



USE OF STRUCTURAL ALERTS OF HAZARD IN MANAGING RISK

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MANAGING NANOTECHNOLOGY RISK

Why?



- **Safety & Sustainability**
 - Prevention of harm
 - Perception (real vs perceived risk)



commentary

The insurability of nanomaterial production risk

Martin Mullins, Finbarr Murphy, Lijana Baublyte, Eamonn M. McAlea and Syed A. M. Tofail

Without insurance the long-term sustainability of nanotechnology is questionable, but insurance companies are encumbered by their institutional memory of losses from the asbestos crisis and the absence of suitable actuarial models to measure the potential risks of nanotechnology. Here we propose a framework that supports the transfer of nanomaterial production risk to the insurance sector.

Nature Nanotechnology, February 2007

DEALING WITH RISK

How?

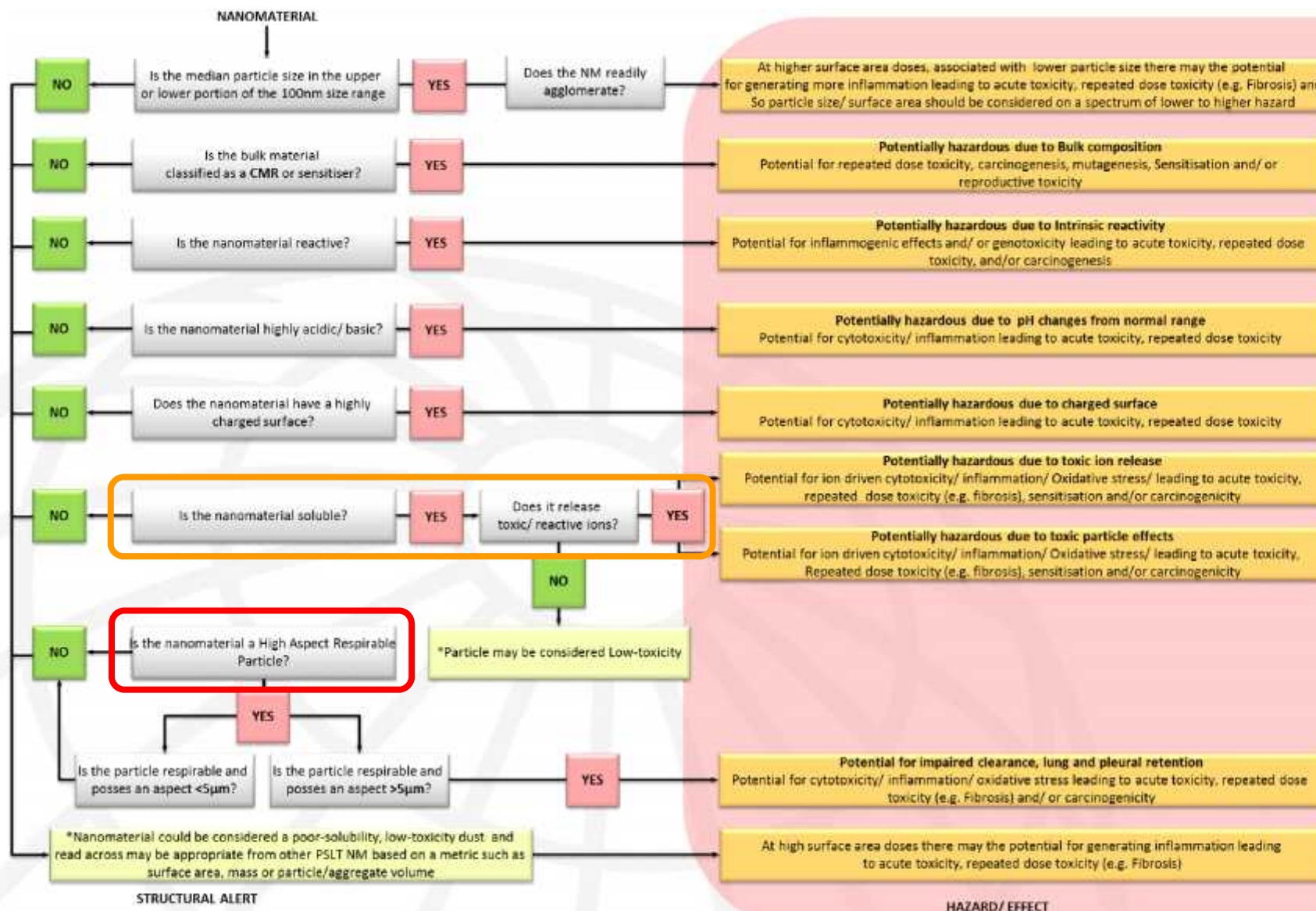


- Concerns over risk are dealt with through knowledge – unknowns cause uncertainty, fear and speculation
- Once risk are identified, they can be dealt with by:
