SUN-SNO-GUIDENANO Sustainable
Nanotechnology Conference 2015
Monday, Mar. 9 – Wednesday, Mar. 11
Venice, Italy

The role of biological monitoring in nano-safety

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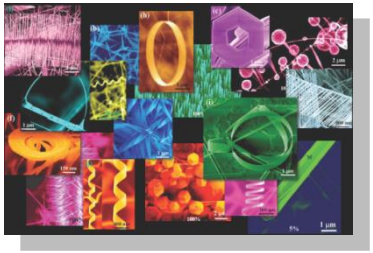
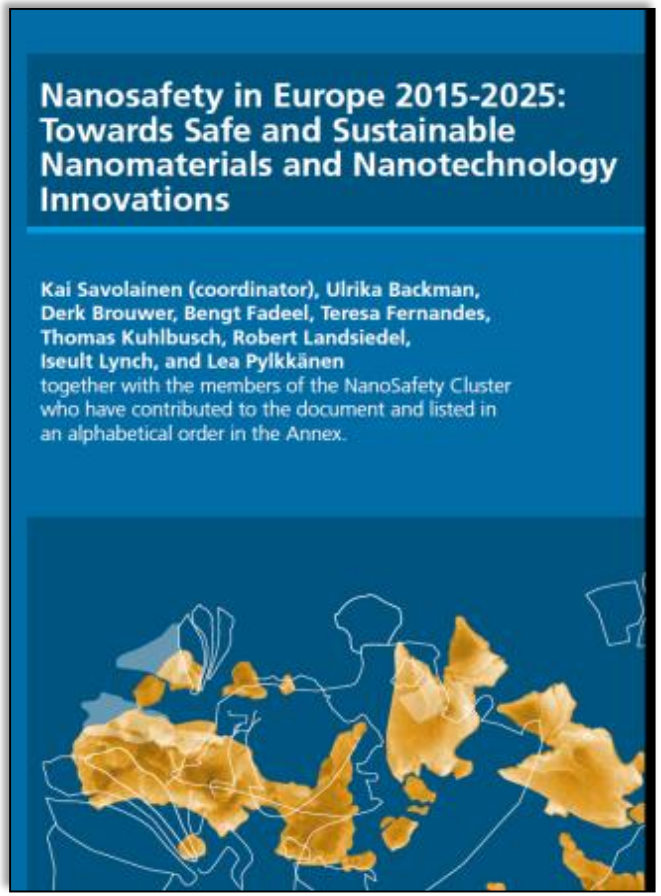


The principal challenges in RA



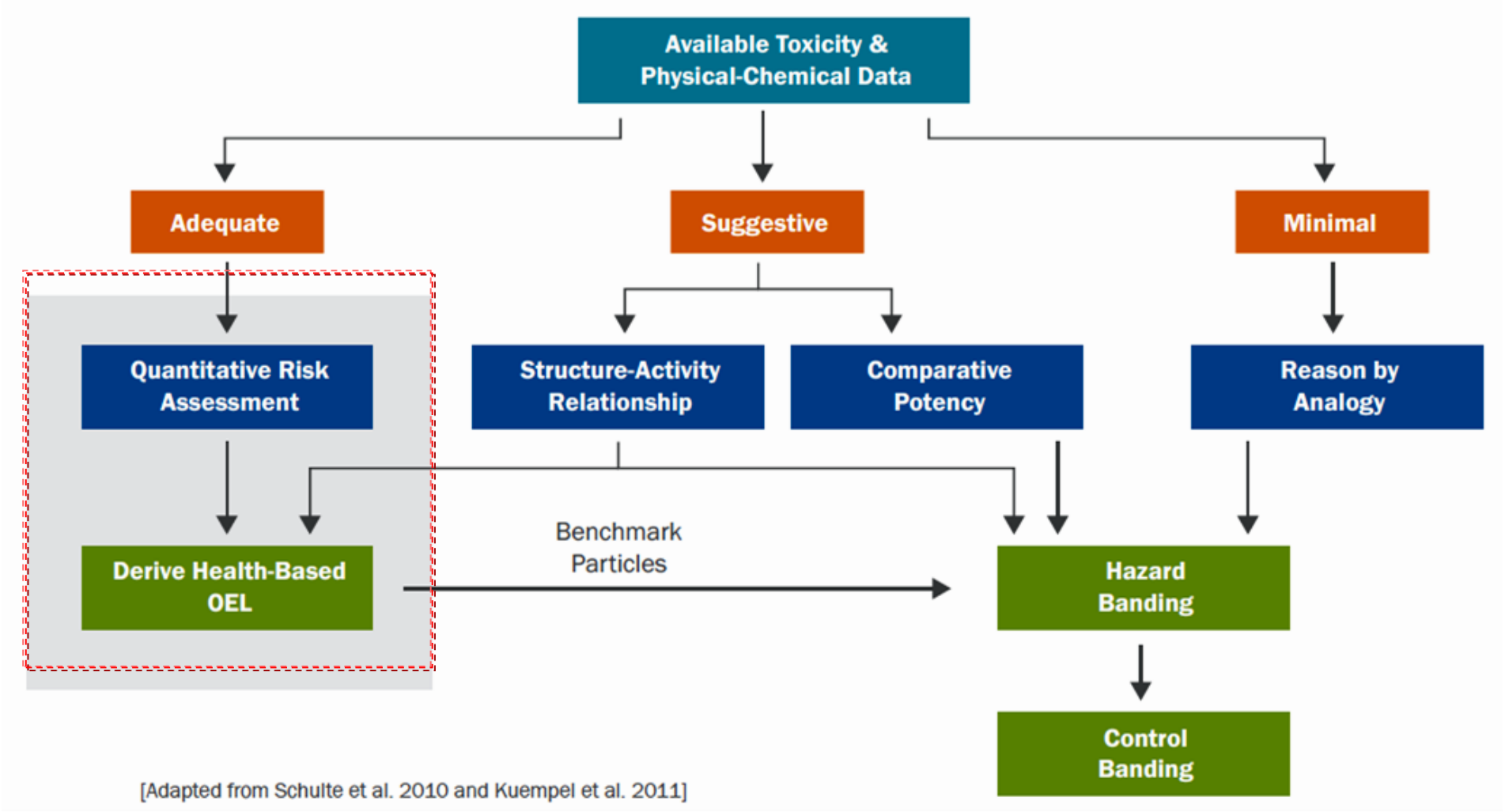
(1) introduction or establishment of a systematic and standardized metrology for physically characterizing NM (*multiple metrics needed*);

(2) uncertainty in the nature of the dose-response relationship between exposure of NM and biological effects, whether they are - or not - "**nano-specific**" (*hazard characterization*);

(3) the difficulties associated with measuring exposure to NM and surveillance once they are introduced into the environment (*Life-cycle assessment*).

