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Responsible and safe nano-innovations: How to address nano-related safety issues in industrial innovation processes

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Introduction

Nanomaterials: Properties & applications

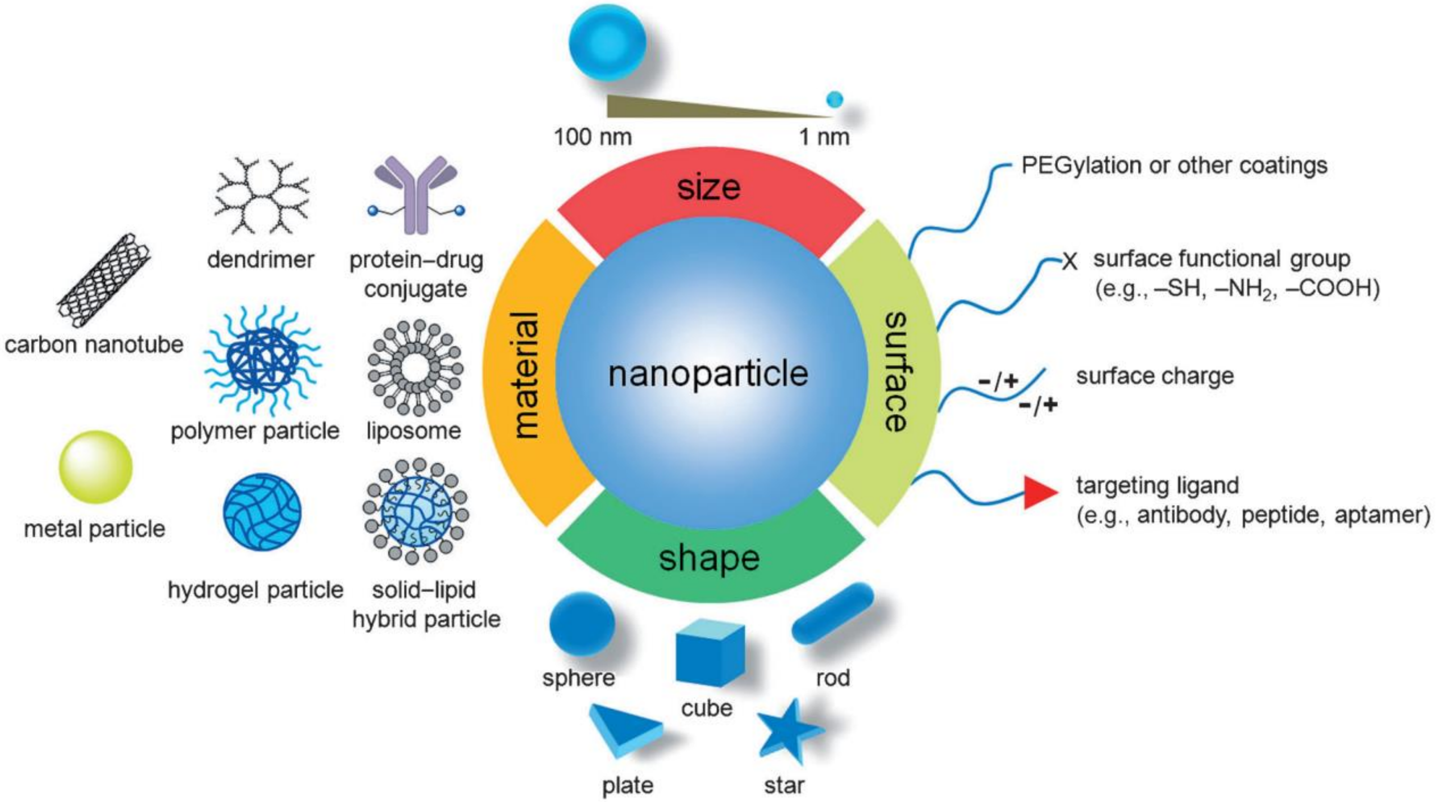
"A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.

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 %.

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

EC Recommendation on the definition of a nanomaterial (2011/696/EU)

Nanomaterials: Properties & applications



Sun, Tianmeng, et al. "Engineered nanoparticles for drug delivery in cancer therapy." *Angewandte Chemie International Edition* 53.46 (2014): 12320-12364.

