree of misalignment between the supply and demand for skills is inevitable. However, the costs of persistent mismatch and shortages are substantial, and is most evident in public sector bodies were staff turnover is often quite low (OECD, 2018) Skill shortages can, for example, constrain the ability of organisation to innovate and adopt to new technologies, and often requires rapid policy intervention to address skills imbalances. However, this intervention relies on having good information on

current resources and future skill needs. It requires appropriate allocation of existing skill resources between organisations on a formal and/or temporary basis. A successful skill needs anticipation systems is user oriented, stakeholder owned, and is well co-ordinated. Stakeholder engagement, notably through dialogue, is key to ensuring that skills assessment and anticipation of future needs are meet. In this regard, regulatory bodies and enforcement agencies engagement with HEI programme design is also crucial, with future priorities been clearly mapped. Questions on the necessary skill set to enforce Nano regulation were raised in both the FSAI and Safefood reports of 2008 and 20013 respectively. However, the absence of nano legislation and the erroneous perception by 80% of the regulatory and enforcement respondents that such legislation is approximately 5 years away is likely to have hampered the development of a nano- specific skill set in the regulatory community. Overall, the data clearly points to a significant shortfall in open communication channels between stakeholders highlighted in Figure 4.2. It also highlights discrepancies with respect to other EU MS, where a more integrated approach is taken, ensuring a fluid dynamic between fundamental scientific research and policy enforcement. This is something that the EU research strategy may ultimately address, with greater EU wide representation of regulatory bodies and national risk assessors who will collaborate directly with academic bodies in horizon Europe partnerships.

Indeed the 'Horizon Europe Partnership for the Assessment of Risk from Chemicals (PARC)' proposed to do just this. PARC is an EU-wide research and innovation programme to support; EU, and national chemical risk assessment and risk management bodies, with new data, knowledge, methods, networks, and skills to address current, emerging and novel chemical safety challenges, one of which is nanomaterials (PARC, 2020). Implicit in the concept of PARC is the open and direct communication by all stakeholders, from academia through to the competent risk assessment bodies, at national, and subsequently at EU level. Currently only two EU MS states have not entered into the partnership programme. Irish risk assessment agencies failed to reach an agreement to engage with PARC, at this time we again highlight the lack of appropriate collaboration between agencies. However, while the partnership work packages for PARC have been determined, Ireland can still seek to engage in such a programme as an observer. It is likely that

such partnerships will shape future legislative approaches in the Nano agrifood sector, and similarly develop an open forum for risk assessment, to align agendas across the EU, and facilitate knowledge transfer and infrastructure.

4.6 Conclusion

The results of this chapter strong highlight significant national disjoins which need to be addressed in order to fully facilitate the partnerships engagement at an international level. However these need to be further investigated using more targeted engagement strategies such as focus groups and expert interviews. Key elements which have emerged and subsequent will be explored further in the coming chapters include:

- The need to gain an understanding of the level of awareness of 'nano' applications and technologies amongst the stakeholder cohort
- To establish the level of awareness of nano-legislation, national agendas/priorities and legislative enforcement concerns
- To determine the sampling and analytical testing requirements
- To review and consider the national Infrastructure in-situ and to determine if there are any potential access requirements or possible restrictions

4.7 References

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5.1 Introduction

In comparison to the survey data presented in chapter 4, focus group discussions traditionally provide qualitative information about attitude and opinions (Doody, 2013). A well organised focus group facilitates and encourages open discussions on topics which can be probed in real time and expanded upon by participants. In addition, focus groups can be used to explore and distil interpretations of wider survey data, to yield information that is more direct. Indeed the focus group design in this thesis is used to scrutinise and explore further the key conclusions derived from the survey data while providing an opportunity to refine questions for subsequent expert interviews.

Although laborious using quantitative techniques to understand, qualitative data can offer new insights and interpretations, and when appropriately applied can remove subjectiveness and/or bias from the analysis. Nevertheless, no one framework exists that delineates the types of analysis techniques that focus group researchers have at their disposal. This is surprising, bearing in mind the relatively long history of focus group research (Morgan and Spanish, 1984) and the array of both qualitative and more recently quantitative analysis techniques available to researchers (Leech and Onwuegbuzie, 2007 and 2008). The analytical techniques that lend themselves to focus group data are constant comparison analysis, keywords-in-context, discourse analysis and frequency distributions. Constant comparison analysis can be used to analyse many types of data, including focus group data. Three major stages characterize the constant comparison analysis. During the first stage (i.e., open coding), the data are chunked into small units. The researcher attaches a descriptor, or code, to each of the units. Then, during the second stage, these codes are grouped into categories. Finally, in the third and final stage the researcher develops one or more themes that express the content of each of the groups. This approach works well when there are multiple independent focus groups within the same study, as in this thesis. The keywords-in-context approach represents an analysis of the culture of the use of the word or term, in this regard words such as ‘nano-risk’, ‘nano characterisation’ or even more specific words such as ‘size’ or ‘area’. would be representative examples. The major assumption underlying keywords-in-context is that people use the same words differently, necessitating the examination of how words are used in context. Furthermore, the

contexts within words are especially important in focus groups because of the interactive nature of focus groups. Thus, for each word uttered by a focus group member, not only should it be interpreted as a function of all the other words uttered during the focus group, but it should be interpreted with respect to the overall context preceding and proceeding its use, including contributions from other members of the focus group. For example, has a particular word or phrase been used in a negative or a positive context within the group dynamic. By mapping keywords, a level of knowledge and understanding of participants can be gauged, but also between groups it can be extrapolated that if a term is used again, then it may be interpreted as accepted terminology within the area. Keywords-in-context involves a contextualization of words that are considered central to the development of themes from a qualitative prospective, and can be quite subjective, with caution required from the moderator not to influence keywords. However, quantitative analysis can be subsequently preformed to establish if the context of a keyword used is statistically significant, and if an association of the keyword and the context of its use is correlated.

Chapter 4 used broad survey methodologies to gather diverse and wide ranging opinions from community stakeholders in the area of nano regulation and enforcement. Each stakeholder as detailed in figure 4.2 chapter 4 contributes to various aspects and stages of the enforcement process. Academic research identities potential emerging concerns. National and international risk assessment bodies develop risk assessments and management strategies to be communicated to the official control laboratories and enforcement officers. The data collated in chapter 4 indicated a broad overview of the process of engagement across each stakeholder, and identified potential areas of concern and knowledge gaps. The focus group study provides an opportunity to; examine the results of the surveys in more detail within a smaller group context, and identify if the responses represent a true reflection of the area. Another key function of the focus groups is to distil down the ideas and thoughts extrapolated from the surveys into thematic areas, which can be further explored to identify sector specific knowledge and skill gaps, and to develop a set of informed questions for subsequent expert interviews.

5.2 General observations of focus group opinions.

Anecdotally there was a good level of awareness of nanotechnology and food amongst the focus groups. Many participants demonstrated an awareness of the general applications of nanotechnology in society such as electronic devices, novel coatings and even novel approaches to drug delivery. Many of the acknowledged applications may have been garnered from their own preparatory background reading prior to their participation in the focus group. A limited number of participants were aware of 'nanofoods' or of food related nanotechnology applications both on the domestic and international market. Examples given included colloidal silver, novel coatings, food contact materials and food additives like TiO_2 The specific awareness of food related applications predominantly stemmed from those participants who professionally had an interest or obligation to be aware of such developments, for example participants from regulatory bodies. Nevertheless, open discussions between participants revealed that they all acknowledged the potential of nanotechnology to contribute to the development of innovative applications in the food sector.

Interestingly many participants were keen to reference size criteria as the predominant characteristics which they considered as essential to categorize something as 'nano,' but they struggled with the concept of the nanoscale and how the size criteria could be effectively included into a working regulatory definition for nano-food technology. Indeed most notable, issues that arose as part of all group discussions continually reverted back to concerns and/or confusion in relation to what was/was not considered to be a 'nanofood'. Moreover several participants expressed concerns about the possible negative implications of referencing food as 'nano' in the consumer domain. A variation in relation to the broad awareness of nanotechnology is somewhat expected in any group study. However, these groups stemmed from professionals working in the regulatory area of food and/or academics with research profiles that included a nanotechnology and or nano-food research profile. In light of this, significant and well informed discussions around the definition occurred in all groups, and considered the pros and cons of the EU definition for nanotechnology in food (European Commission, 2011). This often resulted in opposing views, with the general consensus that a uniform terminology was somewhat absent from the area. This absent was suggested therefore to result

in misinterpretations in the application of the definition, subsequently giving rise to analytical and enforcement issues. It was acknowledged by all groups that to overcome the challenges associated with the awareness for nanotechnology in the food sector that greater communication and interaction between stakeholders would be necessary, to help identify potential applications at early stages of the innovation process. This would help categorize and capture existing applications more efficiently with respect to the accepted definitions. In addition, such close collaborations would facilitate knowledge and skill transfer between stakeholders to assist in the characterisation, analysis, and enforcement protocols of this emerging technology.

5.3 Focus Group Awareness of 'nano'

5.3.1 Qualitative analysis of the Awareness of nano food-technology

Participants were asked what their understanding was of the term 'nanofood,' and were they aware of any 'nanofoods', technology related to nanotechnology, a food, or non-food related technology that is currently on the market? Participants mentioned an array of foods, food contact materials, applications and functions of nanotechnology associated with food various utensils and other sector nanomaterials. Many of these are well known and are reflective of what is outlined in chapter 1 section 1.9. More interesting however, was a certain degree of confusion and ensuing discussions about some aspects of specificity around the term 'nanofood'. For example common discussion points within groups included:

> *"Does the term 'nanofood' include 'naturally occurring nanoparticles in food?"*

Each group essentially acknowledged that the term 'nanofood' is used as a type of 'catch all term' which could be inclusive of many things already present in a food, or things introduced into a food for a particular purpose. As one participant indicated:

> *"Well aren't all foods nano really, because aren't molecules in particles?"*

As stated by another participant:

"What's the difference between a nanofood and a normal food?"

Where confusion was evident, attempts to provide clarification from group members were potentially vague, or in some cases the explanations given were somewhat inconsistent. Many participants referred to criteria outlined in definitions, indicating that this would be the ultimate defining features or property of a nanomaterial, be it for food or any other material. There was general agreement within all of the groups on this particular point, as one individual stated:

"Without a definition, what is it? That's the benchmark!"

This raised concerns about how inclusive a definition should be? With the discussion often focused upon how novel food contact materials with nano-innovations e.g. silver based food packaging, or active packaging could be considered in the context of a 'nanofood'? It was clear from conversations that such food packaging was considered by some individuals to be 'nanofood'. Indeed, a number of participants indicated that such products were already available in the marketplace. Defining novel 'food contact materials' as 'nanofood' was seen by many as complex and potentially confusing, and requests for clarity were sought from some individuals. An interesting point of note was the apparent separation of the food itself from the 'nano' functionality imparted by the food packaging per se. A secondary concern was raised by several members with regards to nanoparticles leaching into the food from the packaging, which gave rise to concepts surrounding the potential negative perception of nano food-technologies.

As interested stakeholders, and as consumers, participants voiced strong views that awareness of 'nanofoods' or applications of nanotechnology in food was very low. They acknowledged that products were already on the market, and they were possibly beneficial for food production. However, consumers probably were not aware that nanotechnology was applied to the food. Caution, or possible reluctance by producers, and even by some EU MS to refer to the word 'nano' was mentioned, as it could be perceived as having a similar association to GMO's, a technology which was widely rejected by consumers. As one individual stated:

"I think there is going to be a big gulf when it comes to communication of the risks associated."

The potential problem arising from the banning of titanium dioxide was referred to for various reasons, on a number of occasions throughout the course of the discussions. The implications of this was viewed as the most imminent difficulty which needed to be managed as outlined by one speaker:

> *"The biggest most controversial one [nanomaterial] at the moment is probably titanium dioxide … we know it's readily available in products on the Irish market …. There's the potential for a number of these to be in the nano size, or nanoparticle range, which is obviously problematic in terms of risk assessment."*

5.3.2 Quantitative analysis of the awareness of nanotechnology in food technology

In order to develop a quantitative approach to the awareness of nanotechnology in the food sector across the five independent focus group discussions, a number of generic keywords, or terms associated with the awareness and understanding of the application of nanotechnology, and the use of the term 'nanofood' where selected as shown in table 5.1.

Table 5.1 Word/phrase associated with a nano application chosen for transcript analysis

Word/phrase associated with an Application	**p- value for significance of statistical occurrence***
Ingredient	*p = .020552.*
Additive	*p < .000001.*
Food contact material	*p= .000038*
Food packaging	*p < .000001*
Delivery/encapsulation	*p= .029208*

**p-values obtained via Binomial testing*

Word mining was subsequently used to analyse the relevant discussion sections of the focus group transcripts, and to extract the occurrence of each phrase (or related phrases) along with the context of its use. The latter was then used to assess understanding, and/or negative or positive viewpoints of nanofood technologies amongst the focus groups. For example, the word 'ingredient' appears 47 times across all focus groups, in discussions on awareness and terminology. Below represents one instance of the context of its use by a participant to explain their interpretation of the term 'nanofood':

> *"It is any food which has something in it at the nanoscale, it could be in contact with food or an added* ***ingredient,*** *perhaps something added directly into the food, or a packaging."*

Analysis of the text that precedes and follows this statement reveals more details with regards the context of the statement, the group dynamic, and whether the statement was received in a positive of negative light. Indeed in this specific case the statement led to questions regarding the inclusion of natural nanomaterials in the description of a nanofood, and the negative consequences of such an inclusion for the sector. However such interpretation of isolated statements, leading to a negative disclosure, does not yield any overarching validation of whether or not a 'nano-ingredient' would be perceived in a negative light by the wider focus groups, or if such an opinion represents a statistically significant distribution of responses. Figure 5.1, below indicates the relevant numeric occurrence, in terms of context of each of the key phrases about awareness and terminology.

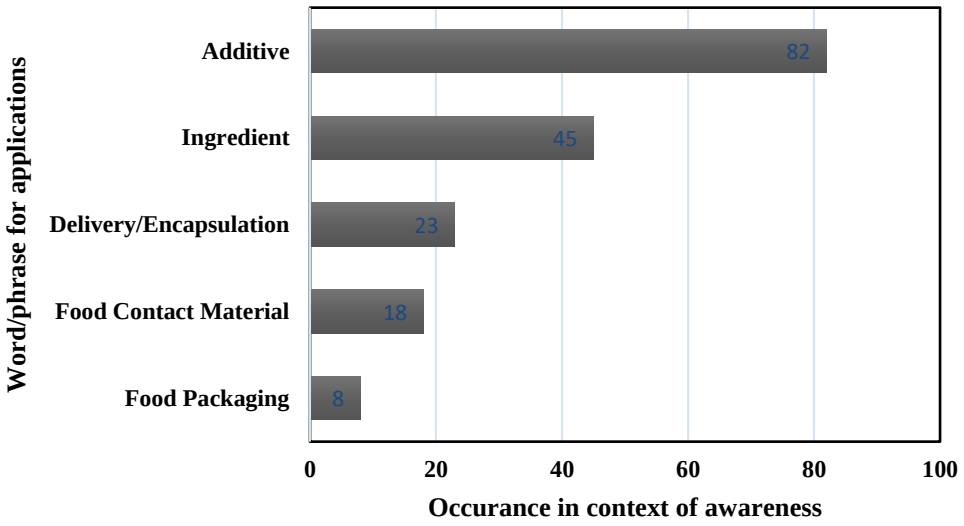

Figure 5.1: Keywords: Awareness of nano-food technology applications

From figure 5.1 it is evident that in terms of the awareness of the application of nanotechnology that food additives featured strongly, with 84 mentions. This was particularly evident for later focus groups in the second half of 2021, due to the publication of the revised EFSA opinion on the use of TiO_2 as a food additive (Younes, *et al*., 2021). Nevertheless, the use of binominal testing indicated that the responses obtained from all focus groups were all statistically significant, with p-values <0.05 (Hung 2020). Similarly a Chi squared test also indicated a p-value <0.00001 (Chi squared equalled 107.112) for the distribution, suggesting that this was not a random distribution. This indicates, as expected, that the focus groups consisted of members who exhibited some degree of prior knowledge, and/or awareness with respect to applications of nanotechnology, confirming that the vast majority of focus group members were correctly chosen to act as informed participants. An uninformed sample of participants such as the public, would give rise to a random distribution.

The majority of applications mentioned by participants can be grouped into two broad categories, equating to either an ‘ingredient’ (additive) in food, or a ‘food contact material’. To identify any correlation between negative or positive viewpoints between applications a cross correlation using the Pearson’s correlation method was employed. The test was assessed for the context in which a statement was made, for example with respect to food packaging, one participant stated:

"The nano plastics from food packaging, which is a really big thing now… it break offs, even more so than the micro plastics…and could be a risk."

This statement, in terms of 'food packaging' was deemed to have a negative connotation, in comparison to the other statements such as:

"Food packaging…we don't consume it as such, it's not part of the food. It might be part of the food technology, but we don't consume it…so that's fine."

"Food packaging application to increase the shelf life are good but other applications…"

These statements were deemed to have been made with a positive bias towards the application of nanotechnology to food packaging. It should be noted that in some cases the post focus group analysis of transcripts is subjective, as emotional tone and expression of the participants are not overtly evident, and this can lead to an error in the analysis (Rabiee, 2004). Nevertheless, 99 negative comments, or expressions of uncertainty from the group directly followed the 178 identified word/phrase associated with the applications listed in table 5.1. A Pearsons correlation test found a strong positive correlation between negative viewpoints and those higher occurring phrases, such as 'additives' and 'ingredients'. This implies that the addition of nano scale materials directly into a food was negatively received by group members, whereas aspects such as food contact materials were not associated with as many negative impressions $r(176)=.98$, $p < .00001$. Interestingly, many of the negative reflections expressed on applications were followed with comments regarding uncertainty associated with the terminology and definition of a nanofood. For example, participants express concern about the broadness of the area of nanotechnology, and subsequent attempts to apply these broad techniques and approaches to a narrow field such as food, as indicated by the following comments:

"If you actually took a definition (of nano) and went into a supermarket shelf you'd end up, at the end of the day, with hundreds of examples of nanotechnology or its application."

"Nano is such a broad terminology in relation to what it is, and what it is in. It would be a massive…"

5.4 Focus Group understanding of 'nano' terminology

5.4.1 Qualitative analysis of the terminology

The focus group participants were drawn from regulatory bodies, official control laboratories and academic backgrounds, many of who had a direct or indirect association with nanofood professionally. It was apparent, that while discussing applications of nanotechnology to food, that vastly different interpretations of the terminology were evident.

The concept of 'nano' as applied to food, when referring to the EU definition, or indeed the definition chosen for this thesis and stated in chapter 1 section 1.13, caused some confusion, especially for those who are not directly involved in interpreting legislation. Indeed many participants agreed with the generic statement that;

"All foods can be considered a nano food, if you get down to the small enough scale."

Additionally questions were raised about 'natural/incidental/unintended nanoparticles' which may be inherently present in the food, or as a consequence of processing or other activities. The general response to this was that 'nano-food' would be food which has been deliberately 'engineered' for a 'technological' purpose, "the fact that it's being introduced".

Specialist Knowledge revealed by participants from the Regulatory Control Authorities indicated that many different components of food could be classified as 'nano'. It was stated that 'additives' incorporated for "a technological purpose or functional purpose" would be classed as 'nano', similarly food flavourings and colorants, or other ingredients added for a 'functional purpose' could be considered as 'nano'. Novel foods was clearly indicated as potentially 'nano' as stated;

"Foods containing 'nano' ingredients, or produced using nanotechnology, may be considered as a novel food."

In fact, each participant essentially expressed their own variation of a definition specific to their own professional experience i.e.

The participants were presented with the definition of a 'nano food' as used in the context of this thesis and presented in chapter 1 section 1.13, i.e.

> Any engineered material or particle (typically, but not exclusively, below 100 nanometres in one or more dimensions) that is introduced into a food (or feed) product or contact surface, which exhibits or is proposed to exhibit a functional purpose on the nanoscale ($x10^{-9}$) or influence the bulk properties of the final product' (FSAI, 2008).

Significant discussion revolved around the statement 'typically, but not exclusively, below 100nm'. Some participants, asked;

> *"Why 100nm? What happens if it's greater than 100nm? What about a product containing different proportions of different sizes? Is it a sliding scale? What about measurement uncertainty?"*

It was clarified by those in the regulatory sector that the 100nm is 'not exclusively' so, and that there is room for consideration of nanomaterials above 100nm in size. This clarification however caused greater confusion, as stated:

> *"The fact that it says 'not exclusively' below 100 nanometers then it leaves it open to what's meant by that? It's a bit of a grey area. Can you say 151 nanometers? 110? 120?"*

This aspect of the definition was largely seen as ambiguous, and appears to be a problem for regulatory control authorities in general, as stated by a participant from the regulatory control authority

> *"Thats a problem that we all face with definitions …. I don't know how you fix it, you can be wishy washy about it in the definition and say, typically anything below 100, but not exclusively, because you do know that some particles could be slightly above 100 which still have or exhibit a functional process, on purpose, that would be my concern."*

The possibility of inclusion of other physical properties within the definition was mentioned e.g. the inclusion of terminology to include differentiation for either

organic/inorganic, bound/unbound, natural/engineered nanomaterials, or surface area.

The importance of agreement on a very clear definition was openly discussed by the focus groups, and concerns were raised about the consequences of applying too broad a 'nano-food' definition in the regulatory control context. It was acknowledged that a definition is necessary for enforcement of food standards, and to bring clarification to relevant stakeholders. Indeed the current EU definition was specifically designed for the novel food regulation, and it puts the responsibility onto the industry to prove that a new product is safe. The difficulty with this is that 'nanomaterials' are referred to in a number of other food legislation in addition to the 'novel food legislation'. It was stated that:

> *"This could actually create problems from a regulatory point of view .... You might find that you have different nanomaterials under different authorisation regimes, depending on what they are going to be used for."*

All participants agreed that a national regulatory definition of 'nano' for regulatory purposes should have clear parameters conducive to measuring, and detecting limits of a material under consideration. This was agreed on the basis of discussions, and group conclusions drawn, implying that enforcement would ultimately come down to identifying and characterizing 'nano' in a food matrix. The groups were also in agreement that from a risk assessment point of view, the establishment of limits of exposure, ADI's and thresholds were deemed essential, although it was expressed that such a definition would evolve from international bodies such as CODEX or the European Commission.

5.4.2 Quantitative analysis of the understanding of terminology

Despite significant debate around the definition, it was noted that size was central to this, with most querying the 100nm limit, but nonetheless emphasising the physical characteristic of size being vital to the formulation of a definition. Figure 5.2 emphasises this with particle size appearing a total of 98 times in the text associated with the discussion of 'definition' or 'terminology'. This can be subsequently broken-down into 25 individual times where it was first stated by participants as the number one physical parameter defining a nanofood. This is

despite the reluctant to consider setting a 100nm size limit as previously discussed. Other parameters mentioned included surface charge, shape, surface area and purity/composition. Interestingly crystallinity was not mentioned (despite many groups referencing TiO_2 as an emerging concern). Nevertheless, for consistency with the outlined physicochemical characteristics in appendix 6 it has been included here. A Chi-Square Goodness of Fit analysis of the data in figure 5.2 yielded a chi-square value of 35.333 with a p-value < .00001 indicating the distribution is statistically significant amongst the cohort. Moreover a cross correlation between occurrence of the phrase 'particle size' in connection with its inclusion in the definition of a nanofood yielded a Pearson's correlation coefficient r(139)= .9924, p-value <0.00001, indicating a statistically significant association amongst participants, that size is indeed the predominate physical parameter required in the definition of a nanofood.

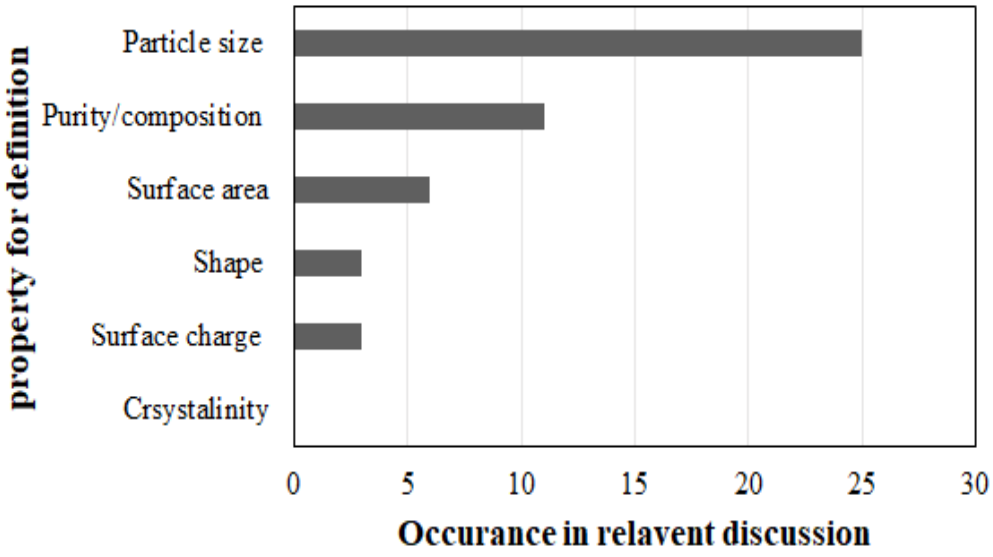

Figure 5.2 keyword in context of physiochemical property inclusion in nanomaterial definition

Another key parameter raised by the focus groups was the concept of an 'engineered nanomaterial' as opposed to natural nanomaterial, and how this can be successfully captured in the formulation of a definition, and more broadly in terminology in general. Indeed participants clearly indicated their difficulty in understanding the context of the term 'engineered' as applied to food.

"I know engineered is used in the labelling regulation … but I'm not quite sure that it does have to be engineered, maybe it (nanoparticles) could be there at that level anyway, without any processing."

"Engineered maybe discounts accidental by-products in a process."

In addition the groups struggled with the separation of the scientific /regulatory definition from how consumers would perceive the use of such terms:

"Engineered and introduced, from a consumer acceptability perspective, these are challenging."

Indeed in relation to the discussions on the definition of nanofoods, the term engineered appeared 38 times, and upon each appearance it is proceeded, or followed with a level of confusion which is explicitly indicated in 26 of those appearance. This undoubtedly suggests a level of misinterpretation and misunderstanding amongst the cohort with respect to how the term engineered nanomaterial is applied to a nanofood. Moreover, it may have subsequent consequences for the enforcement of a regulatory framework or the formulation of legislation, as indicated by participants:

"It needs a qualifying caveat"

for enforcement and for legislation.

5.5 Focus Group Awareness of nano-legislation, national agendas and legislative enforcement concerns.

5.5.1 Qualitative analysis of 'nano' legislation

Anecdotally, focus groups appeared to have a mixed interpretation and awareness of the legislation relevant to 'nano', with many referencing the general food law as the overarching legislation to protect consumers with respect to potential risk from nanofood technologies. This was in itself not surprising, as knowledge of any legislation can be very specific to an individual's background, for example, an academic researcher in the area of nano-safety may be partly familiar with REACH regulations in the area, but may not be familiar with nanofood specific legislation.

Likewise for a regulator in the area of food additives, who will be expected to have an intimate knowledge of the legislation and regulation pertaining to food additives, but not for the area of novel foods. As a result, the aim of this element of the focus groups was to estimate if participants were aware of any legislation, as opposed to having any in-depth knowledge or understanding of that legislation. Over the course of the research this question became more relevant, especially due to the introduction of EU legislation with respect to food additives for TiO_2 (Younes, *et al*., 2021). Nevertheless, it was noted by one participant who had moved from a regulatory environment dealing with novel foods into an academic environment several years ago, that;

> *"It's, sad seeing that things like regulation (for nano), haven't changed much…"*

Chapter 1 sections 1.11 and 1.12 presented an extensive literature review of the current legislation and regulations (at the time of writing) which discuss nanotechnology. Participants were explicitly asked, in terms of specific 'nano' legislation," does anybody have any knowledge of any legislation that is actually in existence at the moment?" While it was acknowledged that there was no legislation specifically dedicated to 'nano', there was mention of various legislation where the term 'nano' was referred to, and where specific requirements for the control of these substances were outlined within the legislation.