 - Replacement
 - Control/ reduce exposure or,
 - Addressing the hazardous component
- Generating knowledge can be expensive, time consuming
- Paradigms in toxicology can help identify physicochemical properties that can infer potential hazards – structural alerts
- The Sanowork project aimed to identify these and interrogate a panel of nanomaterials before and after modification with an aim reduce intrinsic risks through a safe-by-design strategy based on physchem properties then test them to see if such an approach was predictive



STRUCTURAL INDICATORS OF TOXICITY

Rapid Identification of Potential Problem Properties



Toxicological Testing Recommended to Quantify Hazard

HIGH ASPECT RESPIRABLE PARTICLES

High Aspect Particles - a Problem for the Lungs



Fibres are a well known example of large yet respirable particles which can cause problems for clearance in the deep lung

Thin

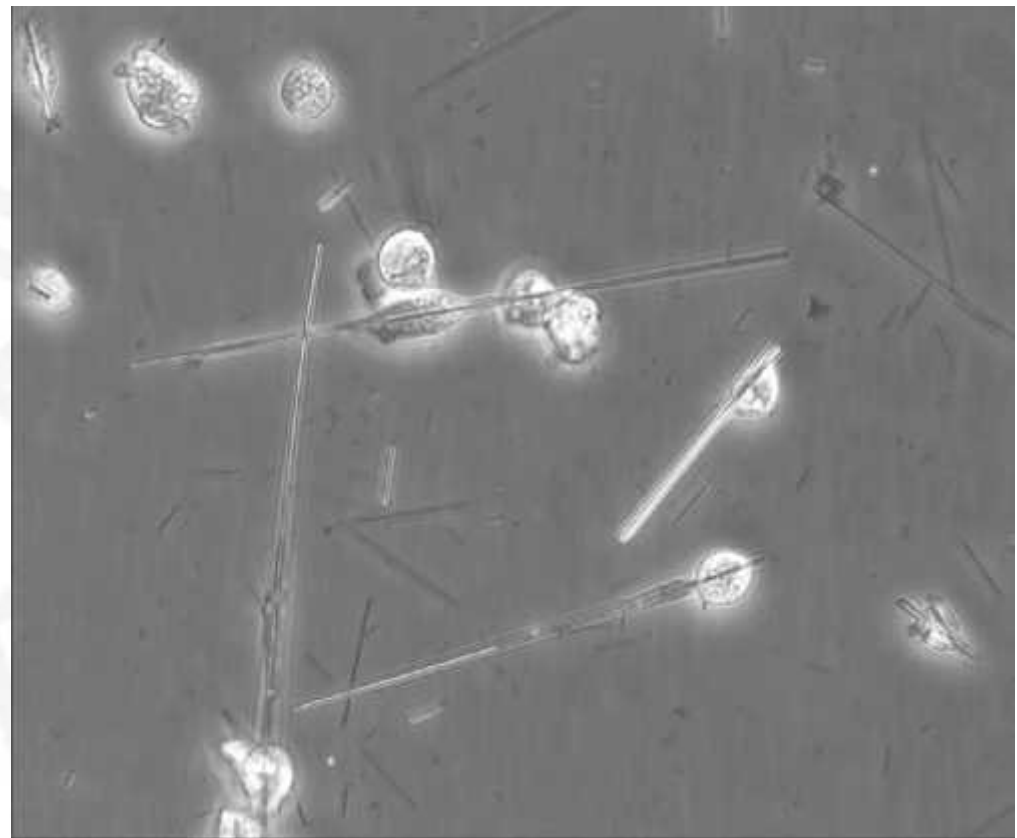
Small aerodynamic diameter
enables deposition beyond the
ciliated airways