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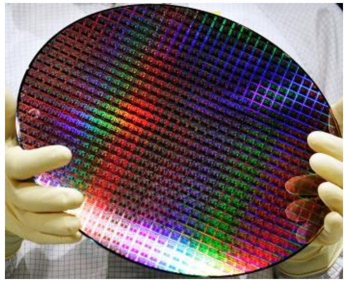
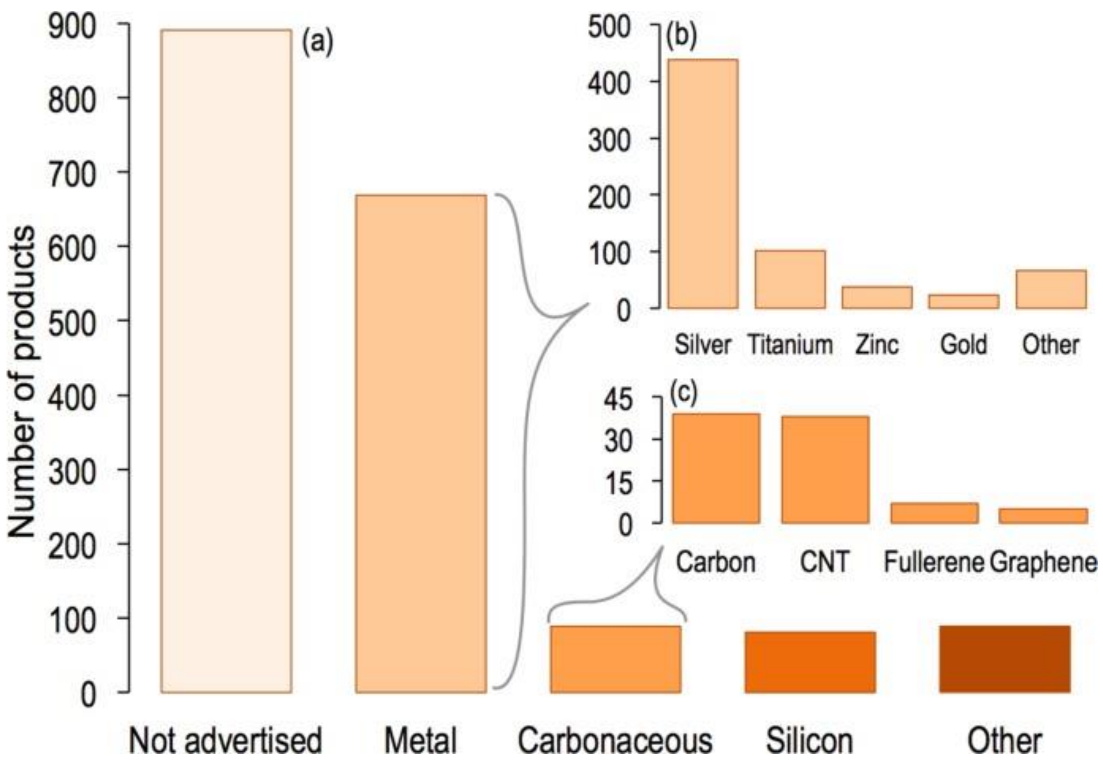
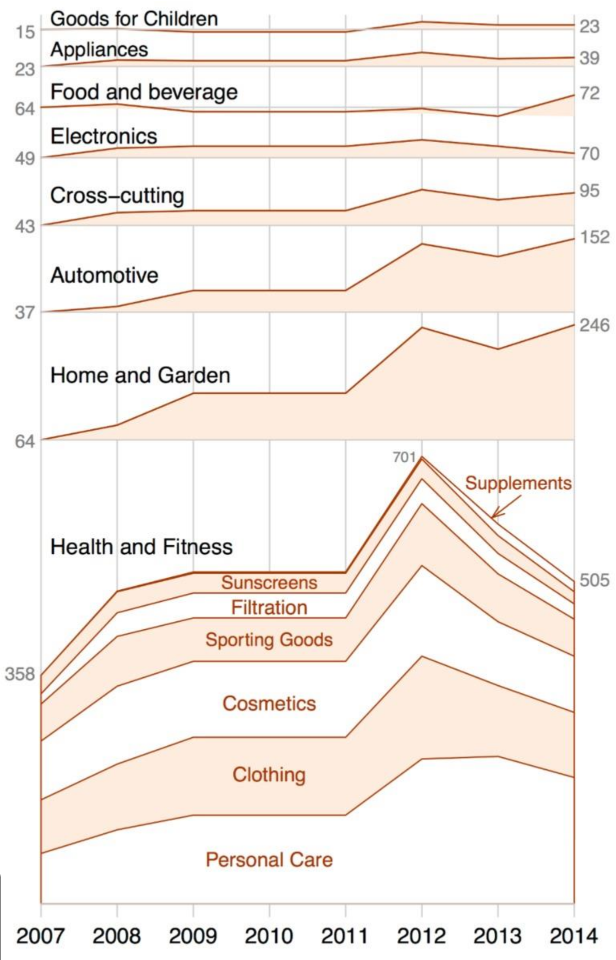
Nanomaterials: Properties & applications

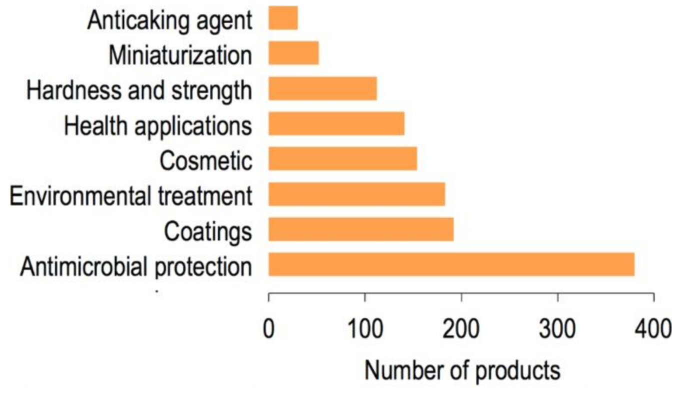
- Nanomaterials have a great variety of applications used in everyday life



Nanomaterials: Properties & applications







Vance, Marina E., et al. "Nanotechnology in the real world: Redeveloping the nanomaterial consumer products inventory." *Beilstein journal of nanotechnology* 6 (2015): 1769.