> *"There's no specific legislation on nanotechnology per se, but there is reference to nanotechnology in other legislation."*

Participants referred to 'nano' in the following food specific legislation; Food Contact Materials, Food Information for Consumers, the Novel Foods regulation, Additives, Flavorings and also the Enzyme regulation. They also mentioned the Commission recommendation that included the definition of nano (European Commission, 2011), EFSA publications on 'nano and EU guidance documents for carrying out risk assessments of nanomaterials.

Participants concerns in relation to the practical application of 'nano' specific legislation requirements, mainly focused on the requirement for sampling and testing of materials containing 'nano', and how this can be applied in practice for regulatory and analytical control purposes.

The follow statement typifies the sentiment:

> *"You can have legislation, but if you can't match it in terms of the analytical side then obviously that's another challenge."*

Nevertheless it was acknowledged by the focus groups that MS are required to carry out testing and sampling of foodstuff specified in legislation.

> *"As Member states we are also supposed to be testing the purity of these (nano) additives that are going to be added to various foodstuffs*."

However the reality of infrastructure, (both analytical and human), budget, and sample volume often present challenges to the implementation of legislative requirements cross the sector in Ireland. Moreover, the process is often not a simple task, and this is particularly true in situations where new novel contaminants are identified, as indicated by one participant from an official control laboratory;

> *"Testing of nanoparticles isn't trivial!"*

Which is compounded by the fact that the legislation to date has been somewhat vague in testing protocols and in specifying standards. Members of the official control laboratories pointed out that proficiency testing was one route used to develop new methods and effectively test their capabilities. However there was consternation amongst participants that facilities and infrastructure were not available to official control laboratories to participate fully in nano-related PT schemes with respect to the availability of an electron microscopy in particular.

> *"We didn't have the equipment to participant!"*

> *"I'm not sure how widely available electron microscopy is … from the official controls perspective, whether the state lab for example have one, or the Dublin PAL or any of the other (official controls) labs that test."*

> *"We don't have an electron scanning microscope, so that is a downside for us… Maybe that's different around Europe."*

In fact, a review of equipment and inventory in official control laboratories in Ireland for food and feed reveals that no laboratory has electron microscopy. This greatly compromises their ability to fulfill the necessary assessment requirements specified in guidance documents by bodies such as EFSA. As demonstrated in

chapter 7, the participation of official control laboratories in PT schemes provide significant confidence building in a laboratories capability, and moreover when combined with the wider infrastructure capabilities of academia it works well for fact finding, and for method screening approaches. However, for enforcement purposes the requirement in the official controls legislation ((EU) 2017/625) for the regulatory competent authority specifies the need to use an accredited laboratory, and an accredited test method for food testing (European Parliament and Council, 2017). For some participants this was an essential component, separating traditional analysis in academia from enforcement-based analysis.

> *"For enforcement …you need accreditation… Once you have an accredited laboratory you can stand over the results."*

The requirement for accreditation, despite being specified in legislation, was somewhat the subject of debate amongst participants, although it was acknowledged by all, that for enforcement:

> *"Accreditation … is your first port of call"*

Anecdotally most academics aired on the side of accreditation being a necessary requirement for enforcement. The largest discrepancy in opinion for the need for accreditation actually occurred between participants who professionally were directly associated with enforcement. Capacity issues in official control laboratories was one element highlighted for situations where unaccredited facilities could be explored, in particular with respect to infrastructure access or method development.

> *"We've gone outside of the official control laboratories in the past for analysis, because sometimes that analysis capacity is not available in the official laboratories."*

Others indicated that the restrictions associated with accreditation made it difficult for analysts to deviate from the set methods, in order to assess more difficult samples, or samples in different matrices, for example, adapting an accredited method for tissue analysis, to food analysis. As indicated by the following participant:

> *"The strength of accreditation is it is a standardised method, but it is also a weakness of accreditation, that there is no flexibility….. So if you have a*

different matrix or a different food, all of a sudden you can't use it anymore."

Moreover, participants expressed views that novel, new areas, have less stringent requirements for accreditation;

"There's an awful lot of tests which don't have accreditation. But they are used because that's what we have. That's the best we have."

Indeed reference was made to legislation which facilitates derogations from the requirements of official controls legislation ((EU) 2017/625) (European Parliament and Council, 2017).

"There is new legislation out there which allows member states to make derogation to laboratories to carry out tests which might not necessarily be accredited. So nano could actually fall into that category."

Although such derogations would only ever be temporary to facilitate the build-up of expertise and facilities in a member state, in order to properly enforce the legislation. Indeed for emerging areas it was pointed out by a participant that:

"We need to know what our limits are, and then working within our European scope with other member states to build those methods."

This was a point of discussion, as currently Ireland has no accredited laboratory for nanotechnology based testing in food, and so we would be dependent on the support of other member states if such a requirement was enforced.

The debate over the requirement for accreditation to enforce legislation was surprising. Typically accreditation can be expensive and time consuming to maintain, but it generally distinguishes official control laboratories from other academic or commercial laboratories. The restrictions imposed by accreditation are designed to ensure standardization, traceability and control over any; analysis, instrument or methodology. The focus group debate therefore represents a degree of uncertainty amongst the enforcement stakeholders, as to the flexibility of accreditation to address emerging concerns and enforce legislation in these areas. This element will be further explored in direct interviews with experts (chapter 6) in particular, from the point of view of other member states, to assess if similar

accreditation restrictions apply, and if a greater level of engagement across all the stakeholders, including academia, exists in other member states.

Another analytical difficulty which was raised with respect to applying legislative requirements were concerns about criteria stipulated in guidance documents, most notably around purity, particle size/distribution, and/or concentration. Concerns were expressed that there is no clear specification on how to evaluate the 'nano' criteria in the actual food products, with guidance documents focusing on non-representative samples. Queries were also raised around the availability of certified reference materials and/or standards to test that a method is effective for accreditation requirements. In the absence of standards and traceability one member of an official control laboratory emphasized:

> *"We do have a problem in that there is no EURL reference laboratory…so what are you gonna do with the results if you do find something? …it would need to be something that's repeatable, robust, which will be commonly available to countries."*

In areas of emerging contaminants, much of the sought after guidance for official control laboratories stems from academic reports and guidance documents, from bodies such as the JRC, OECD and EFSA. Knowledge of national, EU reports, recommendations or dissemination strategies were therefore also investigated amongst the focus group participants.

5.5.2 Awareness of National Reports

When probed about nano-reports many of the reports referenced by focus group participants were quite old. Nationally three key reports exist the ICSTI, FSAI and Safe-Food reports (Forfas, 2004, FSAI, 2008, Hanford, 2014). Anecdotally the focus groups knowledge of these reports was low with approximately <20% of participants being aware of only two of the three reports, while most participants were aware of the FSAI report, potentially due to independent preparation for their focus group participation. The awareness of the overarching recommendations from these reports was not noticeable as part of the initial discussions. The recommendations were therefore presented to participants, who were subsequently asked if they had seen any progress towards the implementation of the

recommendations in their professional capacity. Opinions expressed were varied, but there was broad agreement that some progress existed. Although it was judged potentially to be a natural, repositioning of agendas, as opposed to a specific directional change in response to the recommendations of these reports. This was particularly true in terms of the development of 'nano' skillsets in academia, which have not transitioned into regulatory bodies.

> *"I think it (skill-set) appears to be there in the academic arena, but I haven't come across a huge amount of skills in the regulatory laboratories, or discussion around nanoparticles or nanoparticle analysis."*

As highlighted in chapter 3, Ireland has invested heavily in supporting the National infrastructure, and participants referred to the fact that Ireland would be recognized as one of the world leaders in nanotechnology, in terms of the academic skill set, and the level of infrastructure. It was also acknowledged, that analytical methods for characterization and measurement of nanomaterials for risk assessments, and toxicity assessments were well developed in Ireland. There appears to be some progress made also regarding DAFM funded research, as one participant stated:

> *"They (DAFM) are building a network of academic researchers out there, to make sure that we have a colloquial here in Ireland, if they need that research or they need their input later on, that they've built that network."*

Although it was acknowledged that this was not nano-specific. Participants from regulatory control authorities, viewed the implementation of the recommendations primarily from their perspective, and generally were of the opinion that there had been only limited progress.

> *"All of them (recommendations) could probably do with more work, or either more support, more funding."*

As previously mentioned, it was emphasized by participants that the transfer of this knowledge from academia into regulatory bodies is vital, and that this has not been addressed.

> *"There's that gap between academia and regulatory bodies…. the transfer of knowledge back to the state sector labs, that is what I would see as important, that would be important for the next steps."*

It was also noted that the regulatory framework in Ireland is more reactive then proactive, and that the progress was in keeping with the relatively low level of development of nano-food, in comparison to other priority areas. However the continued advancement of the technology, and the emergence of more applications today, in comparison to 2008 may necessitate a review of progress.

> *"Now, is the time to get them (recommendations) back on the agenda and decide whether they are needed or not …. it will help promote that these recommendations get a higher visibility."*

5.5.3 Quantitative analysis of awareness of nano-legislation, national agendas and legislative enforcement concerns.

A quantitative approach to awareness of legislation, reports and guidance documents is somewhat difficult to perform, as no uniformity across the groups where achieved. Views differed significantly based on an individual's background. However, using word mining and associations, a degree of analysis was attempted, albeit descriptive. The small numbers, and the vague nature of participant's responses prohibited any statistical analysis of meaning. Figure 5.3 shows the relative percentage breakdown of participants who indicated knowledge of national nanotechnology based reports. During the discussion on reports, the FSAI report was acknowledged 61% of the time, indicating that this report is the predominant national reference source for the participants exploring nano-food technology. This is no surprise, as the report published in 2008 was followed up with a series of workshops and subsequent summary booklets, which greatly assisted in promoting and communicating the findings of the report. In comparison, the SafeFood report was only referenced 22% of the time, while no participants acknowledged the ICTSI report. Other reports were mentioned to a lesser extent, but these tended to be from another MS or NGOs. Examples of such reports included the Royal Society of Chemistry in the UK (The Royal Society, 2004) and recent opinion on pertaining TiO_2.

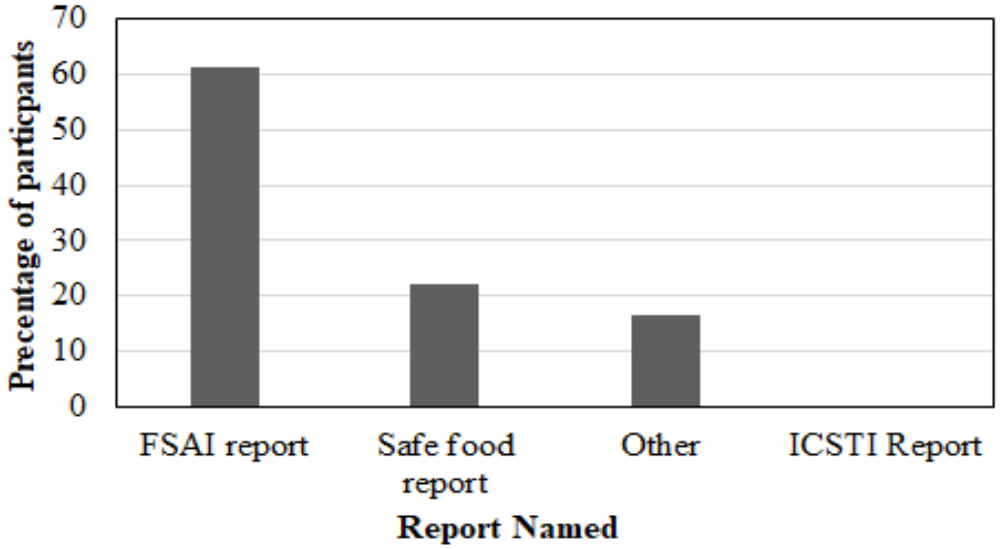

Figure 5.3 Breakdown of participants who indicated knowledge of national nanotechnology reports.

Figure. 5.4 explores the correlation between negative perceptions of the implementation of the recommendations, and the positive perceptions associated with the same recommendations. It can be seen quite clearly that the recommendation on engagement was split, with many feeling that the engagement process between agencies was good. This included interactions linearly through the regulatory control stakeholders, as indicated in Figure 4.2 in chapter 4. However there was less confidence in engagement laterally between agencies at the same level, for example, between different control laboratories or risk assessment agencies. Likewise, the opinions were split with respect to funding. Many felt that funding was sufficient, and was getting better with a more targeted approach. This was particularly true of DFAM funding, where it was acknowledged that the targeted approach often focused on emerging issues of concern. In contrast, recommendations on method development were perceived predominantly with a negative outcome. Many suggested that little or no progress was made on method development since the FSAI report. One key issue highlighted was infrastructure access across the stakeholder community. Indeed analytical concerns and legislative enforcement concerns were routinely coupled together in discussions extracted from the transcripts. The occurrences revealed a statistical significance ($p<0.02275$) between the concerns, suggesting that both issues were strongly coupled in the minds of the participants. This is somewhat similar to what emerges from the purely descriptive point of view, as indicated in figure 5.4.

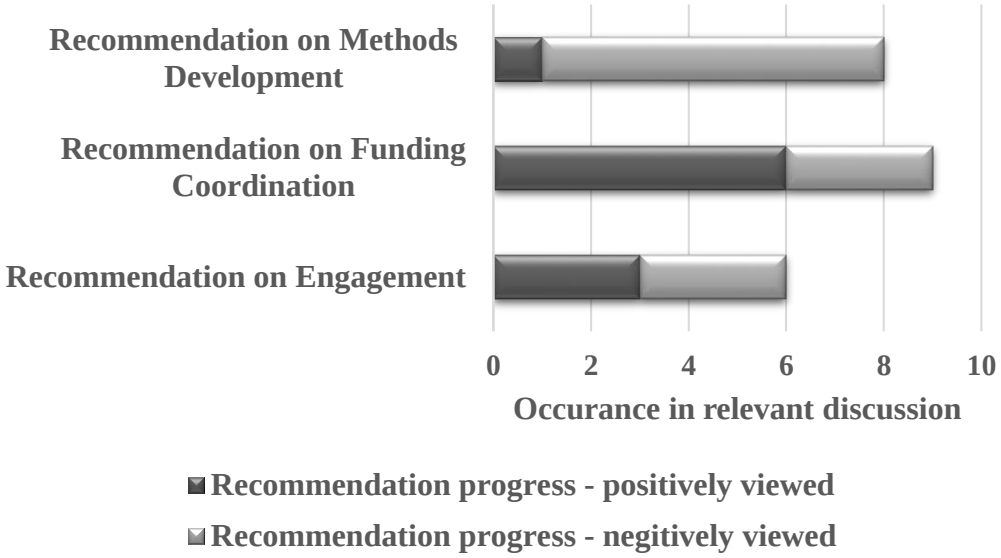

Figure 5.4. Positive and negative perception of the progress made towards the implementation of national nano-report recommendations.

Figure 5.4 highlights the perception amongst participants that recommendations on method development for 'nano' analysis in the regulatory domain have not significantly advanced since the report publication. In contrast, the recommendation of a coordinated approach to funding was better described as an even distribution of opinions. As aforementioned, DAFM have embarked on a prioritized funding approach to their research calls, as have the EPA and other funding bodies. Although the prioritization may not always feature 'nano'-based research as a priority. In terms of engagement, figure 5.4 does not express the true reflection of the groups' interpretation of engagement across all stakeholder groups. Analysis of the transcripts reveals an expressed concern of a reduced role of academia, in comparison to other jurisdictions. Indeed it was acknowledged that a vibrant active academic network of laboratories exist nationally, as described by participants,

> *"Ireland would be recognized as one of the leaders in nanotechnology (research) … we have that skill set and …the infrastructure."*
>
> *"Engagement between the (academic) laboratories, the regulatory authority, and the official control laboratories, that would be useful. That type of engagement with academia…the skillset is there, it definitely is there, the equipment is there too, but it's not in the right place for us (regulators). We don't have that type of equipment, we don't have access to the academic laboratories."*

The latter point above, representing an expressed view from many participants involved with control laboratories and regulatory bodies. The suggestion potentially being, that there is a lack of direct channels of communication between the enforcement stakeholders and academia. The potential for greater engagement of these sectors would open several avenues of exploratory research into method testing, while providing direct access to the exchequer funded infrastructure of academia and state run research laboratories such as Teagasc.

5.6 Infrastructure Access and Restrictions

Central to managing the regulatory control and subsequent testing of nanomaterials in food products, is the requirement to consider the availability and the suitability of the national analytical infrastructure that is potentially available to the regulatory control authorities. Having an awareness of the analytical equipment needed for testing, two of the regulatory control laboratories clarified that they could support some aspects of testing i.e. compositional analysis, using the existing equipment within their current remit. However, it was acknowledged that the laboratories in question do not have the analytical infrastructural capacity to carry out the full characterization suite of analysis, which would be expected for regulatory control purposes.

> *"Aspects of the testing might be available. I mean, for characterization, the State lab would have instrumentation suitable for elemental composition or concentration, this would be available by ICP Mass Spec, OES, XRF technology."*

It was suggested that the national competent control laboratory for "nano" in food DPAL has been working on developing facilities to measure 'nano', although no specifics of the approach used by DPAL was available from those participating in the focus group.

> *"The Dublin Public Analysts are looking at this, I think it's just the ICP-MS that they are using, with single particle, but I don't know if they've actually developing a method."*

DPAL were contacted subsequently, but declined to confirm the stage of

development of methodologies, but did however acknowledge that they were only using sp-ICP-MS for analysis of inorganic nano materials, and that they were following JRC guidelines. A number of participants expressed an opinion that; in their experience, electron microscopy is the recommended method based on guidelines;

> *"The Commission said that the EM was the method preferred by EFSA, in their opinion they suggested that this was the best method for the analysis of the particle size, and also that it was recommended as well by the JRC. So that was the reason why it was placed in the regulations."*

> *"They specifically mention 'to be analysed with electron microscopy' and that was after consultation I think as well with the JRC. And I wondered why they would say that if it cannot be done, I presume it can be done, because otherwise it wouldn't be specified in the legislation."*

> *"I know in the latest regulation on the specifications for titanium dioxide, it does say that the particle size should be measured by electron microscopy, so that's the technique that they've recommended."*

Needless to say the absence of electron microscopies within official control laboratories was a cause of some concern amongst participants, particularly academics, who's' response is typified in the following statement of surprise by one participant:

> *"Ireland is probably considered as one of the top destinations for nanotechnology research. Suitable equipment is widely available, in any part of Ireland you could see those facilities."*

Indeed results from chapter 7 (Infrastructure chapter) demonstrated that equipment suitable for 'nano' analysis is widely available within academic institutions throughout Ireland. The potential for state funded laboratories to access equipment in academic institutions was proposed as a way to resolve the barriers to testing. This was considered to be unlikely to happen, without having established links and relationships between the relevant institutions and a funding stream.

> *"Unless there's a strong link between the Labs and academia, I can't see how we (official control laboratories) would ever get access to the*

equipment."

"We'll go into the university and say, look, we're interested in looking at this work with a view to bringing it to the official laboratory at a later stage, but you have to have a budget for it!"

Nevertheless, some participants did indicate that existing collaborations with the academic sector, or Teagasc have worked well in the past, and have delivered results on an *ad hoc* basis. Additionally, some doubt was cast by the regulatory control authority in relation to how this arrangement would work in practical terms, specifically for the purpose of accredited 'nano-food' analysis. The lack of available funding, and/or access to Exchequer funding proposals was deemed to be a significant restraining factor experienced by regulatory control laboratories. It was highlighted that the equipment required is very expensive, and procurement procedures are often complex or protracted.

"If we've only got a small amount of sampling and a small amount of testing we might not be able to justify the expense to develop methods in house,"

"The technologies are very, very, expensive, and from a regulatory perspective, the official laboratories certainly …you have to get the funding authorized, then you have to get the equipment, train the staff and so on. So there is a bit more bureaucracy."

It was emphasized from instrument procurement, to staff training, and equipment validation, that official control laboratories experience significant bureaucracy, and they are required to justify exchequer 'value for money' more so then academic institutes would be required to do. Despite a shortfall in the capacity, participants clearly acknowledged the skillset possibly was available within the official control laboratories, with transferability of skills/expertise easily managed by training/upskilling, potentially being provided by the academic sector.

To be in a position to deliver such upskilling, academia would also require a degree of knowledge with respect to regulatory control, and the demand for reliable, consistent, and absolute standards in detection. One participant from the official control laboratories reiterated the need for accreditation stating that:

"The technology might be there to identify it, but to go that one step further

and develop established methods that are internationally recognized, and really get a handle on that variability piece, and that uncertainty of measurement piece through an ISO 17025 method, I don't think it is."

Of course academic research has a flexibility and a freedom in methodology, but nevertheless academic research can be representative of the highest standards in science, and is often held accountable. Indeed the review and subsequent banning of TiO_2 was the direct result of an academic paper reporting anomalies in testing of food grade TiO_2 (Bettini, 2017). In addition, academic research underpins much of the regulatory and legislative development at EU level and ISO standard development. Ireland has a network of technology gateways located in third level academic institutes which provide valuable resources; in terms of capacity, knowledge and skill set, to industry and to other sectors (EI, 2022). One participant from a technology gateway indicated this latter point, suggesting a need for a technology gateway to support official control labs and the regulatory sector.

"I suppose it's just what the demand is in the nano space for food in the future. Is it that we want to have a technology gateway positioned in one of the universities that will take in all of these kind of questions and queries coming in from the sector, that would be in an accredited lab space specifically for those queries, …or in Teagasc, where they can do that high throughput, again in an accredited space…"

Indeed, it has been noted that Teagasc research facilities are well established, and could facilitate a bridge between academia and control laboratories. Nevertheless, the establishment of such a facility would still need to overcome many fundamental issues e.g. lack of clarity on; technical specifications, how to interpret legislative requirements (if available), variations relating to technology requirements, different types of food and extraction of the particles themselves from different matrices.

A reoccurring stumbling point in discussions around the accessibility of equipment, procedures and standards, was the ongoing concern over the perception of a lack of certified reference materials or standards for testing nanomaterials. Participants highlighted the need for a centralized European reference laboratory:

"We do have a problem in that there is no EURL reference laboratory … it's an ongoing issue … produce standards, doing trials … and help the

laboratories to develop methods."

The establishment a European Union Reference Laboratory (EURL), would support method development, produce standards, and coordination of PT schemes. However, there would still need to be capacity, with respect to the infrastructure of official control laboratories and competent authorities to facilitate real engagement with the EURL's on emerging areas such as 'nano'. As such, an accredited technology gateway could enhance engagement, and support endeavors with respect to supporting, and supplementing capacity shortfalls in official control laboratories and the competent authority.

5.7 Nano-food prioritization as a part of the national agenda

A theme which repeatedly occurred during focus groups was the need, or otherwise, to prioritise 'nano' as an emerging risk of concern. Several participants expressed the view that currently the volume of products is simply not there.

> *"Is there a need for it? Is there enough of this stuff on the market to ask those questions … is there enough of a risk there?"*

Of course this view considers only those products which fall explicitly under a clear nano definition, and excludes aspects such as food additives which are included in multiple market products, for example TiO_2, nano-silver, or nano-iron. Nevertheless, it is recognised that the FSAI do focus on future planning and horizon scanning activities, and this was referred at all of the focus group meetings. Each year the FSAI produce a document outlining their research priorities, and what the:

> *"Laboratories could start looking at, in terms of developing methods, so this is outside of the official control perspective."*

In addition, a National Chemical Surveillance Programme (NCSP) has been established. The NCSP is an agreed sampling and analysis programme between the FSAI and the Health Service Executive (HSE), comprising of the Environmental Health Service (EHS) and the Public Analysts Laboratories (PALs). The NCSP is an essential element in facilitating Ireland to meet its obligations under EU legislation, which requires each member state to sample, and to carry out analysis on a range of foodstuffs to determine legislative compliance (European

Commission, 2006). The NCSP covers a range of analytes for monitoring and surveillance, including contaminants, additives, flavourings, food contact materials, vitamins, minerals, allergens, GMOs and food fraud parameters, among others. The NCSP is generally an FSAI/HSE administered programme, but in more recent years other official agencies such as DAFM and the SL have also participated, through the submission of samples to the official laboratories, for testing of specific parameters as part of their official controls. The initial step in developing the NSCP is that the FSAI would internally establish a list of potential chemicals for surveillance and sampling. The list is typically drawn from legislation, previous surveillance programmes, and suggested emerging risks. This list is subsequently collated into the FSAI priorities document of chemicals for the NCSP, and it is circulated to the external stakeholders for discussion and consideration. The reasons why a certain priority parameter/test proposed by the FSAI may not be taken up by the EHS and the laboratories, has often been due to a lack of accredited methods for the testing, or it may have been due to resources and capacity issues within the service. As a result, it is extremely important to have a solid scientific foundation to underpin the FSAIs priorities for inclusion in the NCSP, and to ensure sufficient allocation of resources, to enable the plan to be brought to fruition. In terms of nano, uncertainty in the definition, standards and methodologies have potentially hindered its prioritisation. Nevertheless, it was indicated by participants, and confirmed subsequently, that FSAI had embarked on a number of fact finding initiatives in the nano-area;

> *"FSAI, the Dublin PAL and the State Lab had meetings to discuss nano issues, … it was just an initiative to get people who are doing work in the nano area talking, but I don't think thats' progressed any further."*

In addition, it was emphasised that going forward, with new legislation requiring more targeted testing of nano or nano related materials, that future proofing aspects are always considered.

> *"We try to be a bit more proactive every year and we do identify priorities across the organization that people see as sometimes an issue."*

A significant restriction however for the FSAI, is that it does not have a budget to fund research, or to explore in great detail potential emerging risks or concerns.

That is, they are not in a position to make payments for, or to tender for completion of research activities.

> *"It's more about the funding and the money that's available. If we had the money to do it, and there was a structure in place to do it, by all means I'm sure the FSAI would …"*

In contrast, the EPA, DAFM and other state agencies do have a research budget, allowing them to focus on research activities of relevance to their particular priorities. While DAFM have numerous research activities ongoing, they also benefit from administering funding calls to academia and Teagasc. Indeed Teagasc could be considered a 'defacto' research arm of DAFM.

In terms of prioritization, at various times in focus group discussions participants made reference to the dioxin contamination incident in 2008, which led to an international recall of pork products, and forced capacity and capability in dioxin analysis onto the agenda nationally. Indeed it was suggested that:

> *"If there was an (nano) issue in the morning that emerged in Ireland, or in Europe we would have to start analysis of different foodstuffs."*

An alternative opinion from a different authority was that appropriate actions would be quickly put in place to manage an issue, as stated:

> *"If there is a scare, like the dioxins, obviously you'd remobilize, you'd re-task, like we have had to do for the COVID crises. So there could be a driver, but at the moment there isn't. So it's very hard to speculate what would be needed to be done*."

Expanding upon this further, and focusing more on the imminent requirement to regulate for titanium dioxide, which has been banned from use as an additive in foodstuffs, participants were asked, "In the absence of a national accredited facility, who could carry out this testing? What options would be available in that situation? Would it be possible to use an 'unaccredited method" for this testing, or would the competent authority need to outsource this testing to another member state who have the capacity, and the accreditation status?" There appeared to be some disparity regarding the approach which would be taken by regulatory control authorities. However, it was stated that,

"Preference wise, it would be to source from another member state, especially with titanium dioxide, it probably will be challenged, and if it is relating to a particular company that's manufacturing that additive, then more than likely it will be challenged."

In summary the prioritization of nano as an emerging risk requiring focused method development was not broadly seen as an over-arching concern, and it was believed that interim arrangements via derogations to use non-accredited methods, or access to accredited methods via other member states would be sufficient to bridge any immediate gaps in infrastructure and knowledge. It was also acknowledged however, that this reactive approach was partly due to funding restrictions and capacity issues across the stakeholders.

5.8 Summary and Conclusions

Issues and concerns identified by participants centered mainly on identification of requirements for 'nano' testing with respect to; why is needed? What exactly is the risk? Is there skilled graduates to carry out testing? When should testing be done and how results should be interpreted?

