

(Occupational) Dermal Exposure to NOAA

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TNO innovation
for life

Report of Pre-normative Research project



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods

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M/461 EN

**MANDATE ADDRESSED TO CEN, CENELEC AND ETSI FOR
STANDARDIZATION ACTIVITIES REGARDING NANOTECHNOLOGIES AND
NANOMATERIALS**



Scope of PreNormative Research (PNR)

- › Guidance on the assessment of **occupational** dermal exposure to nanomaterials (and nano enabled products) NOAA relevant for consequential (potential for), local effects, skin permeation and inadvertent ingestion.

INCLUDED

- › Types of nano enabled products that contain nanomaterials that are not completely incorporated in a solid matrix (for example in an article), but suspended in a liquid matrix, e.g., **highly concentrated intermediates, spray liquids (for surface coating), coatings, paints, etc.**

EXCLUDED

- › **Consumer exposure**, e.g. intended exposure to personal care products or unintended exposure due to release of nanoparticles from articles

Examples of nano (enabled) products for professional use

Variety in physical state

- Powders
- Dispersions
 - Solvent-based e.g. metallic, magnetic, spray liquids
- Aqueous dispersion e.g. liposomes
- Cream or gel-based
- Nano capsules

Outline

- › Conceptual approach
- › Evidence for skin penetration of NOAA
- › Evidence for exposure to NOAA
- › Exploration of measurement methods for NOAA
- › Summary & Guidance Framework

Exposure Assessment

Repenetration/
permeation

SCSC integrity

'Core' parameters

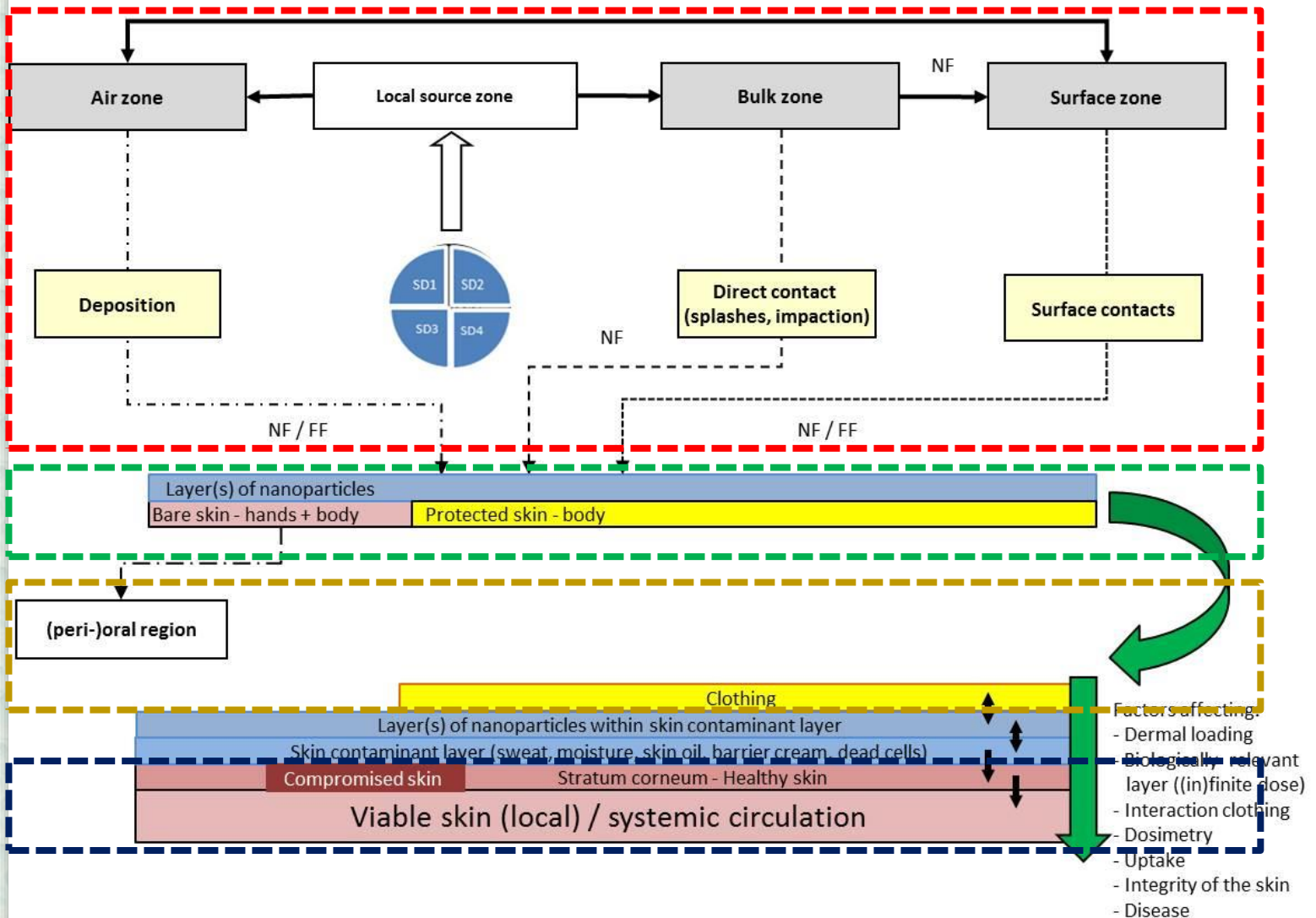
- Identification of NM, e.g. identity NP, coating, charge, state of appearance/ physical state, surfactants, etc...
- Identification of exposure route
- Frequency of contact/ exposure
- Duration of exposure
- Body location and surface area exposed
- Loading (metric ?)

ingestion

Contextual information

- Potential for alteration properties NM
- Identification of co-exposures (solvents, oils, ..etc)
- Wet work , (de)hydration
- Evidence of work/ task related abrasion of SC
- Potential for mechanical damage, cuts, lesions..etc
- Potential for burns
- UV-IR irradiation
- Frequency of hand-mouth contact