There are inadequate data to inform quantitative risk assessments on current and emerging NM. At most, only qualitative risk assessments are feasible, given the current state of knowledge

Impact of the level of information on the guidance development (e.g. Occupational Exposure Limits)



[Adapted from Schulte et al. 2010 and Kuempel et al. 2011]

Opinion

WIREs Nanomed Nanobiotechnol 2012, 4:1–15. doi: 10.1002/wnan.162

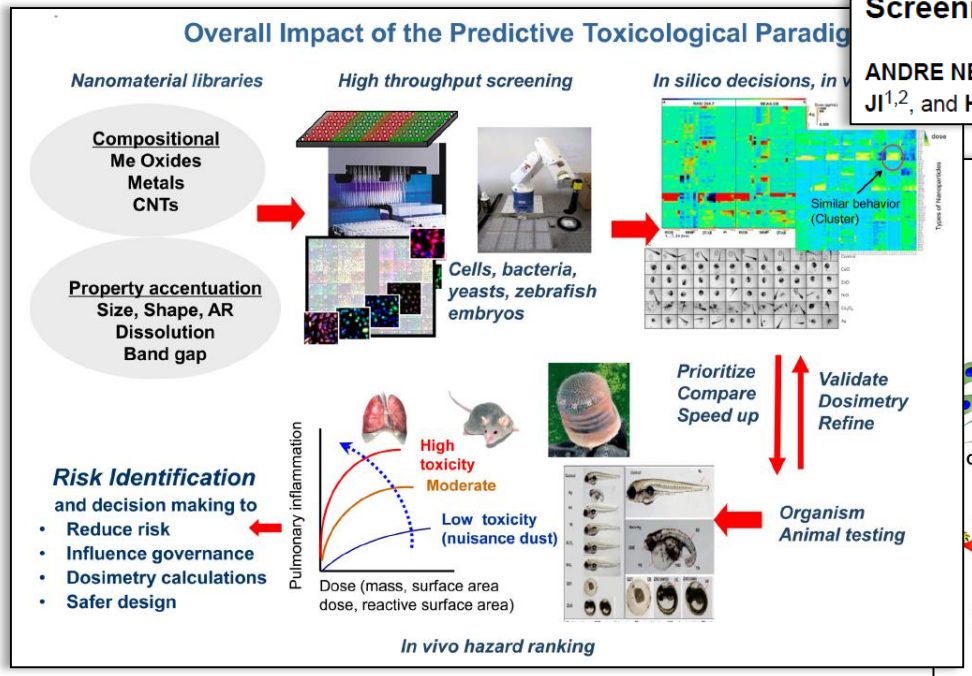
Toward toxicity testing of nanomaterials in the 21st century: a paradigm for moving forward

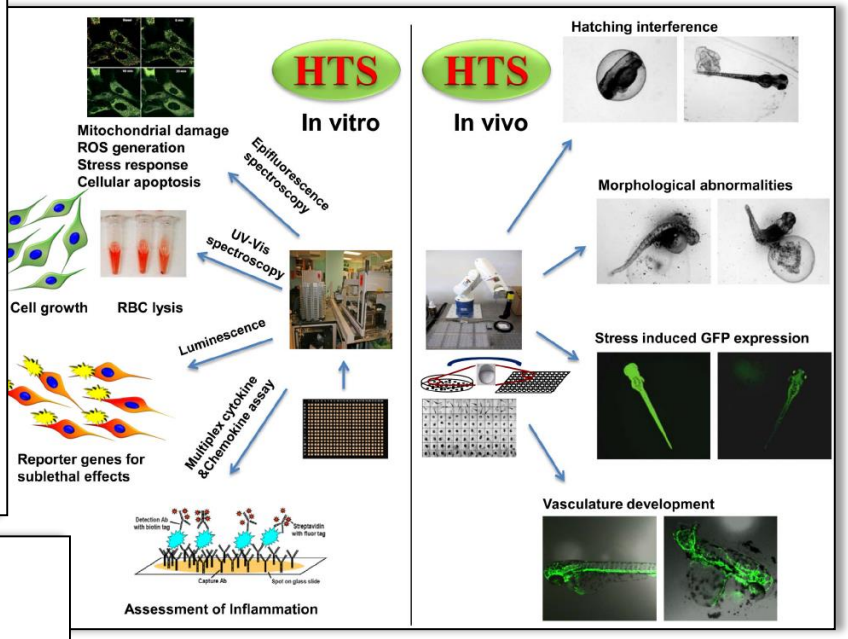
David Y. Lai*

Acc Chem Res. 2013 March 19; 46(3): 607–621. doi:10.1021/ar300022h.

Nanomaterial Toxicity Testing in the 21st Century: Use of a Predictive Toxicological Approach and High Throughput Screening

ANDRE NEL[1,2,3,4,*], **TIAN XIA**[1,2,3], **HUAN MENG**[1,2], **XIANG WANG**[1,2], **SIJIE LIN**[1,2], **ZHAOXIA JI**[1,2], and **HAIYUAN ZHANG**[1,2]





J Intern Med. 2013 December ; 274(6): 561–577. doi:10.1111/joim.12109.