The need for controlled, planned testing of applications of nanotechnology was not evident. Nevertheless, participants were concerned about uncertainties going forward, and the need for national preparedness. The implications of the EFSA opinion on TiO_2 (Younes, *et al*., 2021) and the requirement for testing to determine if particles were in the 'nano' range was identified as a source of concern. Additionally, the consequence of this for other materials/additives was identified as an issue. There was an anticipation that legislation would be revised to indicate a requirement to test many different products for 'nanoparticles' in food products. While it was evident that the academic infrastructure has been sufficiently funded to support the availability of skilled graduates and capacity, significant concerns existed around standards and accreditation, if such academia 'facilities' were to be used. Furthermore, currently there is no formal arrangement in place whereby regulatory control laboratories can avail of infrastructure within the academic institutions. Indeed it was recognized that infrastructure and expertise is diminishing in some state research facilities, leading to outsourcing of analysis

Evidence of 'horizon scanning or future proofing was investigated particularly with a focus on the requirements of regulatory control authorities. While opinions differed in many ways, there was evidence provided that a degree of proactively managing controls, and future issues existed. It was acknowledged by a number of participants that:

> "*There is a requirement for member states to look at emerging issues, to look to emerging risks and so on, and to put in place contingencies for those emerging issues, emerging risks*."

Indeed the FSAI have an in-house group who actively review the impact of 'novel technologies,' and the potential impact of nanotechnology is included as part of this topic. However a significant restriction in this regard is the inability of the FSAI to access research laboratories, and/or to provide funding to commission research for horizon scanning.

In conclusion the key finding of the focus group study can be summarise into the following aspects.

1. The need for greater communication between stakeholders to facilitate knowledge transfer, resource sharing, enhance skill bases and method development.
2. A targeted research arm or budget for the competent authority in the area to facilitate genuine horizon scanning and greater autonomy in formulating the NCSP.
3. Uncertainty in regards to the requirement and level of accreditation required for new and emerging areas of risk.
4. The formation of a technology gateway to support method development for regulatory enforcement of new and novel emerging contaminants.
5. The urgent need to establish a EURL in nanotechnology to address concerns in knowledge gaps, standards and methodology.

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6.1 Introduction

Individual interviews are often used in exploratory, descriptive type research studies; to obtain detailed information about a specific topic or situation, and/or to get access to opinions, perceptions, experiences, and even knowledge of a given phenomenon (Ryan, Coughlan and Cronin, 2009). The individual interview data gathering approach involved one-on-one communication between the researcher and 'selected' participating interviewees, in this case selected because of their professional status. The individuals purposely 'selected' for participation in this interview process were specialists who are; involved in implementing policy, or monitoring control of policy strategies, and those who are in positions where they influence legislative/policy decisions at EU level. This approach was deemed appropriate as a follow on from the focus group discussions (chapter 5), which are a form of interview also, but with several people attending (Rabiee, 2004). While a broad and comprehensive range of issues and perceptions were discussed at length during the focus group discussions, the main purpose of the 'specialist' interviews was to explore specific issues, opinions and/or misconceptions expressed at the focus group discussions. Individual interviews were conducted on-line in a similar fashion to the focus group discussions, in line with national policy prohibiting face-to face meetings due to Covid based restrictions in place at the time.

The interview methodology for this research involved the use of 'non-standardised, semi-structured' interviews (Saunders *et al,* 2009). In this case a pre-arranged list of themes and questions which needed to be explored at interviews were prepared prior to the individual interviews. The list of 'proposed' questions were sent to all participants prior to attending the interviews. The interview questions were focussed, to gain in-depth information from the respondents. It is appropriate that questions were phrased differently, depending on the participant and on the professional context which they are representing. The main emphasis of the interviewer was to involve the interviewee in discussions on specific topics, so that the desired information is freely provided by the interviewee, as opposed to the interviewee responding to prompts from the interviewer (Gordon-Hunter, 2006). The interviews were based on broad open-ended questions, giving the interviewer and the interviewee opportunities to discuss some areas in greater detail if they wished to do so (Fox, 2009). The semi-structured interview format allows the

researcher to add additional pertinent questions, or to skip certain questions from the 'proposed' list of questions provided to participants, in order to probe certain areas more deeply, if it becomes apparent that questions are not relevant, or indeed if the participant is unable to answer questions for some reason (Alamri, 2019). With the semi-structured approach, if the interviewee had difficulty answering specific questions, or if they provided only a brief response, the interviewer was able to provide prompts to encourage the interviewee to consider the question in a different way, and the interviewer also had the possibility to follow a line of inquiry introduced by the interviewee (Fox, 2009).

The data collated from chapter 4 survey and chapter 5 focus groups provided the researcher with a refined list of themes of relevance for further discussion with specialists working in the 'nano' area. The main themes related to;

- Roles and responsibilities,
- Official controls,
- Potentials, gaps and deficiencies,

Questions were directed to individuals specifically within these area to provide evidence to; corroborate findings from the surveys and focus group discussions, refute findings or to gain new information which was not evident from the previous enquiries.

Previous enquiries demonstrated the need to probe more deeply into aspects on regulatory control strategies such as; legislative responsibility, awareness of technical/analytical requirements, access to national testing facilities, stakeholder engagement and suggestions for future policy.

6.2 Roles and responsibilities

6.2.1 Specialist roles

The targeted interview participants included specialists from

- The National competent control authority (FSAI) working in different focus areas covering a range of legislative responsibilities.
- Policy enforcement

- Official control testing laboratory
- European Food Safety Authority

Participants were asked to clarify their specific role from both an organisational prospective and as individuals within the organisation, with the key response in italics in the following text.

The national competent authority (CA) working with the relevant stakeholders were deemed responsible for:

> *"Drawing up the FSAI priorities for the National Chemical Surveillance Programme (NCSP) for agreement with the relevant agencies (EHS and PALs)."*
> *"One of our main roles in the chemical safety team is that of risk assessment."*

Policy enforcement officials, namely the Environmental Health Officers (EHO) who are employed under the remit of the Environmental Health Service (EHS) were considered as being responsible for:

> *"Our main function as EHOs is to protect public health."*
> *"This involves sampling of foodstuffs from various premises to assess compliance against food law under service contract to FSAI."*

Analytical competent controls/testing laboratory facilities which are contracted to the FSAI for food analysis are the regional Public Analyst Laboratories (PAL) and the State Laboratory (SL). Responsibilities of these laboratories within the regulatory enforcement stakeholders include:

> *"Apply testing requirements based on legislative requirements."*
> *"Testing for 'banned' substances i.e. substances which are not allowed to be present in food, and also a large amount of testing is devoted to our legislative responsibilities, which we must complete."*

Finally, as an overarching organisation the European Food Safety Authority (EFSA) provides independent scientific advice on existing and emerging food-related risks.

"We (EFSA) are responsible for the risk assessment, for the demonstration of the safety of the materials."

"EFSA have issued many guidance documents on nanotechnology over the years"

New technologies come along all the time, and for food additives, the manufacturing process is assessed as part of the risk assessment process, when an additive is being authorised at EU level."

6.2.2 Legislative responsibility

Food law requires that official controls are carried out on a risk basis. Specialists from the FSAI indicate that; testing requirements are based on; legislative requirements and monitoring compliance of parameters which specifically are of:

"High risk to the consumer."

"Discussions at EU level also influence what should and should not be covered by various sampling plans."

It was acknowledged by focus group participants that:

"You can have legislation, but if you can't match it in terms of the analytical side then obviously that's another challenge."

This statement raises the question about how much input regulatory control authorities have towards the formulation of legislation. Focus group participants agreed that a definition of 'nano' for regulatory purposes should have clear parameters conducive to measuring, and detecting limits of a material under consideration. However most legislative testing requirements are often based on establishing if a parameter has been found to be in breach of maximum permitted levels, or for the detection of banned/unauthorised substances. It is the case with 'nano' that measurements of test samples should confirm the 'presence' of 'nano' as well as other 'nano' parameters e.g. particle size, size distribution, shape, and/or crystallinity. This implicit concept was confirmed by the interviewee participants for the FSAI whose responsibility it is to interpret legislation and to provide direction to other stakeholder in the enforcement area.

6.2.3 Impact for testing

The principal means of determining priorities for testing of foods/products is laid out in the NCSP. The FSAI present the annual plan to the relevant stakeholders, the document is discussed amongst the stakeholders, with the final sampling plan negotiated and agreed with each stakeholder, before being scheduled on the EHO sampling plans and the PAL analysis plans. A particular constraint highlighted by different stakeholders within the regulatory control community was that sampling and testing is:

> *"Based on resources and capacity to collect the foodstuffs identified (EHO's) and methodology permitting (Testing Laboratory)."*

When regulators were asked specifically about the inclusion of nano products or applications of nanotechnology on the annual control plans the authority indicated;

> *"We don't test for any nanomaterials at the moment, at the moment we don't have that facility."*

> *"Any actions we would take on the basis of something having a nano component would be based on, maybe other member state measuring for us."*

> *"We may test some of the products out there for various ingredients such as additives/contaminants, but particle size and particle size distribution are currently not being checked."*

Putting the future analytical determination of nanomaterials into context, and using the example of the impending requirement for analysis of products potentially containing TiO_2, interviewees were asked about their thoughts on the impact of the Commission decision to ban TiO_2 as an additive in foodstuffs. Competent control authorities indicated that this:

> *"Could mean a requirement for testing in the future and along with that all of the other additives or compounds which are in 'nano' form which EFSA consider to be compounds of concern."*

The Competent authority elaborated on the need to ensure that no products containing E 171 will remain on the market following the end of the legislation transitional period ending on the 7th of August 2022, indicating that:

> *"This will entail some market surveillance activities to ensure this is the case, and also potential testing of food products to verify that this is the case."*
>
> *"Testing for titanium dioxide has not commenced yet, but it has been highlighted as one of the FSAI's priorities for 2022."*

When asked about the approach which would be taken in an emergency situation, or if a major issue was identified requiring testing for e.g. titanium dioxide in food. Participants were asked what route the competent authority would take to ensure that testing was carried out, with the awareness that the national 'State' laboratories are currently unable to complete this testing. Different approaches were identified as follows;

> *"In the event of an emergency, we usually consult our own official control laboratories to see if they can carry out the analysis for the parameter concerned, and if not then other avenues are looked at such as testing in other member states, or in research environments if necessary, until such time as we have the capacity developed within the labs nationally to analyse the parameter of concern."*
>
> *"We would source alternative laboratories (within the EU) capable of testing the parameter of concern."*
>
> *"We would probably get the samples to a Public Analyst, or a State Lab, and then they would probably have to delegate the testing to an outside laboratory."*

Sampling Offices (EHO's) expressed concerns about the impact for them, the professional body consults with the laboratories prior to taking samples for testing to determine if the analysis can be carried out within the national infrastructure, or if indeed the samples and the analysis can be outsourced to another MS laboratory for testing. For them the difficulties are that if testing of samples to determine the presence of TiO_2 does become an issue:

"They don't have a plan developed yet."

In relation to their knowledge about the current infrastructure status within the PAL national network, it was stated that

"There is no testing available, I don't think that any of our Public Analysts Labs can actually analyse for nano particles."

"They (laboratory) probably would have to send it into somewhere where there would be a Scanning Electron Microscope."

This level of acceptance that no official approach has been decided upon with a wait and see approach is somewhat disconcerting, as uncertainty in relation to how and where the analysis will occur, will undoubtedly impact upon the type and timing of product sampling. Reducing the potential for a timely response from the enforcement stakeholders to an emerging concern. Moreover, as the TiO_2 legislation has been enacted, the requirement for sampling is a real and tangible possibility post 7th of August 2022.

6.3 Official Controls

6.3.1 Awareness of technical/analytical requirements

There appears to be some disparities regarding the approaches which would be taken to ensure that testing of relevant materials is carried out i.e. whether the competent authority would outsource directly to another member state official laboratory or send the samples to a national control laboratory to allow them to manage outsource testing. It was stated by competent authority specialists that:

"We (IE) currently do not have the analytical technical capacity to carry out testing of nanomaterials in food/products."

A proactive approach to managing this matter has been taken by the competent authority along with some of the regional Public Analyst Laboratories, where discussions took place with a number of large additive manufacturers about the potential impact of TiO_2. Discussions were also held with GPAL (Galway Public Analyst Laboratory) about establishing an accredited method for such testing. It

was indicated that the DPAL (Dublin Public Analyst Laboratory) have confirmed that they have the:

> *"Capability to carry out this analysis, but they have not completed method development/validation yet."*

It would appear therefore that IE are in a position to progress this testing, pending the advancement of method development/validation.

It was perceived by competent control authorities that there is a requirement for the use of an electron microscope for analytical testing of 'nano' samples in general, and that this would be reflected in the analytical requirements for TiO_2 samples also. This opinion was also mentioned amongst different focus group participants. As the competent control laboratories do not have direct access to an electron microscope it is important to establish if there is a need for analysis using electron microscopy.

Clarification on this point was sought from the EFSA technical specialist, who indicated that the technical requirement for titanium is relatively easy, i.e.

> *"The assessment is for all particles of titanium, it's not for specific sizes. So, there is no need to go for electron microscopy, or to have a full characterization of the particles."*

> *"As I said, it is very easy to measure titanium and obviously if you measure titanium it is assumed that is, as particles."*

Additionally the specialist gave reassurances that there are some techniques/methods which could easily be utilised in a testing laboratory without the need for the use of a scanning electron microscope. In the EFSA guidance document for particle technical requirements (More, *et al*. (2021). analytical methods are presented to exclude the presence of a fraction of concern. As stated by the EFSA Specialist:

> *"Those methods are relatively simple … even the screening methods, these are methods that can be easily implemented in a control laboratory, and they do not require electron microscopy."*

Discussions amongst focus group participants regarding the need for accredited facilities and test methods generated varying opinions as to whether accreditation is necessary for regulatory control testing. This was one of the important points which was raised at the specialist interviews, to gain an understanding of the official requirements. Specialists made reference to the requirements outlined in official controls and other official activities regulation i.e. (EU) 2017/625 (European Parliament and Council, 2017). In relation to the regulations, It was stated that:

> *"It is a requirement in the official controls regulation that control laboratories must be accredited for official control purposes."*

In Ireland the official control laboratories are designated under SI 79 of 2020 (Statutory Instrument, 2020). Regulation (EU) 2017/625 indicates that for designated official control laboratories the scope of accreditation should include all of the accredited methods of analysis when the laboratory operates in an official control capacity (European Parliament and Council, 2017). It was highlighted, with the exception of some derogations provided for in the official controls regulation:

> *"All designated official control laboratories should be operating in accordance with the standard EN ISO/IEC 17025 (ISO/IEC, 2005), and should be accredited in accordance with that standard by a national accreditation body operating in accordance with Regulation (EC) No 765/2008."* (European Parliament and Council. (2008).

The derogations referred to are often temporary and are however:

> *"Limited to newly required methods, substantial changes to existing methods, or testing related to emergency or emerging situations and are limited in time."*

This would substantiate the claims made within focus group discussions that test results obtained outside of accredited procedures would be deemed acceptable under certain circumstances, e.g. in an emergency or emerging risk scenario.

Specialists were asked about the possibility of using any of the national control testing laboratories as a designated 'accredited laboratory' not necessarily accredited for 'nano' but as accredited facilities, while they work towards gaining accreditation? It was clear that different approaches may be deemed acceptable i.e.

"We could get the testing completed elsewhere while we wait for the laboratories to get the accreditation status."

"The way food law is set up it doesn't matter what technique you use however, sloppy as it is, or unaccredited, et cetera, if you can fairly scientifically demonstrate a food safety concern you can act straight away and then ask questions, or answer questions later on."

An example of where this logic was applied was for the 'Horse Meat Scandal' in 2013, where preliminary investigations by the FSAI resulted in detection of the presence of horse meat, in meat for human consumption. At that time the national competent control laboratories did not have competency for official control testing, so the competent authority outsourced the analysis until such time as the capacity was suitably established. The competent authority were justified in this case to remove unauthorised products from the marketplace prior to initiating control plans through 'official' analytical testing procedures.

Considering the uncertainty of approach which would be assumed towards the requirement to use 'accredited' test methods or 'unaccredited' test methods, it seemed prudent to explore this ambiguity further. The possible option of using "unaccredited" test methods was queried with the EFSA Specialist, the response was very much in line with the requirements set out in Regulation (EU) 2017/625 (European Parliament and Council, 2017), as follows;

"I don't think that this is feasible for official control purposes."

Further evidence of the requirement for accreditation was provided by the CA Specialist who referred to the 'Official Control Rules (OCR) ((European Parliament and Council. (2017) for testing laboratories, for official control purposes'. The OCR does stipulate that official control laboratories must hold accreditation to ISO/IEC 17025 standards (ISO/IEC, 2005), ensuring that a robust quality assurance system is in place to guarantee sound and reliable results using a method which is included within the scope of the existing accreditation schedule. There is mention of specific derogations, with terms and conditions, where accreditation is not necessary for official control laboratories. However the temporary designation shall not exceed a period of one year. An interesting point which was made was that the:

"The official laboratories designated shall be located in the Member States in whose territory the competent authorities which have designated them are located."

With this in mind it would appear that the option of outsourcing analysis of samples to other MS is not feasible on a long term basis, in this regard it is important the official control laboratories do obtain accreditation status for official control testing requirements as soon as possible.

6.3.2 Issues identified by laboratories for appropriate technical/analytical resources.

In order to satisfy the criteria for gaining laboratory accreditation to EN ISO 17025 standards, laboratories need to have internal and external quality control activities in place for accredited test methods. Along with a lot of other criteria, the laboratory must have appropriately validated methods; which generally involves the regular use of certified reference materials (CRM), and participation in proficiency testing schemes (PTS) and/or inter-laboratory comparisons (ILC) studies where appropriate. With the knowledge that the laboratories are developing their capacity to carry out nano analysis, and that they have not completed method development/validation yet, specific queries were directed towards specialists to determine if the applicant laboratories would have the appropriate technical/analytical resources available to help them to progress this activity.

Some of the potential issues raised include the following:

- **Effect of matrices;**

  "Let's say you have a powder of titanium dioxide in a food matrix. It would be physically impossible to determine what fraction of the titanium dioxide, which is dispersed throughout the whole food, how much of it is in the nano form?"

  "It's one thing to look at a pure source of titanium dioxide, but there's a difference to looking at a food matrix, which contains, you know, tiny amounts of the actual additive as such, you're looking for needles in haystacks!"

- **Quality Control Criteria, i.e. Availability of reference materials e.g. CRM, PTS and ILC**

  "Obviously, it (Test method) does have to have some kind of standards, whether it's accreditation or ring trials or whatever."

  "If you have a brand new technique then there is no accreditation. There's no ring trials." (i.e. PTS)

- **Provision of technical assistance and training, e.g. through a European Union Reference Laboratory (EURL))**

  "One of the problems with the testing of food additives in food in particular is that there is no EURL in this area, whereas there is one on the feed side."

  "It would be subject to challenge. If you found it, there's the problem of what is compliant and what is not compliant?"

6.3.3 Identified Concerns for nanomaterial characterisation

Some general concerns raised about nanomaterial analysis in general relate to the following;

- Control labs potentially do not have suitable equipment for this type of testing and the validation is not complete yet.
- Acknowledgement that there are safety concerns about nanomaterials in general and particularly about 'engineered' nanomaterials.
- It is anticipated that after the banning of TiO_2 that EFSA will instigate a retrospective look at materials like silicon dioxide, iron, silver and other nanomaterials in additive form.

The specialist from EFSA confirmed that they have indeed completed further evaluations on some materials covering food and feed, including food additives, and they have opinions of the EFSA panels:

"Where they have indicated possible concerns regarding possible presence of nanoparticles for other materials."

The advice from the specialist referred very much to EFSA guidance document to establish the presence of small particles, with the advice being:

"If the member states have concerns they can carry out checks. They can follow the guidance to see if some of the materials which they have concerns about contains (or does not contain) a fraction of nanoparticles, and then they can alert the Commission, and then the Commission may request EFSA to do a new assessment."

Competent authority specialists explained the basis of the requirement for testing TiO_2 in particular, in response to the EFSA decision to ban the additive. As outlined by one specialist:

"There was concern about the fraction of TiO_2 particles in the 'nano' size range. This is the first mention really about the 'nano' component and reference to the small particle size."

The impact of the ban for competent authority sampling officers was discussed with the EHO specialist, who stated that the professional body had communicated to food business operators (FBO) that TiO_2 was banned, and that FBO's needed to source an alternative material for use in the production process where applicable. The concern however expressed by the practicing EHO was that:

"The food businesses, they'll start thinking of ways of saying "I'm not stopping using this!"

With this in mind the interviewee stated:

"That's where the analysis will be critical, because it is possible that you're gonna have people saying "well no, this isn't the type of titanium dioxide that has any impact….."

Which would imply that the competent authority would be particularly reliant on the analytical results in order for them to be able to take any actions against those FBO's who flouted the legislation and continued to use TiO_2 despite the ban.

In an attempt to explain the health and safety concerns and the rationale for the decision taken by EFSA to ban TiO_2 as an additive, the EFSA specialist highlighted some issues of concern i.e. on review of the literature:

"Uncertainties and data gaps previously identified …."

by ANSES and EFSA still exist. Additionally the specialist indicated:

"There is a classification for carcinogenicity for inhalation. So there are several concerns about TiO_2."

6.4 Potentials, gaps and deficiencies

6.4.1 Access to national testing facilities

As illustrated earlier there are many limiting factors for the various national stakeholders. A particular difficulty is that there is no national laboratory set up for the testing of nano food/feed products for official control purposes. This has an impact for the sampling officers (EHO's) who cannot take such samples from food business operators/customer supply premises because they may not be in a position to have the samples tested. As stated by the EHO Specialist;

"There might not be a method there for that analysis, so you might just have to maybe do monitoring analysis."

"For us (EHO's) that's quite difficult because we take samples from food businesses so you want to be able to give them a test result. We can't just take samples ad hoc from premises and just give them a letter without a result."

"The main thing we want is (EHO), basically that the analysis can be done in a timely manner, and that it can be designated, (For official control purposes) so that we can go back with a very clear result to the food business"

Additionally, the competent control authority indicated that the lack of testing facilities at national level is a restraining factor, as stated earlier:

"Any actions we would take on the basis of something having a nano component would be based on, maybe other member states measuring."

This is not in alignment with the requirements of the Official Control Rules for testing laboratories, for official control purposes, i.e. under Article 42 of the OCR 'the official laboratories designated shall be located in the Member States in whose territory the competent authorities which have designated them are located' (European Parliament and Council, 2017).

The FSAI sampling priorities are outlined on their NCSP, however it is not always possible to have sampling/testing in place for everything included in the document. The competent authority indicates that there are many products/parameters which need to be tested for, to demonstrate legislative compliance and the list of parameters increases annually. As stated by the competent authority specialist:

> *"The list is ever growing but there are constraints on the staff/resource capacity which in some instances is not increasing in line with the requirements. A lot more testing could be carried out if the resources were increased."*

It was explained by one specialist that parameters can be added to the plan which are not included in the sampling/testing agreement, however some parameters are taken on board by the control laboratories for method development, with the aim of including sampling and analysis of these parameters in future plans.

6.4.2 Research and Development (R&D)

Beyond the range of services and responsibilities of the competent authorities listed earlier, some EU member states competent authorities are actively involved in research and development activities, in collaboration with the applicant producer. The competent authority supports the product application dossier process by providing risk assessment, health and safety evaluations/advice, before products are sent to EFSA for authorisation and approved use. The example given related to the experienced specialist involvement with a group of researchers in:

> *"Public institutions who were providing support to the applicants."*

This research infrastructure was funded by the Spanish government, as explained by the specialist:

> *"It was covered by the Ministry of the Environment, the Ministry of Agriculture and Food and the Ministry of Health. They created a kind of partnership between different research institutions, providing very high level technical and scientific support for the applicants."*

Further evidence of where this activity becomes relevant is where some legislation provides specific roles and responsibilities to member states in different areas. The example of this was given for the pesticides area where:

> *"The competent authority in the member state has the main responsibility, as rapporteur or as collaborator of this activity (supporting the applicant producer)."*

> *"In other areas even the dossiers are received firstly by the member states, and then it is submitted to the Commission or to EFSA" (through the competent authority)."*

The dual function where member states competent authorities have remits for research and development, as well as regulatory control activities is illustrated well in Germany, where the BfR is a research institution and it is the national competent authority also. Further evidence of this in other EU MS includes; in Italy, the Istituto Superiore di Sanità (ISS), and ANSES in France. While this is not the case in all member states the EFSA specialist indicated that:

> *"Most of the countries have at least a kind of national body that produces both research and regulatory advice for nanotechnology. For example, Belgium Sciensano is doing similar activities."*

An alternative suggested approach discussed with the EFSA specialist was where some member states avail of the research and development resources of research organizations, which are ideally "not linked to universities", i.e. it is preferable to use:

> "*Public research organizations."*

It was highlighted by the EFSA specialist:

> *"If a member state does not have a sufficient way of carrying out research, using public researchers, or public organizations, then the logic is to include universities as well."*

6.4.3 Future proofing

Having discussed the awareness of technical/analytical requirements, the issues and concerns identified by focus group participants and at specialist interviews a number of actions have been identified where action can be taken to facilitate future proofing of this official control activity.

A brief overview of the actions are presented below;

1) Establishing the priority needs

Upon review of the available laboratory resources, (people and equipment) and the technical requirements necessary for control testing of nanomaterials, it is important to determine the needs, and potentially the timelines to put systems in place for control testing purposes. With the banning of TiO_2 in force since 2022 this parameter has now been included on the FSAI 2022 NCSP i.e.

> *"To alert the laboratories and sampling staff to this, so they are aware of stuff that is also coming down the track and for which future/pending test requirements will be needed."*

In saying this it would appear that the level of priority is not high, as explained by one individual;

> *"At the moment, given that food additives have to go through an extensive safety assessment before they are even authorised, this means that they are not seen as a high priority for testing compared to contaminants for example."*

Additionally the regulation allows manufacturers a 'grace' (transitional) period of 6mts to remove products containing TiO_2 from the market place. This grace period will hopefully; allow time for manufacturer reformulation to take place, and allow MS to get plans in place to remove products containing E 171 from the marketplace. The process will involve competent control authorities ensuring no products containing E 171 remain on the market following the end of the transitional period. As stated by the practicing EHO:

"This will entail some market surveillance activities to ensure this is the case, and also potential testing of food products to verify that this is the case."

2) Identifying resources constraints

In many instances additional resources may be required to progress the testing requirements outlined in the NCSP. This issue was highlighted by different stakeholders as follows:

"A list of parameters and foodstuffs concerned, which require testing is proposed by the FSAI and these are incorporated into the national chemical sampling plan, based on resources and capability of the EHS to collect the necessary samples and on the PALs ability to analyse for the parameter concerned (methodology permitting)."

"This document is discussed among the stakeholders and various parameters are chosen for inclusion in the overall NCSP, based on resources and capacity to collect the foodstuffs identified."

"There are constraints on the staff/resource capacity, which in some instances is not increasing in line with the requirements. A lot more testing could be carried out if the resources were increased."

"They are included in the plan for testing, as and when the resources are available."

While the resource issue was highlighted by different stakeholders suggestions/options for how this might be addressed were not given.

3) Identifying training requirements/opportunities

Training for sampling officers (EHOs) is provided by the EHS Food Product Safety Operational Unit where applicable, the units also attend the BTSF (European Union) training courses, they receive support from the FSAI and the PAL's appear to be are supportive too. As acknowledged by the EHO specialist:

"The FSAI play a huge role in training as well. They provide a lot of eLearning through SafetyNet."

"What we (EHO's) find anyway with the laboratories, is that they're great, in that they're quite willing to do training with us."

It was not possible to explore the training needs of the competent control laboratory directly due to lack of participation in the interview process, the laboratory did provide written responses to preapproved interview questions. The written response to the questions indicated that nationally there has been some support from the FSAI in terms of information, however the majority of the support has come from EU. This support has come in the form of technical information and training from JRC projects e.g. NanoDefine and NanoForFood. As outlined in the DPAL written response to approved interview questions:

"The associated information sharing from contacts made during these projects has also been beneficial. We have also been involved in a CEN project, part of TC352. Other sources of support has come from participation in PTs organised by e.g. RIKILT and JRC."