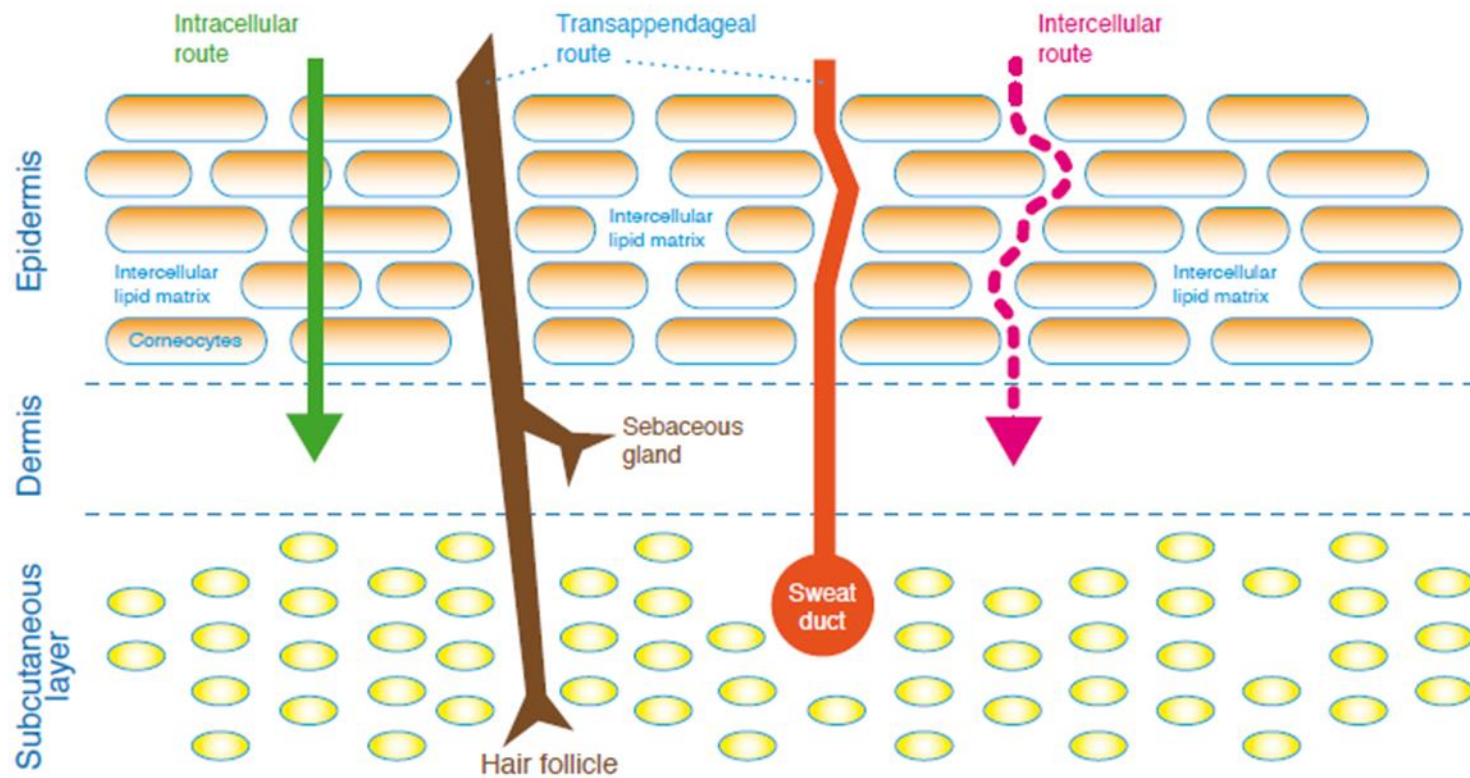
Conceptual framework for dermal exposure to nanoparticles (and relevance for ingestion exposure)



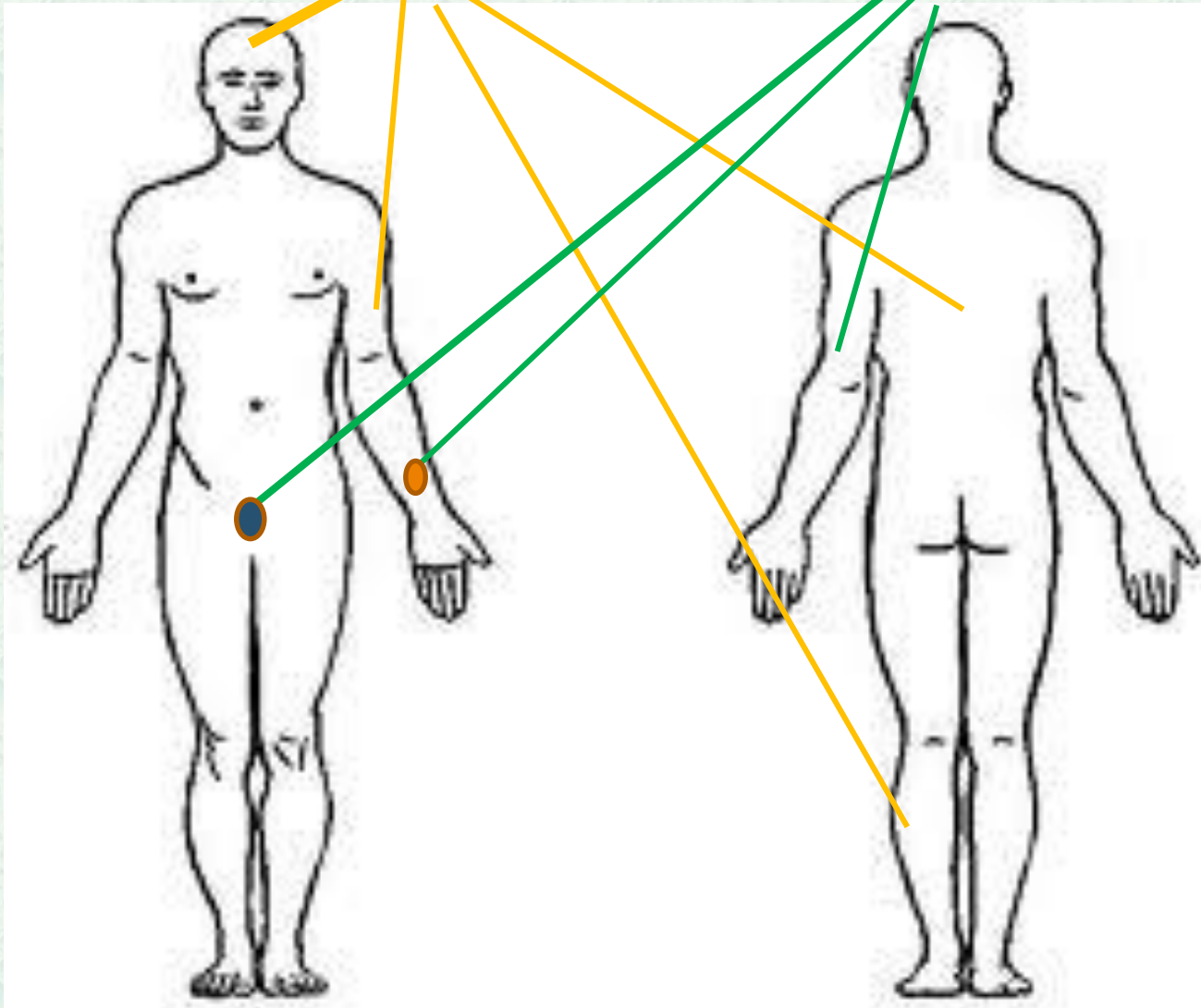
Assumptions on effect of dermal exposure pathway