Bio-persistent

Retains its shape
over long-term
residence in the
lungs

Long

Cannot be completely
enclosed by a macrophages
producing frustrated
phagocytosis



TITANIUM DIOXIDE NANOFIBRES

Hazard Identification & Mitigation Based on Length

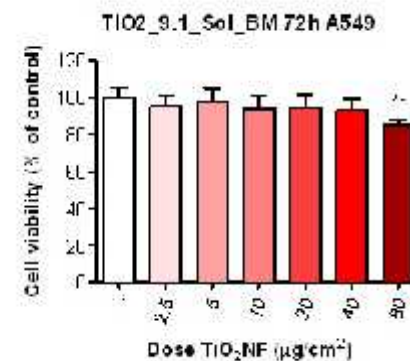
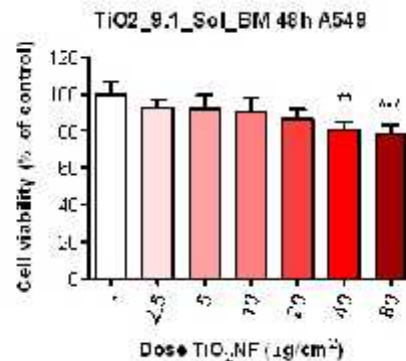
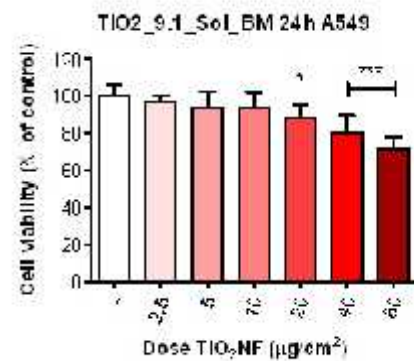
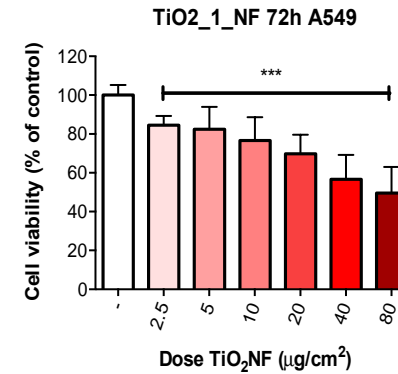
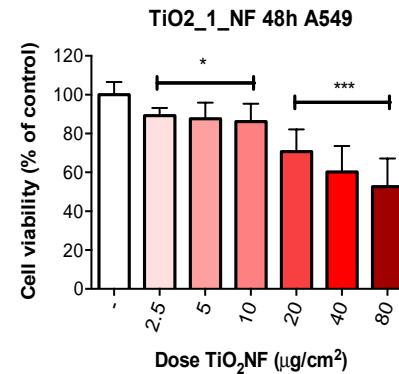
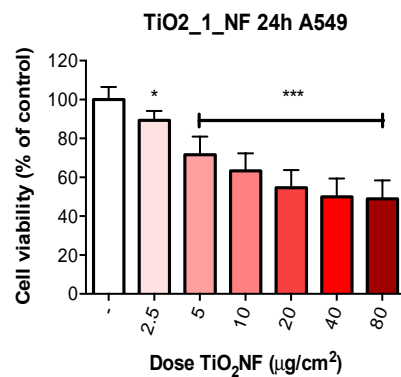


Pristine Material

= TiO₂ Nanofibres (Ti_{9.1}_NF) – 9.9µm (29:1)

Modified Material

= Ball milled TiO₂ nanofibres (TiO₂_9.1_Sol.BM) – 2.1µm (5:1)