Training for member state competent control authorities is provided by the JRC in Ispra, it was stated by the EFSA specialist that the training is:

"Specifically focusing on control laboratories." The JRC have already conducted several training sessions online…"

"They (JRC) requested that the information is passed through the nano network, because they will continue now with physical training in Ispra."

The idea of using the professional knowledge and technical experience of academics and researchers was suggested by a number of focus group and interview participants, i.e., that this could be possible by way of:

"A potential link up with academia involved in nanotechnology."

This idea was viewed in a positive light in the case of the EHO specialist, who indicated that research institutions like Teagasc have proven to be very beneficial in the past, and that they still run a lot of courses and webinars. The idea that training/upskilling could be provided from university/research institutions was viewed in a positive light also, the example of a successful collaboration was given where TU Dublin and the EHS Continuous Professional Development (CPD) unit

provided a bespoke research training course for Environmental Health Officers to try to encourage more EHOs to do research projects, it was acknowledged that the training:

> *"Was really interesting and I was thinking, this is great, it gives you an idea of where do you start with research."*

4) Establishing an EURL

The most prominent support system for competent control laboratories is usually the relevant European Union Reference Laboratory (EURL). This is usually a facility for member state laboratories to avail of the scientific and technical expertise of experts in the relevant area of interest. The facility usually has 'state of the art' equipment at its disposal, and it is usually a repository of certified reference materials. It is also responsible for organising proficiency testing schemes (PTS) and/or inter-laboratory comparisons (ILC) studies. This facility is highly valuable for laboratories who are in the process of developing methods, expertise and who are working towards validation of methods for accreditation purposes. It was highlighted by the competent control authority that the lack of availability of an EURL for food additives in particular was perhaps a limiting factor for laboratories who have not yet reached the stage of testing, as stated:

> *"One of the problems with the testing of food additives in food in particular is that there is no EURL in this area, whereas there is one on the feed side."*

The Commission committed to establishing an EURL for food additives in early 2021, and with the increased focus on nano additives:

> *"It is hoped that testing will improve in this area, once the EURL is in place."*

Considering that this was identified as a significant indicator enabling progress to be potentially achieved by control laboratories, clarification was sought from the EFSA specialist on the current status of an EURL for food additives. It was stated that:

> *"There is no EURL specifically for nanotechnology, but the JRC is for feed additives as well as for food contact materials."*

"It is envisaged that the JRC will be designated at the EURL for food additives."

The JRC is the contact point, for queries and they will provide support while member state competent control laboratories who are arranging to get accreditation for this testing. It was acknowledged by the EFSA specialist that:

"Member state competent authorities and their official laboratories will be able to refer to the JRC as the EU wide reference facility."

This will bring a range of benefits for national laboratories such as advice on analytical methodologies, technical expertise, use of specialised equipment and training where relevant.

5) Queried uptake of the infrastructure available in research institutions

In Ireland the competent authority does not have direct recourse to research professionals and the associated infrastructure. However this is not the case with other member states e.g. RIKILT (RIKILT, 2022) has been recognised by the Dutch Accreditation Board for national official control testing and for research and development. The Technological University of Denmark (DTU, 2022) is also another example of this, and as mentioned previously this is similar with ANSES in France (ANSES, 2022), Istituto Superiore di Sanità in Italy (ISI, 2022) and Sciensano in Belgium (Sciensano, 2022). Exploring the possibility for the use of the national academic infrastructure/research facilities as an option for outsource testing was raised as a query. The responses from both the national and European specialists were very much non-committal, the concerns primarily related to accreditation status and the fact that academic research institutions usually do not hold the requisite accredited status. The European Specialist provided reassurances that:

"The Joint Research Centre (JRC) will provide support while MS's competent laboratories are arranging to get accreditation for this testing."

6.4.4 Stakeholder engagement

Engagement between 'state' stakeholders appears to be the established norm for the routine work requirements and technical updates, particularly amongst the Environmental Health Service stakeholders. Regular meetings are also held

between the competent authority, the Environmental Health Officers and the Public Analysts Laboratories, to discuss and plan for future needs. For example the competent authority communicates technical updates:

> *"On various topics to the EHS for dissemination to the relevant personnel and (Relevant stakeholders) receive our (FSAI) back to office reports from all EU WG meetings to keep them abreast of developments at EU level."*

It would appear however that some aspects of lateral communication is either not happening or is not effective e.g. when the national competent control laboratory with responsibility for 'nano' were asked the following question in the preapproved interview questions, i.e. "following the EFSA evaluation and banning of TiO_2 do you envisage that the competent authority (FSAI) will require the relevant Public Analyst Laboratory to carry out analysis of products which potentially have TiO_2 present as an ingredient/food additive? An interesting point of note taken from the written response provided by the laboratory was the statement;

> *"My understanding is that Galway PAL is looking into this."*

This is not a definitive statement, and as outlined earlier the competent authority specialist indicated that the DPAL (Dublin Public Analyst Laboratory) have confirmed that they have the:

> *"Capability to carry out this analysis but they have not completed method development/validation yet."*

It would seem that the competent authority and the national competent control laboratory have some different opinions relating to the designation of this testing. When the Galway PAL were contacted about this testing and they were invited to participate at the interview stage they referred to the Dublin Public Analyst Laboratory as the competent control laboratory for this type of testing.

Building upon the existing stakeholder engagement that appears to be reasonably well established within the EHS institutional setting, and similarly between the competent authority and the control labs, discussions with the different national specialists centred on how stakeholder engagement could become more all-encompassing across the entire stakeholder network. Exploring the potential use of Irish research facilities, either publically funded research facilities (e.g. Teagasc) or

university research facilities, participants were asked their views on whether they think there may be any role for academia, or the research institutions to support method development, validation or possibly technical upskilling. It appears that there is not much engagement between the relevant stakeholders and the research institutions. The national competent authority with responsibility for food does appear to have some level of engagement with the academic institutions, but it does not appear to be on any established or formal basis. Additionally it would seem that there is not much engagement between the control labs and the academic institutions, as stated by one specialist:

> *"I'm not sure how that might work. It might be something that could be explored."*

The competent authority would be aware of research project calls from FIRM (DAFM), Enterprise Ireland and SFI, however it was stated that:

> *"We never see anything to do with nanomaterials, not on the food side anyway."*

Communications with the Food Business Operators (FBO's) is also proceeding, to proactively manage sampling and testing of TiO_2. In this regard the Competent are involved in discussions with a number of large additive manufacturers about the potential impact of TiO_2, as a result of these discussions:

> *"They (FBO's) are certainly aware of the outcome of the TiO_2 decision and the implications of this when it comes into law."*

At the meetings

> *"Manufacturers indicate that there is very little TiO_2 in food in Ireland, with the exception of confectionary and food supplements."*

Discussions regarding how best to prepare for sampling requirements, and how to manage official control testing activities are ongoing, i.e. the competent authority regularly meets with the official control labs (PALs and SL: competent testing labs), and:

> *"This could be considered as pre-market surveillance, 'preparations' for upcoming testing requirements."*

In relation to the potential testing of TiO_2 the competent authority has;

- Provided information on this issue to the FSAI retail forum, industry stakeholders and the Food Safety Consultative Council.
- Presented information on this on their official website (FSAI).
- Discussed the topic at FSAI/EHS-PAL meetings over the last year.
- Discussed the issue of testing with one of the PAL laboratories, and sought insight on the best approaches to do this via the Titanium Dioxide Manufacturers Association (TMDA).
- Held discussions with the Galway Public Analyst Laboratory about getting a method accredited for such testing.

6.5 Suggestions for future policy implications and requirement for future policy development

Specialists were invited to present their opinions on the best approaches to support future policy developments for nanofood

As one participant stated;

> *"I think there should be more communication and discussions, engagement between the different agencies, the authority, the control labs and the sampling officers to agree on priorities and to build capacity for the future. There is not enough of this at the moment."*

> *"If this were to happen we could plan for the future in a more targeted and effective way."*

It is acknowledged that the 'state' stakeholders could benefit from more engagement with the researcher institutions, as stated by one specialist:

> *"I'm aware that academia have been involved in this type of work for a long time now."*

Efforts to proactively manage future food safety requirements have been underway within the FSAI, who have established a national Chemical Safety Regulatory Forum, where:

"One of the ideas for this group was to meet with researchers nationally to discuss potential projects of mutual interest."

Finally suggestions from the EFSA specialist included making suitable advancements within the member state to facilitate monitoring and control testing of 'nano' applications as follows;

"My recommendation would be to focus on two different activities. The first one would be for the detection of nanomaterials or nanoparticles. Obviously the best offer is the training that the JRC is proposing. You do need to have electron microscopy, so that's clear, and they are offering that."

"There is a second issue, in the guidance for particle technical requirements. We are offering other methods to exclude the presence of a fraction of concern. And those methods are relatively simple. Even the screening methods, these are methods that can be easily implemented in a control laboratory, and they do not require electron microscopy."

"I think that I would put the effort in both activities, training for the characterization by electron microscopy, and also to be ready for the screening."

"If it is a case that, in the screening you detect the presence of nanoparticles, then you need to go and maybe get some partnership with the other EU institutions to do the characterisation."

6.6 Summary and Conclusions

As outlined at the beginning of this chapter the main purpose of the 'specialist' interviews was to explore specific issues, opinions and/or misconceptions expressed at the focus group discussions with the intention of providing clarification and if possible definitive answers. This section of the report also provides some suggestions for future policy.

While it is clear that member state competent authorities apply testing requirements based on the legislative requirements, there does not appear to be an immediate requirement for 'nano' food additives (e.g. TiO_2) specific testing at this point in

time, as the competent authority are satisfied that food additives go through an extensive safety assessment before they are even authorized for market supply. Therefore these products are not potentially seen as a high priority concern affecting consumers. Additionally the sampling officers (EHO's) do not have a sampling plan ready for either market surveillance or for routine testing. The accessibility of laboratory testing for this type of analysis is not clear either, with two different PAL laboratories nationally involved in evaluating testing requirements, and neither laboratory has indicated that they intend to apply to include this testing in their scope of accreditation.

The need for TiO_2 (E171) specific testing has been identified in the FSAI NCSP for 2022, and the EHS in general recognize that some form of market surveillance activities will be required to ensure that no products containing E 171 remain on the market following the end of the legislation transitional period, i.e. 7th August 2022.

The perception that the laboratories are not suitably equipped to carry out testing was explored, specifically the need to carry out analysis by electron microscopy, as well the requirement for the use of accredited analysis for control testing. It was clarified by the EFSA technical expert that analysis by electron microscopy was not necessary for TiO_2 determinations, and simple screening techniques outlined in the EFSA guidance document for technical particle requirements should be possible for control laboratories. It was emphasised however that accreditation status is a requirement for official control purposes.

Stakeholder difficulties identified due to the lack of an EURL can be lessened to some extent by the acknowledgement that the JRC in Ispra is the European contact point for queries, and they will provide support while member state competent control laboratories are arranging to get accreditation for this testing.

The potential use of 'public' research institutions e.g. Teagasc, or even university research facilities was explored. There was good level of positive support for this idea. However it was emphasized that this should mainly take the form of high level technical/scientific support for method development purposes, rather than for official control purposes. This would be very beneficial (for those laboratories who do not engage in research activities) at the initial stages of method development and

validation, and indeed if the 'public' research institutions involved did manage to attain accreditation for this testing then they could become the national' designated' laboratory assigned by the competent authority.

The key findings arising from the specialist interviews can be summarised into the following points.

1. The need to establish the priority needs, to plan for imminent testing requirements of TiO_2 and other potential future nanomaterials.
2. Identifying any resources constraints either personnel, equipment, knowledge or skill deficits to ensure that the infrastructure is in place to support legislative testing requirements.
3. The requirement for accredited analysis for control testing and clarity regarding the designation of the national competent control laboratory.
4. The availability of the JRC as the EURL for nanotechnology, and the potential use of such expertise/equipment and technical data by the competent authority and the national control laboratory.
5. The benefits which can be accrued through uptake of the infrastructure available in research institutions, and the potential use of 'public' research institutions for control testing if they attained accreditation for this testing.

The most important suggestions for future policy relate to the need for:

> *"More communication and discussions, engagement between the different agencies, the Authority, the control labs and the sampling officers to agree on priorities and to build capacity for the future. There is not enough of this at the moment."*

If this were to happen planning for future policy development and implementation could be improved significantly involving the multi-organisational stakeholders referenced in chapter 4, figure 4.2.

Suggestions from EFSA to facilitate monitoring and control testing of ‘nano’ applications include the following:

- To avail of the training that the JRC is proposing.
- For monitoring of TiO_2 in particular, refer to the EFSA guidance for particle technical requirements, specifically the methods to exclude the presence of a fraction of concern.
- Screening methods can be easily implemented in a control laboratory, and they do not require Electron Microscopy.

➢ If the presence of nanoparticle is evident from the screening stage the characterization and confirmation will be required using electron microscopy.

6.7 References

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7.1 Prelude and abbreviations

The first portion of this chapter is partially reproduced from a paper submitted by the report author to Talanta: The International Journal of Pure and Applied Analytical Chemistry, a review of Nano-characterisation techniques for customs laboratories. As a review, the paper outlined the basic concepts of nanotechnology and accepted characterisation techniques. Crucial to the review is the notion of enforcement of legislation and policy. The later aspects covered in the chapter focus on the Irish capacity to deliver regulatory supports and standardised methods in the area of Nano characterisation. This will outline, the key parameters and methods suggested by the EFSA for food, and will review the requirements for official control laboratories to meet the needs for enforcement within the food and feed sector. Finally, a series of proficiency tests carried out as part of an EU wide collaboration, and an Ireland based PT scheme comprising of academic institutions involved in aspects of Nano characterisation is presented, which the author participated in and facilitated through TU Dublin.

Commission Regulation (EU) 2022/63 effective from 14th January 2022 legislation indicates that titanium dioxide (E 171) can no longer be authorised for use as an additive in foods (European Commission, 2022), consequently member states will be required to have suitable characterisation techniques in place within appropriately accredited laboratories, to facilitate control testing of the banned substance. The challenges identified here will thus play a crucial part in closing any infrastructure gaps going forward.

Abbreviations: Atomic Absorption Spectroscopy (AAS), Atomic force microscopy (AFM), Dynamic light scattering (DLS), Energy Dispersive X-ray spectroscopy (EDX/EDS), Field Flow Fractionation (FFF), Fourier Transform Infrared Spectroscopy (FT-IR), Inductively Coupled Plasma – Mass Spectroscopy (ICP-MS), Inductively Coupled Plasma – Optical Emission Spectroscopy (ICP-OES), Particle tracking analysis (PTA), Scanning electron microscopy (SEM), Scanning transmission electron microscopy (STEM),Scanning transmission X-ray microscopy (STXM), Single particle spICP-MS (spICP-MS), Small angle x-ray scattering (SAXS), Transmission electron microscopy (TEM), Ultra Violet-Visible Spectroscopy UV/VIS, X-ray Diffraction (XRD), *X-ray fluorescence* (*XRF*).

7.2 Introduction

7.2.1 Nano: the technology and the materials

Nanotechnology is the manipulation, application, and study of matter conducted at the nanoscale (one in a billion/nanometer/10^{-9}). Ultimately, it is the ability to control and restructure matter at the atomic and molecular level, to create materials, devices and systems, which exhibit different properties and functions at the nanoscale, as compared to those of the bulk material (Roco, 2011). Nanotechnology is an enabling technology, facilitating new product design, enhancing existing products or processes. It is multidisciplinary in nature, with numerous applications in the fields of science, engineering, and technology (Porter and Youtie, 2009).

The most abundant commercial products emerging from nanotechnology innovation are engineered nanomaterials. Nanomaterials are the largest "products" produced from nanotechnologies, as nano-scale particles, tubes, rods, or fibres. Nanomaterials are normally defined as being smaller than 100nm in at least one dimension (Turney, 2009). The European Commission (EC) *Recommendation on the definition of a nanomaterial* defines a nanomaterial as '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' (European Commission, 2011).

7.2.2 Nanotechnology and nanomaterials in the consumer domain

In the early 2000's significant progress was made translating nanotechnology from the laboratory towards the production of practical applications and consumer products that are now widely available in the market place. Applications of nanotechnology include, but are not limited to the following:

- Appliances (Heating, cooling and air; large kitchen appliances; laundry and clothing care)
- Automotive (Exterior; maintenance and accessories, coatings)
- Goods for Children (Basics; toys and games)
- Electronics and Computers (Television, video/cameras, computer hardware/display, mobile devices)

- Food and Beverage (Cooking; food; storage; supplements)
- Health and Fitness (Clothing; cosmetics; filtration; personal care; sporting goods; sunscreen)
- Home and Garden (Cleaning; construction materials; home furnishings; luxury; paint)

(Project on Emerging Nanotechnologies, 2013).

In Europe revenue from nanomaterials was valued at more than '€2.2 billion in 2015 and is expected to reach €8.2 billion by 2022 (Inshakova and Inshakov, 2017). As the number of nanotechnology applications and products continues to grow, with many novel products currently at developmental stage it is important that regulatory policies are in place to manage and control applications of nanotechnology. Regulation is necessary for the control of economies, to facilitate global trade and for the protection of society. It is applied through the creation of "rules" for citizens, businesses, governments and society. The rules 'underpin the markets, protect the rights and safety of citizens and ensure the delivery of public goods and services' (OECD, 2011). To date, there is no specific legislation in the European Union (EU), which is solely dedicated to the regulation of nanomaterials although Commissions concerns about TiO_2 has potentially brought about the beginnings of change. To date it has been considered that existing sector specific legislation, covering materials in the macro form is generally considered sufficient to cover applications of nanotechnology/nanomaterials in current use (Amenta, *et al*, 2015). While some sector specific legislation can be applied to some applications of nanotechnology, which are currently available to consumers, this is not the case for all applications of nanotechnology. A review of current legislation was given in chapter 1 Section 1.11 and is available for reference in Appendix 1 Table A2). Of course vital to enforcing a legislative regime is the ability of risk assessment agencies and enforcement officers to have access to expertise and facilities, to correctly identify and characterise materials for enforcement. The preliminary results from the survey outlined in chapter 4 indicated a number of concerns amongst these stakeholders with respect to access. This chapter looks to investigate if Irish risk assessment agencies, namely the FSAI for food, do indeed have appropriate access to such facilities and expertise, if such access is suitable for regulatory purposes, and if not, how it could be made available. This is in keeping

with the research questions outlined in chapter 1. It will also ascertain and investigate challenges to standardising nano-characterisation methodologies across multiple laboratories.

7.2.3 Characterisation of nanomaterials

Nanotechnology tools and techniques allow a great degree of control over matter at the molecular level. By using nano-scale techniques and developing nano specific methodologies, we are developing systems that can measure 'Nano'. Regulatory controls and measurement of applications of nanotechnology will be dependent upon the application of knowledge and skills relating to the use of different types of analytical technology, applying various tools of metrology that can adequately define the physiochemical and functional properties of materials at the nanoscale.
In general, it is recognised that characterisation of nanomaterials requires the determination of a more comprehensive range of properties compared to those required for regular authorised chemicals (Rasmussen *et al*, 2018, Peters *et al*, 2011). Sample preparation, separation and characterization of nanomaterials is considerably challenging (Peters *et al*, 2011). While many technologies and analytical approaches are described in literature, standardised methods for the detection and characterisation of nanomaterials are limited in many respects. In addition, these methods may not be suitable for the nano form of the chemical, and often more than one technique will be needed to confirm the various properties that are required to be measured. Instrumental capability to determine various materials/matrices at the nanoscale level has not been sufficiently demonstrated, or validated to date, and current test methods are often based on conventional methodologies, which may not be appropriate at the nanoscale.

In recognition of the importance of adequate testing procedures, and the need for harmonization within the scientific community, various regulatory authorities, working groups and organisations, and research institutes have set out to establish comprehensive approaches and reviews of suggested methodologies. These have been published with recommendations relating to the key properties required for the characterisation of nanomaterials (Rasmussen *et al*, 2018). Table 7.1 was assembled from many of these published reports using data and word mining to identify the most common properties proposed. The EU funded 'Gracious' research

programme for nanomaterial characterisation, a framework and strategy for risk analysis, identified the following physicochemical properties: chemical composition, crystallinity, particle size, particle shape, surface chemistry and specific surface area (SSA), which are considered to be "priority properties"; for regulatory purposes, when applying specific requirements for characterisation of nanoforms of a substance under the REACH regulation (Comandella *et al*, 2020). Table 7.1 also shows the most suitable techniques used to measure the aforementioned prioritized properties.

Table 7.1: Physio-chemical property and Instrumentation

Property characterised	**Suitable characterisation techniques**
Elemental Composition/mass concentration,	AAS, ICP-OES, ICP-MS, UV-Vis, XRF, EDX, FTIR
Crystallinity	XRD, STEM, Raman
Particle Size (structural properties)	TEM, XRD, DLS, SEM, AFM, spICP-MS, UV-Vis,
Size distribution	spICP-MS, SEM
Particle Shape	TEM, AFM
Surface area, specific surface area (SSA)	BET, liquid

Literature presents numerous lists of prioritised properties (Tiede *et al*, 2008, Mourdikoudis *et al*, 2018, Modena, *et al*, 2019, Comandella *et al*, 2020). However EU legislation with respect to food still has to denominate priority properties beyond size and surface area. Table A2 Appendix 1 outlines the REACH and EC specifications for nanomaterial testing and defining properties for general nanomaterials. As aforementioned in chapter one the EU definition focuses more on aspects of regulation and general risk assessments than on any scientific understanding.

7.2.3.1 Measurement of nanomaterials

Table A4 (Appendix 6) presents an overview of the potential suitability of some of the more commonly recommended analytical technologies of relevance for the

physio-chemical characterisation of nanomaterials, for regulatory authorities, or indeed for use by EU customs laboratories. Some specialized techniques with multiple end points are included in this review, as these techniques expand upon the range of information available to give greater awareness of specific nanoparticle properties. Given the large variety of technology available and the potential use of different "hyphenated" techniques, this review does not provide an extensive list of all the available technology for nanoparticle characterisation. The aim of this review is to provide guidance for laboratories, using techniques that may be commonplace in many regulatory laboratories. Table A4 (Appendix 6) provides a snap-shot of the key techniques with aspects such as detection limits quoted for the most common commercial specifications.

7.3 Characterisation Capacity

7.3.1 European Food Safety Authority (ESFA) key parameters

The European food safety authority is an independent scientific body that provides advice on food related issues to the EU commission. A number of working groups established by EFSA have investigated potential approaches to nanomaterial characterisation in food matrices, with a focus on risk assessment (EFSA Scientific Committee, 2009, EFSA Scientific Committee, 2011). EFSA have summarised much of the work of these working groups via a set of proposed evaluation steps as shown in figure 7.1.

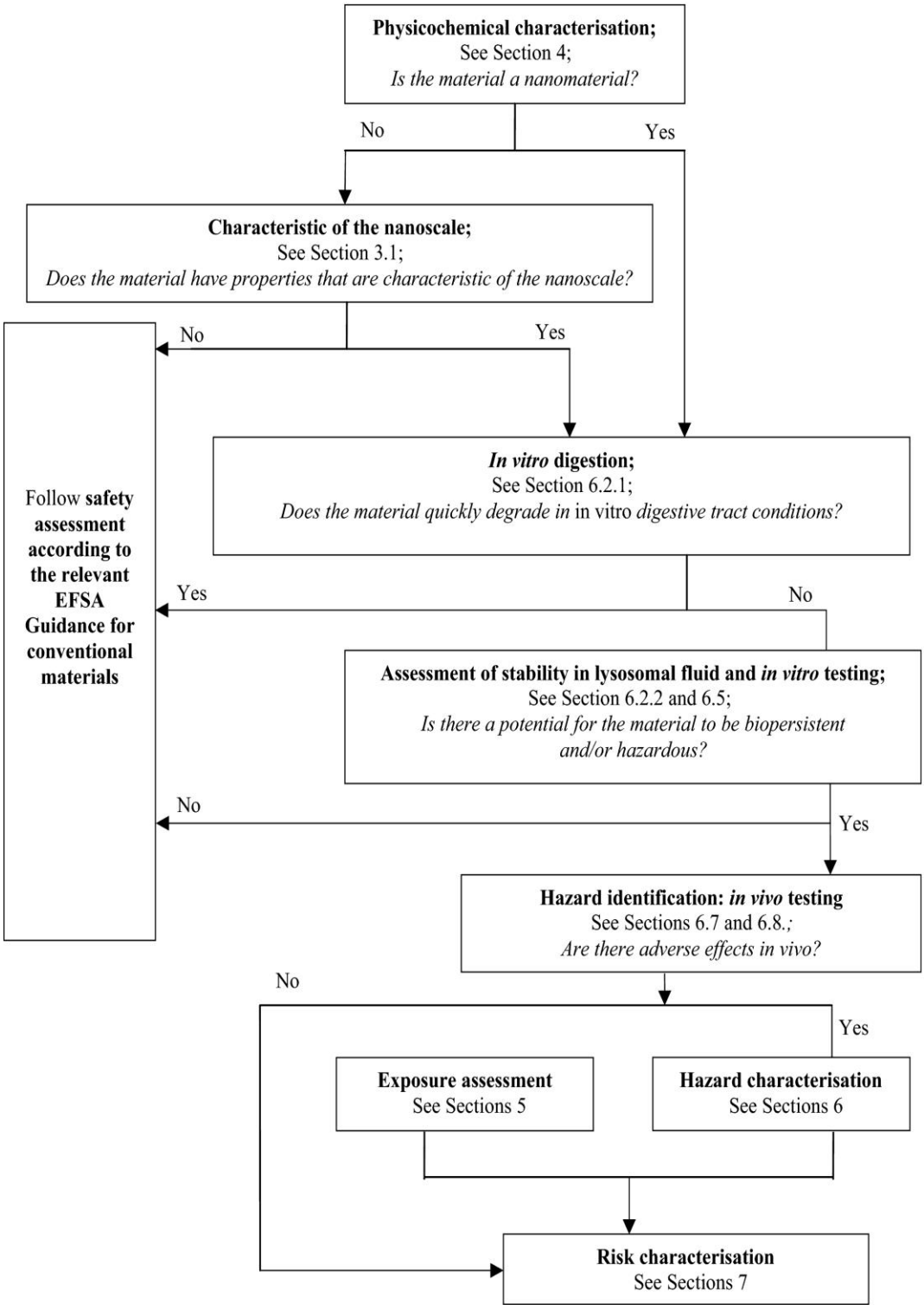

Figure 7.1: Schematic outline for risk assessment of ingested nanomaterials for human and animal health, focussing on hazard characterisation (Hardy *et al*, 2018)

From a regulatory enforcement point of view step one and two in figure 7.1 are crucially important. However the guidance document merely suggests that 'adequate characterisation of a nanomaterial will generally require multiple

methodologies' it further states that 'the best suited technique depends largely on the material characteristics'. The guidance recommends that standardised methods should be used if available, but in itself does not recommend any specific method (Hardy *et al*, 2018). However, the EFSA nano-project consortium 2021 has proposed that a complete analysis would include a screening process based on the 'Nanotechnologies –Guidance on detection and identification of nano-objects in complex matrices', which was developed in the context of CEN/TC 352 (CEN, 2018). The analysis initially requires a screening step to determine the presence of particles in food matrices, typically using descriptive EM and/or spICP-MS if applicable. This is followed by the measurement of the size and shape distributions of the particles by quantitative EM, and the subsequently determination of the concentration of the fraction of nanoparticles by ICP-MS and spICP-MS. In addition, it is strongly advised that all measurements be confirmed by a second technique such as DLS for particle size.

EFSA's role is to provide scientific advice and their opinions are not legally binding. However, much of their advice does inform EU policy in food and food safety, and it is typically accepted by the commission. In light of EFSA's revaluation of several known nanofood additives' for example TiO_2, SiO_2, nano-silver and nano-cellulose, it is therefore crucial that the facilities and infrastructure necessary to comply with potential legislation are identified nationally, and where necessary appropriate planning strategies should be developed to prevent any deficiencies.