Pathway	Potential for (size) alterations from source to skin	Remarks
Direct contact : Accidental (splashes, spills, immersion)	Low	No forces involved
Intentional e.g. Rubbing	High	Shear forces (shove / press) may enhance agglomeration
Transfer/ surface contact	High	Shear forces may enhance agglomeration
Deposition	Medium/high	Dispersion and transport (aerosol formation) Unequal (size) distribution on skin

Pathways for penetration of substances through skin

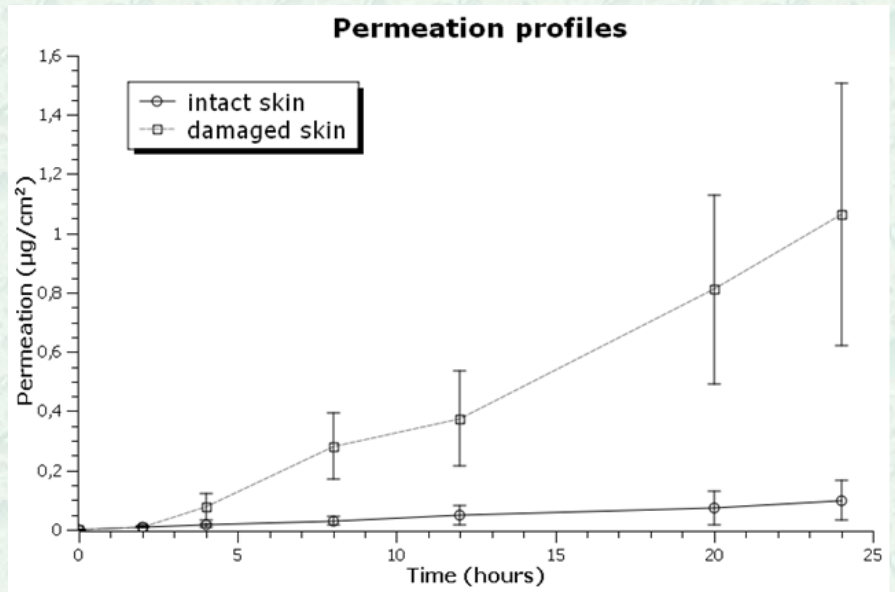
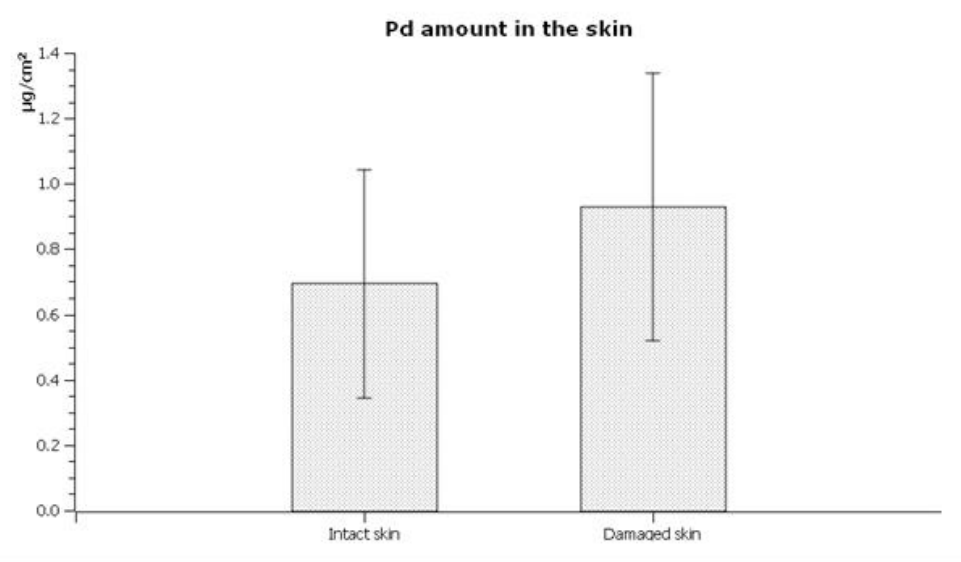
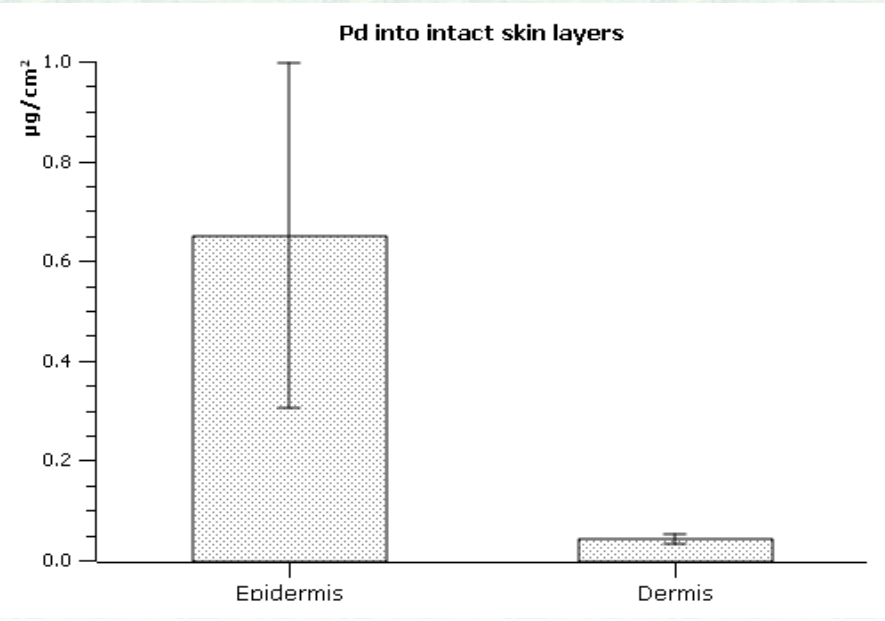


Hot spots for high hair follicle density and thin SC



Examples of NP penetration (experimental work (Crosera ...Larese Filon, 2015))

Palladium: size = 10.7 ± 2.8 nm



Summary of literature and experimental data

NPs	Critical size (nm)	Penetration	Permeation	Possible mechanism
TiO ₂	-	No	No	-
ZnO	-	No	No	-
QDs (CdSe)	12	Yes	Yes	Cd release
Silica	42	Yes	No	To be studied
Co	80	Yes	Yes	Ions release
Ni	77	Yes	Yes	Ions release
Pd	13	Yes	Yes	Ions release
Pt	5	Very low (only in damaged skin)	No	-
Rh	5	Very low (only in damaged skin)	No	-

Critical considerations for skin penetration and local effects

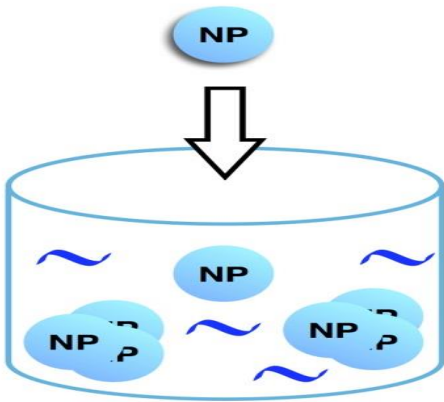
- › Size (in physiological media/ on skin) and skin condition:
 - › ≤ 4 nm penetrate and permeate intact skin
 - › 4-20 nm potential for permeation damaged / intact skin
 - › 21-40 nm penetration/permeation **only** in damaged skin
 - › ≥ 40 nm **NO** penetration/permeation