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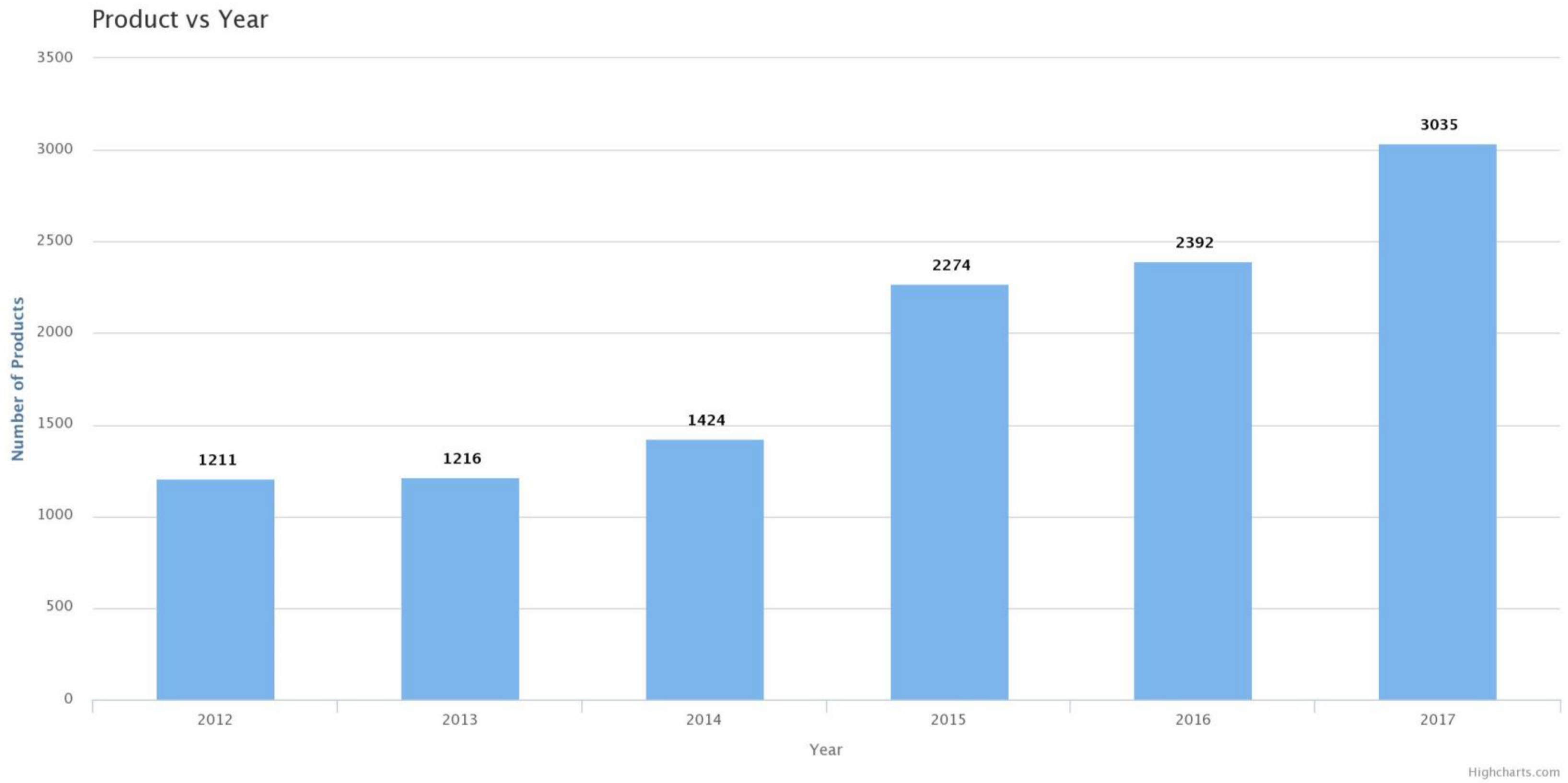
Nanomaterials: Properties & applications

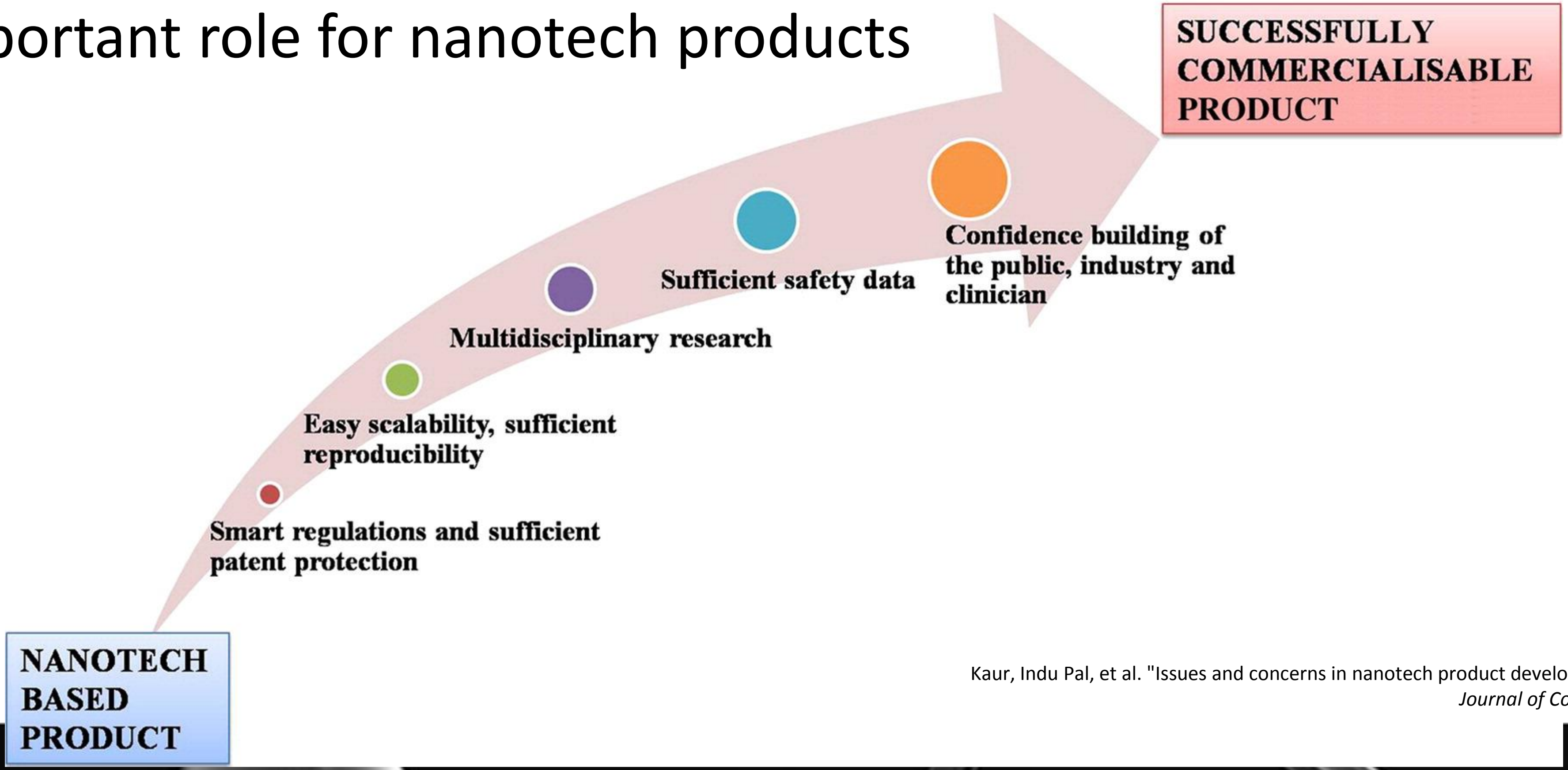
- Increasing number of available nano-enabled products over time



