Institution: Heriot-Watt University

Unit of Assessment: UoA8 – Chemistry

Title of case study: Intelligent Testing Strategies for Nanomaterial Safety

Period when the underpinning research was undertaken: 2012 – 2014

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Vicki Stone	Professor (Director of IB3)	Nov 2010 – present
Helinor Johnston	Assoc Prof	Jan 2011 – present
Teresa Fernandes	Prof (Director of ILES)	Feb 2011 – present

Period when the claimed impact occurred: 2017 – Dec 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Heriot-Watt University led the European Commission FP7 project, ITS-NANO, which developed new terminologies that were adopted by European Chemicals Agency (ECHA) to clarify the requirements needed when chemical companies submit dossiers to comply with the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation, which includes the safety of nanomaterials. The outputs of ITS-NANO also identified the gaps in nanomaterial risk knowledge, and developed a strategy to fill these gaps, which was used by the industry-funded Centre for Chemical Safety Assessment ECETOC to develop grouping strategies for nanomaterials to streamline risk assessment. ITS-NANO outputs were also utilised by several international research consortia to formulate risk assessment strategies used by regulators and industry.

2. Underpinning research

The vast array of nanomaterials generated by nanotechnologies requires efficient mechanisms to assess safety according to regulatory requirements, and to ensure that nanotechnologies are sustainable. Industry is required to provide specific information to ECHA (and other regulators) regarding the risks of using and being exposed to the substances that they manufacture and market in Europe. Understanding of the safety of nanomaterials has lagged behind the enormous expansion in the variety of nanomaterials used in a wide variety of products (e.g. cosmetics, clothing, medicines, construction, electronics, coatings, biocides). Regulators and industry therefore need robust, clear and evidence-based strategies to provide exposure, toxicity and risk information. It is impossible to assess every nanomaterial on the market or under development on a case-by-case basis due to cost, time and the number of animals required.

The ITS-NANO project was funded via the European Commission Framework Programme 7 between 2012 and 2014. ITS-NANO, coordinated and led by Heriot-Watt University, defined what an intelligent testing strategy (ITS) for nanomaterial risk assessment should include, and a road-map to allow usable ITS to be developed in future.

Defining the components needed to make an ITS required an understanding of the underlying chemistry, exposure, ecotoxicity, and human hazard, as well as potential methods to combine different sources of existing information with new modelling approaches and experimental testing, to inform risk assessment [3.1]. Heriot-Watt led research inputs in relation to ecotoxicology by Fernandes and for human health by Johnston and Stone. This work allowed Heriot-Watt to identify the knowledge gaps relevant to assessing nanomaterial risks and developed novel tabulated summaries of information availability across all relevant discipline areas [3.3]. The gap analysis informed development of a roadmap to detail and strategically structure the research needed to allow ITS generation and use.
A major part involved stakeholder engagement with regulators (e.g. ECHA), policy makers (e.g. Danish NRCWE and Netherlands RIVM), industry (e.g. FIAT) and academics from across Europe and the USA. Heriot-Watt led the stakeholder engagement in terms of organising and chairing several workshops, as well as leading several of the breakout groups, combining the feedback from stakeholders and feeding this feedback into the roadmap.

A roadmap was generated that addressed the key disciplines. Within each section the key research priorities were represented by hexagonal stepping-stones that interlock. Heriot-Watt generated this innovative design of the roadmap, allowing multiple developments in parallel, feeding into a final common goal: development of an ITS. The vertical orientation of some hexagons demonstrated the need to consider multiple priorities simultaneously. In addition, the horizontal orientation indicated the direction of travel with time, with hexagons interlinked logically in order to provide the knowledge base for subsequent key priorities to develop upon. Each section interlinked to provide the information to logically group nanomaterials according to shared attributes that subsequently allows effective, streamlined risk assessment [3.2]. The output was designed to be visual, logical and scientifically evidence based. Furthermore, the roadmap was flexible with the ability to easily update and reorganise as knowledge becomes available.

The project included 10 partners from across Europe (Heriot-Watt University (UK), Veneto Nanotech (Italy), Aarhus University (Denmark), Italian Institute of Technology (Italy), Centro Ricerche Fiat (Italy), Fraunhover IME (Germany), Institute of Occupational Medicine (UK), National Research Centre for the Working Environment (Denmark), Joint Research Centre (Italy) and European Research Services (Germany)

3. References to the research

[3.1] Scott-Fordsmand, JJ, Pozzi-Mucelli, S, Tran, L, Aschberger, K, Sabella, S, Vogel, U, Poland, C, Balharry, D, Fernandes, T, Gottardo, S, Hankin, S, Hartl, MGJ, Hartmann, NB, Hristozov, D, Hund-Rinke, K, Johnston, H, Marcomini, A, Panzer, O, Roncato, D, Saber, AT, Wallin, H & Stone, V 2014, 'A unified framework for nanosafety is needed', *Nano Today*, vol. 9, no. 5, pp. 546-549. https://doi.org/10.1016/j.nantod.2014.07.001