Effective Remediation

TITANIUM DIOXIDE NANOFIBRES

Hazard Identification & Mitigation Based on Length

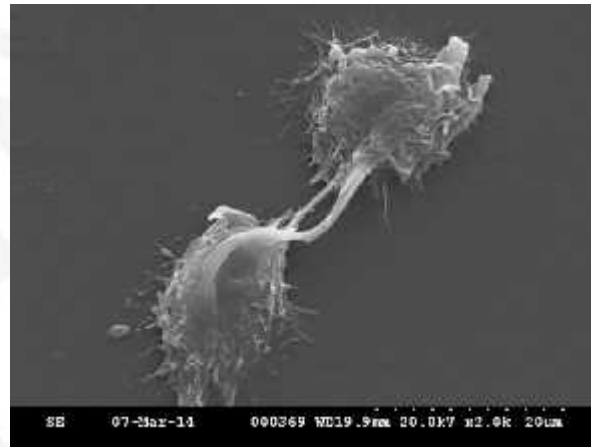


Macrophage interactions with TiO_2 Nanofibres

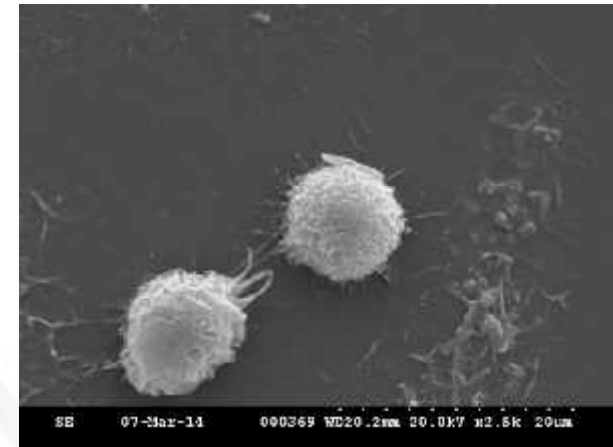
Crocidolite Fibres



TiO_2 Long Nanofibres



Ball Milled TiO_2 NF



Effective Remediation

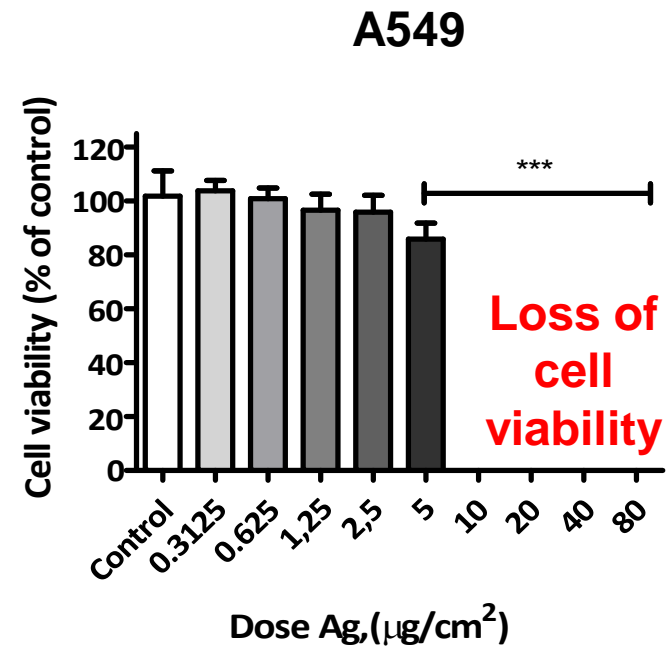
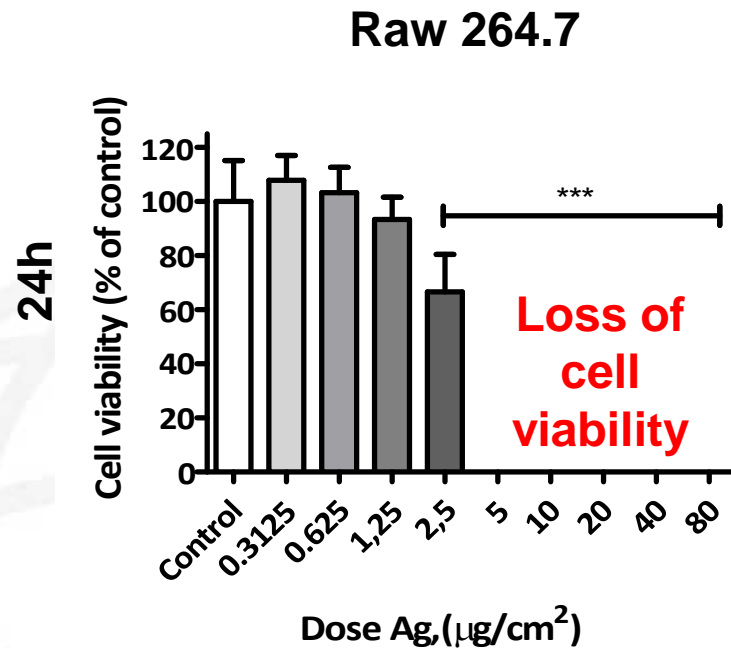
SILVER NANOPARTICLES

Hazard Identification & Mitigation Based on Toxic Ion Release



Pristine Material = Silver Nanoparticles (Ag_1_sol)

Modified Material = Spray dried, silica coated, gel coated, ultra-filtrated



IC_{50} (Raw 264.7) = $2.8 \mu\text{g}/\text{cm}^2$

IC_{50} (A549) = $5.9 \mu\text{g}/\text{cm}^2$

High Cytotoxicity

Mitigation of toxicity with modified materials?