Implementation of Alternative Test Strategies for the Safety Assessment of Engineered Nanomaterials

Andre Nel

Definition and meaning of biological monitoring in occupational health

BM deals with the "systematic, continuous or repetitive activity for collection of biological samples for analysis of concentrations of pollutants, metabolites or specific non-adverse biological effect parameters, with the objective to assess exposure and health risk to exposed subjects, comparing the data observed with the reference level and - if necessary - leading to corrective actions"

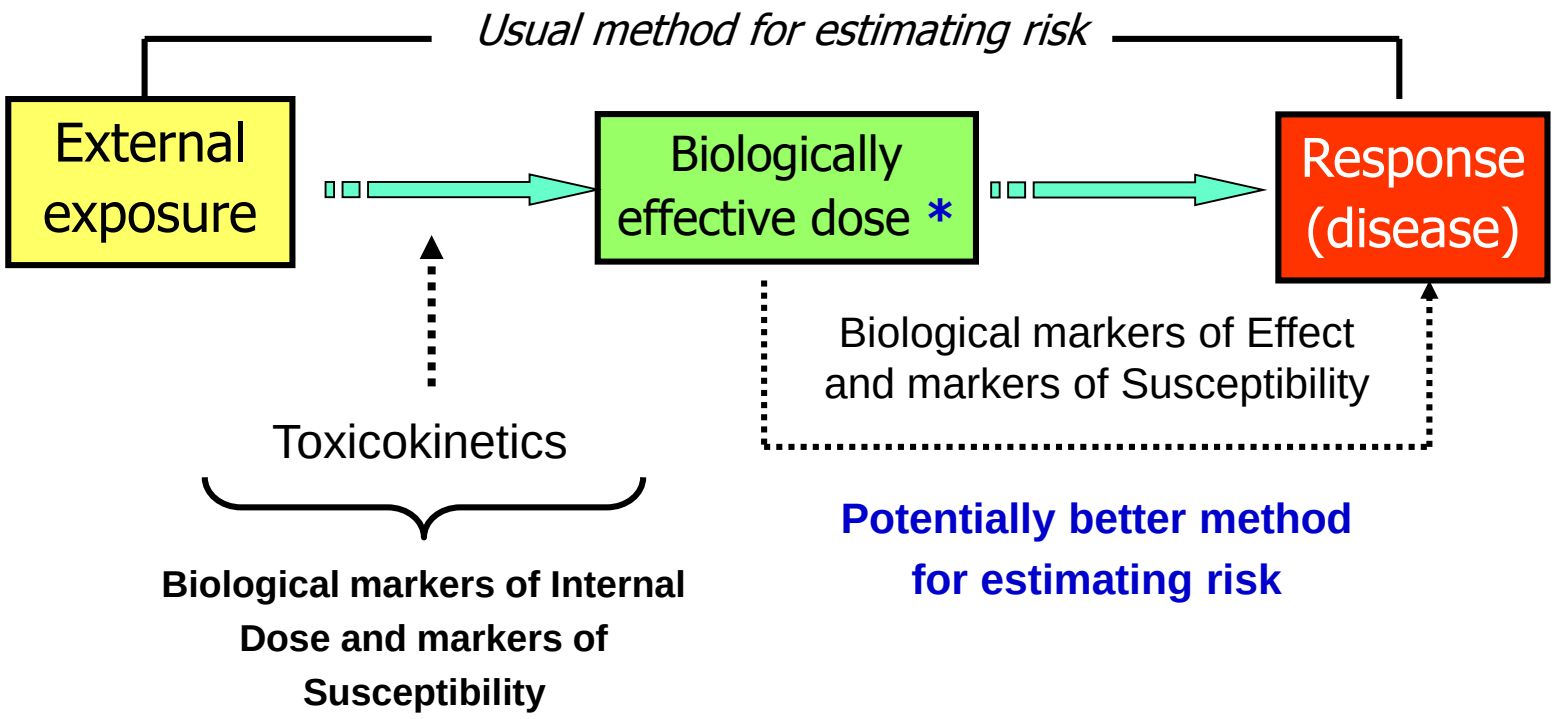
[R.L. Zielhuis and P.T. Henderson, 1986]

Biomarkers (NRC, 1987)

- ✓ **EXPOSURE**: an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism .
- ✓ **EFFECT**: any measurable biochemical, physiological or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease
- ✓ **SUSCEPTIBILITY**: effect-modifying factors, including both genetic (e.g., genetic polymorphisms of drug metabolizing and DNA repair enzymes) and acquired conditions

Rationale for using biomarkers in risk assessment

IPCS, 1998



*** In particle toxicology, the BED is defined as "the entity within any dose of particles in tissue that drives a critical pathophysiogically relevant form of toxicity (e.g., oxidative stress, inflammation, genotoxicity, or proliferation) or a process that leads to it.**

Donaldson *et al*., Acc. Chem. Res., 2013, 46 (3), pp 723–732

Available online at www.sciencedirect.com
SciVerse ScienceDirect
Current Opinion in Biotechnology

Nanotoxicity: challenging the myth of nano-specific toxicity

Ken Donaldson[1,2] and Craig A Poland[2]

- ✓ **The Biologically Effective Dose (BED) is the mechanistic entity that actually drives toxicity.**
- ✓ **Mechanisms of nanoparticle (NP) toxicity need to be considered in relation to conventional particles (CPs).**
- ✓ **Recognition of similar mechanisms would aid in benchmarking the NP hazard.**
- ✓ **Currently known NP BEDs include surface area, soluble species, charge and shape (AR).**
- ✓ **All of these BEDs also drive CP toxicity so, whilst nano-relevant, they are not nano-specific.**

TOXICOLOGICAL SCIENCES **107(2)**, 553–569 (2009)
doi:10.1093/toxsci/kfn250
Advance Access publication December 10, 2008

Macrophage Responses to Silica Nanoparticles are Highly Conserved Across Particle Sizes

Katrina M. Waters,*,†,[1] Lisa M. Masiello,*,‡,[1] Richard C. Zangar,*,‡ Barbara J. Tarasevich,*,§ Norman J. Karin,*,‡ Ryan D. Quesenberry,*,‡ Somnath Bandyopadhyay,*,† Justin G. Teeguarden,*,¶ Joel G. Pounds,*,‡ and Brian D. Thrall*,‡,[2]