7.3.2 Irelands Capacity to characterise Nano food for legislative enforcement

The Official Control laboratory service in Ireland includes nineteen chemical and microbiological laboratories, eight of which are classed as Irish National Reference Laboratories (NRL), under the auspices of different Competent Authorities. The specific requirements for official laboratories and national reference laboratories (NRLs) are outlined in Regulation (EC) No. 2017/652 (European Parliament and Council, 2017). The list of Irish NRLs and official laboratories designated under the regulation for use by the FSAI are available at https://www.fsai.ie/enforcement_audit/laboratories/labs.html#official_labs.

In Ireland the Department of Agriculture, Food and the Marine, the Department of Health and relevant government departments have designated the NRLs for official controls of feed and food law, animal health and animal welfare rules. Official control laboratories and NRLs are required to be accredited to ISO 17025, for relevant parameters, for which the laboratory will maintain competence. In addition, they are required to meet all obligations under Regulation (EC) No. 882/2004 (European Parliament and Council, 2004) with respect to collaboration with the European Union Reference Laboratory (EURL) in their area of competence. They are required to ensure the dissemination of analytical test methods, results of analysis and to provide technical guidance and appropriate advice on the same to the competent authority, and to other official laboratories. Interestingly, they also are required to notify the competent authorities in a timely manner of any deficiencies, gaps and overlaps in sampling programmes in official laboratories, which may affect the outcomes of official control testing. These laboratories can only formally report to the competent authority on the responsibilities for which they hold accreditation status, with respect to a specific individual test, or group of tests. At present the Irish National Accreditation Board (INAB) does not list any Irish laboratory who are authorised for testing nanomaterials in food. Furthermore, no laboratory has ISO 17025 authorisation for electron microscopy analysis, nor for particle sizing using DLS. The ICPMS technique is authorised in several laboratories for metal analysis, but there is no specific mention of nano-metals or nanomaterials included, indeed the processes and methods for determining bulk materials and nano materials differ significantly in this regard. In addition, private or other laboratories can be subcontracted to carry out this work, provided they also hold ISO 17025 accreditation status. However, again it appears that nationally there are no laboratories who are accredited for nano- characterisation.

In situations where no official national control laboratory can provide the service required, the regulation stipulates that an alternative laboratory can be designated from another EU-MS official control laboratories. Article 42 of the regulation provides for a temporary derogation from the conditions of the mandatory accreditation for official laboratories, if no laboratory can provide the service, and/or if the method is a new required by way of Union rules. Nevertheless, the

temporary designation is still subject to holding ISO7025 accreditation status. This subsequently restricts Ireland to seeking the assistance from other MS, if the need to enforce nano legislation should arise.

Nationally however many private laboratories and university laboratories have ISO 9001:2015 Quality Management Systems in place. ISO9001, is a global standard for quality management of resources and processes, and is a general standard for any industry. Accreditation to an ISO 17025 standard is more specific and detailed for testing and calibration laboratories. However similarities can be drawn with the ISO9001 standard regarding the management system requirements of ISO 17025. In other words, the minimum management requirements are very similar to those found in ISO 9001:2015. As ISO 9001:2015 is applicable across several sectors it has a broader appeal to generic laboratories looking for accreditation. However, on its own it is not sufficient to comply with Regulation (EC) No. 882/2004, and hence it cannot be used for enforcement purposes. Nationally some of the top exchequer funded research and academic centres hold 1SO19001 accreditation status, with facilities and expertise capable of characterising nanomaterials to the highest standards. Examples of such centres include Enterprise Ireland (EI) gateway centres, Science Foundation Ireland (SFI) research centres and Higher Education Authorities (HEA) Research Institutes. Of particular note, with regards EM measurements is the Centre for Microscopy and Analysis in Trinity College Dublin (TCD), the Materials Surface Science Institute (MSSI) in University of Limerick (UL), and the CREST centre in TU Dublin. All of which boost extensive material characterisation and microscopy facilities in line with the EFSA guidance documents, and they hold ISO19901 accreditation status. In addition to accreditation however, the importance of participation in proficiency testing (PT) schemes is also crucial, to verify the test methodologies and to provide a degree of standardisation and traceability of results. In chapter 4 it was noted that approx. 80% of academics surveyed indicated that they had not participated in any national or international programmes/projects relating to the development of nano-standards or proficiency testing. While the numbers surveyed were low, it is not surprising that the majority of academics have not participated in such PT tests, as inter laboratory test are typically coordinated and delivered by a single person in an organisation.

7.4 Proficiency testing

Despite holding appropriate accreditation status it is vitally important to acknowledge the potential for variability in the characterisation process, and the importance of inter-laboratory confirmation of results. Proficiency testing offers an avenue for laboratories to establish confidence in their methodology and their procedures, which from a purely academic point of view is potentially more important than accreditation. Along with validation and accreditation, proficiency testing is a requirement of the EU Additional Measures Directive 93/99/EC (European Commission, 1993) and is required in ISO17025.

7.4.1 EU wide PT schemes

As part of the work for this chapter, participation in a number of EU wide PT schemes which were coordinated by RIKILT Wageningen University was undertaken, combining the infrastructure of the State Laboratory and TU Dublin. The work assignment was directed by the thesis author. The purpose of this undertaking was to demonstrate that a national collaborative approach, using infrastructure in both an official controls laboratory and a university laboratory could potentially facilitate a complete nano-analysis, as directed by EFSA, and that it could meet the highest international standards. Indeed, it is not uncommon for risk assessment agencies across Europe to fully engage with academic institutes in; research projects, method development, and elements of characterisation for enforcement purposes. For example the University of Wageningen Food Safety Research conducts high-quality independent research into safe and reliable food, working mainly for the Netherlands Food and Consumer Product Safety Authority (NVWA). Similarly ANSES in France has strong links across the French university sector, and it is emerging as a significant research body in Horizon Europe research projects. The BFR in Germany also has active research dedicated laboratories, and nurtures close contacts with the academic sector with exchange of experts becoming increasingly important.

The proficiency testing scheme coordinated by RIKILT Wageningen University as part of the EU ACEnano project focused on specific predetermined nano-samples, predominately commercial gold nanoparticles from NanoCompsix

(www.nanocomposix.com), which were prepared and subsequently tested by multiple laboratories across Europe using DLS, spICP-MS, and EM.

7.4.1.1 DLS proficiency test

Sixteen laboratories participated in the DLS proficiency test. Samples were produced blind from a NanoComposix citrate stabilised gold nanoparticle suspension. Three batches were produced and they were split between the participating laboratories. The batch specification provided were:

Batch A contained single sized spherical gold colloids <50nm

Batch B contained single sized spherical gold colloids >50nm

Batch C contained a mixture of two differently size spherical gold colloids.

Upon receipt of the samples they were immediately refrigerated at 4^{o}C, to preserve the particle stability. Prior to sample analysis particles were equilibrated to room temperature over a 30 minute period. Samples were then sonicated for 30s, they were diluted 1:10 with ultrapure water, and were subjected to further sonication. The standard default, in-house procedure was used to determine the particle distribution, which briefly included setting the backscatter angle to 173^{o}, refractive index of 0.3, and absorption of 3.3. A short measurement period of 3s was used, with 50 repetitions. All measurements where performed in triplicate and a calculated average result was reported.

DLS proficiency test results

The results of the in-house analysis indicated that sample A was 43.99 ±0.2nm with a poly dispersion index (PDI) of 0.17 ±0.01nm. Sample B was 176.0 ±0.5nm with a PDI of 0.16±0.03nm. While sample C, consisting of a mixture of particles was found to be 137.7±0.3nm and 34.52 ±0.3nm with a PDI of 0.22±0.08. The data obtained from all participants is shown in table 7.3. TU Dublin and the State Laboratory are labelled lab 1.

Table 7.3: DLS proficiency test data obtained from RIKILT Wageningen University as a proficiency test collaborator

Lab	Batch A		Batch B		Batch C Large		Batch C Small	
	Result	z_{ai}*	Result	z_{ai}*	Result	z_{ai}*	Result	z_{ai}*
1	**43.99**	**0.26**	**176.00**	**-0.46**	**137.70**	**-0.99**	**34.52**	**-1.53**
2	41.19	-0.26	181.30	-0.17	200.60	1.25	47.60	0.70
3	41.83	-0.11	178.60	-0.32	165.40	-0.27	39.93	-0.43
4	47.84	0.84	180.02	-0.24	158.60	-0.45	42.43	0.05
5	40.94	-0.32	197.63	0.39	8.61	-4.36	43.36	0.18
6	32.00	-2.34	176.00	-0.46	176.00	0.01	35.00	-1.43
7	42.30	0.00	247.70	1.89	268.70	4.67	54.30	1.54
8	48.72	0.97	186.79	0.07	184.21	0.43	37.39	-0.94
9	38.60	-0.87	197.10	0.38	162.80	-0.34	21.40	-4.20
10	43.00	0.11	185.00	0.02	210.00	1.72	49.00	0.87
11	42.77	0.07	181.50	0.21	198.70	1.15	47.90	0.74
12	40.99	-0.31	189.00	0.14	175.30	-0.01	42.58	0.07
13	52.90	1.60	184.50	0.00	99.60	-1.98	14.30	-5.65
14	51.00	1.31	182.00	-0.13	-	-	-	-
15	40.80	-0.35	178.00	-0.35	182.00	0.32	46.60	0.57
16	41.80	-0.02	176.80	-0.41	193.10	0.87	47.60	0.70

*** Zai = accuracy Z-score taking into account the uncertainty of the consensus value**

The lowest value reported for Batch A is 32nm and 52.9nm is the highest. Using robust statistic the median value is 42nm (rounded) which represents the consensus value i.e. as it is a random distribution of particles, this consensus value represents the most probable distribution maximum. Robust statistical methods for the data analysis were used as traditional statistics assumes that the data comprises of a random sample from a normal distribution. However, analytical data often departs from normal distributions, and this is particularly true for proficiency tests. Proficiency tests results are often heavily tailed, containing a higher than expected proportion of results far from the mean, and can often contain outliers, resulting in a non-normal distribution. Robust statistical methods are optimised for analysing data which is drawn from a wide range of probability distributions, but especially for distributions that are not normal. The specific statistical approaches are outlined in the methods chapter.

Using the robust statistical approach a modified performance or accuracy score Z_{ai} for each measurement was determined. The accuracy score Z_{ai} was calculated for

each participant with a correction made for the instability (ISO-13528 was employed to do this). To determine if the calculated accuracy score was satisfactory, the following limits were set:

Table 7.4: Classification of accuracy score based on robust statistics

$\|z_{ai}\| \leq 2$	Satisfactory
$2 < \|z_{ai}\| < 3$	Questionable
$\|z_{ai}\| \geq 3$	Unsatisfactory

The scores were modified to accommodate particle instability issues, as it was reported by the proficient test coordinators that each batch experienced an increase in particle size, due to aggregation over the course of the trial. Batch A was reported to have a maximum increase of 12% while Batch B was 15%. The mixed sample indicated a potential 15% and 19% for the smallest and largest particles respectively. The TU Dublin analysis for batch A had an accuracy score of 0.26. A score of less than 2 is deemed statistically satisfactory, with a score approaching zero being optimum. The accuracy is gauged based on the consensus value. Similarly for batch B the TU Dublin analysis had a calculated accuracy score Z_{ai} of 0.46. Although it was 8nm smaller than the consensus value it still was within the 15% expected for the instability in the particle size. In contrast, batch C posed a number of analytical issues stemming from the mixed particle size, and the higher potential for particle instability across the test period. Unsurprising then, the PDI was high for this bath reflecting the size mixture. Indeed all participants in the proficiency test reported increases in the PDI for Batch C, and laboratory 14 reporting no discernible result in the nano-range. Nevertheless TU Dublin again performed well with a calculated accuracy value of less than 2. In comparison to other participating laboratories the TU Dublin scores can be classed as being optimal across the proficiency test.

Applying the same accuracy calculations to all participating laboratories it can be seen that ten participants returned optimal results for all batches, suggesting that almost 40% of participating laboratories failed to achieve a satisfactory score across all batches. This clearly highlights concerns with respect to reproducibility, and the ability to fully standardise via an inter-laboratory comparison of DLS measurements of nanoparticles. Interesting almost all of the questionable Z_{ai} scores

were obtained for the mixed particles of batch C. This may reflect a higher degree of difficulty in analysing matrices containing more than one particle size, which is a worrying prospect for nanofood analysis where there would be significantly more than two distinct particle sizes in samples for analysis. Nevertheless, a clear positive outcome, is the fact that academic laboratories performance can be comparable to that of accredited laboratories, such as the laboratory at RIKILT Wageningen University, which coordinated the inter-laboratory PT scheme. This illustrates that an academic laboratory could provide a support mechanism to supplement the national infrastructure.

7.4.1.2 Single particle ICP-MS proficiency test

Twenty six laboratories participated in the spICP-MS proficiency test, to determine particle diameter and the particle number concentration of an unknown gold nanoparticles suspension. The particle number concentration is particularly important with respect to EU definitions as described in Appendix 1 Table A2. As with the DLS proficiency test the report author coordinated the State Laboratory and TU Dublin response. In this case the sp-ICP-MS, facilities of the State Laboratory where used. The NanoComposix citrate stabilised gold nanoparticles used in the DLS study were used again here. However, for this study only one single sample was prepared with an unknown size given to participants. Homogeneity and stability studies were undertaken by the coordinators, and it was determined that the samples were sufficiently homogeneous for the proficiency test. In terms of the stability it was observed that the particle size had a statistically significant decrease in size by 6%. Therefore, for this work this decrease was included in the determination of the accuracy score, as was done for the DLS proficiency test. However, the coordinators also reported a particle per litre difference over the period of the proficiency test, indicating an 11% increase. The change could not be incorporated into the accuracy score, as no additional details were provided with respect to the aggregation state, or the particle stability with respect to the zeta potential. It was therefore difficult to ascertain if the reported increase was due to environmental conditions of the coordinators stored particles. The NanoComposix supplier however reports no such increase for the product once appropriately stored.

Upon receipt of the sample it was stored at 4^{o}C in a refrigerator. For analysis the sample was allowed to equilibrate for 30 minutes to reach room temperature. For spICP-MS the sample was diluted using tri-sodium citrate buffer 1 mM in ultra-pure water. An ionic gold standard and reference material was used for calibration and determination of transport efficiency. The standard operating procedure of the State Laboratory was used for choosing the dwell time, determining the transport efficiency, and for all subsequent calculations of sample parameters. The standard operating procedure employed was based on ISO/TS 19590: 2017 (ISO, 2017).

spICP-MS proficiency test results

All laboratories reported results for the particle diameter, with the lowest value reported as 30.2nm and the highest value as 80nm. The consensus value was 61nm, with a robust standard deviation of 5.3nm. The accuracy score Z_{ai} was calculated for each participant with a correction made for the instability.

Table 7.5 shows the reported results from each participant. The State Laboratory measurements are labelled lab 1 in table 7.5. It can be seen that the reported diameter for the particle diameter was 65.24nm, and an accuracy score of 0.65 was achieved, which, with respect to the accuracy criteria given in table 7.4 can be deemed to be a satisfactory result. In addition, the reported diameter is within the expected 6% increase of size over time. In comparison to the other laboratories one participant had a questionable result i.e. lab 6. In addition, lab 8 and 23 were deemed to have reported unsatisfactory particle diameters, based upon the calculated accuracy score. This represents 88% success rate for satisfactory reporting of the spICP-MS data on the particle size.

In terms of the particle number concentration, the results were more mixed. The coordinators reported that seven laboratories where asked to redo or check their data as it appeared that dilution factors were not appropriately applied. Furthermore one laboratory was not in a position to determine the particle number due to instrumentation restrictions. Indeed much of the variation may be due to algorithms and software used to perform the calculation, particularly on older spICP-MS instruments.

Table 7.5: spICP-MS proficiency test data obtained from RIKILT Wageningen University as a proficiency test collaborator.

Lab code	**Particle diameter in nm** Census value 61nm		**particle number concentration per litre** consensus value 1.44 x10^{13}particles/l	
	Result (nm)	**z_{ai}*score**	**Result (µg/kg)**	**z'$_a$*score**
1	**65.24**	**0.65**	**1.82x10^{13}**	**1.14**
2	62.40	0.18	1.45 x10^{13}	0.03
3	59.52	-0.25	1.50 x10^{13}	0.19
4	61.00	-0.04	2.19 x10^{7}	-4.35
5	65.00	0.61	1.57 x10^{13}	0.39
6	74.00	-2.08	1.73 x10^{7}	-4.35
7	64.00	0.44	1.10 x10^{13}	-1.03
8	80.00	-3.05	7.61 x10^{12}	-2.05
9	55.50	-0.81	2.34 x10^{13}	-2.72
10	60.00	-0.18	1.90 x10^{13}	1.39
11	61.60	0.05	1.27 x10^{13}	-0.51
12	58.16	-0.44	1.60 x10^{13}	0.48
13	63.00	0.28	4.43 x10^{7}	-4.35
14	68.80	1.23	1.01 x10^{13}	-1.30
15	52.00	-1.31	2.00 x10^{13}	1.69
16	57.00	-0.60	4.10 x10^{13}	-8.04
17	60.20	-0.15	1.34 x10^{13}	-0.30
18	61.60	0.05	1.70 x10^{13}	0.79
19	61.25	0.00	1.61 x10^{13}	0.51
20	66.00	0.77	1.14 x10^{13}	-0.92
21	49.90	-1.60		
22	63.00	0.28	6.73 x10^{12}	-2.32
23	30.20	-4.37	9.78 x10^{13}	-25.20
24	54.00	-1.02	2.10 x10^{13}	1.99
25	60.00	-0.18	1.69 x10^{13}	0.76
26	66.40	0.84	7.98 x10^{12}	-1.94

***Zai = accuracy Z-score taking into account the uncertainty of the consensus value, Z'a = accuracy Z-score**

Interestingly, for the particle number concentration there are 8 questionable or unsatisfactory results. Overall this reflects the difficulty of performing spICP-MS analysis, which requires additional sample preparation, with appropriate instrumentation with software add-ons. The State Laboratory and indeed most official control laboratories have state of the art spICP-MS systems which are maintained in accordance with ISO-17025. In contrast, the ICP-MS systems in academic institutions may not be as well managed or maintained. It is speculated that this may have been a contributing factor to the variation in the data. Indeed the

three laboratories with unsatisfactory results for the reported particle size were among the eight laboratories with questionable or unsatisfactory results for the particle number concentration, potentially indicating that operator inexperience, sample handling errors, or instrumentation variations may have played a significant part in the proficiency test results.

The State Laboratory reported a size of $1.8x10^{13}$ µg/litre, with a calculated accuracy score Z_{ai} of 1.14 thereby meeting the satisfactory criteria for both properties reported. Overall only seventeen laboratories managed to achieve a satisfactory score when accessing both the particle size and the particle number concentration properties. In order words 35% of laboratories failed to achieve successfully results using spICP-MS in the inter-laboratory comparison for this gold nanoparticle.

7.4.1.3 Electron microscopy (EM) proficiency test

The final proficiency test which TU Dublin and the State Laboratory participated in was analysis using electron microscopy. EFSA and the European Union have deemed electron microscopy to be an essential instrument for characterization of nano parameters, as well as it being specified in other international guidelines (EFSA Scientific Committee, 2011, Hardy *et al*, 2018). Indeed, many of the test protocols for nano-characterisation explicitly specify that some form of electron microscopy should be used to confirm particle size and distribution (Williams *et al*, 2006). EM can cover the entire nano-range, and with image analysis it can provide a high enough resolution to detect most types of nanoparticles, providing individual particle sizes, particle distributions, and information regarding particles aggregation state and shape. However, time and cost-inefficiency are the main difficulties generally associated with characterization of nanomaterials by EM, plus many control laboratories do not have direct access to such systems. In this proficiency test participants were required to measure particle size using TEM or SEM for three different samples. Sample 1 was a powdered sample of BaSO4 particles with a particle size in the range of 20-100nm. Sample 2 was a powdered sample of TiO2 particles with a particle size in the range of 100-200nm. Sample 3 was a suspension of gold particles with a mass concentration of approximately 100 mg/L and a particle size in the range of 40-100nm.

The SEM facilities in TU Dublin were used to carry out the TU-Dublin-State Laboratory collaboration for this proficiency test. The powdered samples demonstrated no particle instability during the test period, whereas the gold suspension had the same instability profile as the NanoComposix sample provided for the spICP-MS proficiency test.

Upon receipt, the powdered samples were stored at room temperature in the dark, while the gold suspension was store at 4°C in a refrigerator. The suspension of gold particles were allowed to equilibrate to room temperature prior to analysis, and were subsequently sonicated for 1 min prior to use. The powdered samples were prepared as a dispersion of the particles in ultrapure water to transfer to the SEM-grid. The samples were then analysed and the primary particle sizes reported as the Feret min diameter, defined as the distance between the two parallel planes restricting the object perpendicular to its minimum dimension. In the case of the TU Dublin system the diameter was measured using a semi-automatic approach based on the grey values. A size distribution of at least 250 particles per sample was sized to produce a mean particle size. CEN/TS 17273, "Nanotechnologies - Guidance on detection and identification of nano-objects in complex matrices" was used as a guidance document for the analysis.

In total twenty two laboratories participated in the study, contributing results of the diameter obtained from either TEM, SEM or TSEM analysis.

Electron Microscopy Proficient Test Results

The data obtained from all participants using Electron Microscopy for the PT scheme is shown in table 7.6. For barium sulphate the largest value reported was 68.7nm, with the lowest value of 20nm reported as the TU Dublin measurement. The consensus value for barium sulphate was 34nm with an uncertainty of 6.2nm. The uncertainty placed the reported diameter just outside of the target standard deviation of 20%. However, the robust standard deviation which was calculated as 15nm resulted in a calculated accuracy score Z_{ai} score of -1.78, which was deemed to be satisfactory (i.e. $z_{ai}<2$). However this also highlights one of the difficulties of measuring a wide distribution of particles, and using statistical analysis to subsequently justify the validity of the result. Indeed many of the accuracy scores while less than two did indicate a higher degree of variation. Only one laboratory

returned an unsatisfactory result, i.e. lab 12 with a diameter of 68.7nm and an accuracy score of 4.2. The solubility, and the dispersibility of barium sulphate in ultrapure water for drop casting onto the grid could have played a key factor in these reported results, as nano barium sulphate is not easily dispersed in water. This was confirmed by measuring the zeta potential of barium sulphate in ultra-pure water as +1.52±1.1 mV. It was also noted that barium sulphate readily agglomerated in aqueous media, again confirming its poor dispersibility. As a result particle handling in this proficiency test and sample preparation prior to performing the analysis is crucial and very dependent upon the operator.

7.4.2 Ireland PT scheme

Following on from the successful participation of TU Dublin in the EU wide it was decided to set up a national PT scheme to determine the capacity and the capability nationally. Participation in this PT scheme involved the use of the infrastructure in seven Irish universities. Unfortunately the national competent control laboratory and other control laboratories were not involved in this PT scheme for reasons due to lack of resources, (methods, equipment, personnel), or due to other priority testing requirements. The PT scheme was facilitated by TU Dublin and the work assignment was directed by the thesis author. Participating laboratories were supplied with three spherical colloid silver nanoparticles suspensions (aqueous). Testing requirements involved estimating the particle size distribution and reporting the average size. Measurements using either DLS and/or electron microscopy (EM) (SEM, STEM or TEM) was a stipulated requirement.

Samples: The samples provided for testing by DLS and/or EM were as follows;

> Sample A: An aqueous colloidal suspension of spherical silver nanoparticles stabilised with citrate. Particle mass concentration is approximately 100 mg/L. Typical particle size distribution is <50nm.
>
> Sample B: An aqueous colloidal suspension of spherical silver nanoparticles stabilised with PVP. Particle mass concentration is approximately 100 mg/L. Typical particle size distribution is <100nm.

Sample C: An aqueous suspension of spherical silver nanoparticles uncoated. Particle mass concentration is approximately 100 mg/L. Typical particle size distribution is <50nm.

Participants were advised on the appropriate storage conditions and the measurement procedures for DLS and TEM/SEM. (Refer to Appendix 7 for Inter-laboratory study for Irelands nano-characterisation capability procedures and reporting instructions).

Robust statistical methods were utilised for data evaluation of results in a similar manner to the EU PT scheme.

8.4.2.1 DLS Stability test

At the beginning of the study (day 0) eleven replicates of each of samples A, B and C were analysed by DLS to determine the average particle size, eleven sample replicates of A, B and C were also stored in the dark at room temperature. At the end of the study (day 40) the stored samples were analysed to determine the average particle size, in order to establish if there was any evidence of 'instability', potentially due to aggregation and/or agglomeration.

The data obtained and the statistical functions are shown in table 7.6. There was no evidence of instability for any of the samples analysed when results were evaluated according to robust statistical approaches. The specific statistical approach used to determine if 'consequential instability' was evident is outlined in the methods section of this thesis in chapter 2.

All measurements where performed in triplicate and a calculated average result was reported.

Table 7.6: DLS Stability test data as determined by TU Dublin laboratory

	Sample A Manufacturer specification 20+/-4nm		**Sample B Manufacturer specification 40+/-2nm**		**Sample C Manufacturer specification 15+/-4nm**	
	Result day 0	**Result day 40**	**Result day 0**	**Result day 40**	**Result day 0**	**Result day 40**
Rep. 1	23.4	23.6	45.3	45.2	18.72	18.90
Rep. 2	23.5	23.4	45.7	45.3	18.71	18.82
Rep. 3	23.2	22.9	45.2	45.4	18.19	18.83
Rep. 4	23.2	22.7	45.9	45.0	19.01	18.90
Rep. 5	23.1	23.6	45.3	44.9	18.40	18.94
Rep. 6	23.5	24.1	45.4	45.2	18.71	18.88
Rep. 7	23.7	23.6	44.8	45.2	17.98	18.23
Rep. 8	23.4	23.3	44.8	45.3	18.30	19.10
Rep. 9	23.2	22.4	45.2	45.3	18.25	19.00
Rep. 10	23.2	23.5	45.3	45.6	18.23	19.01
Rep. 11	23.3	23.5	45.1	46.3	18.43	19.20
Avg.	23.34	23.33	45.27	45.34	18.45	18.89
Diff.		0.01		-0.06		-0.44
Std. dev.	0.1804	0.4819	0.3289	0.3695	0.3040	0.2477
0.3σp		0.7001		1.3581		0.5534
Signif.	**Not signif.**	Diff < 0.7001	**Not signif.**	Diff < 1.3581	**Not signif.**	Diff < 0.5534

7.4.2.2 DLS proficiency test results

The overall results from the DLS measurements were very good, with only two results i.e. lab 2B and 6F returning 'questionable' results. Notable the Z scores were only slightly above 2. The PDI values across all batches were all <1. For Samples A and B in particular, with the exception of lab 6F, the PDI values were relatively low ranging from 0.13 – 0.34, which indicates stable, uniform particle size distribution in solution, as would be expected with nanoparticle solutions stabilised with either citrate or PVP. Sample C, the laboratory synthesised nanoparticle solution of uncoated particles showed higher PDI's values ranging from 0.32 – 0.63, with lab 6F again being the exception, giving a higher PDI value than the other participant laboratories. It is not unusual to see higher PDI values for the laboratory specific synthesised nanoparticle solution as compared to the commercially prepared (Sigma Aldrich) solutions, as the latter solutions would have been subjected to stringent quality control procedures before being released for sale or supply. Results from six of the participating laboratories are resented in table 7.7.