- › (potential for) **Release** (in physiological media/ on skin):
 - › Toxic metal, e.g. Cd from QDs
 - › Me ions from Me and MeOx NP and **impurities in C-NPs**

NANOMATERIALS

OTHER NPs

METAL BASED NPs

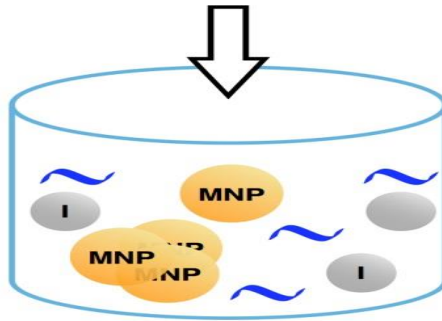


PRIMARY SIZE

NPs in physiological media (physiologic solution, synthetic sweat, etc)

- Size
- Shape
- Surface charge
- Z potential
- Aggregation
- Precipitation
- Dissolution
- ...

MNP



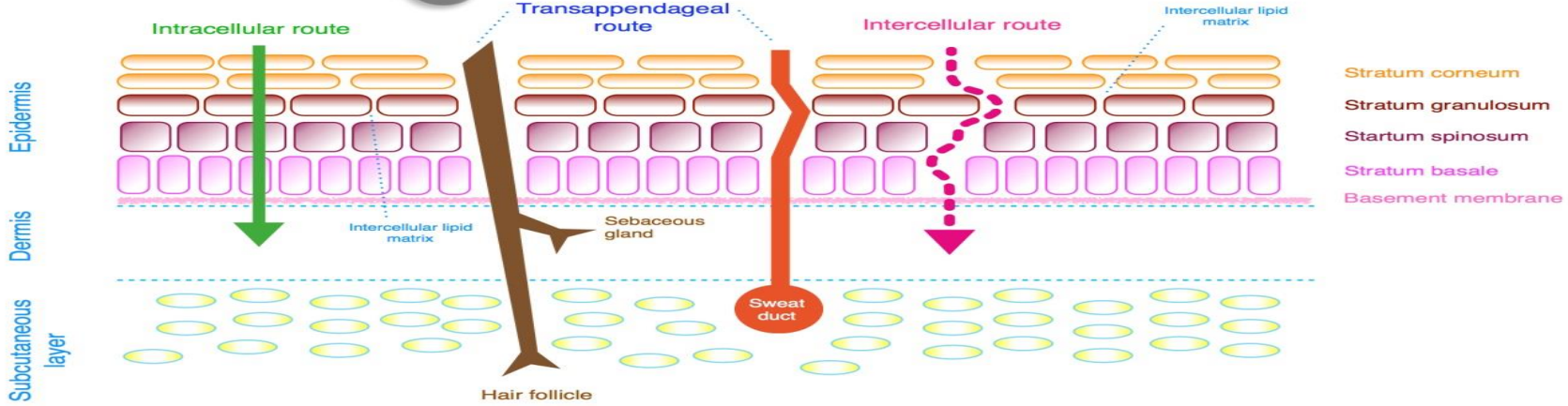
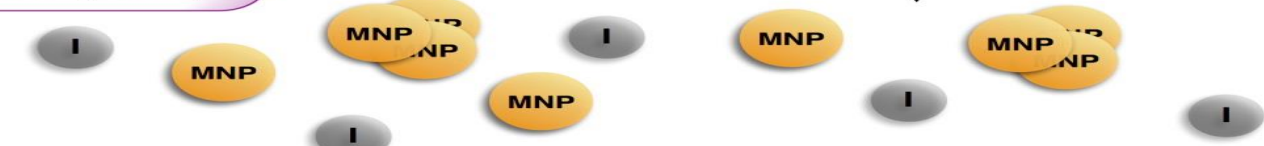
SECONDARY SIZE

STABILIZED NPs:
Low size-dependent skin permeation (i.e.: Au, Ag, Pt, < 20 nm);

AGGREGATION OF NPs:
Aggregation lead to a growth of dimensions and to a reduction of skin permeation. (i.e: Metal Oxides)

RELEASE OF IONS
Metal permeation is mainly due to ions released by the NPs (i.e.: Ag, Ni, Co)

Some evidence of skin permeation in damaged or flexed skin (<45 nm)



Skin barrier disruption

Individual level

Clinical observations

Questionnaires

- › Redness
- › Swelling
- › Oozing/crusting
- › Thickening
- › Cracking
- › Dryness



Biophysical measurements

TEWL (Trans Epidermal Water Loss)

Industrial sector/ job title level

Reported incidence of Allergic or Irritant Contact
Dermatitis (ACD/ICD)

Industry sectors/ job titles with high incidence of occupational skin diseases

Product / Sector / Industry	Jobs with high incidence of contact dermatitis	Factors influencing integrity skin barrier ⁵					Causes of contact dermatitis (CD) ⁶											
		Abrasion	Cuts	Puncture	Temperature	Vibration	wet work ⁴	soaps and cleaners ⁴	hairdressing products	preservatives	rubber chemicals	nickel, chromium, chromates, cobalt	cement	resins and acrylics	cosmetics & fragrances	petroleum and products	disinfectants	degreasers, cutting oils, coolants
Automotive / Automobile ²	Mechanics, vehicle assemblers	x	x					x										x
ICT/Electronics ¹	Electroplater ³				x						x		x			x		x
Surfaces and Coatings							(x)											
Cosmetics / Personal care ²	Hairdressers, beauticians		x	x			x	x	x					x			x	
Health care ¹	Dental practitioners/ nurses	x	x	x			x	x		x							x	
Textiles							x	x										
Construction ¹	Construction workers	x	x			x	(x)					x	(x)					(x)
Energy & Environment / Green nanotechnology / Energy applications					x													
Plastics					x								x			x		
Food industry ¹	Cooks, catering workers		x		x		x	x									x	x
Agriculture ¹	Florists	x	x							x								x
Chemical industry ¹	Chemical process workers				x						x		x		x			x
Micellaneous																		
Sports														(x)				
Aerospace / aviation																		
Ceramics & glass ²	Ceramics / glass process workers				x													
Cleaning ²	Cleaners	x			x	x	x	x									x	
Paper industry																		
Printing & packaging					x													
Home and garden										x								
Research & Development (general)																		
Security / Defense																		
Trade / Retail																		
Metal industry ²	Metal working machine workers	x			x	x	x											x
Stone		x				x												
Watches / Optics																		
Rubber industry ²	Rubber process workers										x							