TOXICOLOGICAL SCIENCES **120(1)**, 123–135 (2011)
doi:10.1093/toxsci/kfq363
Advance Access publication December 6, 2010

Comparative Proteomics and Pulmonary Toxicity of Instilled Single-Walled Carbon Nanotubes, Crocidolite Asbestos, and Ultrafine Carbon Black in Mice

Justin G. Teeguarden,*,[1] Bobbie-Jo Webb-Robertson,* Katrina M. Waters,* Ashley R. Murray,† Elena R. Kisin,† Susan M. Varnum,* Jon M. Jacobs,* Joel G. Pounds,* Richard C. Zanger,* and Anna A. Shvedova†

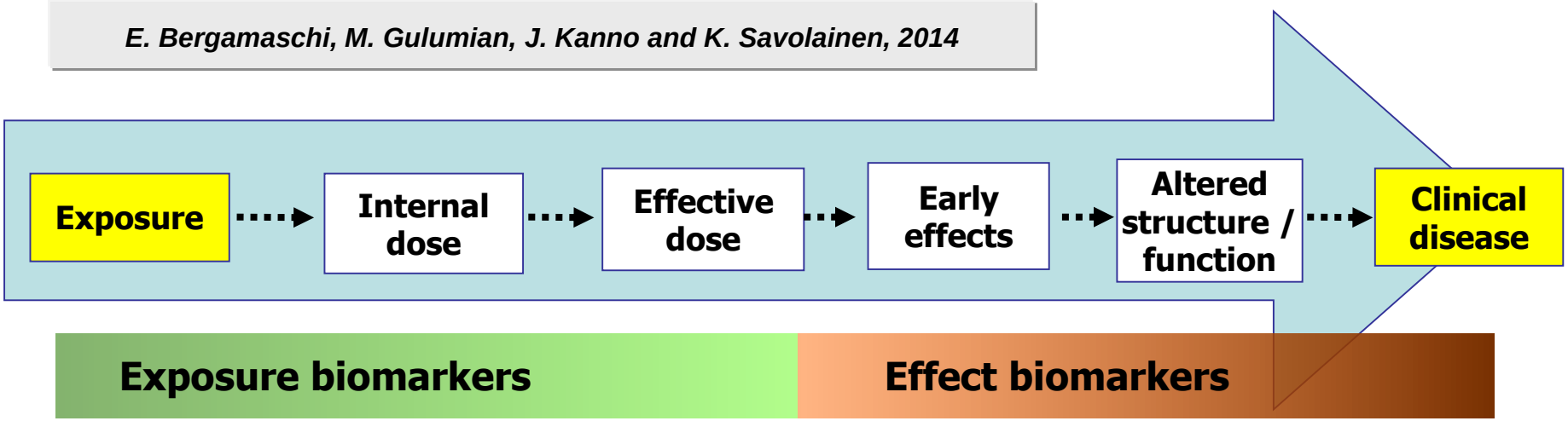
OPEN ACCESS Freely available online

Particle-Induced Pulmonary Acute Phase Response Correlates with Neutrophil Influx Linking Inhaled Particles and Cardiovascular Risk

Anne Thoustrup Saber[1]*, Jacob Stuart Lamson[1], Nicklas Raun Jacobsen[1], Gitte Ravn-Haren[2], Karin Sørig Hougaard[1], Allen Njimeri Nyendi[1], Pia Wahlberg[3], Anne Mette Madsen[1], Petra Jackson[1], Håkan Wallin[1,4], Ulla Vogel[1,5]

An appraisal of available biomarkers associated with exposure to UFP & NMs (manufactured/engineered)

E. Bergamaschi, M. Gulumian, J. Kanno and K. Savolainen, 2014



- **Exhaled particles and/or elements in EBC** (estimate of the "deposited dose")
- *Particles/break down products in biological media*
- **Elements analysis** in biological fluids (excretion, body burden)
- Protein modification ("corona")

- **Lipid peroxidation products** in EBC or blood (MDA, T-BARS, conjugated dienes, LTB_4, F2- and 8-isoprostane)
- **DNA excision base products** (8-OH-dG, 8-oxo-Gua)
- **Exhaled NO (FeNO)** and **nitrosative stress** products (3-nitrotyrosine)
- **Carbonyl compounds (4-HNE) in EBC**
- Serum pneumoproteins (CC16)
- Platelet activation/aggregation; pro-thrombotic changes
- **Acute phase proteins** (hsCRP), **Haptoglobin**
- **IL-6, IL-8, TNFα and sTNF-RII**
- **Clotting factors** (fibrinogen, **PAI-1**)
- **Vascular adhesion molecules** (V-CAM-1)

- Fibrogenic markers (osteopontin)
- Cell transformation
- **Micronucleus**
- **DNA strand breaks** (Comet assay + FPG-ENDO III)
- **DNA (hypo)methylation**
- **MicroRNAs** (miRNAs)