[3.2] Stone, V, Pozzi-Mucelli, S, Tran, L, Aschberger, K, Sabella, S, Vogel, U, Poland, C, Balharry, D, Fernandes, T, Gottardo, S, Hankin, S, Hartl, MGJ, Hartmann, N, Hristozov, D, Hund-Rinke, K, Johnston, H, Marcomini, A, Panzer, O, Roncato, D, Saber, AT, Wallin, H & Scott-Fordsmand, JJ 2014, 'ITS-NANO - Prioritising nanosafety research to develop a stakeholder driven intelligent testing strategy', *Particle and Fibre Toxicology*, vol. 11, no. 9, 9. https://doi.org/10.1186/1743-8977-11-9

The third publication was invited following an invited keynote presentation at a Society of Risk Analysis workshop in Washington. The paper incorporates some of the gap analysis tables derived from the ITS-NANO project:

[3.3] Stone, V, Johnston, HJ, Balharry, DC, Gernand, JM & Gulumian, M 2016, 'Approaches to Develop Alternative Testing Strategies to Inform Human Health Risk Assessment of Nanomaterials', *Risk Analysis*, vol. 36, no. 8, pp. 1538-1550. https://doi.org/10.1111/risa.12645

4. Details of the impact

The global market for nanotechnology products was valued at USD22,900,000,000 in 2013 and increased to about USD39,200,000,000 in 2016. This market is expected to reach about USD90,500,000,000 in 2021, a compound annual growth rate (CAGR) of 18.2% from 2016 to 2021. (https://www.bccresearch.com/market-research/nanotechnology). It is impossible to assess every nanomaterial on the market or under development on a case-by-case basis due to cost, time and the number of animals required. ITS were therefore urgently required to improve efficiency and to enhance the ethics of nanotechnologies. ITS application combined with grouping approaches increased the confidence in the safe use of nanomaterials and the sustainable development of nanotechnology industries.

The outputs of ITS-NANO are relevant to industry, regulators and policy makers, because ITS:

- Reduces the cost and time of safety testing, not only for risk assessment under REACH, but also under e.g. the Biocides, Cosmetics, and Foods Directives. The ITS addresses the urgent need to increase the efficiency of testing and reduce the use of experimental animals in relation to regulatory risk assessment and support the safer design of quality products.
- Enables grouping of nanomaterials based upon a range of descriptors of both hazard and exposure, including physicochemical, (eco) toxicological, toxicokinetic and/or environmental fate properties. Groupings reduce the need for case-by-case assessment of nanomaterials and enable read-across from source to target nanomaterials to facilitate industry to generate dossiers for consideration under regulations such as REACH.
- Aids development of safer products and consequently enhancing the trust of consumers and society in nanotechnology.

The project included significant and extensive stakeholder engagement. A series of stakeholder workshops took place in September 2012 and March 2013. Each workshop included key experts from academia (e.g. Duke University, USA), industry (e.g. Unilever, BASF, Nanotechnologies Industries Association) and regulatory bodies (e.g. ECHA, Dutch RIVM, European MHRA). The final project report was launched at a large international conference (EuroNanoForum) in Dublin (2013). Through these sequential stakeholder workshops, we translated knowledge gaps into research priorities, which were prioritised in terms of both urgency and feasibility. This stakeholder engagement ensured the relevance of the project, but also aided in the dissemination, as those who participated became the strongest advocates leading to inclusion of ITS-NANO concepts in a number of international initiatives, events and publications.

Policy Impact

The outputs and terminology of ITS-NANO are used by the regulator ECHA within the guidance/best practice documents for nanomaterial grouping/read-across relevant to

REACH. ECHA, Recommendations for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals V2 [5.1] include [3.2] in the citation list, and the ITS-NANO coined terminology in the text and diagrams (with citation number) as a mechanism for structuring the exposure, hazard and risk information requirements for industries. The relevance to industry is expanded below. As a consequence of the impact of ITS-NANO, Stone was invited by the EU to lead the Research Regulatory Roadmap for Nanomaterials.

Industrial Impact

REACH affects any company internationally (inside or outside Europe) who wishes to sell their products within Europe. Therefore, industries making and using nanotechnologies (e.g. BASF), are also beneficiaries of the ITS-NANO outputs when generating regulatory dossiers required to allow marketing and sale of products within the EU. The outputs of ITS-NANO have helped such companies in the design of safety assessment strategies for nano-enabled products, e.g. Senior Principal Scientist, BASF stated: '*The ITS nano results were used within BASF to anticipate the integration of different aspects in the risk assessment of nanomaterials. The hexagon graphics presented how the properties are interlinked. We initiated research projects to support the developments along these linkages.'* [5.2]
The outputs of ITS-NANO are cited by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), which is funded by 35 international chemical industries, including BASF, ECHA, Solvay, Nouryon, L'Oreal, Evonik, Dupont, Dow, Bayer. ECETOC used [3.2] to guide proposals on grouping of inhaled nanomaterials [5.3, 5.4, 5.5]. In addition the outputs informed joint projects between regulators, policy makers, industry and academics, in order to provide tools for evidence-based risk assessment and regulation of nanomaterials [5.6]. The ECETOC tool has been cited over 139 times in the peer reviewed literature (04/11/20 PubMed).