SILVER NANOPARTICLES

Hazard Identification & Mitigation Based on Toxic Ion Release



-Ag_15_Sil_Sol
-Ag_16_Sil_Sol
-Ag_25_Sil_Sol_SD_US
-Ag_26_Sil_Sol_SD_US
-Ag_27_Sol_SD_US
-Ag_30.3_Gel_Sol

IC₅₀ not
significantly
different from
pristine

No remediation

-Ag_23_Sil_Sol
-Ag_24_Sil_Sol

Partial remediation

Ag_31.3 Sol UF

Effective remediation

IC₅₀ (Raw 264.7)= 42.3 µg/cm² (vs. 2.8 µg/cm²)

IC₅₀ (A549)= >80 µg/cm² (vs. 5.9 µg/cm²)

WAS THE USE OF STRUCTURAL ALERTS PREDICTIVE OF TOXICITY?



- **Titanium Dioxide Nanofibres** - The analysis of the properties of TiO₂ nanofibers suggested that the long fibres within the pristine TiO₂ NF was of greatest concern, although the ball milled version was not without concern.
 - Analysis showed confirmed fibre shape/ length as a issue significant issue.
 - However, the ball-milled TiO₂ NF caused higher levels of macrophage stimulation and inflammation - not predicted
- **Silver Nanoparticles** – The analysis of the properties of AgNP suggested that the presence of silver ions was the greatest concern for toxicity and those samples with reduced availability of silver ions (e.g. solubility) would display lower toxicity.
 - The toxicological analysis showed this was the case and that ultra-filtration was a successful remediation strategy.



PERFORMANCE



The use of structural alerts to estimate the relative toxicity of pristine vs. remediated forms of various nanomaterials was effective in indicating toxicity and modifications of this. **However:**

- the tool and approach lacks a quantitative aspect such as being able to band properties into low, medium, or high hazard based on parameter quantities (e.g. redox activity) – **unless this is done based on biological effect/ outcome, it is meaningless**
- the approach, due to a lack of quantitative measures, lacks resolution to estimate differences between materials which, to the most part appear the same across many properties and differ only in a small way.
- Not all endpoints correlated toxicological outcome (e.g. acid/basicity, surface charge)



Thank You for your Attention

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SUMMARY



PL	Material	Evaluated endpoints	Benchmark	Successful strategy	Remediated endpoint
PL1	ZrO ₂ NP (P + 3 modified)	Cell viability/cytotoxicity* Oxidative stress**, Hemolysis Macrophage activation***, TEER	TiO ₂ NP	No	----
PL4	TiO ₂ NF (P + 1 modified)	Cell viability/cytotoxicity* Oxidative stress**, Hemolysis Macrophage activation***, TEER	Crocidolite MWCNT	Yes (1/1) Ball milling	All but macrophage activation
PL5	Ag NP (P + 9 modified)	Cell viability/cytotoxicity* Oxidative stress**	AgNO ₃	Yes (3/9) Ultrafiltration Coating with Silica (heterogeneous nucleation)	All
PL5	TiO ₂ NP (P + 6 modified)	Cell viability/cytotoxicity* Oxidative stress**, Hemolysis Macrophage activation***, TEER	TiO ₂ NP	No	----
PL6	MWCNT (P + 2 modified)	Cell viability/cytotoxicity* Oxidative stress**, Hemolysis Macrophage activation***, TEER	---	Yes (2/2) Freeze granulation Spray Drying	Macrophage activation

* Cell viability/cytotoxicity have been assessed with 6 different types of tests

** Oxidative stress has been assessed with 5 different types of tests

*** Macrophage activation (pro-inflammatory activity) has been assessed with 5 different types of tests

WHAT IS A PREVENTABLE EVENT?

The Extreme Example That Has Shaped Perception



Global estimates suggest at least **90,000** people a year die from asbestos related disease

Source: WHO 2006 Elimination of asbestos-related disease