Industrial sectors and use of nanomaterials/- products

Sector	Subcategory	Sector	Subcategory
ICT/Electronics	Electronics, computers (incl. display), electrotechnics, electrical devices, IT, ICT	Cosmetics Personal care	Sunscreens
	Sensors, microelectronics		Cosmetics (production)
	Magnetics and magnetic materials		Cosmetics and personal care products
	Quantum computing		Clothing / shoes
	(Lithium-ion) batteries		Sports appliances / goods / equipment
Energy & Environment / Green nanotechnology / Energy applications	Lights	Watches / Optics	
	(Renewable) energy	Paper industry	Paper (production)
	Fossil fuel power plants	Printing & packaging	Ink and toners (production)
	Power/energy storage, distribution and transmission	Plastics	Plastics and synthetics production
	Water purification, filtration and desalination	Cleaning	Composites in plastics / synthetics
	Sensing		Cleaning products
	Environmental remediation /Air emissions reduction	Automotive Automobile	Air freshener / spray
	Catalysis		Automotive /automotive panels / motor vehicles
	Photovoltaics		Tire production
	Optics and optical devices		Car body repair
Natural and green products	Car garages		
Healthcare	Photonics and photonic devices	Lubricants	
	Nanomedicine: drug-delivery vehicles, contrast agents, and diagnostic devices	Tires	
Aerospace / aviation	Textiles for medical applications	Fuel / diesel	
	Aerospace / aviation	Car window	
Construction	Cement / concrete // Concrete repair / Concrete prefab	Shock absorber	
	Steel	Trade / retail	
	Wood	Trade / retail	
	Milling machines	Metal industry	
	Applications in construction	Home and garden	
	Insulation material		
	Coatings and paints	Agriculture	
	Infrastructure		
	Masonry and building materials		
	Coatings (paints), surface coating surface modification	Production / manufacture of nanomaterials	
Surfaces Coatings	Paint production	Manufacture of nanomaterials	
	Polish (other)	Manufacture of materials (intermediates)	
	Painters / coaters	Manufacture of dyes and pigments	
Ceramics & glass		Manufacture of other inorganic basic chemicals n.e.c.	
Security / Defence		Manufacturers of plastics in primary forms	
Chemical industry	Sustainable chemistry – catalysts	Research & Development (general)	
	Chemicals industry (production)		
Food industry	Food production, processing, safety and packaging	Micellaneous	
	Nutrition	Assembly / recycling	
Textiles	Textiles	Appliances	
	Shoes	Goods for children	
	Shoe repair shops	Reinforced composites	
	Textile cleaning	Anti-oxidants	
		Absorbents	

Example of 'flagged' job titles with high incidence of occupational skin diseases and potential for dermal exposure to nanomaterials / nanoproducts

Sector	Job title	Example of nanomaterials/ products
Health Care	Dental practitioner/ assistant/ technician	Nanocomposites
	Nurses	Nanomedicine
Personal care	Hairdresser	Variety of personal care products
	Beauticians/ visagists	
Construction	Construction painters	Coatings, paints
	Concrete repair workers	Mortars
Cleaning	Cleaners	Cleaning and dirt repellent coatings
Automotive	Car (body) repair workers	Primers, paints, nanocomposites

Evidence for dermal exposure during handling of nanopowders

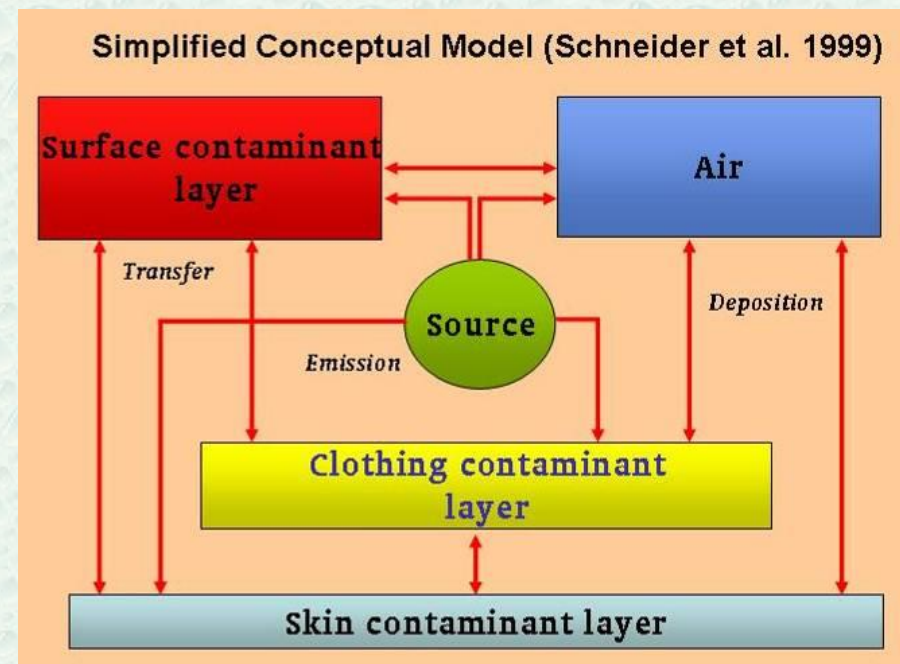


Pictures
courtesy
Dhimiter
Bello

Subjective Assessment of dermal exposure during handling nanopowders (van Duuren et al, 2010, JOEH)