The Nanodatabase
http://nanodb.dk/en/

Nanomaterials: Properties & applications

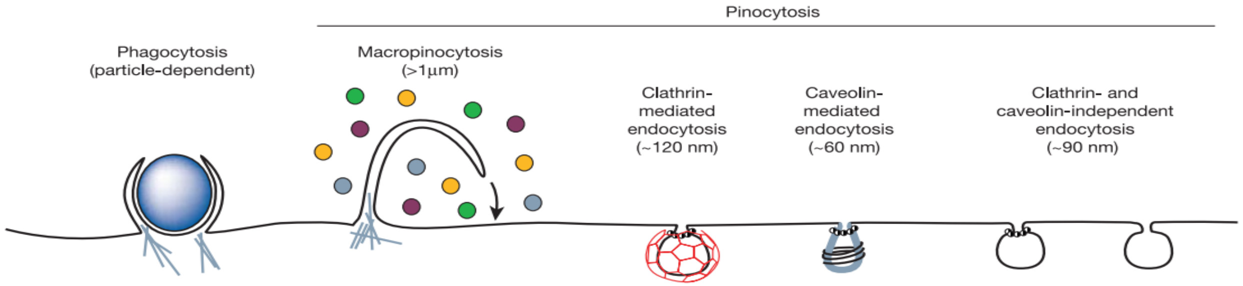
- Sufficient safety data
  play important role for nanotech products

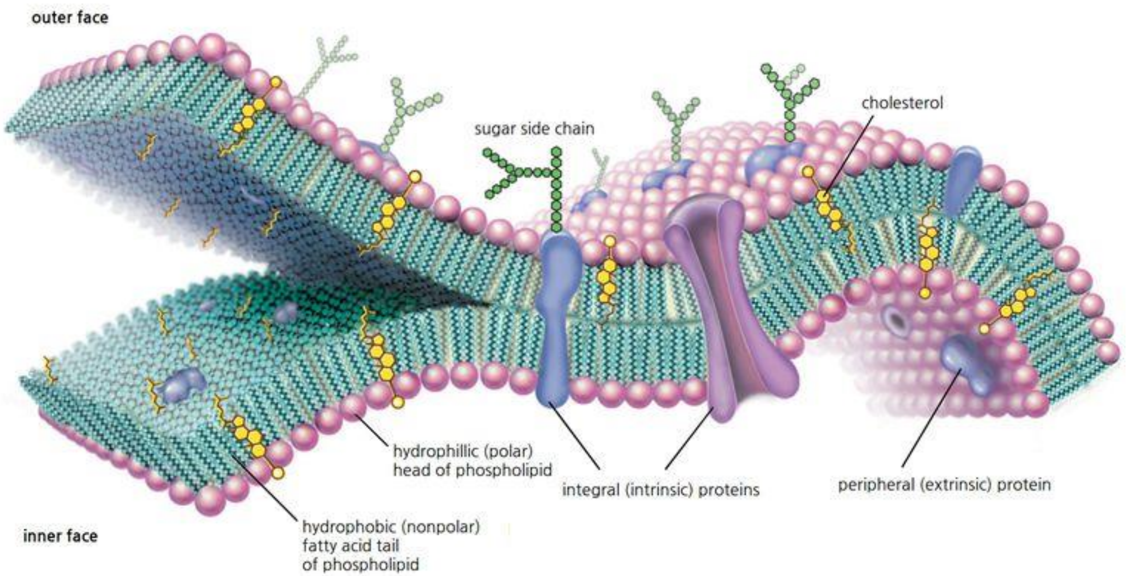


Kaur, Indu Pal, et al. "Issues and concerns in nanotech product development and its commercialization." *Journal of Controlled Release* 193 (2014): 51-62.

Nano-related safety issues

- Nanoparticles can overcome biological barriers that protect physiological environments
- Different transport mechanisms
  - Paracellular vs. transcellular transport