Health hazards among workers occupationally exposed to ENM

Liou et al., J Nanopart Res (2012) 14:878

NM handled by the workers

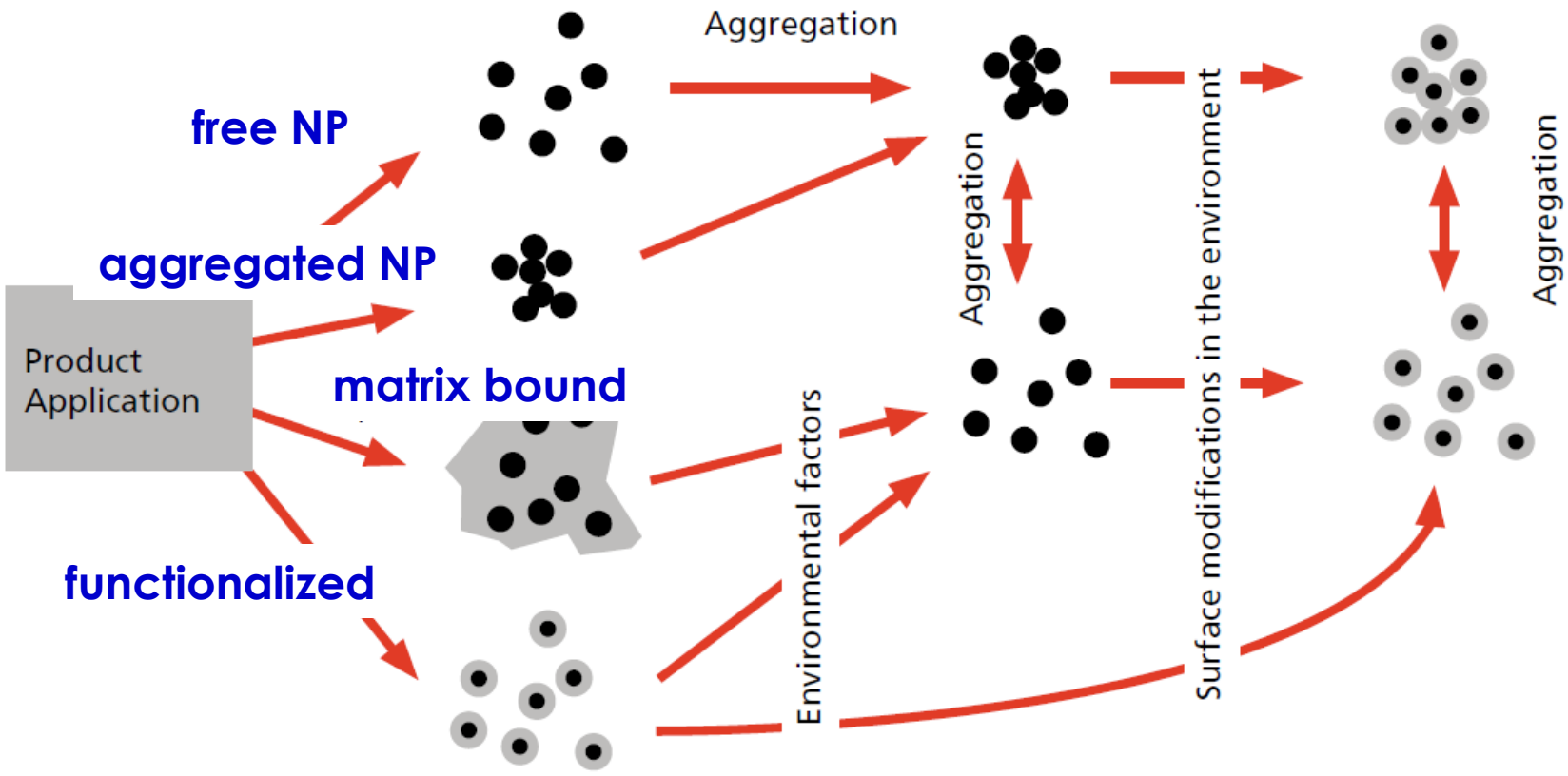
Nanomaterials	Frequency	% of Total (% of exposed group)
Carbon nanotube	52	14.3 (22.9)
Nanoscale silicon dioxide (SiO_2)	37	10.2 (16.3)
Nanoscale titanium dioxide (TiO_2)	19	5.2 (8.4)
Nanosilver	15	4.1 (6.6)
Nanoresins	10	2.7 (4.4)
Mixed materials	94	25.8 (41.4)
Exposed group	227	62.4 (100)
Control group	137	37.6
Total	364	100

Summary of significant findings after adjustement for confounders

Biomarkers	RL1 vs. control	RL2 vs. control	Trend (RL2, RL1, control)
Antioxidant enzymatic activity	SOD↓, GPX↓	SOD↓	SOD↓
Lung inflammation and oxidative damage	–	–	–
Cardiovascular disease markers	IL6↑	Fibrinogen↑, ICAM↑	Fibrinogen↑, ICAM↑
DNA damage and genotoxicity	–	–	–
Pulmonary function	–	–	–
Neurobehavioral function	–	Backward 7-digit memory↓	–

Release of nanoparticles (NP)