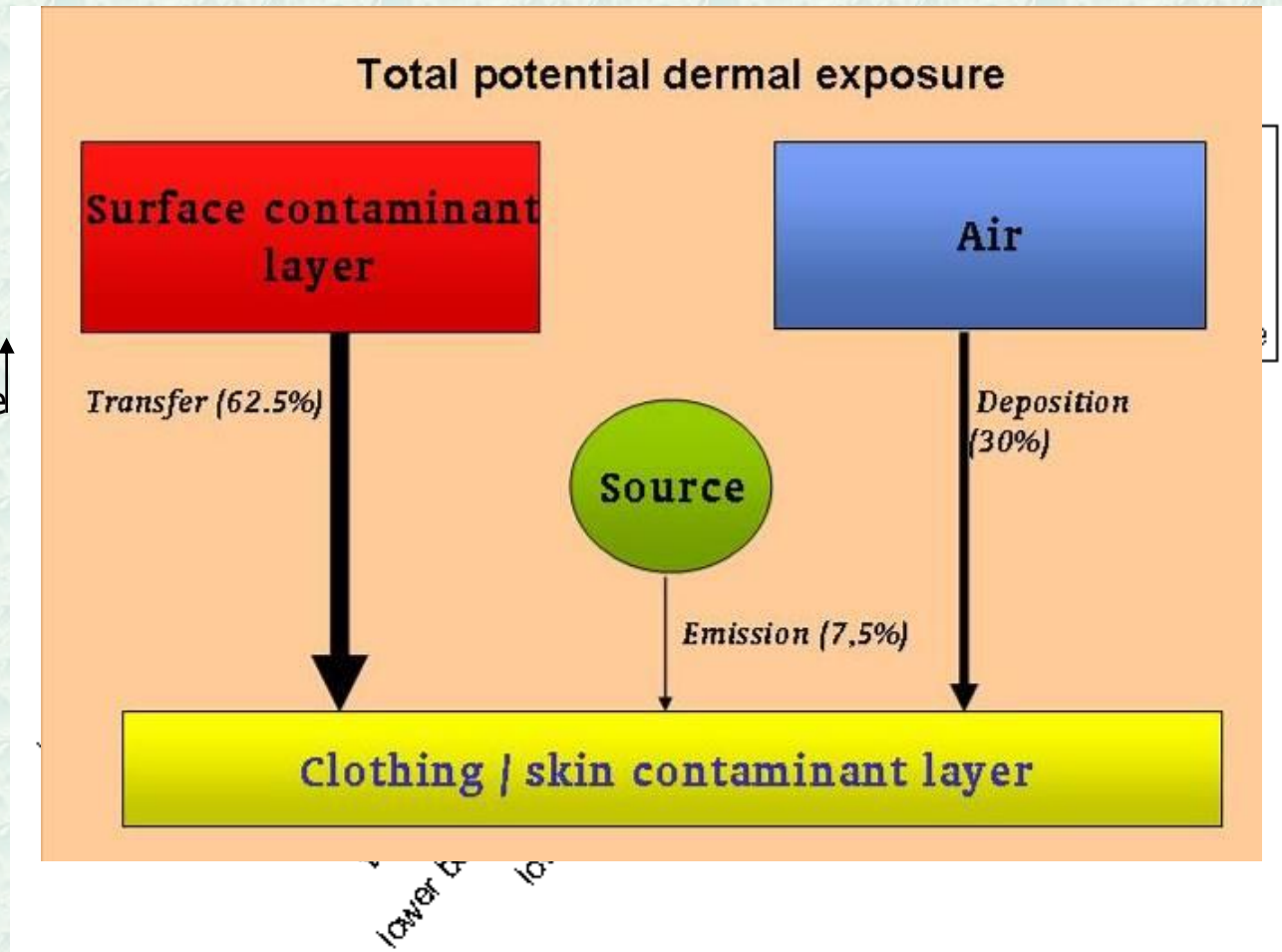
(excerpts of) DREAM model described by Van Wendel de Joode et al. (2003) based on:

- Conceptual model (Schneider et al., 1999)
- Method for structured subjective assessment of airborne concentrations (Cherrie et al., 1996)



Example Bag dumping fumed silica

DREAM
estimate ↑

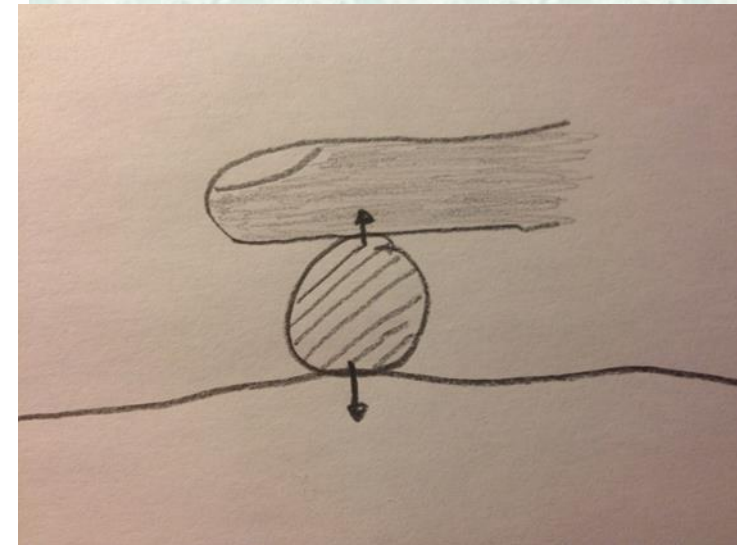
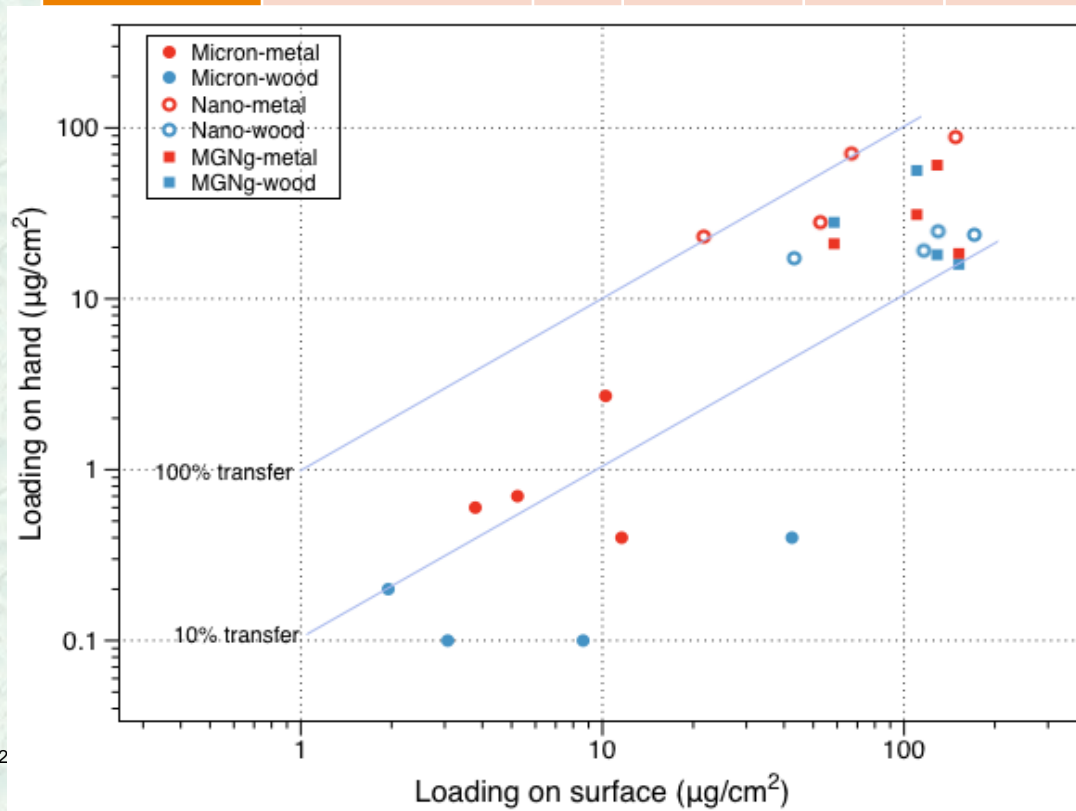


Transfer surface to hands; results of experimental study (Sleeuwenhoek & Cherrie, 2014)