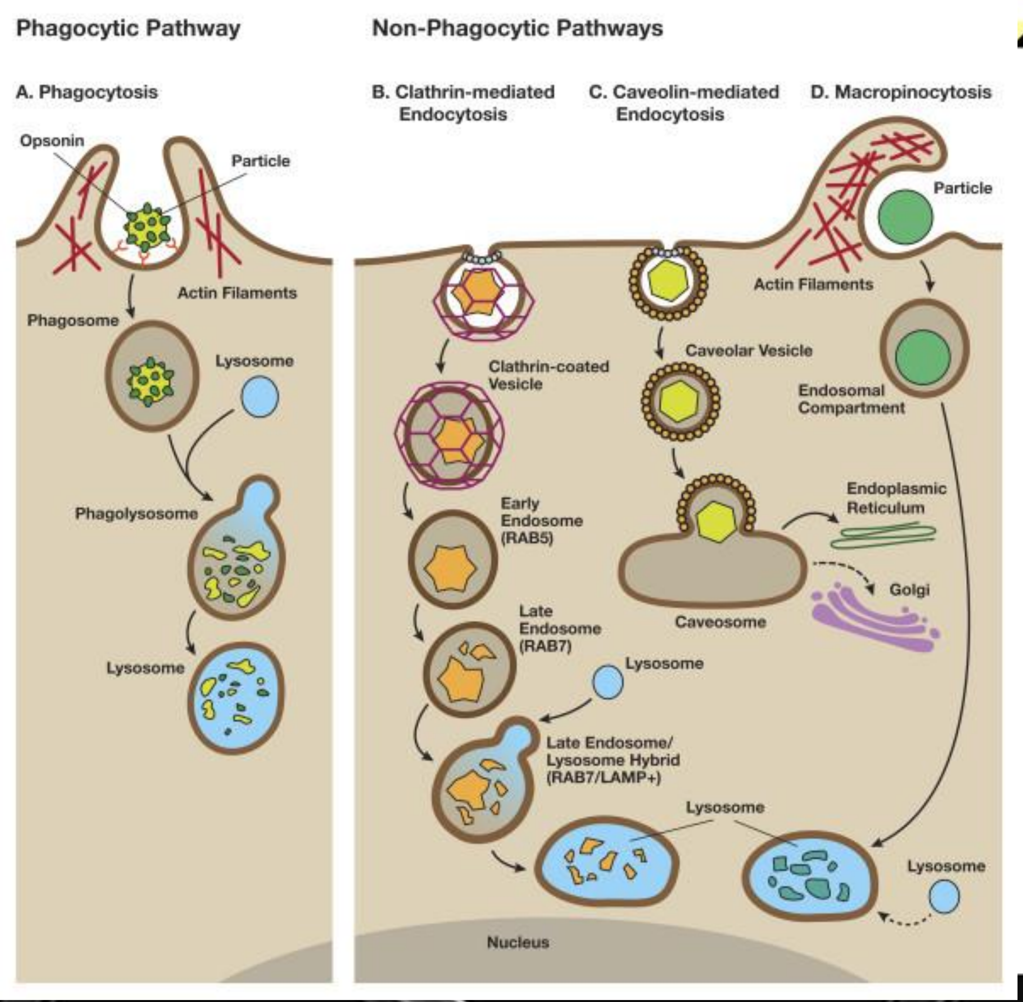




Conner, Sean D., and Sandra L. Schmid. "Regulated portals of entry into the cell." *Nature* 422.6927 (2003): 37.

Nano-related safety issues

- Due to their small size, nanoparticles can be internalized by cells, and may have adverse effects to humans and the environment
- Different endocytosis-mechanisms
- Influenced by nanoparticle size, shape, charge, surface
- Biological fate of nanoparticles → long-term effects?



Stern, Stephan T., Pavan P. Adiseshaiah, and Rachael M. Crist. "Autophagy and lysosomal dysfunction as emerging mechanisms of nanomaterial toxicity." *Particle and fibre toxicology* 9.1 (2012): 20.

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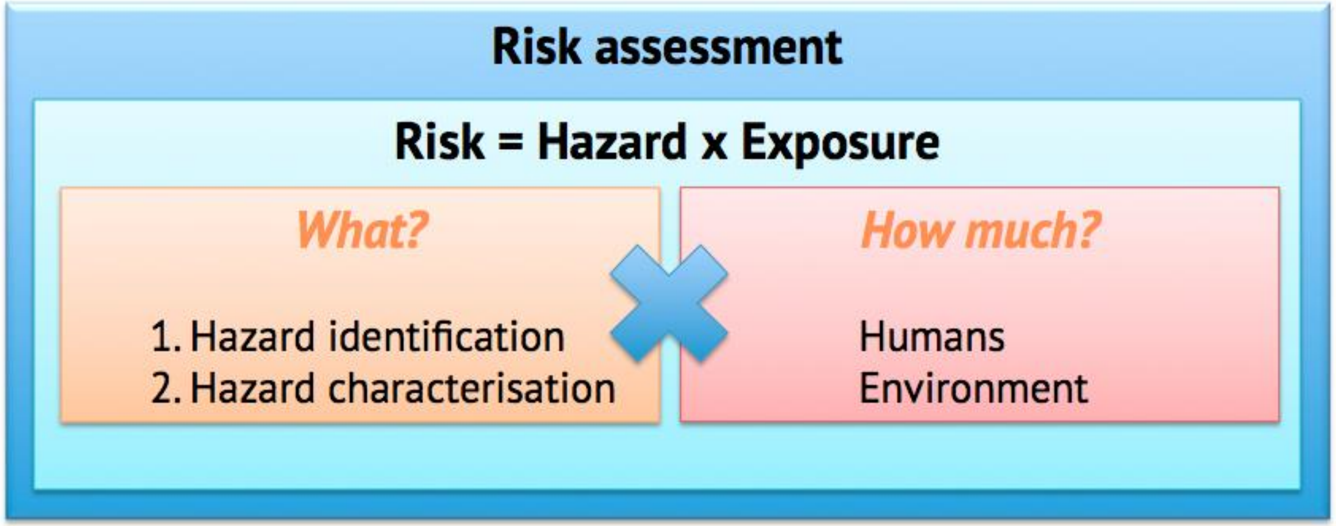
Safety assessment

Safety assessment

- Chemical Safety Assessment according to REACH:



- REACH → EU regulation since 2006
  Registration, **E**valuation, **A**uthorisation and Restriction of **Ch**emicals

Safety assessment

	HAZARD	EXPOSURE	RISK
A			hazard, but no exposure → no risk indicated
B			exposure, but no hazard → no risk indicated

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Safety assessment

- REACH definition of **hazard assessment**:
  Collection and evaluation of all available and relevant information on the used substance in order to identify potential hazards of the substance
  - Safety data sheets
  - EC recommendations
  - Exposure limit values
  - Peer reviewed data, scientific literature, relevant databases
  - Lack of data → further tests needed

Safety assessment

- OECD recommended list of endpoints for testing nanomaterials

Nanomaterial information
(e.g., structural formula, composition, morphology, catalytic activity)

Environmental fate
(e.g., dispersion stability in water, biodegradability, soil simulation testing, sediment simulation testing, degradation products)

Mammalian toxicology
(e.g., pharmacokinetics, toxicokinetics (ADME), acute toxicity, repeated dose toxicity)