Table 7.7: DLS test data obtained from six university laboratories

Lab	Batch A Consensus value 24.01			Batch B Consensus value 43.32			Batch C Consensus value 19.96		
	Result	**PDI**	**Z'$_a$***	**Result**	**PDI**	**Z$_a$***	**Result**	**PDI**	**Z$_a$***
1A	21.0	0.13	-1.17	35.8	0.16	-1.75	21.3	0.41	0.71
2B	24.5	0.24	0. 20	34.6	0.34	-2.03	18.7	0.63	-0.66
3C	20.2	0.15	-1.48	42.3	0.2	-0.24	16.6	0.32	-1.77
4D	28.2	n/a	1.65	48.9	n/a	1.30	22.5	n/a	1.34
6F	29.2	0.34	2.05	44.3	0.67	0.23	21.2	0.91	0.65
7G	23.5	0.26	-0.20	45.2	0.14	0.44	18.7	0.37	-0.65

***Z'a = accuracy Z-score taking into account the uncertainty of the consensus value, Za = accuracy Z-score**

7.4.2.3 Electron Microscopy Proficient Test Results

Results from all seven laboratories participating in the PT scheme were presented for analysis by electron microscopy. One laboratory provided results for both Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Overall the results were quite good with only four results classified as either questionable/unsatisfactory results with an accuracy score greater than two. This represents an 83% success rate for reporting of the electron microscope results for the particle size. In practical application of quality control monitoring procedures, reported results where the Z scores are >2 but < 3 would not be rejected outright. Internal quality control checks would be instigated using alternative reference materials/sources and/or the laboratory performance reported by the external PT schemes would be monitored over time, to establish if a trend and/or a bias exists. As was the case with the DLS results, Sample C was the most problematic sample, with two laboratories reporting 'unsatisfactory' results and one laboratory reporting a 'questionable' result for this sample. The range of results reported was more diverse for the EM as compared to the DLS for all three samples. For Sample A there was a 38% difference between the lowest and the highest value, for Sample B there was an almost 30% difference and for Sample C the difference was very stark at 55% difference, with values reported from the lowest result of 15.3nm to the highest of 34.2nm. This would explain why these result were deemed 'unsatisfactory' and they could indeed be considered to be 'outliers' within the overall results. Feedback/additional comments made by two participating laboratories indicated for EM that "Sample C was difficult to image with aggregates

visible initially, further dilution and additional sonication was used". Results from seven of the participating laboratories are resented in table 7.8.

Table 7.8: Electron Microscopy test data obtained from seven university laboratories

Lab code	Batch A Consensus value 28.35		Batch B Consensus value 51.05		Batch C Consensus value 25.00	
	Result	Z_a-score	Result	Z_a-score	Result	Z'_a-score
1A	36.20	2.76	50.10	-0.19	34.20	3.30
2B (SEM)	30.30	0.69	61.20	1.99	18.30	-2.40
2B (TEM)	28.70	0.12	54.30	0.64	24.80	-0.07
3C	25.20	-1.11	58.10	1.38	25.23	0.08
4D	30.00	0.58	46.00	-0.99	30.00	1.79
5E	22.30	-2.13	43.00	-1.58	15.30	-3.48
6F	28.00	-0.12	52.00	0.19	25.20	0.07
7G	27.10	-0.44	49.30	-0.34	24.80	-0.07

*** Za = accuracy Z-score, Z'a = accuracy Z-score taking into account the uncertainty of the consensus value,**

As indicated previously, results of the EU PT scheme where EM was used, highlights the difficulties involved in this type of measurement, where variation in results is quite apparent across a number of laboratories. This was evident in the smaller Ireland based PT scheme also. The use of electron microscopy for characterisation of nanomaterials in food and feed has been recommended by EFSA and EM is included in EC documented procedures for official controls and confirmation of nanoparticles in food/feed. What is concerning here is that evidence from both PT schemes demonstrate that this techniques is subject to high levels of variability, it is prone to sample preparation inconsistencies, possible measurement uncertainties associated with sample dilution procedures, and it is very much dependent upon operator technical skill and expertise to ensure accuracy of results.

7.5 Discussion

This chapter explored the basic concepts of nano characterization, from a regulatory enforcement point of view. Such characterization differs significantly from the needs or requirements of an academic laboratory. Typically in academia, nanoparticle characterization serves merely to confirm a starting material and/or to underpin further observations. As such academic laboratories can exert significant control over the experimental parameters and variables. In contrast from a regulatory perspective, samples can be diverse and challenging, and results are needed to enforce policy and legislation, with little room for interpretation or approximation of results. For this reason risk assessment bodies and competent authorities are required to use accredited laboratories, where practises and procedures are adhered to rigorously. In the agrifood sector accreditation to the ISO 17025 standard is required by European legislation. This restricts regulatory bodies like the FSAI from accessing the services of the rich exchequer infrastructure that is available in many of the countries third level institutes, thereby limiting potential engagement, for method development and horizon scanning for new methodologies and/or emerging risks. Furthermore, the FSAI is dependent upon service contracts which have been agreed with third party national reference laboratories, and it does not have its own specific laboratory or research division to develop and explore new methods or approaches. In contrast, many EU competent authorities have direct access to the third level infrastructure, and/or they have dedicated research labs and facilitates of their own.

Nevertheless, nationally Ireland does appear to have considerable expertise and infrastructure, including; laboratories within the remit of a number of ministerial departments, Teagasc, and the ISO 19001 accredited laboratories in the third level education sector. As such, a national collaborative agreement could be instigated; to support the nano food regulatory framework development, and to encourage horizon scanning for method development, that is, if the political will deemed it necessary. Indeed, such recommendations were made by both the FSAI and SafeFood in 2008 and 2013 respectively. Yet almost a decade later as we face into implementing the regulation for titanium dioxide as a food additive, it is still the case that none of the recommendations have been acted upon, additionally the infrastructure has not been made more available to the competent authority to fulfil

its obligations. The chapter also reported on proficiency test schemes which the report author coordination on behalf of TU Dublin and the State Laboratory, as well as an Ireland based PT scheme. The PT schemes focused on three of the main techniques that are commonly used for nano analysis, i.e. DLS, spICP-MS and electron microscopy, as proposed by EFSA for the initial physiochemical characterization of nanomaterials in the risk assessment model for nano hazard identification, identified in figure 7.1. The first technique considered was DLS, which showed good agreement across all laboratories involved in the proficiency test, for simple monodispersed particle sizes. However, significantly more difficulties arose as a binary mixture of two particle sizes was measured. Similarly spICP-MS was demonstrated as being a valuable technique, which is capable of giving good agreement for simple systems across a number of laboratories. Although it highlighted that once a degree of sample preparation was involved, or specific instrumentation requirements were needed, than results did vary, and ultimately this impacted upon the reproducibility of data across multiple laboratories. This is further emphasised by the EM proficiency test, which as 'the gold standard' for particle size determination showed significant variation across all laboratories when analysing powdered samples of barium sulphate and titanium dioxide. Interestingly the model dispersed citrate stabilise gold particle was analysed in all three proficiency schemes. A cross comparison between each technique showed good agreement between sp-ICP-MS and the EM.

Proficiency test schemes provide valuable insight in facilitating member states to overcome characterization problems associated with materials. Both proficiency test schemes demonstrated collaboration between a national reference laboratory and academic institution laboratory facilities/equipment can facilitate successful participation in three of the key nano-characterisation techniques. Furthermore, the participation demonstrated that overall satisfactory scores could be achieved across all of the proficiency test standards and techniques. While academic institutes cannot contribute to enforcement elements due to accreditation restrictions, they can clearly provide valuable infrastructure to facilitate forward planning, and procurement planning for national reference laboratories.

The proficiency tests also highlighted difficulties in applying the current EU definition of a nanomaterial to food and complex food matrices, where more than

one particle size is likely. Indeed, based on the current state of the art with respect to suitability methodology and analytical techniques, the EC definition presents a number of analytical challenges which include:

- *Difficulties measuring down to 1 nm*

There is only a limited number of techniques which can measure 1nm particles e.g. Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM), Small Angle X-ray Scattering (SAXS) and Brunauer Emmett Teller method (BET).

- *Size limit 100nm, broad analytical range from 1-100nm*

While there is a limited number of techniques which can measure 1nm particles, there is also a limited number of techniques which can cover the range from 1-100nm and beyond. This is required in order to decide when a material is a nanomaterial according to the definition, it is necessary to be able to measure all particles, including those above 100nm. This requires a measurement technique which is capable of measuring over at least three orders of magnitude.

- *Number/size distribution particle counting, and conversion to a number base value*

Not all analytical techniques are capable of producing a number based size distribution result, some counting techniques e.g. Electron Microscope (EM), Particle Tracking Analysis (PTA) and single particle Inductively Coupled Plasma – Mass Spectroscopy (spICP-MS) produce a number based distribution output. However, many techniques yield results expressed by volume, mass, surface, or physical property. These results need to be converted using a suitable conversion algorithm/appropriate model, which has the potential to introduce further variance based on measurement uncertainties.

- *The ability to distinguishing constituent particles within agglomerates and aggregates*

The EC definition defines the following the terms: ‘agglomerate’ meaning “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;

and ‘aggregate’ means “a particle comprising of strongly bound or fused particles” (2011/696/EU). Suitable sample preparation procedures are required to enable separation and measurement of particles within matrices, especially those which are bound or clustered within the sample. In addition, few methods are capable of the analysis of this range of constituents within matrices, especially those which are bound or clustered within the sample. In addition, few methods are capable of the analysis of this range of constituents.

- *The term ‘external dimension’ and the determination of this parameter*

If particles have an irregular shape, then it is not clear how this dimension can be measured. Only a very limited number of techniques are capable of measuring external dimensions, e.g. imaging techniques, such as TEM, SEM and AFM, and ensemble techniques such as SAXS, X-ray Diffraction (XRD) (peak width) and BET.

- *The means to prove that a material is not a nanomaterial, and the role of the volume specific surface area (VSSA)*

The EC recommendation provides clarification and technical details as follows: “VSSA measurements are highly sensitive to the techniques used and are very material dependent” in addition “VSSA is not validated for multimodal distributions or mixtures, and is not applicable to suspensions, formulations, articles, and consumer products” (Adapted from Gaillard, Mech and Rauscher, 2015).

In conclusion, in order to appropriately enforce potential nano regulation in Ireland the FSAI will most likely require the assistance of other member states national reference laboratories. Currently no laboratory nationally is accredited for electron microscopy to the ISO 17025 standard. Nevertheless, in the absence of such a laboratory, accessible third level infrastructure could be used for method development and for participation in proficiency test schemes, to gain experience and to upskill staff, as well as facilitating future planning for aspects such as instrument procurement.

7.6 References

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8.1 Background to the research

In 2008, the Food Safety Authority of Ireland (FSAI) published its statement on nanotechnology in the food and feed industries in Ireland (FSAI, 2008). In 2013 'Safefood' commissioned Teagasc to carry out a review of the applications of nanotechnologies in the agrifood sector (Handford *et al*., 2014). A key conclusion of these reports was the need for a multi-organisational approach between state agencies, industry and academia to ensure that safe innovations of nanotechnology are applied in the sector. The aim of this research, more than a decade after the FSAI statement, was to assess the 'state of the art' and to establish the national baseline capacity, to assist the development of safe nano-food technology, and to fully implement any potential nano-legislation arising from an informed regulatory process.

This research has assessed the national capacity in an attempt to identify any regulatory and/or monitoring challenges presented to Irish state agencies due to the rapid evolution of nanotechnologies in the agrifood industry, and the changing nano-legislative environment.

8.2 Discussions

The requirement to establish the national baseline capacity appears to have become more crucial as policy decisions relating to 'nano' have recently gained momentum, more so than at any time over the past 10 years or more. The most important policy decision being the recent EU reviews and decisions on the potential safety concerns of a number of 'nano' food additives, with more reviews and decisions expected on additional additives. The most pertinent additive in the context of this research is the EFSA opinion on the use of TiO_2. On May 2021 the European Food Safety Authority revised its opinion on the safety of titanium dioxide as a food additive (Younes *et al.*, 2021).

There has been a lot of uncertainties surrounding the use of titanium dioxide as a food additive, many focusing particularly on the toxicity of the nano component of this food additive. EFSA's opinion indicated a significant level of uncertainty surrounding the genotoxicity of titanium dioxide. From a review of 11,000 publications they could not conclusively associate any of the observed adverse

effects with the nano fraction. Nevertheless, it is highly probable that the properties such as size, surface area and surface charge do contribute to the toxicity, indeed isolated literature does indicate such correlations could potentially exist. Under pressure from competent authorities in France, Belgium, the Netherlands and Germany, who have repeatedly expressed concern over nano titanium dioxide, including the body of evidence, it was inevitable that the safety of titanium dioxide would be called into question. The association of the oxide with genotoxicity necessitated immediate action from the European Commission, to legislate and to protect consumer health. Legislation was enacted on 14th of January 2022 and the national competent authorities will be required to enforce the legislation (European Commission, 2022). This will require the FSAI to begin testing for this food additive in consumer foods.

The European Food safety Authority has in the past issued guidance on the risk assessment and hazard identification for nanomaterials. However, the specific methods used for characterization and to identify the nanomaterial are still the subject of debate by many in the regulatory controls area. At the moment several techniques have been identified to aid characterization, these have been identified throughout this thesis, and they have been thoroughly reviewed in chapter 7. To date in Ireland no single laboratory is accredited to perform any nano food characterization or identification. This will require the competent authority to source an alternative reference laboratory within another EU member state. This is despite the Food Safety Authority of Ireland recommending in 2008 that appropriate infrastructure, skilled personnel, and investment would be required to safeguard and protect Irish consumers from potential nano food risks.

The main research question guiding this research was the requirement to determine: **What are the gaps and deficiencies in Ireland's 'analytical and research infrastructure', in order to support state agencies who are responsible for the regulatory control of nanotechnology in Ireland's agri-food sector?**

Chapter one discussed in detail the logic behind posing this question and suggested several related questions which underpinned the elucidation of the answer to the main research question (chapter 1, section 1.5). In the following paragraphs these questions are revisited in the context of the work reported and the outcomes of the research activities.

Q.1 What is the current status of nanotechnology in Ireland's agri-food sector?

This question was addressed in the literature review, and extensively the Safefood report (Handford *et al*., 2014) which established a baseline of nanotechnology applications in the nano agri-food sector in Ireland. Little has changed in this regard, but it is clear that nanotechnology has continued to grow in the agrifood sector in the intermittent period between the Safefood report and now. Initially reported in chapter one was a review of national and international projects such as European Union (EU) programmes and published reports and position papers on nanotechnology in the agri-food sector. This review aided in developing the key theories and main hypothesis of the subsequent work. Additionally, a technical review was carried out to identify applications, technology and methodology which could be suitable for the characterization of nanomaterials. Based on the review, four potential key themes or deliverables for national nanotechnology agendas were identified for further consideration in an Irish context these include:

- Development of comprehensive regulatory controls for applications of nanotechnology in the agri-food sector.
- Development of a national coordinated approach between government departments and agencies regarding applications of nanotechnology.
- Co-ordination of funding to support the national infrastructure, for the supply of skilled personnel, and funding to facilitate access to this infrastructure.
- Development of analytical methods for the characterization and measurement of nanomaterials, and methods to determine; toxicity, adverse risks to health, and environmental effects resulting from the use of nanoparticles in the agri- food sector.

Q.2. &Q.3 What are the knowledge gaps for state agencies in assessing the safety of potential nanotechnology innovations with respect to legislative requirements? And are there identifiable skill shortages within state agencies.

This question combines two questions reposed in section 1.5 of chapter one, that is the identification of knowledge gaps and skill shortages within state agencies. Chapters 4, 5 and 6 highlighted a number of knowledge gaps **for risk assessors**, based on data obtained from a set of surveys, focus group discussions and interviews. Knowledge gaps through lack of, or low levels of engagement was evident between the academic community and each of the key stakeholders i.e. the competent authorities, control laboratories and enforcement officers is not strongly apparent, or supported. While it was acknowledged that there is a good level of engagement laterally, particularly within the EHS, meaningful engagement across agencies, government departments, academia and other relevant stakeholders does not appear to have been strategically advanced. As highlighted in chapter 4, when academics were asked about engagement with regulatory control agencies 80% of them indicated that they have had no involvement, or requests to participate in the development of national nanomaterial standards or method development. In fact 95% of academics surveyed ranked 'collaboration with the 'relevant government department' and/or 'with a state or semi-state body (e.g. State Lab/PAL)' as their least preferred collaboration option, the vast majority preferred an industrial collaboration. This was in contrast to other EU member states, where direct engagement is encouraged through funding schemes and active research divisions of the competent authority.

Communications with regulatory control agency personnel demonstrated that they believed they had insufficient analytical infrastructure, and/or the skill/knowledge base to support testing of 'nano' for 'official control', characterisation purposes. In addition, uncertainties surrounding the availability of, and access to infrastructure for method development, training and upskilling of staff was also identified. Despite this, regulators generally demonstrated a good level of understanding of the commonly used techniques for nano characterization. Although they did acknowledge limited, if any access to the analytical infrastructure. The academic community indicated that they believed sufficient research grade facilities do exist nationally to suitably characterise nano foods if required. It was surprising however

that less than one in three of the academics surveyed believed they have suitable analytical infrastructure available to them within their own institution, in terms of 'supporting teaching and training of undergraduates' on techniques for the characterization of nanoparticles. This could indicate that there seems to be a dependency upon national access programmes to access equipment across the higher education sector nationally. This is not unusual, as collaboration across the third level sector is normal. On a positive note, most of the academics surveyed did however appear to be confident that they would have access to L&D/training programmes in organisations outside of their own institution.

In addition to potential communication issues, training needs, and skills shortages surrounding nanotechnology regulation, serious concerns were raised about analytical methods and approaches to 'nano' characterisation. Anecdotally it was found that confusion existed with respect to the most relevant approaches required to characterise nanomaterials. The perception amongst regulators was that the laboratories are not suitably equipped to carry out 'nano' testing. This was explored at the in-depth interview stage of this research. The overarching concern expressed by multiple participants across all regulatory control authorities was that; testing is contingent upon the availability of an electron microscope for routine testing and for confirmatory analysis. This is also borne out by the international literature in the area. Clarification was sought, and was provided by the EFSA specialist who confirmed that; analysis using electron microscopy is not an essential requirement, specifically in the case of analysis of TiO_2, and that simple screening techniques, that are most probably accessible to many regulatory control laboratories would be sufficient. EFSA have indicated several techniques of value in their literature, nevertheless the area is still the subject of much debate.

Knowledge gaps with respect to the legislation were also identified across the general stakeholder cohort. Unsurprisingly, the majority of academics were unaware of any legislation associated with nanotechnology. While the competent authority will have specialist knowledge in food related legislation generally, the sampling officers (EHO's) demonstrated a low level of awareness of 'pending legislation,' despite the fact that the TiO_2 legislation was enacted on 14th of January this year (European Commission, 2022). Overall, the regulatory control authorities were not confident that the regulatory frameworks are 'sufficiently evolved in order

to support nanotechnology testing procedures'. This was emphasised by the sampling officers (EHO's), who overwhelmingly (93%) indicated that they would require training and/or upskilling to enforce any potential legislation in the area of nanotechnology.

Q4. Could Irelands 'exchequer funded' research infrastructure, support state agencies in closing any identified gaps and shortages?

Chapter 7 explored the most relevant characteristic techniques and infrastructure required for nano characterization. The chapter was underpinned by participation in a proficiency test scheme for DLS, spICP-MS and electron microscopy. The physiochemical characteristics focused on in the proficiency test were particle size and number concentration, across a range of nanomaterials in keeping with the EU nano definition. The participation demonstrated a cross stakeholder collaboration, utilising infrastructure in a national reference laboratory and a university. The results of the PT scheme demonstrated how, by facilitating collaboration between universities and national reference laboratory stakeholders, that adherence to the characterization criteria of the EU nano definition is extremely possible nationally. The Irish exchequer has invested heavily in developing the university and the third level research infrastructure, as demonstrated in chapter 3, where a desk-based review of Ireland's nano investments over the last 10 years was conducted. In this period ultimately €29 billion was invested on nano related activities, of which almost one third was from direct exchequer funding sources. The largest research funder in the state is Science Foundation Ireland, over the same timeframe this funder invested €95 million on nanotechnology based research. Much of this investment was directed towards Science Foundation Irelands research centres, to build the national infrastructure. In addition, other funders such as Enterprise Ireland and the Higher Education Authority have also established centres of research excellence with strong research infrastructure, with respect to Enterprise Ireland Gateway Centres and Higher Education Authority research institutes.

It is therefore not surprising that 64% of academics surveyed believe that the equipment (physical) infrastructure for 'nano' food characterization is readily achievable nationally. However, from a regulatory point of view accreditation is essential with legislation requiring compliance to ISO 17025 standards for

laboratories participating in enforcement activities (ISO/IEC, 2005). Currently in Ireland no laboratory has accreditation status for the analysis of nanomaterials in food. The potential use of 'public' research institutions e.g. Teagasc, or even university research facilities was explored as a potential source of high level technical/scientific support for method development and or validation purposes, rather than for official control activities. It was suggested that if the 'public' research institutions involved did manage to attain accreditation for this testing then they could become the national' designated' laboratory assigned by the competent authority. This is evident in many European member states, the examples given include; in Italy, the Istituto Superiore di Sanità (ISS), and Anses in France. While this is not the case in all member states the EFSA specialist interviewed indicated that: "Most of the countries have at least a kind of national body that produces both research and regulatory advice for nanotechnology".

The results of this study however do indicate that the use of universities or non-accredited infrastructure could provide an opportunity to develop approaches in a cost effective, risk free environment. It could also be used for training and future planning with respect to procurement.

Q5. How can Ireland establish and promote an accessible inventory of national nanotechnology infrastructure which is suitable for the characterisation of nano-food technologies?

This aspect of the work packages as depicted in chapter 2 figure 2.1 was not fully achieved during the research process. This research question is best answered as part of the research recommendations (8.6) and the potential future work (8.7) paragraphs of this chapter.

8.3 Limitations of the research

Over the course of this research, a number of limitations were identified mainly related to; scope, lack of secondary research data, the research methodology chosen, sample size, and subsequent analysis of the results.

- Scope: The purpose of this research was to assess the nanotechnology skill and capacity shortages in Ireland's agri-food sector. On commencement of

the study it was hoped that the results and the outputs would be, to establish an inventory detailing the available national nanotechnology infrastructure which would be suitable for the characterisation of nano-food technologies, for use by 'state regulatory authorities'. This was not fully achieved due to the shortage of relevant infrastructure identifiable and possible restrictions on the use of 'state-university research facilities' mainly relating to the requirement for accreditation. Recommendations from this research will enable such an inventory to be established.

- Lack of prior research studies on the topic: This research problem was focused on the 'Irish' 'state of the art' and the potential for developing a strategic plan for the future. It was apparent from the literature review that very little literature/documents/reports, or prior research on this topic existed in the Irish context, to help gain an in-depth understanding the research problem been investigated. Comparisons with the systems in place in other European states was not conducted as part of this research, as the regulatory control – research infrastructure setting is, in most cases not comparable to the Irish situation. Future research work could include a 'compare and contrast' with other member states of similar; size or population to Ireland, to expand the literature review process.
- Research methodology: As the secondary research data was limited and the primary data collected was based on low sample numbers, it was necessary to streamline the research methodology to best describe the approach taken due to the unavailability of a lot of data. The interpretative research philosophy was chosen as the 'best fit' for this research. This approach involves the research building the theory based on interpretation of the data. The difficulty with this approach is the possibility of unconscious bias of the researcher, this was considered throughout the research process, with moderation by the supervisor who was independent of the interpretative process. Future research could explore the possibility of using an alternative research design, if additional data is available.
- Sample size limitations: The sample population available, particularly for focus groups and the interviews was limited. In the case of the regulatory control personnel there are only a limited number of people and agencies

specifically involved in the ‘nano’ area, as such the sample size available for focus group and interview was limited to a small population of individuals nationally. In addition, it was not possible for some people to participate in the survey due to organizational restrictions on completion of electronic surveys/communications from outside of their organization. This applied in the case of the regulator and the academic surveys. It is common to assume that a study’s statistical power (i.e., the probability that a significant effect will be detected, if it exists) is directly tied to its sample size. Indeed, as sample size decreases, the ability of a study to detect small or even moderate effects diminish. Thus, it is likely that for small sample studies only very large effects will be able to be detected, which for this work was relevant, since it is has already been established that overarching aspects such as perception of access to equipment is an overriding concern. Nevertheless caution should be applied to interpretations, as the reduced sample size may inhibit any assumptions made from inferential statistics (Burian, Rogerson and Maffei III, 2010). Therefore, where relevant statistics purposely designed for low sample size were used as presented in chapter 2, section 2.7. Future enhancement of survey numbers and more robust statistical evaluations could be achieved through face-to- face interactions at training/conferences and networking events, or when the restrictions noted above have been eradicated.

- Analysis of the results: It was difficult to conduct statistical analysis of results in a lot of the cases, as the sample numbers were too low to provide trends and meaningful evaluation of possible relationships, if they exist. While qualitative evaluations are plentiful within the review process, quantitative evaluations are less frequently presented within the thesis. However attempts at providing qualitative statistics are presented where possible, this is most evident in the case of the analysis of national PT scheme results. If this study were to be repeated at a future date, the results to date could be included, and with the additional sample numbers a more representative distribution of the population could be considered, incorporating a greater number of representatives of groups of people to

whom results would be relevant. A possible expansion of the national PT scheme would also provide a larger sample size for statistical evaluations.

8.4 Impact of COVID-19 restrictions on this research

While some aspects of this work were mainly desk based e.g. literature reviews and surveys, a significant element of the work involves meeting people, for the purpose of conducting focus group discussions, interviews and attending networking events. By the very nature of this research the direct dialogue, communications with personnel was scheduled for completion after the review stage, and as the surveys were well underway.

The direct communications with personnel element of this research has been significantly impacted throughout 2020, 2021 and 2022, due to restrictions imposed nationally as a result of the global pandemic. The methodology used for the focus group discussions and the interviews had to be adapted due to government restrictions on face-to-face meetings/close contact, and indeed all personal interactions.

The survey numbers were significantly impacted due to the fact that face-to-face; events, workshops, meetings and even conversations were prohibited, thereby eliminating the ability to recruit willing participants to take part in the survey, forcing an entirely online survey approach.

The restrictions posed as a result of the pandemic had a significant impact on the ability to recruit large numbers of people for participation in the focus group discussions also. The traditional focus group discussion format, comprising of scheduled gatherings with many attendees present, perhaps twenty or more, who are divided into four or five groups to discuss the topic of interest, was not possible throughout the scheduling of the focus group discussions for all of this research. The focus group discussions were performed virtually, online, using the Cisco Webex platform. While this was a deviation from the more traditional format of the focus group experience known to many people, this format was convenient for many attendees, there was less time commitment required by participants, and there were less administrative requirements relating to venue availability. However, only

a limited number of attendees were involved in each of the focus group discussions, in order to manage the exchange of communication effectively and to encourage input from all in attendance. A number of people who were invited to participate declined the invitation. Some of the individuals declined due to the nature of the forum used for the meeting (electronic format) and others declined because they were of the opinion that they had insufficient involvement in the area of nanomaterial analysis. It is also worth noting that the unexpected absence of individuals who had committed to attend the meetings, and who subsequently did not attend, this had an impact on the reduced level of participation in the focus groups discussions.

Similarly individual interviews were also performed virtually, online, using the Cisco Webex platform. As the interviews were scheduled for the later part of the research project, after the surveys and the focus group discussions, it was hoped that these individual interactions could be carried out in-person, if government restrictions on close contact interactions had been lifted. Unfortunately, the restrictions on close contact interactions on remained in place within the workplace and the academic environments for the entire two years, and they still remain in place. Therefore it was decided that the interviews needed to be progressed in a similar format to the focus group discussions. The same advantages and constraints apply to the interviews as those which applied to the focus group discussions. A notable advantage of the virtual interview process was the greater ease of availability of designated persons for interview, i.e. it would potentially not have been possible to arrange an interview with some EU stakeholders' in-person whereas these people were these people were happy to make themselves available for the virtual interviews.

8.5 Potential impact of thesis for regulatory control/policy advancements

- Having established that the requisite equipment for 'nano' testing is available within many HEI/university institutional settings nationally, and while the equipment cannot be used for 'official control testing' it could be used for other purposes. With the implementation of formal agreements detailing 'instrumentation hubs' and the availability of practical-technical

specialised expertise, instruments within the academic institutions could be used for the development of research and for method development. Such an arrangement would support development of specialised expertise, it would facilitate training of regulatory control personnel, and could be used as 'trial' instrumentation to help prospective purchasers make an informed choice prior to making the commitment to purchase highly specialised instruments. It has been demonstrated through the EU PT scheme participation (chapter 7, section 7.4.1) that this type of collaboration between a regulatory control laboratory and a university proved to be beneficial towards the achievement of successful results in an international laboratory comparison study.