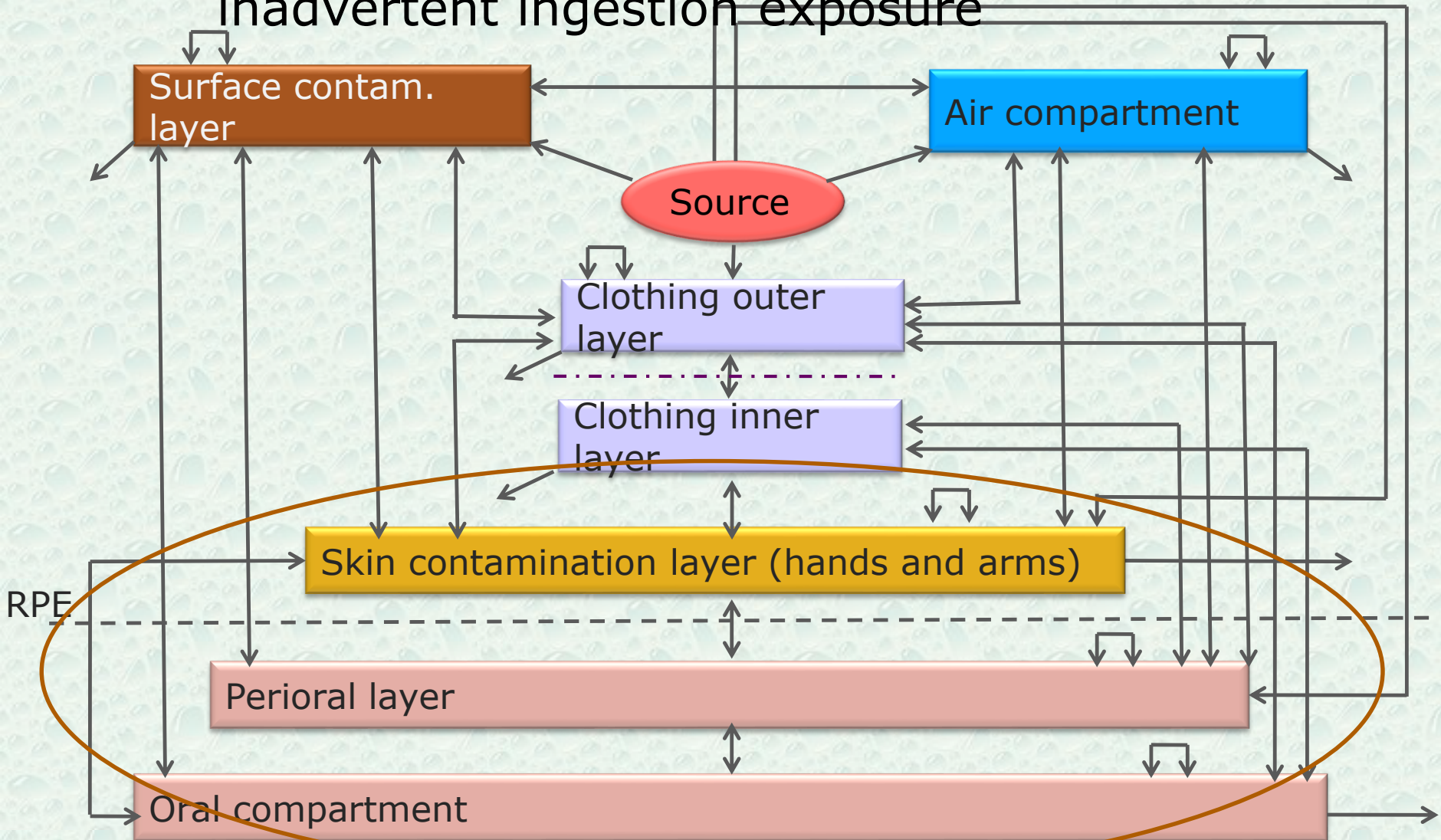
SURFACE	Particle Size	N	TRANSFER EFFICIENCY		
			Range	GM	GSD
Metal	micron	4	3.5-27	12	2.4
	nano	4	53-106	77	1.4
Wood	micron	4	0.9-10	2	3.2
	nano	4	14-40	20	1.6

Main observations

- Nano > micro
- Smooth > rough
- Loading no determinant of transfer?



inadvertent ingestion exposure



Inadvertent ingestion

- › Experimental work (Gorman Ng et al. 2013, 2014)
 - › Coarser powders transfer more readily from **hands to mouth** (peri-oral region)
 - › Lower transfer from rough surface (cotton glove) compared to smooth surface (bare hands, nitrile glove)
 - › Quantification
 - › **Ingestion Exposure Assessment Tool (IEAT)**
 - › **Estimates mass loading of Perioral region (μg) from hand exposure ($\mu\text{g}/\text{cm}^2$)**
 - › Parameterised for micron-sized particles

N.B For nanoparticles the adherence to skin and surfaces may reduce ingestion exposure; however, agglomerates may behave differently

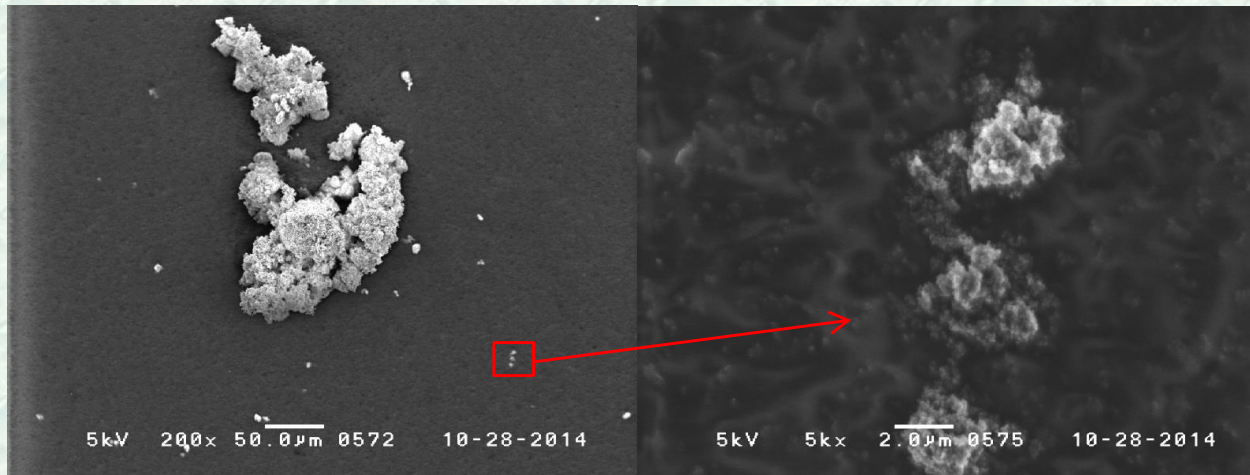
Assessment and measurement methods

- › CEN/TR 15278 (2007)/ ISO/TR 14294 (2011)
DERMAL Exposure Assessment Strategies
- › *Observational / Qualitative methods*
 - › Structured observations, e.g. DREAM.
e.g van Duuren e al, 2010 and modifications
proposed by IOM/ John Cherrie)
- › CEN/TS 15279 (2007)/ ISO/TR 14294 (2011)
Measurements: Methods and Requirements