Phys-chem properties
(e.g., agglomeration, aggregation, dispersability, dustiness, TEM, particle size distribution, specific surface area, zetapotential)

Environmental toxicology
(e.g., short term/long term effects on sediment species, soil species, terrestrial species, micro-organsisms; effects on activated sludge at WWTP)

Material safety
(e.g., flammability, explosivity, incompatibility)

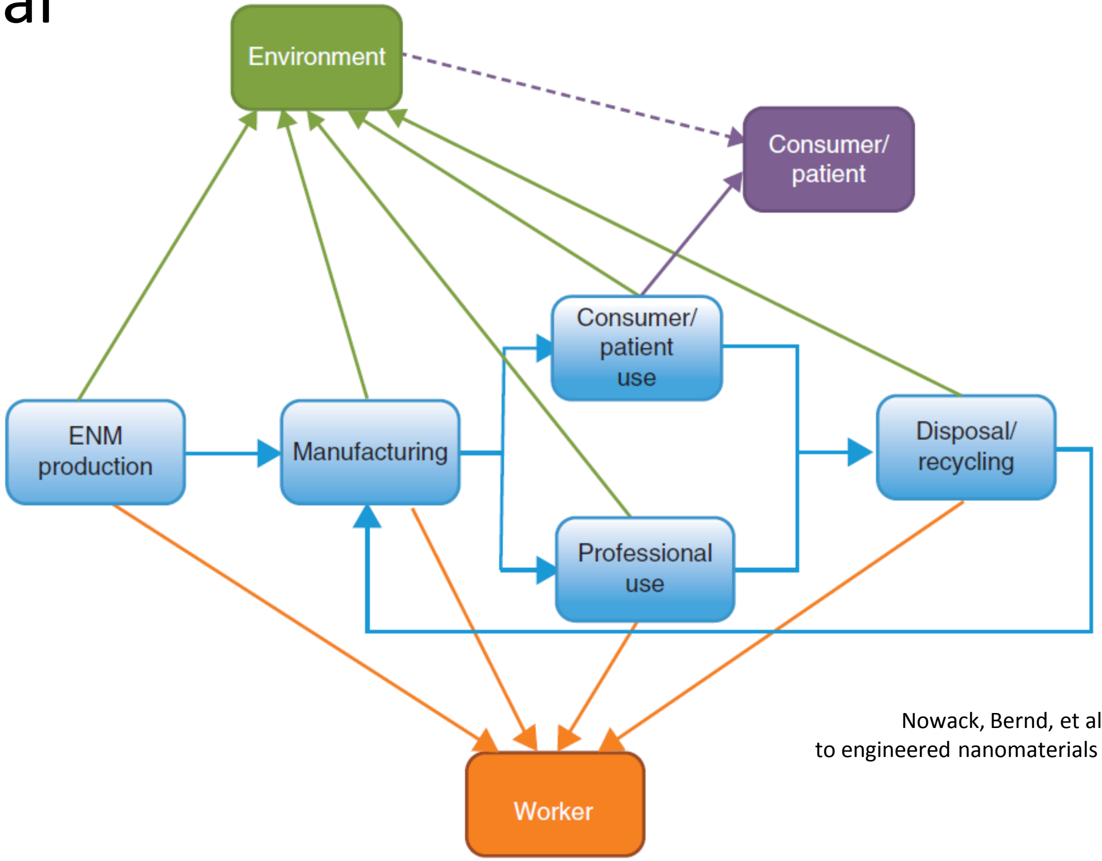
OECD Environment, Health and Safety Publications
Series on the Safety of Manufactured Nanomaterials No. 27

Safety assessment

- REACH definition of **exposure assessment**:
  Definition of possible levels of exposure under reasonable conditions of use
- Different types of exposure:
  - Occupational exposure
  - Environmental exposure
  - Consumer exposure
- Considering biological pathways along the whole life cycle

Safety assessment

- Exposure assessment includes the entire life cycle of nanomaterials from synthesis to disposal



Nowack, Bernd, et al. "Analysis of the occupational, consumer and environmental exposure to engineered nanomaterials used in 10 technology sectors." *Nanotoxicology* 7.6 (2012): 1152-1156.

Safety assessment

- Different exposure routes
  - Inhalative: most common route; breathing in aerosols, fibres, particles, etc.
  - Dermal: absorption through skin
  - Ingestive (oral uptake): mouth contact with contaminated item
  - Injective: contact with needles or sharp items

Safety assessment

- REACH definition of **risk assessment**:
  Characterization of risk by comparing the levels of exposure and threshold levels below which risks for human health and for the environment
- Threshold levels:
  - **D**erived **N**o **E**ffect **L**evel (DNEL) → limit for occupational exposure
  - **P**redicted **N**o **E**ffect **C**oncentration (PNEC) → limit for environmental exposure
- Risk Characterization Ratio (RCR)
  - RCR > 1: risk is indicated under selected conditions
  - RCR < 1: no risk is present under selected conditions

$$RCR\ human\ health = \frac{Exposure}{DNEL} \qquad RCR\ enviroment = \frac{PEC}{PNEC}$$

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Safety assessment: bulk vs. nano

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"Classic" chemical safety assessment

REACH recommended tool to calculate RCRs: ECETOC TRA

- Based on mandatory inputs related to materials phys-chem properties, operational settings and RMM in place
- Calculates RCRs under selected conditions
- Considers worker, environment and consumer exposure