- It has been recognised by the competent authority, the FSAI, that horizon scanning for new methodologies and/or emerging risks is an important part of their remit. The FSAI does not have its own laboratory, research division or indeed research funding to develop and to explore new methods or approaches for regulatory control purposes. The authority is dependent upon service contract agreements with competent control laboratories, and with third party laboratories, who are not within the authority's direct control, thereby limiting what testing may or may not be completed within the national control testing plan. In contrast, many other EU competent authorities have direct access to the third level infrastructure, and/or they have dedicated research labs and facilitates of their own, the examples given included; RIKILT (responsible for the Dutch national official control testing and for research and development), the Technological University of Denmark (DTU), ANSES in France, Istituto Superiore di Sanità (ISI) in Italy and Sciensano in Belgium. A significant improvement for the competent control authority would be an exchequer commitment to dedicate funding for a targeted research arm or research budget for the competent authority to facilitate regulatory preparedness, horizon scanning and to give greater control to the authority in formulating the NCSP.
- Details of the 'Horizon Europe Partnership for the Assessment of Risk from Chemicals (PARC)' were briefly presented in chapter 4. As outlined in section 4.5 Irish risk assessment agencies have not engaged with the EU PARC partnership. Concerted efforts should be made by all national

stakeholders involved in food regulation, along with the academic partners, to engage in some part of this programme. Similar activities involving other member states demonstrate how national control authorities can influence and direct EU policy through their involvement in research activities, and through their collaborating they may be able to highlight issues, influence policy and standards to support their own national priorities. Additionally where appropriate this experience/network opportunity could facilitate a greater level of knowledge transfer and possible infrastructure sharing.

- Throughout the research it was evident that there is a need for greater communication between all stakeholders. Co-ordination of priorities should be discussed amongst the various regulatory control authorities, along with the involvement of the 'publicly' funded research/academic institutions, to facilitate information sharing, knowledge transfer and equipment resource sharing, to enhance training, skill development and method validations. Such cross collaboration would greatly enhance development of a national risk assessment strategy which could be applicable to other areas of concern e.g. contaminants, toxicants and other emerging risks. A clear plan to facilitate horizon scanning, and to build capacity to quickly respond to crisis situations could be accommodated within this forum also.

8.6 Recommendations

A number of recommendations can be presented arising from the interpretation, analysis and review of all of the data from the completed PhD research. These recommendations include:

- A greater degree of communication between stakeholders via a round table forum and/or a national risk assessment conference.
- A greater degree of engagement of enforcement officials and risk assessment agencies with academic research and development. This could be achieved through incentivised funding schemes and appropriate lobbying of funding bodies.
- A national proficiency test scheme for nanomaterials of interest within the Agri food sector.

- A searchable database available and accessible infrastructure for nanomaterial characterization.
- The formation of a technology gateway within a 'public' research institution or designated academic research institution to support method development for regulatory enforcement of new and novel emerging contaminants.
- The urgent need to advance establishment of an EURL in nanotechnology to address concerns in knowledge gaps, standards and methodology.

8.7 Potential Future Work

Potential future work arising from this research would be to consider; those aspects of the existing research questions and knowledge gaps which remain to be identified, and some aspects of the questions could be explored further or may warrant further investigation. Anticipated aspects for potential future work have been highlighted in the bullet points below.

- To expand upon the existing knowledge gaps for state agencies in assessing the safety of potential nanotechnology innovations with respect to legislative requirements.
    - Legislation/Policy responsibility: Strategy statement identifying and outlining explicitly the regulatory controls governing applications of nanotechnology in the agri-food sector.
    - Accreditation: Identification of the practical and technical requirements for accreditation, and upskilling of relevant stakeholders if required, to enable them to participate in the regulatory control and policy decision processes.
    - Training/workshops/knowledge sharing networks and events: Relevant to all stakeholders within the different institutions and government departments or agencies.
- To identify skill shortages within state agencies, in order to facilitate closing any knowledge gaps.
    - Future work comprising: additional surveys, focus groups, interviews to identify the skill shortages and barriers to capability for regulatory

authorities, with the outcomes providing recommendations for the attention of relevant stakeholders.

- Procurement/participation: in 'nano' technical training, potentially involving funding from the EU, and to encourage attendance at network training/conferences and networking.

- To influence government departments and state funding agencies to ensure that the exchequer provides dedicated funding to establish and/or expand upon the current research infrastructure to support state agencies in closing any identified gaps and shortages.

  - National oversight: highlight 'priority areas' for exchequer funding, to support the national infrastructure.
  - National Research Infrastructure: provide details of the availability and location of resources and infrastructure for the use of state departments and agencies.
  - Explore the potential role of academia or dedicated research hubs: What role can academia play in supporting state agencies who are responsible for the regulatory control of nanotechnology in Ireland's agri-food sector? Is there a role for dedicated research hubs, within IE/EU MS's?

- To establish and promote an accessible inventory of national nanotechnology infrastructure which is suitable for the characterisation of nano-food technologies.

  - Construction of a searchable database of expertise and capacity with verifiable 'nano capabilities: - A searchable database could be constructed to obtain details of access points to national; accredited laboratories, academic institutions, industry, public/state laboratories collaboration potentials with nano capabilities. The database would be most relevant for state agencies who are involved in regulatory controls, however it would not be a publically accessible resource. The database could be maintained and updated by the competent authority (FSAI), or by a designated agency who have been assigned national responsibility for managing Ireland's analytical and research infrastructure.

- To futureproof Ireland's infrastructure and skill needs going forward with respect to nano-food technology.
    - Mapping of Irelands capacity and infrastructure.
    - Focused research and funding structure applicable to regulatory controls/application of policy.
    - Upskilling and/or establishment of dedicated accredited testing facilities.

8.8 Conclusions

This research sought to assess; the 'state of the art' of nano-food technology developments, to establish the national regulatory control baseline capacity, and the potential implications for policy enforcement in line with regulatory requirements.

From communications with the relevant stakeholders it was apparent that issues and concerns exist generally about 'nano', and more specifically with respect to 'nano'; nomenclature, applications, legislation, measurement technologies, sampling and policy implementation.

Individuals understanding of the terminology, i.e. what is/is not 'nano' varied, depending on the context of their particular 'nano' involvement. While this is acceptable within the different sectors (academia, regulators) the impact of this research would be greatly enhanced with a clear understanding of nanotechnology terminology, and common terms which can be implemented across all sectors, arising from informed opinion, and from a regulatory point of view.

The need for controlled, planned, testing of applications of nanotechnology was not evident amongst the cohort, which might explain why recommendations from the national reports on 'nano' have not been progressed to a great extent. Applications of nanotechnology, and related regulatory controls are referred to implicitly or explicitly in many food regulations. Indeed the requirement to apply regulatory control is imminent in the case of regulation (EC) 2022/63 regarding the food additive titanium dioxide (E171) (European Commission, 2022).

It would appear that stakeholders have identified the short term need for testing of 'nano', arising from the EFSA decision to ban TiO_2 as a food additive (Younes *et*

al, 2019). The EHS are aware that they will be required to initiate market surveillance activities to determine if TiO_2 is still present in the food chain at the end of the legislation transitional period, (i.e. August 2022). The sampling officers (EHO's) have stated that they do not have a sampling plan ready for either market surveillance activities or for routine testing, and they have identified a need for further training/upskilling in order to implement policy decisions.

While regulatory control laboratories indicate that they have suitable equipment for 'some' aspects of testing, they indicate that they do not have capacity for 'full' characterisation of 'nano'. Opinions expressed by personnel from the regulatory control sector is that they do not have the specialised equipment required to complete the testing requirements, nor do they have access to such equipment i.e. they do not have Electron Microscopy (EM), Dynamic Light scattering (DLS) and other equipment that could be required for characterisation and regulatory control purposes. A review of the infrastructure available within academia suggests that the requisite equipment is available with many HEI/university institutional settings nationally.

The potential use of equipment from within the 'academic' setting was queried as a solution to the perceived lack of infrastructure within the regulatory control laboratories. It was stated that academic facilities and expertise have been availed of in some instances where appropriate testing was not available in regulatory control laboratories e.g. DNA sequencing/profiling. However concerns were raised by many personnel from the regulatory control sector about the use of such facilities, namely that; academic facilities are not accredited to ISO/IEC 17025 accreditation standards, and that there is no formal arrangement in place whereby regulatory control laboratories can avail of infrastructure from within the academic institutions. It was also highlighted that official control legislation specifies that testing must be carried out according to accredited protocols.

At the time of writing no Irish regulatory control laboratory has accredited procedures in place to carry out 'nano' testing, neither have the relevant laboratories made any plans to seek to achieve accreditation status for this testing.

The main research question guiding this research was to determine 'What are the gaps and deficiencies in Ireland's 'analytical and research infrastructure', in order

to support state agencies who are responsible for the regulatory control of nanotechnology in Ireland's agri-food sector?'

The research hypothesis proposed was that "Ireland's analytical and research infrastructure' is not sufficiently future proofed to support State Departments and Agencies who are responsible for the regulatory control of nanotechnology in the agri-food sector".

The results of this research refute the hypothesis, it would appear that the equipment infrastructure is in place within the research/academic institutions, even though it is not in-situ within the state sector regulatory control laboratories.

Resources are potentially available within the regulatory control authorities and the laboratories, however it has been highlighted that some form of training/upskilling would be required by the relevant sampling officers and analytical facility staff concerned.

The requirement, or the driving force, for the laboratories to seek accreditation has not been progressed yet, with the perception amongst the regulators is that this type of testing cannot be progressed without the availability of electron microscopy.

Possible ways to reduce the difficulties encountered within the regulatory control sector, and to establish national priorities for legislative enforcement have been presented throughout this thesis.

8.9 References

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Appendix 1

Table A1: Nanotechnology policy in the European Union and some Member States

Regulation	**Country EU MS**	**Application**	**Specific to Nano**	**Status**
Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) 1907/2006(EC)	EU wide	Chemicals and Raw Materials,	No, but 'substance' covers nanomaterials	Implemented
Regulation on Medical Devices (EU) 2017/745	EU	Medical devices	Yes	Implemented
Cosmetic Products Regulation (EC) 1223/2009	EU	Cosmetic Products	Yes	Implemented
European Commission Recommendation on the Definition of a Nanomaterial (2011/696/EU)	EU	Substances at the nanoscale	Yes	Implemented
Nanomaterials in the Healthcare Sector: Occupational Risks and Prevention - E-fact 73	EU	Medical devices and pharmaceuticals	Yes	Implemented
Decree on the annual declaration on substances at nano-scale - 2012-232	France	Substances at the nano-scale	Yes	Implemented
Guidance on the determination of potential health effects of nanomaterials used in medical devices	EU	Medical devices	Yes	Published
Guidance on the protection of the health and safety of workers from the potential risks related to nanomaterials at work.	EU	Health and Safety of Workers	Yes	Published
Royal Decree regarding the Placement on the Market of Substances manufactured at the Nano-scale	Belgium	Substances manufactured at the nano-scale	Yes	Implemented

Table A2: List of testing requirements and/or definitions which have been referenced in part 2.5 of this thesis

Legislation and Date	**NANOMATERIAL TESTING REQUIREMENT/DEFINITION**
REACH Regulation (EC) No 1907/2006 with consolidated text (EU) 2018/1881 amending the 2006 Regulation	IDENTIFICATION OF THE SUBSTANCE For each substance, the information given in this section shall be sufficient to enable each substance to be identified and the different nanoforms to be characterised. If it is not technically possible or if it does not appear scientifically necessary to give information on one or more of the items below, the reasons shall be clearly stated. Name or other identifier of each substance * Name(s) in the IUPAC nomenclature or other international chemical name(s) * Other names (usual name, trade name, abbreviation) * EINECS or ELINCs number (if available and appropriate) * CAS name and CAS number (if available) * Other identity code (if available) Information related to molecular and structural formula of each substance * Molecular and structural formula (including SMILES notation, if available) * Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate) * Molecular weight or molecular weight range Composition of each substance. Where a registration covers one or more nanoforms, these nanoforms shall be characterised pursuant to section 2.4 of this Annex. * Degree of purity (%) * Nature of impurities, including isomers and by-products * Percentage of (significant) main impurities * Nature and order of magnitude (… ppm, … %) of any additives (e.g. stabilising agents or inhibitors) * Spectral data (e.g. ultra-violet, infra-red, nuclear magnetic resonance or mass spectrum) * High-pressure liquid chromatogram, gas chromatogram * Description of the analytical methods or the appropriate bibliographical references for the identification of the substance and, where appropriate, for the identification of impurities and additives. This information shall be sufficient to allow the methods to be reproduced 2.4. Characterisation of nanoforms of a substance: For each of the characterisation parameters, the information provided may be applicable to either an individual nanoform or a set of similar nanoforms provided that the boundaries of the set are clearly specified. The information in points 2.4.2 – 2.4.5 shall be clearly assigned to the different nanoforms or sets of similar nanoforms identified in point 2.4.1. 2.4.1. Names or other identifiers of the nanoforms or sets of similar nanoforms of the substance 2.4.2. Number based particle size distribution with indication of the number fraction of constituent particles in the size range within 1 nm – 100 nm.

Legislation and Date	NANOMATERIAL TESTING REQUIREMENT/DEFINITION
	2.4.3. Description of surface functionalisation or treatment and identification of each agent including IUPAC name and CAS or EC number. 2.4.4. Shape, aspect ratio and other morphological characterisation: crystallinity, information on assembly structure including e.g. shell like structures or hollow structures, if appropriate 2.4.5. Surface area (specific surface area by volume, specific surface area by mass or both) 2.4.6. Description of the analytical methods or the appropriate bibliographical references for the information elements in this sub-section. This information shall be sufficient to allow the methods to be reproduced.
European Commission (EC) Definition (2011) (European Commission, 2011a)	'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 %. The Recommendation further specifies: By derogation [...], fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials. [...] 'particle', 'agglomerate' and 'aggregate' are defined as follows: (a) 'particle' means a minute piece of matter with defined physical boundaries; (b) '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; (c) 'aggregate' means a particle comprising of strongly bound or fused particles. Where technically feasible and requested in specific legislation, compliance with the definition [...] may be determined on the basis of the specific surface area by volume. A material should be considered as falling under the definition [...] where the specific area by volume of the material is greater than 60 m^2/cm^3. However, a material which, based on its number size distribution, is a nanomaterial should be considered as complying with the definition [...] even if the material has a specific area lower than 60 m^2/cm^3
Food Information to Consumers (2011) (European Parliament and Council, 2011b) **Novel Foods (2015)**	"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.

Legislation and Date	NANOMATERIAL TESTING REQUIREMENT/DEFINITION
(European Parliament and Council 2015)	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 physio-chemical properties that are different from those of the non-Nano form of the same material
Active and Intelligent Materials and Articles (2009) (European Commission, 2009a). **Plastic materials and articles intended to come into contact with food (2011)** (European Commission, 2011b).	New technologies engineer substances in particle size that exhibit chemical and physical properties that significantly differ from those at a larger scale, for example, nanoparticles. These different properties may lead to different toxicological properties and therefore these substances should be assessed on a case-by-case basis by the Authority as regards their risk until more information is known about such new technology. Additional text to the above applicable for 'nanoparticles …. it should be made clear that authorisations which are based on the risk assessment of the conventional particle size of a substance do not cover engineered nanoparticles". "Specific requirements on substances" provides that "Substances in Nano form shall only be used if explicitly authorised and mentioned in the specifications in Annex I."
Biocide Product Regulation (2012) (European Parliament and Council, 2012).	'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
Thesis Definition (2020)	Any engineered material or particle (typically, but not exclusively, below 100 nanometres in one or more dimensions) that is introduced into a food (or feed) product or contact surface, which exhibits or is proposed to exhibit a functional purpose on the nanoscale (x10-9) or influence the bulk properties of the final product' FSAI (2008).

Table A3: EU legislation (implicitly/explicitly) covering nanomaterials in the agri-food/feed sector.

Application area	**Legislation**	Nano-definition
General Chemicals		
Chemical substances	(EC) No 1907/2006 (REACH) (authorisation/pre-market approval required for certain hazardous substances)	No
Agri-Food		
Food information to Consumers (FIC)	(EU) No 1169/2011	No
Novel Food/Feed	(EC) No 258/97 (EU) 2015/2283	No Yes
Common Food Authorisation Procedures	EC) No 1331/2008	No
Enzymes	(EC) No 1332/2008	No
Food additives	(EC) No 1333/2008	No
Flavourings	(EC) No 1334/2008	No
Food supplements	Dir. 2002/46/EC	No
Vitamins, Minerals and other food substances	(EC) No 1925/2006	No
Food contact materials (FCM)		
Active and Intelligent Materials and Articles	(EC) No 450/2009	No
Plastic food contact materials	(EC) No 10/2011	No
Agricultural Products - Biocides	(EU) No 528/2012	Yes

*EU legislation is accessible and searchable on-line at http://EUR-LEX.europa.eu/.

Appendix 2

Specific key word searches used when searching for journals/articles of relevance in web based databases (Scopus, Web of Science and PubMed).

- Nanotechnology + Agriculture + Application
- Nanotechnology + Characterisation + Chemistry
- Nanotechnology + Characterisation + Physiochemical
- Nanotechnology + Engineered Material
- Nanotechnology + Food + Agriculture + Application
- Nanotechnology + Food + Application OR Opportunity OR Risk
- Nanotechnology + Food + Legislation
- Nanotechnology + Food + Production + Application
- Nanotechnology + Food + Production + Risk
- Nanotechnology + Food + Regulation + Application
- Nanotechnology + Food Contact Material OR Food Packaging
- Nanotechnology + Food Packaging + Application
- Nanotechnology + Food Packaging + Risk
- Nanotechnology + Food Processing + Application OR Opportunity
- Nanotechnology + Food Processing + Risk
- Nanotechnology + Food Products + Risk
- Nanotechnology + Food Safety + Application
- Nanotechnology + Food Safety + Risk
- Nanotechnology + Measurement + Instrumentation
- Nanotechnology + Measurement + Properties
- Nanotechnology + Nutrition + Application OR Opportunity OR Risk
- Nanotechnology + Size determination

Appendix 3

Nanotechnology knowledge and skill awareness – Academics

Dear ……

I would like to extend an Invitation to you to participate in a study on the "Identification of Nanotechnology skill shortages in Ireland's Agri-food sector, to aid the safe, innovative, and sustainable development of nano-food technology"

My name is Eileen McCarron. I am a part-time student in the school of Physics, Clinical and Optometric Science, at the Technological University Dublin, I am conducting this survey as part of the research requirements towards the award of a PhD, and I would like to invite you to participate in a short survey. The purpose of the questionnaire is to gather information from representatives of different academic institutions who are involved in nanotechnology. The questionnaire is not designed to obtain your personal views, so please state your opinions relative to the organisation which you represent.

I am aiming to identify 'What are the gaps and deficiencies in Ireland's '*Analytical and Research Infrastructure'*, in order to support state agencies who are responsible for the regulatory control of nanotechnology in Irelands agri-food sector? I am aware that your institution may not be directly involved in the agri-food sector, however your opinion, and the contribution you potentially make to nanotechnology education, and to workforce professional development in general will be valuable to this study. If you agree to participate, you will be asked to complete a survey about skill needs and educational requirements for agrifood nanotechnology. The survey will take about 10-15 minutes to complete.

Although you may not benefit directly from participating in this study, I hope that others involved in regulatory control, and in the research community in general may benefit. Your participation is confidential, and the study information will be kept in a secure location at the Technological University Dublin. The results of the study may be published or presented at professional meetings, but your identity will not be revealed. Your answers will be completely anonymous and will be published only in summary, in statistical form. You will not be identified in any way. If you have any questions or concerns about the survey, or if would like to find out further information about this research, I will be happy to answer any questions you may have. You may contact me at (087) 2104862 and at eileen.mccarron@statelab.ie or you may contact my faculty advisor, Prof. Gordon Chambers, at 01 4022856 and Gordon.chambers@dit.ie. If you have any questions about your rights as a research participant, you may contact the Research Ethics and Integrity Committee directly at researchethics@dit.ie

If you would like to participate, please click on this *link* to proceed to the survey.

Thank in advance for your time.

Kind regards,

Eileen McCarron
Senior Chemist,
Customs and Excise Section,
State Laboratory
Backweston Laboratory Campus
Celbridge, Co. Kildare, W23 VW2C
Ph +353-1-505 7003 Fax +353-1-505 7070

Nanotechnology knowledge and skill awareness – Academics

Invitation to members of academia, where nanotechnology is taught as part of the curriculum, or those who are involved in research relating to nanotechnology. Please attempt to answer as many questions as possible, even though you may not have direct experience of some of the points raised in each question (Q's 1-12 relate to research in general, while Q's 13-22 relate specifically to nanofood/nano-agriculture).

1. What is your role within the academic institution you are affiliated to:

Principal Investigator	
Senior Lecturer	
Lecturer	
Researcher	
Research Manager	
Post-doc Researcher	
Student	

Other (Please specify)

2. Which of the following academic sectors are you affiliated to:

University	
Institute of Technology	
Research Institute or Centre e.g. Teagasc	

Other (Please specify)

3. What is the level of your involvement in the academic sector? (e.g. supervising research, faculty teaching, researcher, student etc.)

Less than 1-2 years	
2-5 years	
5-10 years	

More than 10 years	

4. Which, if any of the following national agencies have you applied for funding from?

SFI	
EPA	
FIRM	
IRC	
HEA	
I have not applied for funding	

Other, has any of this funding been nanofood, nano-agriculture related? (If so Please provide brief details)

5. Which, if any of the following national agencies have you received funding from? (note, this is specifically with respect to nano food/agriculture only), please specify the scheme you received the funding from.

SFI	
EPA	
FIRM	
IRC	
HEA	
I have not received funding	

Other (Please specify), additional comment

6. Are the research activities you are involved in, industry led?

Yes	No

7. In terms of research, how important do you rank the following national collaborations? (On a scale of 1 – 5, please rank each option, with 1 being the most important, and 5 being the least important)

National collaboration	Rank (1-5)
Industry collaboration e.g. Internship/ job funded research/short-term contract	
Another HEI collaboration	
Engagement with a Regulatory body (e.g. FSAI, EPA etc.)	
Collaboration with State or Semi-State body (State Lab, PAL etc.)	
Collaboration with relevant government department	

8. Have you participated in any national, or international programs/projects relating to the development of nano-standards, or method development, for regulatory and traceability purposes?

Yes	No	

If yes please specify the most recent date of participation	

9. In terms of analysing particulates, nanoparticles or ingredient size distributions in complex systems e.g. chemical mixtures or food products, which 3 of the following techniques would you consider as being the most appropriate technique to obtain routine, high throughput, and reliable data on a broad range of nanomaterials? (On a scale of 1 – 3, please rank your preferred choice, with 1 being your highest preference, and 3 being your least preferred choice) Please choose only three techniques.

Analytical Technique	First Preference	Second Preference	Third Preference
Dynamic Light Scattering (DLS)			
Field Flow Fractionation (FFF)			
Inductively Coupled Plasma Mass Spectroscopy (ICP MS)			
Electronic Spectroscopy (Atomic Emission or Absorption, AAS or AES)			
Atomic Force Microscopy (AFM)			
Scanning Electron Microscopies (SEM)			
X-ray Diffraction and Elemental Analysis (XRD)			

Near-infrared spectroscopy (NIR)			

10. In terms of analysing particulates, nanoparticles or nano-ingredients size distributions, in complex systems e.g. chemical mixtures or food products, which of the following techniques have you available to you within your organisation, or you have access to by an alternative means? (Please select as many as apply)

Analytical Technique	Yes	No
Dynamic Light Scattering (DLS)		
Field Flow Fractionation (FFF)		
Inductively Coupled Plasma Mass Spectroscopy (ICP MS)		
Electronic Spectroscopy (Atomic Emission or Absorption, AAS or AES)		
Atomic Force Microscopy (AFM)		
Scanning Electron Microscopies (SEM)		
X-ray Diffraction and Elemental Analysis (XRD)		
Near-infrared spectroscopy (NIR)		

11. In your opinion, what are the most important considerations in relation to gaining an understanding of any potential health risks associated with particulates/nanoparticle applications in the agri-food sector? Please rank the following questions (On a scale of 1 – 5, please rank the importance, with 1 being your most important, and 5 being your least important).

Review of potential health risks	Rank (1-5
What are the hydrophobic/hydrophilic properties of nanoparticles in terms of the GI tract?	
How do particulates/nanoparticles interact with bio-molecules and cellular structures i.e. membranes?	
Are they degradable, and how will their properties change during degradation?	
What is the bioavailability and fate of nanoparticles within the human body?	
Particle size distribution in the initial food formulation (or migrated onto the food)	

12. Is your work/research related to aspects of nano-food or nano-agriculture?

Yes	No

13. Do you believe that you have a suitable analytical infrastructure available within your HEI to fully characterise nanoparticle applications in the agri-food sector?

Yes	No	I do not know

14. Is the infrastructure available nationally, in your opinion?

Yes	No		I do not know

15. In terms of teaching and training, do you have a suitable analytical infrastructure available to undergraduates to support training of the characterization of nanoparticles?

Yes	No	I do not know

16. Is the national infrastructure accessible to you within your organisation?

Yes	No

17. Skills gaps arise when an employer cannot recruit suitably skilled and qualified personnel to meet the requirements for their job functions. As an educational institution, to what extent do you expect developments in nanotechnology to lead to such gaps, and potential recruitment problems in the future?

There will be no future recruitment problems	
There may be limited future recruitment problems	
There will be substantial future recruitment problems	
I do not know	

18. Do you think that the current higher education system in Ireland is able to fulfill the skills and the technical knowledge needs related to present, and to future developments in nanotechnology?

To a great extent	
Somewhat	
Very little	
Not at all	
I Do not know	

19. In your opinion, what is the best strategy to enable you, as educators of the future workforce to address any potential skill needs that may arise in the future? (Please select as many as apply)

Develop stronger cooperation with potential employers	
Increase the supply of graduates in this field	
Start new types of specific/specialized higher level education courses	
Improve the theoretical level of education programs at Bachelor/Masters level. and more possibilities for part-time PhD programs	
More specialization (i.e. in-depth knowledge of specific domains) within science	
Less specialization within science, but more general knowledge of scientific domains	
Greater focus on technical developments within the curriculum	
More opportunities for relevant in-house training courses	
I do not know	

Other (Please specify), additional comment

20. As nanotechnology continues to evolve, what in your opinion are the most important *technical skills* that you anticipate will be needed?

(On a scale of 1 – 5, please rank each of the skills with 1 being the most needed and 5 being the least needed)

General Science:- Chemistry/physics/biology technical knowledge	
General Laboratory analytical and instrumentation skills	
Specialized equipment expertise e.g. Imagery, Microscopy, Spectroscopy etc.	

Knowledge of nanoscale characterization techniques and methods	
Nano - biology specialist expertise	

21. Please rank the following *employability skills* and competencies that you anticipate will be needed most in the area of nanotechnology.

(On a scale of 1 – 4, please rank each of the skills with 1 being the most needed and 4 being the least needed)

Research experience	
Specialist knowledge (e.g. regulations/product development/applications/health and safety)	
Quality/Accreditation experience	
Problem-solving, critical thinking ability	

22. Do you have any other suggestions for policy makers, which could specifically help to fulfill skill needs related to the present, and the future development in nanotechnology, and agrifood nanotechnology development?

Thank you for participating in this research.

Nanotechnology knowledge and skill awareness - Regulators

Dear Colleague
I would like to extend an Invitation to you to participate in a survey questionnaire, which is part of an initiative towards an "Identification of Nanotechnology skill shortages in Ireland's Agri-food sector, to aid the safe, innovative, and sustainable development of nano-food technology"

My name is Eileen McCarron. I am a part-time student in the school of Physics, Clinical & Optometric Science, at the Technological University Dublin. I am conducting this survey as part of the research requirements towards the award of a PhD, and I would like to invite you to participate in a short survey. The purpose of the questionnaire is to gather information from representatives of Irish State departments and agencies who are involved in the agri-food sector. The questionnaire is not designed to obtain your personal views, so please state your opinions relative to the organisation which you represent.

I am aiming to identify 'What are the gaps and deficiencies in Ireland's 'Analytical and Research Infrastructure', in order to support state agencies who are responsible for the regulatory control of nanotechnology in Irelands agri-food sector?' You/your organisation have been identified as an expert/key stakeholder in emerging technologies in the agrifood sector, and your participation will be valuable to this study. If you agree to participate, you will be asked to complete a survey about skill needs and educational requirements for agrifood nanotechnology. The survey will take about 10-15 minutes to complete.