Environmental factors influence agglomeration and de-agglomerations



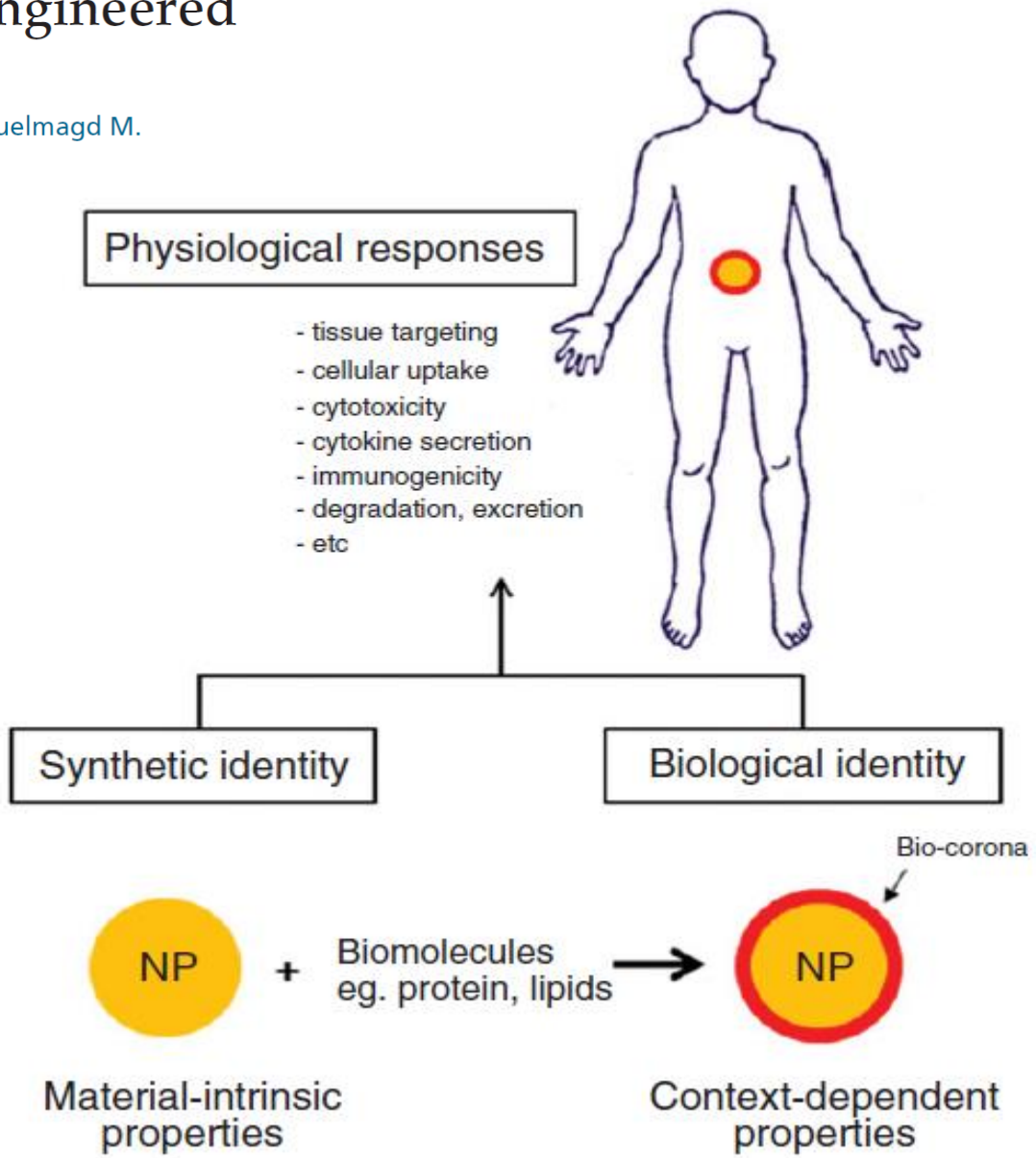
(from Nowack & Bucheli, 2007)

Bridge over troubled waters: understanding the synthetic and biological identities of engineered nanomaterials

WIREs Nanomed Nanobiotechnol 2013, 5:111–129

Bengt Fadeel,[1]* Neus Feliu,[1] Carmen Vogt,[1] Abuelmagd M. Abdelmonem[2] and Wolfgang J. Parak[2]

Synthetic and biological identities of nanomaterials



Hazard determinants of manufactured/engineered NMs

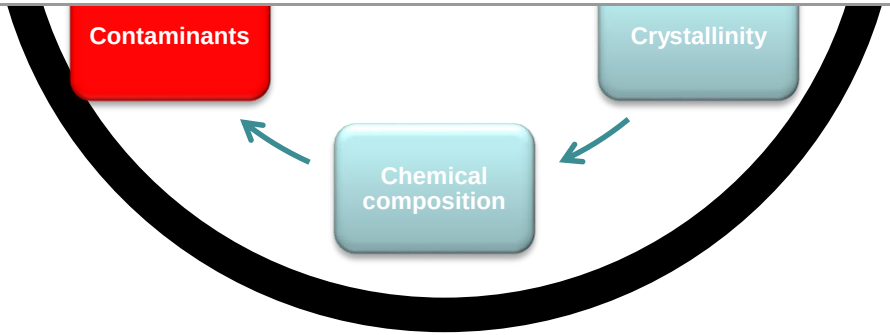
Toxicology Research

PAPER

Titanium dioxide nanoparticles enhance macrophage activation by LPS through a TLR4-dependent intracellular pathway†

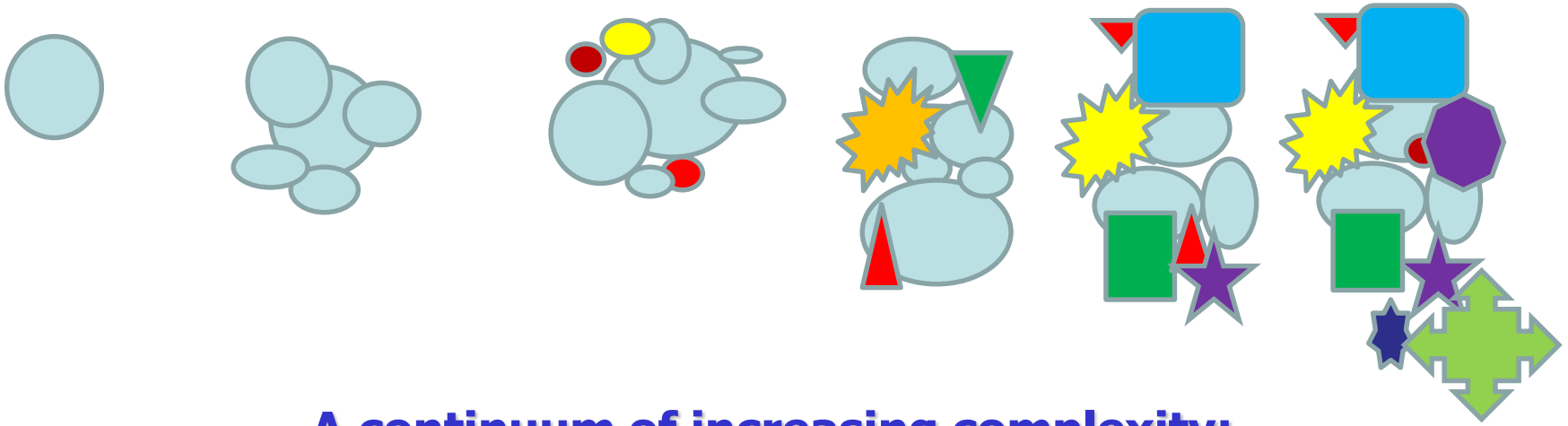
Massimiliano G. Bianchi,‡[a] Manfredi Allegri,‡[b] Anna L. Costa,[c] Magda Blosi,[c] Davide Gardini,[c] Camilla Del Pivo,[c] Adriele Prina-Mello,[d] Luisana Di Cristo,[a] Ovidio Bussolati*[b] and Enrico Bergamaschi[a]

Cite this: *Toxicol. Res.*, 2015, 4, 385

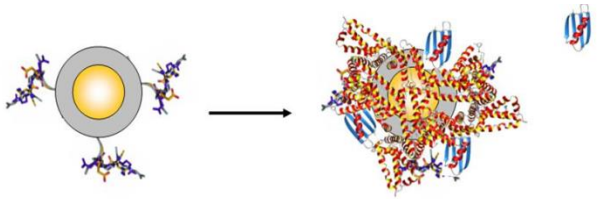


Exposure…to what ENM ??