Feasibility of quantification of skin contamination by nanomaterials (preliminary evaluation)

Sampling principle	Preliminary evaluation
interception techniques	<p>Collection: Pathway direct contact, transfer of powders and aerosol deposition, not for liquids.</p> <p>Chemical extraction and analysis; Huge challenges; information on particle size, state of agglomeration etc will be lost</p>
removal techniques	<p>manual wipe/ hand wash : Collection will/may alter particle size, state of agglomeration etc</p> <p>Extraction and analysis Huge challenges characterization/ analysis</p> <p>tape-stripping: Collection: may not affect particle size, state of agglomeration etc . Challenges for detection may be moderate</p>
direct assessment (e.g. fluorescence)	<p>Huge challenges for detection methods and devices</p>

Explorative experiments measurement methods (Roff 2014)



Direct deposition of nano-TiO₂ on adhesive Carbon tab lift attached to skin



Removal from skin by Carbon tab lift (effect of pressure)

Conclusions experimental work

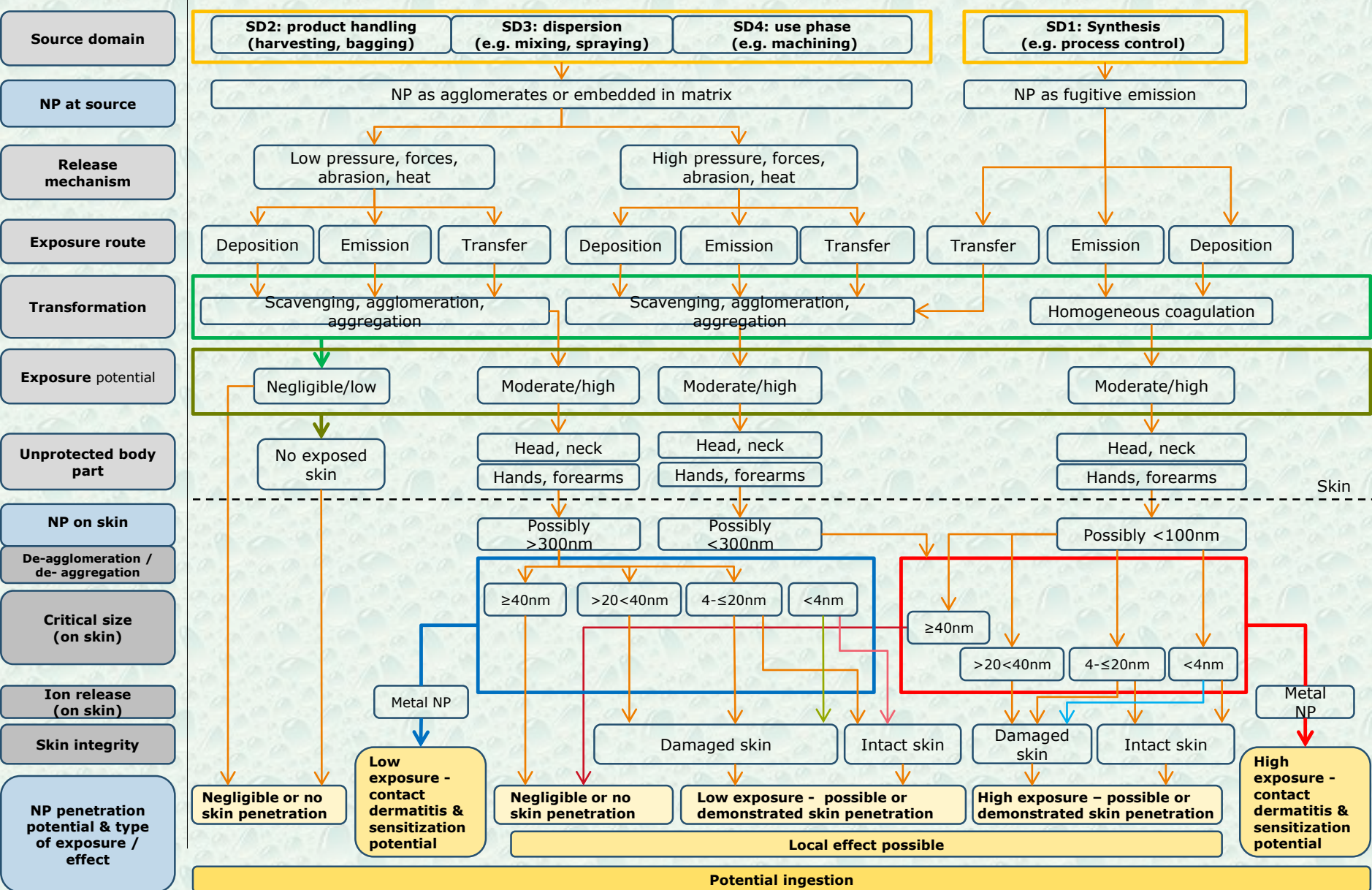
- › Adhesive tape:
 - › Feasible for interception and analysis of composition and size information (SEM)
 - › Feasible for removal and analysis of composition and size information (SEM), however,
 - › Skin cells can mask nanoparticles (pressure!)
 - › Effect of pressure on redistribution in skin layers or on size distribution not known yet
 - › Quantification limited and uncertain

Summary

Exposure route	Exposed Body parts	Physical state	Primary potential effect	Secondary potential effect	Preferred measurement method
Direct contact	<ul style="list-style-type: none"> • hands • forearms 	<ul style="list-style-type: none"> • Agglomerates • Powders) • Dispersion (creams) 	<p>Ingestion</p> <p>Penetration?</p>	<p>Penetration*</p> <p>local effect**</p> <p>Ingestion</p>	<p>Removal:</p> <p>Mass (wash/rinse/wipe)</p> <p>Removal (tab) +size info</p>
Transfer	<ul style="list-style-type: none"> • hands 	<ul style="list-style-type: none"> • agglomerates • clustered/ aggregated particles 	<p>Ingestion</p>	<p>Penetration*</p> <p>local effect**</p>	<p>Removal:</p> <p>Mass (wash/rinse/wipe)</p>
Deposition	<ul style="list-style-type: none"> • All (uncovered) 	<ul style="list-style-type: none"> • discrete particles • agglomerates 	<p>Penetration</p> <p>Local effect</p>	<p>Ingestion</p>	<p>Interception: size (adhesive tab)</p> <p>Removal: size (tab)</p>

*Most likely in disrupted skin
** Me(Ox) NPs and impurities

Guidance framework



Thank you for your attention

(Don't forget to shut the lights)

Mandate 461 Nanotechnologies