Although you may not benefit directly from participating in this study, I hope that others involved in regulatory control, and in the research community in general may benefit. Your participation is confidential, and the study information will be kept in a secure location at the Technological University Dublin. The results of the study may be published or presented at professional meetings, but your identity will not be revealed. Your answers will be completely anonymous and will be published only in summary, in statistical form. You will not be identified in any way.

If you have any questions or concerns about the survey, or if would like to find out further information about this research, I will be happy to answer any questions you may have. You may contact me at (087) 2104862 and at eileen.mccarron@statelab.ie or you may contact my faculty advisor, Prof. Gordon Chambers, at 01 4022856 and Gordon.chambers@dit.ie. If you have any questions about your rights as a research participant, you may contact the Research Ethics and Integrity Committee directly at researchethics@dit.ie

If you would like to participate, please click on this *link* to proceed to the survey. Thanks in advance for your time.

Kind regards,
Eileen McCarron
Senior Chemist,
Customs and Excise Section,
State Laboratory
Backweston Laboratory Campus
Celbridge, Co. Kildare, W23 VW2toC
Ph +353-1-505 7003 Fax +353-1-505 7070

Nanotechnology knowledge and skill awareness - Regulators

Invitation to Regulators, Government departments/Agencies who are responsible for regulation and control of food/feed/products in the agri-food sector. Please answer all questions, even though you may not have direct experience of the points raised in each question.

1. Please indicate which Government department or Agency you belong to:

Department of Agriculture, Food and the Marine	
Teagasc	
The Marine Institute	
Food Safety Authority of Ireland	
Environmental Protection Agency	
The State Laboratory	
The Public Analyst Laboratory	
National Standards Authority of Ireland	
Other, (Please specify)	

2. What is the level of your involvement with nanotechnology in the agrifood/agriculture sector? (Please specify all that apply)

Technical expertise	
Following developments in nanotechnology	
Facilitating research	
Teaching	
Policy Development	
Regulatory monitoring/control function	
No involvement	
Other, (Please specify)	

3. Is developing nanotechnology testing capability a priority for your organisation?

1-5 yrs. time	
5-10 yrs. time	
Now	

Not a priority	
Please elaborate, where applicable	

4. If your organisation is currently involved with agrifood nanotechnology, what is the role of your organisation? (Please select all that apply)

National responsibility for nanotechnology	
Regulatory/legislative function	
Competent Authority	
Analytical function	
Supportive/Advisory capacity	
Other, (Please specify)	

5. Who are your key stakeholders? (Please select all that apply)

European Union	
Government department/Agency	
Research Institutions	
Consumers	
Industry	
Other, (Please specify)	

6. Are you aware of any of the following activities which apply to applications of nanotechnology in the agri-food sector?

Regulatory controls in place	
Risk assessments which have been carried out	
Monitoring/surveillance plans	
Funded research in place	
Testing procedures in place	
Other, (Please specify)	

7 Please select the responsibility of your organisation with respect to the following (please select as many as apply)

Supporting development of legislation	
Carrying out testing procedures	
Responsibility for regulatory control	
Funded research within the agri-food sector	
Responsibility for monitoring and surveillance	
Other, (Please specify)	

8. For each of the following analytical techniques please indicate if you are you familiar with the technology, which could be used for regulatory control/monitoring plans/testing procedures for applications of nanotechnology?

Analytical Technique	Knowledge of	No Knowledge of
Dynamic light scattering (DLS)		
Field flow fractionation (FFF)		
Inductively coupled plasma mass spectroscopy (ICP MS)		
Electronic spectroscopy (atomic emission or absorption, AAS or AES)		
Atomic Force Microscopy (AFM)		
Scanning Electron microscopies (SEM)		
X-ray Diffraction and Elemental Analysis (XRD)		
Other specify_____		

9. If applicable, do you have any of this analytical technology available to you within your institution to facilitate analysis of nanoparticles within the agri-food sector? (Please select as many as apply)

Dynamic light scattering (DLS)	
Field flow fractionation (FFF)	
Inductively coupled plasma mass spectroscopy (ICP MS)	
Electronic spectroscopy (atomic emission or absorption, AAS or AES)	
Atomic Force Microscopy (AFM)	

Scanning Electron microscopies (SEM)	
X-ray Diffraction and Elemental Analysis (XRD)	

10. In your opinion do you have the available resources in terms of analytical capacity/skilled personnel to support nanotechnology testing procedures if you were required to do so?

Yes	No	I do not know

11. In your opinion do you think that existing legislation or the regulatory framework is sufficiently evolved in order to support nanotechnology testing procedures, if you were required to do so?

Yes	No	I do not know

12. To what extent do you expect developments in nanotechnology to lead to such gaps, and potential recruitment problems in the agrifood sector in the future?

There will be no future recruitment problems	
There may be limited future recruitment problems	
There will be substantial future recruitment problems	
I do not know	

13. What do you think are the best strategies to address any potential skill shortages and knowledge gaps that may result from developments in Nanotechnology? (Please select as many as apply)

Recruiting 'skilled' researchers/trained personnel	
Facilitating development of a broader knowledge of nanotechnology topics and applications in academia	
Participation of employees in external training and education programs	
Encouraging specific in-house expertise in nano specific processes and techniques	
Outsourcing the analysis	
Encouraging stronger cooperation between Government departments/Agencies with research institutions	
Improvements in legislation	

Collaboration with industry and academia	
Other, (Please specify)	
I do not know	

14. As nanotechnology continues to evolve, what in your opinion are the most important *technical skills* that you anticipate will be needed?

(On a scale of 1 – 5, please rank each of the skills with 1 being the most needed and 5 being the least needed)

General Science:- Chemistry/physics/biology technical knowledge	
General Laboratory analytical and instrumentation skills	
Specialized equipment expertise e.g. Imagery, Microscopy, Spectroscopy etc.	
Knowledge of nanoscale characterization techniques and methods	
Nano - biology specialist expertise	

15. Please rank the following *employability skills* and competencies that you anticipate will be needed most in the area of nanotechnology.

(On a scale of 1 – 4, please rank each of the skills with 1 being the most needed and 4 being the least needed)

Research experience	
Specialist knowledge (e.g. regulations/product development/applications/health and safety)	
Quality/Accreditation experience	
Problem-solving, critical thinking ability	

16. Do you think that the higher education system in Ireland is able to fulfill the skills and the technical knowledge needs related to present, and to future developments in nanotechnology?

To a great extent	
Somewhat	
Very little	
Not at all	
I Do not know	

What do you think could be added to the curriculum in order to support the development of nanotechnology?	

17. Do you have any other suggestions for policy makers, which could specifically help to fulfill skill needs related to the present, and the future development in nanotechnology, and agrifood nanotechnology development?

Thank you for participating in this research.

EHO Survey

1. What is your awareness of products and/or applications of nanotechnology?
2. Are you aware of any food or beverage products currently on the market that contain nanomaterials or nanotechnology?
3. If you are aware of the use of nanotechnology in food or in food products please indicate some products/product categories/ applications of nanotechnology that you are aware of.
4. In your professional opinion (based on the information supplied below), should the (fictitious) items in the table below be classed as nano or not?
   A. [As Nature intended Colloidal Silver: is easy-to-use and is made up of 10 parts per million (ppm) of the active ingredient, and purified water. It goes through a 9 step purification process to ensure a very small particle size of 0.0006 to 0.005 microns so that they have a proportionately large surface area for better effectiveness.]
   B. [Spot Gone: Acne and Spot Cream. Ingredients Colloidal Silver 50ppm, Aloe Vera Gel, Zinc. Colloidal Silver is 99.99% pure silver and European Pharmaceutical Grade Water.]
   C. [Active silver anti-bacterial spray: Ingredients: Purified water and 99.9% pure silver, at concentration of 10 ppm (parts per million). Colloidal silver is known for its antiseptic properties. Ideal for use around the home, it can be used on any surface or sprayed into the air]
   D. [Colloidal silver soap: Ingredients: sodium cocoate (coconut oil), sodium palmate (palm oil), argentum metallicum (colloidal silver), sodium olivate (olive oil).]
   E. [Antimicrobial nano mask: reusable fitted facemask is protected with silver Ion technology that helps stop the growth of microorganisms and maintains hygiene and cleanliness for a longer period of time.]
   F. [Natural Defence " Colloidal silver: Clear, almost tasteless liquid designed to help boost your immune system containing nano silver with Ag4O4 silver oxide coating. Natural Defence " Colloidal silver contains 10 ppm silver of crystalline structure with multiple modes of action to create superior systematic benefits. 100% vegetarian formula contains no artificial ingredients, preservatives, or additives.]
5. Which of the following do you use to keep up to date with emerging public health and environmental health issues? (You may tick more than one option if relevant)
6. Where applicable, please provide at least one example of a source of information used by you to obtain information about public health and/or environmental health issues."
7. If you had a query regarding a particular nanotechnology application who would you most likely contact for advice? (On a scale on 1-5, please rank each of the sources, with 1 being your most likely choice and 5 being your least likely choice)
   A [Government agency (e.g. FSAI HSE, HSA, EPA etc.)]
   B [Non-government agency (e.g. Safefood, WHO, IBEC etc.)]
   C [Academia]
   D [EU commission]
   E [Nobody, read-up myself using websites, library resources etc.]
8. Are you aware of any of the following activities which might apply to applications of nanotechnology in the agri-food sector? (You may tick as more than one option if relevant)
9. Based on what you know, how would you describe the relative risks and benefits of nanotechnology in relation to agriculture and food?
10. Do you follow any guidelines, or do you conduct risk assessments in relation to nanotechnology products/processes as part of your current job responsibilities?
11. Do you think that applications of nanotechnology may represent an emerging public health and or an environmental health risk?
12. In your opinion do you think that existing legislation or policy directives are sufficiently evolved in order to support the implementation of nanotechnology controls/testing, if you were required to support sampling of products? "
13. Do you think that training in emerging issues such as nanotechnology for practicing EHO's is sufficient?"
14. To what extent do you expect developments in nanotechnology to lead to knowledge gaps, and potential problems for EHOs when implementing relevant policies in the future?
15. What do you think are the best strategies to address any potential knowledge gaps for EHO's, as a result of developments in nanotechnology? (Please select as many as apply)
16. Do you think that the higher education system in Ireland is able to fulfill the skills and technical knowledge needs related to present, and to future developments in nanotechnology?"
17. What do you think could be added to the curriculum in order to support the regulation, health and safety, monitoring and control of nanotechnology? (Please select as many as apply)
18. Are you aware of any recent ESFA or other European Commission opinion on any nanomaterials? If you are, please provide an example and indicate where you heard about the nanomaterial opinion."

19. Do you have any suggestions for policy makers, which could specifically help to fulfill skill needs related to the present, and the future development in nanotechnology development?
20. Please state your professional occupation and for practicing EHO's the HSE county/council/region which you are working in."

Appendix 4: List of the questions/reflections posed by the moderator.

Participants agreed to a recording and were advised that they would be given the transcripts for review/approval.

Moderator (Mod) –

Intro_ Our objective is to ask is Ireland's infrastructure sufficiently future proofed to support State Agencies who are responsible for nanotechnology regulation in the agrifood sector in Ireland.

Our goal is to try to identify gaps and deficiencies in order to support the Agencies and the risk assessors who are responsible for regulation of nanotechnology. Ultimately, we want your personal views, we want to see what you know about nanotechnology, because there may be procedures, and there may be protocols in place in each of the organizations where you work, but what we really want, is to see what is happening on the ground. That is why we want your personal views and personal opinions.

Mod: How do you understand the term Nanofood? Is anyone in the group aware of any nanofoods that are currently on the market, or are they aware of any technology related to nanotechnology that is currently on the market, or a food, or non-food related technology on the market? Is anyone in the group aware of any nano food specific legislation?

Mod: Is anybody aware of Nano products, which are on the market, which are nanofood, or may have nano ingredients within the food and in particular on the Irish market?

Mod: In terms of nanospecific food legislation, is anybody familiar with potential legislation associated with nanofood?

Mod: We want you to look at this definition; this is the definition that Eileen is using for her thesis. This is a nanotechnology definition, indeed there are many definitions across nanotechnology. However, this is what we are using for this study, to try to identify, a nanofood. Can I get you to look at that, and pick out three keywords from that definition that you feel are important? Okay. So the definition there says any engineered material or particle, typically, but not exclusively below 100 nanometers in one or more dimensions. So that 100nm you are looking at is around one thousand times smaller than the diameter of a human hair, this is introduced into a food or a feed product, which exhibits a functional purpose on the nano scale. So, I know you've mentioned in your definitions, or when you were discussing what the term nanofood was, and you did mention size, you did mention functionality. And so we would like to get your views on this, three keywords that you feel are important from this definition.

Mod: Looking at that definition, do you think there is anything missing? Do you think there are any flaws in it? Do you think there could be something else that needs to be included?

Mod: Has anybody come across any alternative definitions, which may be more applicable to the nanofood area?

Mod: Comment Okay. So, in terms of that definition then, does anyone also want to say anything else about that definition?

Mod: The next slide is more to do with how we characterize, and how we consider these products. And so what requirements do regulators need? When we consider that these products could be in a food product? How do we then characterize them from a regulatory point of view?

We also want to consider whether, nationally, do we have that capacity, be it in an academic Institution, be it in the State Lab, in the Department of Agricultural, be it in the public analyst laboratories. Where is that capacity for a risk assessor to assess these products?

Mod: We can start with what properties would be important?

Keep in mind in terms of the requirements a regulator might need, and on the type of product that might land on your desk and you can add to this the type of matrix.

Mod: Does anybody have any feel for whether nano standards are available, and let's just take titanium dioxide let's just take that as an example. Is there a standard material? Is anybody aware where standard materials for nano that could be obtained? Does the legislation specify it?

The other question I'd like to ask is, what about accreditation for the laboratory? So, could a regulator, access an academic Institution? Or if we are doing electron microscopy, does it have to be in an accredited lab?

Mod: Just to summarize what you are saying is the legislation would normally specify an approach or standard, but the real key thing is that it would have to be an accredited laboratory. Is that correct?

Mod: Let's say for instance the Food Safety Authority approached you and said, we have this nano ingredient, we want it characterized, there's the legislation, it specifies that you use electron microscopy, what will be your next port of call knowing that you don't have the instrument available? Would you be aware of an accredited electron microscopy unit nationally?

Mod: So from a regulatory point of view, can I ask a question?

Do you think the capacity is available nationally, would it be available to be able to fully characterize nanomaterials for size, and for any other parameters, but mainly let's focus on that size, is that capacity available in accredited laboratories nationally.

Mod: Can I ask the academics, and after hearing the discussion from the regulatory side of the panels and with respect to the need for accreditation, and that capacity, what would be the academics take in terms of, could you get accreditation easily? And could you maybe be engaged in fact finding approaches?

Mod: Has the exchequer funding supported the National Research infrastructure for Nano risk assessments? And the key there is nano risk assessments, and characterization.

And is there enough engagement between risk assessment agencies and academia as to how exchequer research funding is prioritized?

Mod: There has been something like three billion, or something like that, has been spent on the nanotechnology infrastructure nationally, is that a missed opportunity? Or do you think that there's options there? Maybe those regulatory labs are not aware of all the infrastructure that exists, due to that investment.

Mod: Is the group aware of any national nanotechnology reports on nanotechnology, specifically, but not exclusively focused on the agrifood sector? So is anybody aware of any reports?

Mod: This is a composite of the various recommendations, I'm going to read through them, and just get your opinion based on the discussions that we have had today,

- Whether we reached these recommendations,
- Whether we've surpassed them, or

- Whether we haven't achieved them at all.

And so, the first one there, these are common features throughout all the reports

- Coordination of funding for the supply of skilled personnel.

Mod: In terms of another recommendation that was made, that the development of a National coordinated approach between Government Departments and Agencies regarding applications of Nanotechnology.

Mod: The targeted funding for risk assessments of nanotechnology in food.

Mod: The development of analytical methods for characterization and measurements of nanomaterials and the development of methods to verify, to determine the toxicity, adverse health effects, environmental effects of nanoparticles in the agrifood sector.

Mod: So, taking those recommendations as a whole, Do you think those reports have influenced anything? Do you think that those reports have been listened to? Or maybe now is the time we need to start to implement them? So, would anybody like to consider that?

Mod: Having seen these discussion points these recommendation points. Would this be seen as something of a concern? That these haven't been implemented?

Mod: Are you aware of the hierarchy of national responsibility for nano risk assessment. So we have a little flow diagram here and the yellow boxes are the government body/agency/ministry/risk assessor, whomever that may, or may not be, who has responsibility for overseeing nano risk assessment, or nanotechnology. The green boxes are who you think would be underneath there, and I know some people online already know the answers to this, and so we just wants to get the views of who people think would be the lead organization in this regard. So, who would be in the yellow box?

Mod: Just in terms of some feedback and personal views. So, we'll start with your personal views, and we'll just do it around the table, your personal view of that nanofood area. And whether you feel that today has been of any value in terms of determining the answers to some of the questions that myself and Eileen are posing, so can I have your feedback please?

Mod: And do you have any feedback on the Focus Group process?

Appendix 5: Suggestions given by academics and regulators for the attention of policy makers

- The legislation in relation to nano needs to define what regulation is required.
- More courses or modules on nanotechnology at third level, which would enable the scientists of the future, understand the area. From a policy point of view, agreement on the definition would go a long way.
- An agreed definition would be useful. Also, more courses on nanotechnology itself at third level or even modules on this topic may address some of the skills shortages in this area.
- The development of a network of regulator, industry and academic experts in the area of nano would be a good starting point. Similar to networks already present in academia. A golden pages of nano experts would also be useful and might increase collaborations in the area. In academia, the inclusion of nanotech modules in existing core courses (food engineering, food science, environmental health, etc.) would boost interest in more specialised courses (masters, PhDs) dedicated to nanotechnology. Part time courses on the practical elements of nanotechnology (e.g. regulatory aspects) would also be useful.
- Organise national forums for updates, as a learning knowledge sharing experience.
- Fix the basic problem of underfunding of the university as a good base line funding can help with any future challenge. Rather than boosting specific areas, which will be of topic in 5year, do something to have a healthy solid base capable of quickly reacting to any developments rather than playing catch up every time some "hot" topic appears.
- Lobby for research.
- Annual open forums for engagement with universities
- Engage with academia more
- I have not applied for funding in nanofood it's not my area but I have never seen any nanofood specific calls so it does not seem like a priority for policy makers.
- IT's should be engaged with policy makers more to grow research in the institutes
- I have been involved in European studies with policy makers from other jurisdictions in air quality; Irish policy makers other than EPA do not engage in these enough. May be a resource issue? However to fill skill gaps and continue professional development these projects are crucial to such organisations?
- Prioritise research
- Not very equipped to answer bio-nano questions.

Appendix 6: Review of methodology used for nano characterisation

Table A4: Instrumentation and Performance Criteria (Mech *et al*, 2020*)*

Priority property	Instrument Technology	Nanoparticle (NP) Property	Typical Materials	Sample Preparation	Detection Limit/Range	Type of Technique
Composition	AAS	Mass concentration. Elemental composition.	Metals/Metal Oxides	Suspended in a liquid, as a solution or dispersion	ppm-ppb	Destructive
	ICP-OES	Elemental composition, Mass concentration.	Metals/Metal Oxides	Suspended in a liquid as a solution or dispersion	ppm - ppb	Destructive
	ICP-MS	Elemental composition, Mass concentration.	Metals/Metal Oxides	Suspended in a liquid as a solution or dispersion	ppm – ppt	Destructive
	UV-VIS	Elemental composition, size, shape, Mass concentration, agglomeration state, and refractive index.	Metals Coloured compounds (dyes or pigments). Organic compounds or biological materials.	Suspended in a liquid as a solution or dispersion	ppm-ppb	Destructive
	XRF	Elemental composition, Mass concentration	Solids	Minimal sample preparation (e.g. grinding, pellet formation, or 'as received')	ppm-ppb	Non-destructive
	Priority property	Instrument Technology	Nanoparticle Property	Typical Materials	Sample Preparation	Detection Limit/Range
	EDX	Mass concentration. Elemental composition. Identification of precipitates in alloys, Elemental segregation at grain boundaries, and quantitative composition of multi-component phases.	Metals/Metal Oxides	Solids	0.1ppm-1ppm	Non-destructive

Priority property	Instrument Technology	Nanoparticle (NP) Property	Typical Materials	Sample Preparation	Detection Limit/Range	Type of Technique
Crystallinity	XRD	Crystal/crystallite size, shape, crystal form and phase.	Liquid materials, powders, solids, and thin films.	Suspended as a homogenous material in a suitable sample holder	2-100nm	Non destructive
	STEM	Chemical Composition, Structural, and morphological information	Particles deposited on substrates or particles embedded in an electron-transparent medium	Sample must be prepared on substrates or as thin films, etc.	10 nm -100 µm	Destructive
	Raman	Chemical composition, physical and structural properties. Identification of surface interactions at molecular level.	Organic and inorganic samples, can be solid, liquid, gas, solution or emulsion	Minimal sample prep. Can often be used on samples 'as received')	Sample and/or application dependent	Non destructive
Priority property	Instrument Technology	Nanoparticle (NP) Property	Typical Materials	Sample Preparation	Size Range	Type of Technique
Particle Size and Size Distribution	Electron Microscopy SEM/TEM	Elemental composition, Mass conc. Topography: surface features. Morphology: shape and size of the particles. Crystallinity arrangement of atoms	Particles deposited onto substrates or embedded in an electron-transparent medium	Sample must be prepared on substrates or as thin films, etc.	SEM: 7nm - 1000µm TEM: 1 nm - 1000µm	Destructive
	XRD	(Refer to Crystallinity Priority Property)				
	DLS	Intensity of scattered light	Inorganic, carbon based, organic particulate and non-particulate biological samples.	Suspended particles	1 nm -10µm	Non destructive

Priority property	Instrument Technology	Nanoparticle (NP) Property	Typical Materials	Sample Preparation	Detection Limit/Range	Type of Technique
Particle Size and Size Distribution	AFM	Particle height above the level of a substrate provides info. on particle number, particle size, size distribution and structural information at molecular level	Organic, inorganic, carbon based, biological, core/shell materials and mixtures of different shapes and coatings.	Immobilized particles on a substrate i.e. solids or liquids	1nm >1 µm	Destructive
	Instrument Technology	Nanoparticle (NP) Property	Typical Materials	Sample Preparation	Size Range	Type of Technique
	spICP-MS	Particle number concentration, mass concentration. Calculated from mass, provides information on individual particles, particle number , size distribution, primary particles in non-aggregated and non-agglomerated samples	Metals/Metal Oxides	Suspended particles	Different depending on the element analysed e.g. Au approx. 15-1000nm Ag approx. 20-1000nm TiO_2 approx. 50-1000nm	Destructive
	UV-Vis	(Refer to Composition Priority Property)				
Priority property	Instrument Technology	Nanoparticle (NP) Property	Typical Materials	Sample Preparation	Size Range	Type of Technique
Particle Shape	TEM	(Refer to Particle size and Size Distribution Priority Property)				
	AFM	(Refer to Particle size and Size Distribution Priority Property)				
Priority property	Instrument Technology	Nanoparticle (NP) Property	Typical Materials	Sample Preparation	Detection Limit/Range	Type of Technique
Surface area & Specific Surface Area (SSA)	BET	Specific surface area of a material. inorganic, carbon based, organic particulate and non-particulate and composite samples	Inorganic, carbon based, organic, particulate and non-particulate and composite samples	To determine gas 'adsorbed' as a single or multi molecular layer, on a dry powder or solid material	Sample dependent and/or experimental conditions dependent	Non destructive

Appendix 7:

Inter-laboratory study for Irelands nano-characterisation capability

Dear participant,
Thank you for agree to participate in our study and in this PT scheme to establish the viability of using academic facilities to successfully test nanoparticle size for the assistance of regulatory enforcement organisation.

You have been supplied with three spherical colloid silver nanoparticles suspensions (aqueous). For the study we would greatly appreciate you estimating the particle size distribution and report an average size in the template provided. Measurements can be on either DLS and or electron microscopy (SEM, STEM or TEM).

As previously discussed with you we are unfortunately not in a position to cover your cost or expense in preforming this study. However the long term benefits of being able to demonstrate a potential Inter-laboratory process for measuring nanoparticle size with our Irish academic research institutes and centres will I hope benefit us all in the future with greater engagement with regulators and agencies charged with the enforcement of emerging nanotechnology regulation.

SAMPLES

Sample A

An aqueous colloidal suspension of spherical silver nanoparticles stabilised with citrate. Particle mass concentration is approximately 100 mg/L. Typical particle size distribution is <50nm.

Storage
Should be stored in the dark at room temperature or lower. Do not expose to temperatures above 40 °C or below freezing point. The samples are stable for approximately 2 months under such conditions.

Sample B

An aqueous colloidal suspension of spherical silver nanoparticles stabilised with PVP. Particle mass concentration is approximately 100 mg/L. Typical particle size distribution is <100nm.

Storage
Should be stored in the dark at room temperature or lower. Do not expose to temperatures above 40 °C or below freezing point. The samples are stable for approximately 2 months under such conditions.

Sample C

An aqueous suspension of spherical silver nanoparticles uncoated. Particle mass concentration is approximately 100 mg/L. Typical particle size distribution is <50nm.

Storage
Should be stored in the dark at room temperature or lower. Do not expose to temperatures above 40 °C or below freezing point. The samples are stable for approximately 6 months under such conditions.

DLS MEASUREMENT PROCEDURE

Prior to measurement, the received samples should be vortex/sonicated to re-suspend any settle particles. Samples will be diluted 1:10 in ultrapure water and sonicated prior to analysis. All dilutions should be made gravimetrically where possible.

You should use your own in house method and practice experience to determine particle size, suggested parameters are

- Measure in triplicate.
- recommended backscatter angle (173^{o}) for measurements
- When measuring use general purpose in the data processing parameter for the Malvern instruments
- Refractive index 0.135 and absorption of 3.99
- Allow for the full temperature stabilisation time of 120 seconds
- In order to limit signal contribution from errant large particles, use short measurement times e.g. 3 seconds with multiple runs (>40). This is in contrast to typical instrument settings using long measurement times (10 seconds) with a few runs(~10)

Any significant deviation from this protocol should be reported in your submission.

TEM/SEM MEASUREMENT PROCEDURE

The aqueous suspension may be transferred directly. By bringing this dispersion in contact with the sample carrier (TEM/SEM-grid), specimens suitable for EM analysis are prepared.

Recovering nanoparticles from dispersion is generally done by floating the grid on a droplet of dispersion (grid on drop) or by placing a droplet of dispersion on the grid (drop on grid). The concentration of particles in the dispersion should be adjusted such that the number of particles per micrograph is optimal for later analysis. Preferably, the particles should not touch each other or overlap each other. Optimal concentrations vary from sample to sample.

The nano-objects of interest on the EM-micrographs are detected and the primary particle sizes (Feret min) measured manually or semi-automatically based on their grey value. To obtain a useful size distribution at least 250 particles per sample will be sized ideally. However you should use your own in house method and practice experience to determine the best way to prepare the samples and measure the size.

Significant deviations from the protocols suggested should be reported in template.

Reporting

Please complete the report template including as much of the required data as possible based on your final assessment of particle size for each of the three samples.

If your facility cannot provide a complete data set just insert N/A in the areas where data was not obtained.

Lab ID:					
Method (or deviation)					
Sample preparation					
Internal standard /calibration					
Detection method **Instrumentation**					
Refractive index:		**Absorbance value:**			
Additional comments					
Data report					
Sample A		**Sample B**		**Sample C**	
Size (nm) ***Z average diameter plus/minus uncertainty***	***PDI*** ***Polydispersity index***	***Size (nm)*** ***Z average diameter plus/minus uncertainty***	***PDI*** ***Polydispersity index***	***Size (nm)*** ***Z average diameter plus/minus uncertainty***	***PDI*** ***Polydispersity index***

Lab ID:			
Method (or deviation)			
Sample preparation			
Internal standard /calibration			
Measurement	TEM □ SEM□		
Detection method/Instrumentation			
Additional comments			
Data report			
Sample A	**Sample B**	**Sample C**	
Microscopy SEM			
Microscopy TEM			