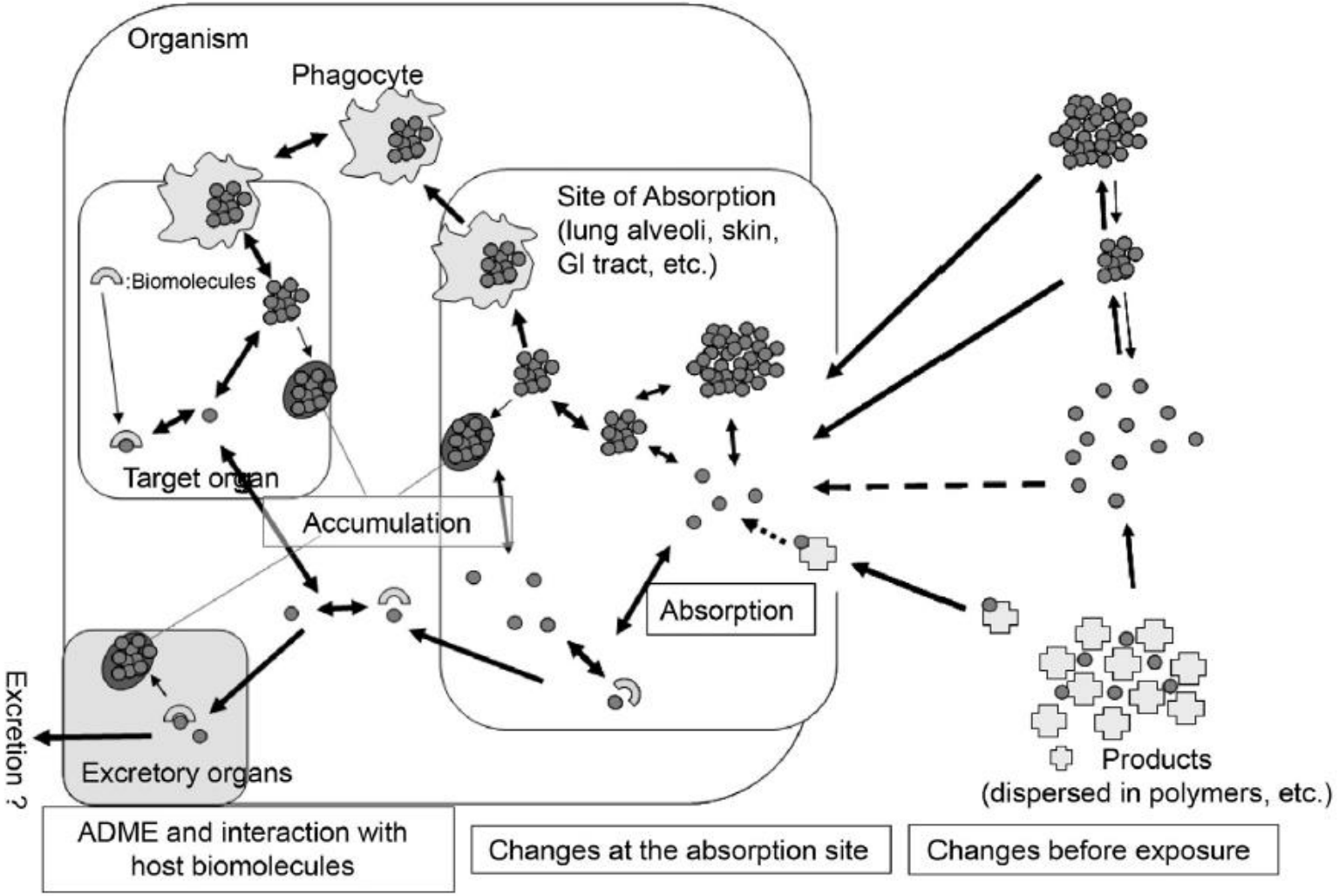
Synthesis Development Manufacture Use (1) Use (2) Product



A continuum of increasing complexity:
Which expected effects on biological systems?