Nanosafety assessment

Various frameworks/tools available

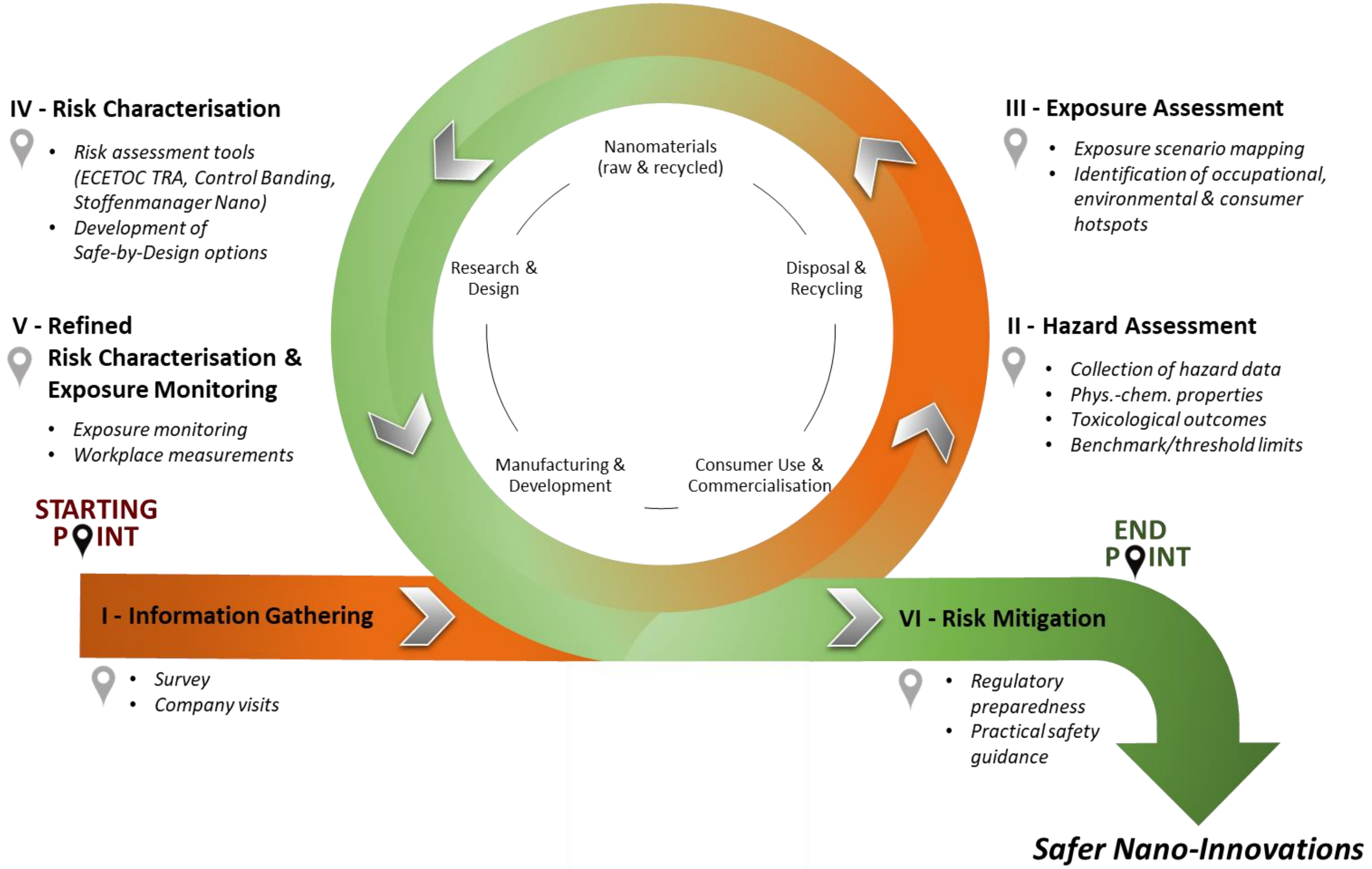
Limited applicability →

- What kind of nanomaterial?
- How is nanomaterial used?
- Worker exposure?
- Environmental exposure?
- Consumer exposure?

Safety assessment: bulk vs. nano

- Challenges in nanosafety assessment
  - Definition of the term nanomaterial
  - Availability of data
  - Centralized database providing hazard data
  - Standardization of test methods
  - Lack of generally accepted, evidence-based exposure limit values (DNELs/PNECs)
  - Harmonized guidelines/approaches easy to implement, especially for SMEs

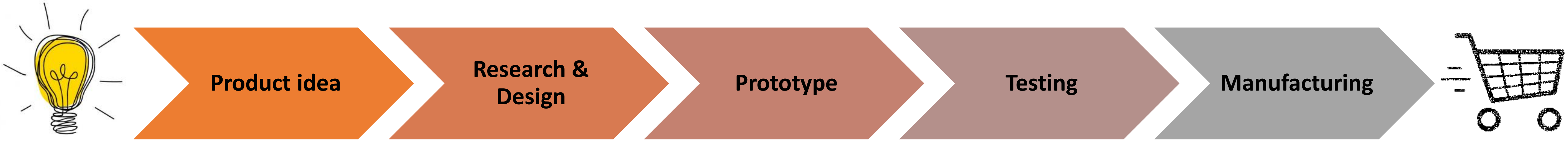
Nanosafety strategy



Safe-by-Design Approaches

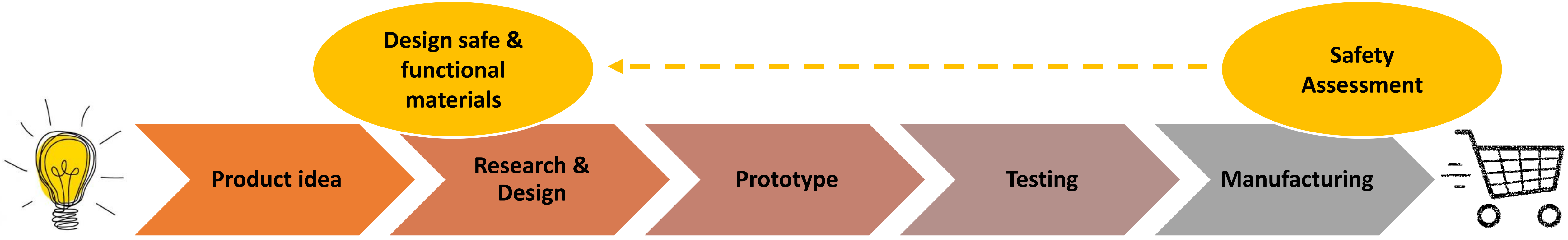
Safe-by-Design Approaches

- Innovation chain scheme:
  From initial idea to market introduction



Safe-by-Design Approaches

- Considering safety aspects already in the design phase
  → „design-out“ hazardous properties to minimize possible risks from the very beginning