Both policy and industrial impacts are sustained as the market for nanomaterials continues to expand, accompanied by the requirement to submit risk assessments according to REACH. Every regulatory dossier submitted to ECHA that includes the use of grouping and read-across of nanomaterials are currently required to structure the information provided according to the terms generated by ITS-NANO, regardless of whether they use the ECETOC tool or not. As of November 2020 there have been 101,634 submissions to REACH. Currently 332 nanomaterials are listed as nanomaterials on the EU market (https://euon.echa.europa.eu/search-for-nanomaterials), with each of these nanomaterials including several-hundreds of forms (e.g. varied length for a carbon nanotube, varied coating for a silica nanoparticle). For chemicals (not just nanomaterials), ECHA state that '*Grouping of substances and read-across is one of the most commonly used alternative approaches for filling data gaps in registrations submitted under REACH'.*

Consultants supporting companies with the generation of dossiers to comply with REACH have also indicated that the phrases and structures generated by ITS-NANO go beyond nanomaterials, to inform regulatory dossier generation for chemicals. Kai Paul, Regulatory Consultant, Blue Frog, on ITS-NANO stated; 'What they are'*, 'where they go' and 'what they do', three fundamental pillars which cut through the jargon and give further clarity to the nanoform data requirements under REACH and why they are there. The simplest terminology but one of the most powerful ways to build a robust, understandable and transparent scientific argument for grouping and to help explain why certain tests will aid in doing this. Digestible for Registrants, Regulators and Trainees'*

The impact of ITS-NANO is ongoing through European H2020 funded project GRACIOUS. GRACIOUS has used the concepts of ITS-NANO and ECETOC (which was limited to inhaled nanomaterials), to inform a more expansive grouping and read-across framework, relevant to all routes of exposure (inhalation, ingestion, dermal) and environmental compartments (air, water, sediments, soil). This Framework is for use by regulators such as ECHA and industries, to support regulatory dossier generation, as well as to inform safe-by-design innovation within industry [5.7]. Stone is the co-ordinator of GRACIOUS, which includes 26 partner institutes from the EU and US, including industry (e.g. BASF), policy makers (e.g. EU-JRC, Netherlands RIVM, Danish NRCWE, German Bfr). Kai Paul of Blue Frog on GRACIOUS said, *'By building not only the framework but the tools to streamline compliance strategies for nanoforms via grouping and read-across of nanoforms, the GRACIOUS project will reduce financial burden and animal testing giving rise to a more ethical, easier pathways to market. Ultimately this can only lead to, a more accessible and larger market, innovation and the wider application of this key enabling technology'.*

5. Sources to corroborate the impact

[5.1] ECHA, Guidance Appendix R.6-1: Recommendations for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals (Draft (Public) Version 2.0. 2019.

[5.2] Letter from BASF which confirms the ITS nano results were used within BASF.

[5.3] Gajewicz, A, et al. 2014, 'Decision tree models to classify nanomaterials according to the DF4nanoGrouping scheme', *Nanotoxicology*, vol. 12, no. 1. https://doi.org/10.1080/17435390.2017.1415388

[5.4] Arts, J, et al. 2015, 'A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping)'. *Regulatory Toxicology and Pharmacology*, vol. 71, no. 2, pp. S1-S27. https://doi.org/10.1016/j.yrtph.2015.03.007

[5.5] Landsiedel, R, et al. 2017, 'Safety assessment of nanomaterials using an advanced decision-making framework, the DF4nanoGrouping'. *Journal of Nanoparticle Research*, vol. 19 no. 5. https://doi.org/10.1007/s11051-017-3850-6

[5.6] Bos, P, et al. 2015 'The MARINA Risk Assessment Strategy: A Flexible Strategy for Efficient Information Collection and Risk Assessment of Nanomaterials', *International Journal of Environmental Research and Public Health*, vol. 12, no.12, pp.15007–15021. http://dx.doi.org/10.3390/ijerph121214961.

[5.7] Stone, V, et al. 2020, 'A framework for grouping and read-across of nanomaterials-supporting innovation and risk assessment', *Nano Today*, vol. 35, 100941. https://doi.org/10.1016/j.nantod.2020.100941

[5.8] Giubilato, E, et al. 2020, 'Risk Management Framework for Nano-Biomaterials Used in Medical Devices and Advanced Therapy Medicinal Products', *Materials*, vol. 13, no. 20, 4532. https://doi.org/10.3390/ma13204532