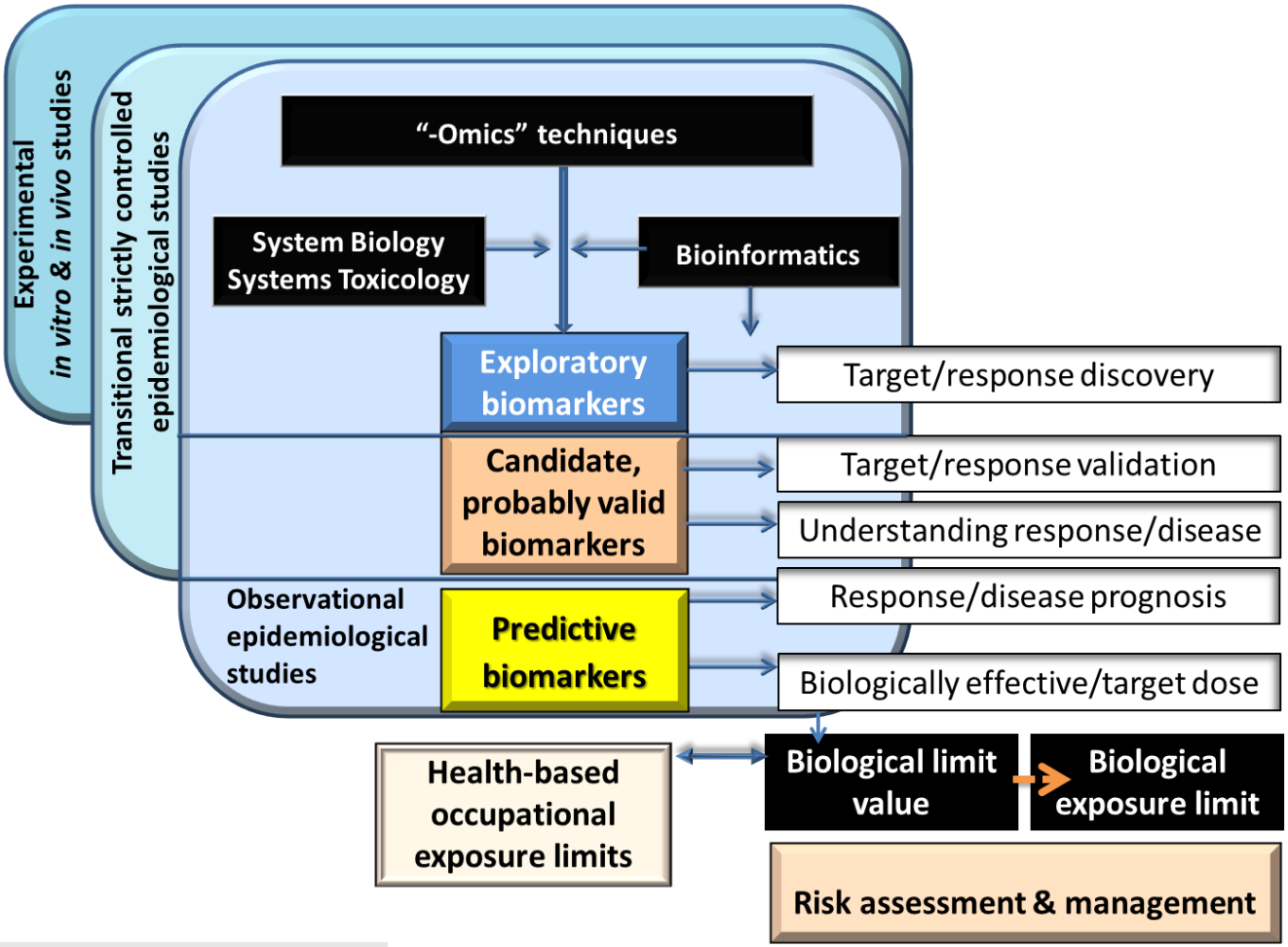


Representation of absorption, distribution, metabolism, excretion, and deposition of ENMs in cells and tissues



E. Bergamaschi, M. Gulumian, J. Kanno and K. Savolainen, 2014

Layout of biomarkers research as condition of the responsible development of nanotechnologies and safety of workers exposed to ENM



E. Bergamaschi et al., 2015

A Road Map Toward a Globally Harmonized Approach for Occupational Health Surveillance and Epidemiology in Nanomaterial Workers

Michael Riediker, Dr.sc.nat., Mary K. Schubauer-Berigan, PhD, Derk H. Brouwer, PhD, Inge Nelissen, PhD, Gudrun Koppen, PhD, Evelien Frijns, MSc, Katherine A. Clark, DrPH, Juergen Hoeck, PhD, Saou-Hsing Liou, MD, PhD, Sweet Far Ho, MBBS, MSc, Enrico Bergamaschi, MD, PhD, and Rosemary Gibson, DPhil

Particularly needed are…

- ✓ Criteria for potentially useful **biomarkers** and (pre)clinical parameters for epidemiological studies about workers in small and medium enterprises and transnational companies.
- ✓ Recommendations on the feasibility of human population studies based on these **biomarkers**.
- ✓ Recommendations on the requirements for harmonized approaches for **human biomonitoring** and health effect studies tailored to nanomaterial workers.

***JOEM* Volume 54, Number 10, October 2012**

NanoSafety Cluster

The risk prediction and management tools

Milestone	Topic	By 2015	By 2020	By 2025
Health	*Health effect*	Markers for short term effect identified	Markers for long term effect identified	Implementation of the markers
	Register	Health surveillance registries developed Exposure registries developed	Using registries for research	Implementation of results for regulations
	Study design	Pilot panel studies completed	Case-control studies completed	Longitudinal studies started

Databases and epidemiological or health studies can be considered as "enabling tools" supporting the processes of RA and RM.

Take-home message

- There is a pressing need to overcome pitfalls in risk assessment (RA) for engineered nanomaterials (ENM)
- Inherent properties of ENM are subject to changes in the environmental settings
- Similar paradigms for particle/nanoparticle hazard do not support "nano-specificity"
- The issue of biomarker specificity for ENM is challenging but should not hamper their use in epidemiological research
- Candidate biomarkers validated in epidemiological studies should consistently support the RA

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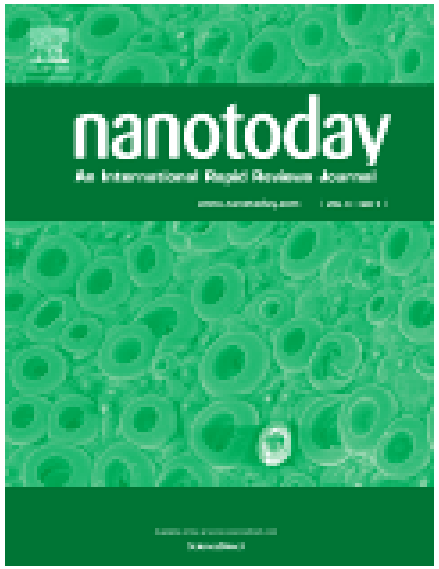

Enrico Bergamaschi, Craig A. Poland, Irina Guseva Canu, Adriele Prina-Mello

DOI information: ***10.1016/j.nantod.2015.02.001***

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