→ moving/integrating safety considerations into design phases

Safe-by-Design Approaches

- Aims and benefits
  - Early and easier identification of uncertainties and risks
  - Reduction of uncertainties and risks
  - Preparedness to meet todays and future regulatory requirements
  - Well-balanced safety, functionality and costs
  - Better design of products and better business models

Safe-by-Design Approaches

- Safe-by-Design provides a safety net…
  - for innovators to avoid confrontation with safety/regulatory issues later on in the innovation process,
  - for investors and insurers to minimize uncertainty about health risks,
  - for regulators to minimize casualties,
  - for society to benefit from safer innovative products.

Application examples in industrial innovation processes

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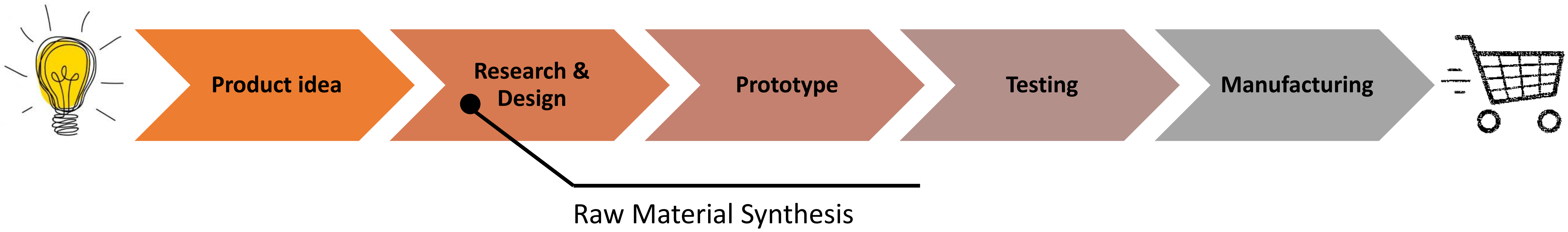
Application examples in industrial innovation processes

- EXAMPLE #1

H2020 Pilot Line Project INSPIRED

- INdustrial Scale Production of Innovative nanomateRials for printEd Devices



http://www.nano-inspired.eu/

Application examples in industrial innovation processes

- Material used: Graphene
- Process: Graphene nanoplatelets production via liquid phase exfoliation
- Hotspots: Possible aerosol generation during graphene manufacturing
- Qualitative/semi-quantitative risk assessment: combining predicted tools
- Quantitative risk assessment outcome:
  - Real time monitoring in the pilot plant area; exposure measurements with Diffusion Size Classifier (DiscMini; 5 nm – 1 µm size range) and two Condensation Particle Counter (near and farfield Scanning Mobility Particle Sizer, TSI, Model 3007; size range of 10 - 500 nm) showed no aerosol release under used conditions

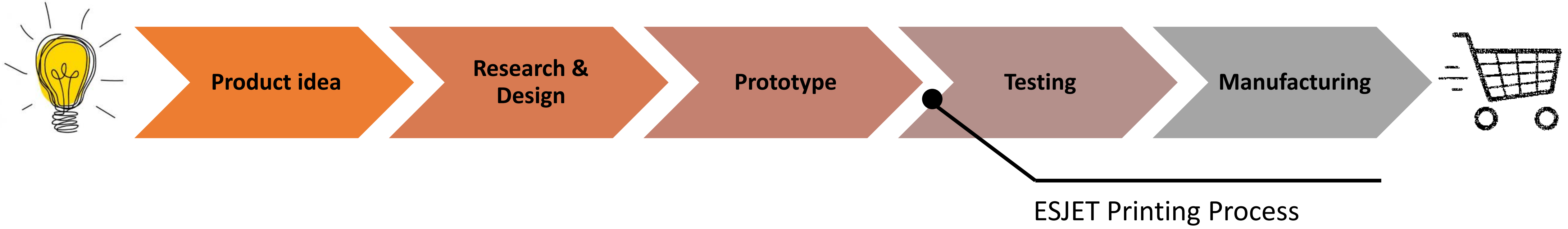
http://www.nano-inspired.eu/

Application examples in industrial innovation processes

- EXAMPLE #2

  H2020 Pilot Line Project Hi-Response

  - High Definition Printing of Multi-functional Materials → Developing new ESJET printing techniques for nano-inks



http://hi-responseh2020.eu/

Application examples in industrial innovation processes

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Hi-Response

- Material used: Nano-Copper ink formulation
- Process: ESJET printing process
- Hotspots: Possible aerosols arising during high-speed printing
- Qualitative/semi-quantitative risk assessment: combining predictive tools
- Quantitative risk assessment outcome:
  - Workplace measurements under real-life conditions in the laboratory; exposure monitoring with SPMS (Scanning Mobility Particle Sizer, TSI; measurement range 14,9 – 697,8nm) showed no aerosol release

http://hi-responseh2020.eu/

Conclusion

Lessons learnt

- Great number of nanomaterials and nanotechnology applications
- Great variety of possible hazards/exposure scenarios
- Case-by-case nanosafety assessment
  - Following the REACH Chemical Safety Assessment
  - Adaptations/modifications required that meet nano-related needs
- Complex, multidisciplinary topic
  (material science, physics, chemistry, biology, mathematics, informatics, etc.)
- Communication/knowledge exchange between technical developers and safety experts is very important

Outlook

- Adequate, nano-specific data (nano-specific DNELs/PNECs)
- Simulation/modeling approaches in early innovation stages
- Implementable Safe-by-Design actions
- Decision support systems for industry, especially for SMEs
- Reliable tools to predict the risk potential of new/advanced materials

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