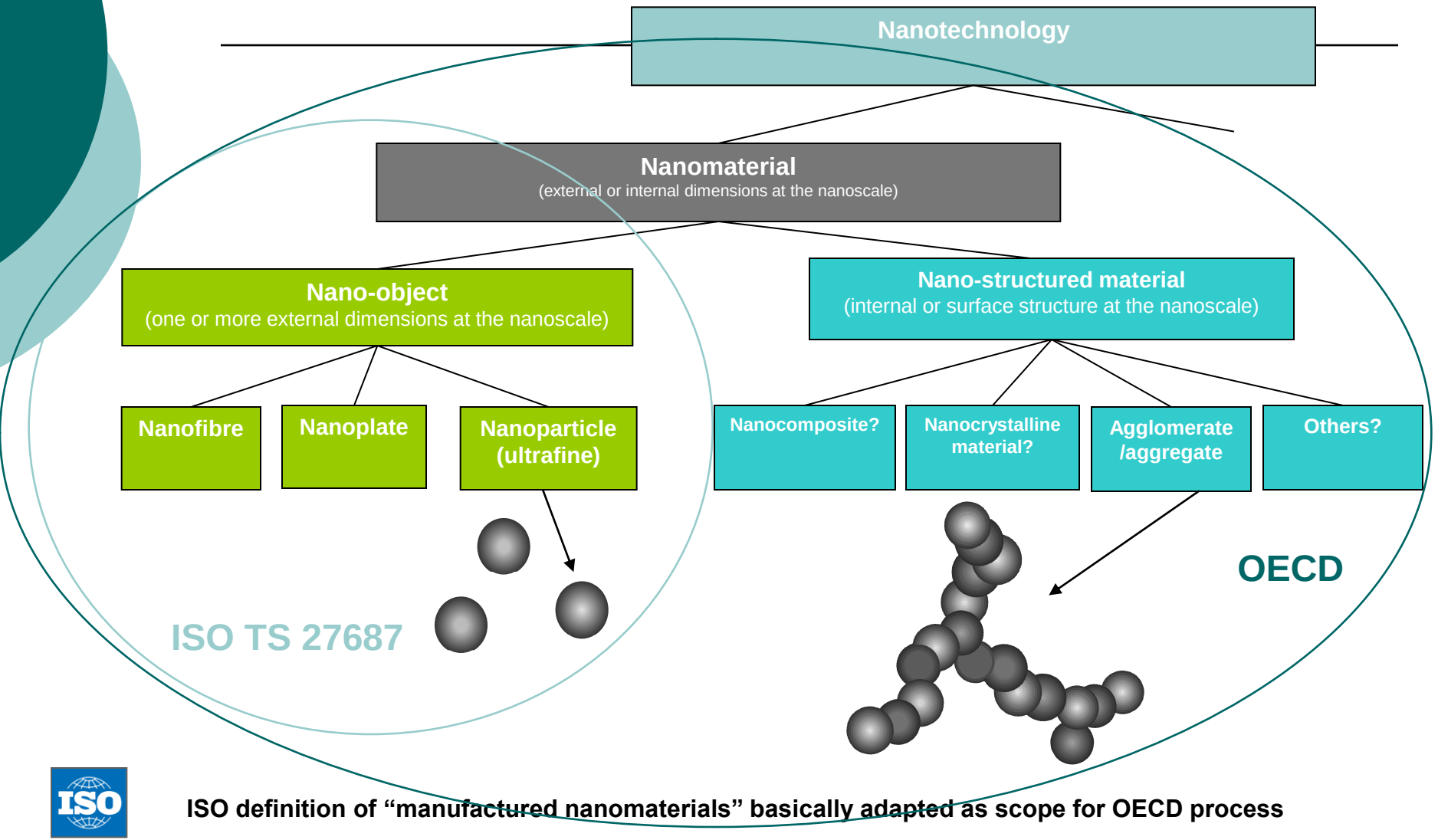
# Current Opinions on the Human Safety of Titanium Dioxide and Zinc Oxide

J F. Nash, Ph.D.
Central Product Safety
The Procter & Gamble Company
Cincinnati, OH 45241
nash.jf@pg.com

# Human Safety: Objective

- There are no human health concerns associated with the use of "nano" $TiO_2$ and ZnO
  - as used in sunscreen products
  - at anticipated exposures
- SCCS favorable opinion for $TiO_2$ and ZnO
  - "nano" supplement for $TiO_2$ is under review
  - for ZnO, a supplement is being prepared

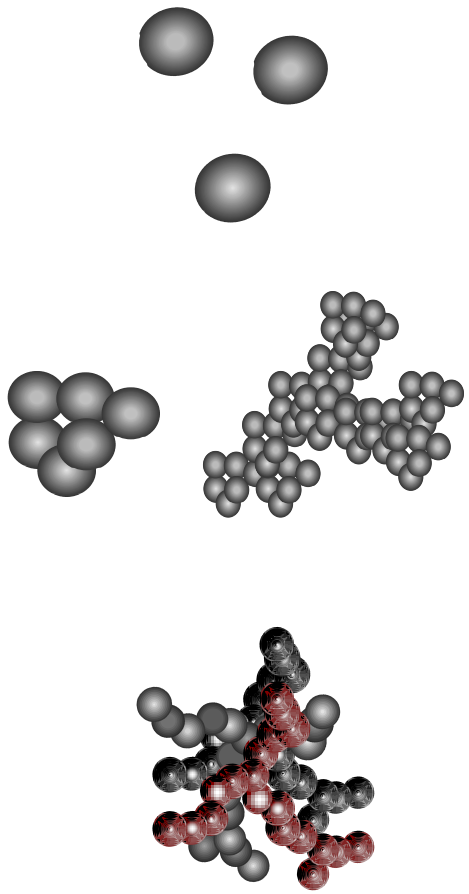
# Definitions of “Nano”




**ISO definition of “manufactured nanomaterials” basically adapted as scope for OECD process**

# Definitions of “Nano”*

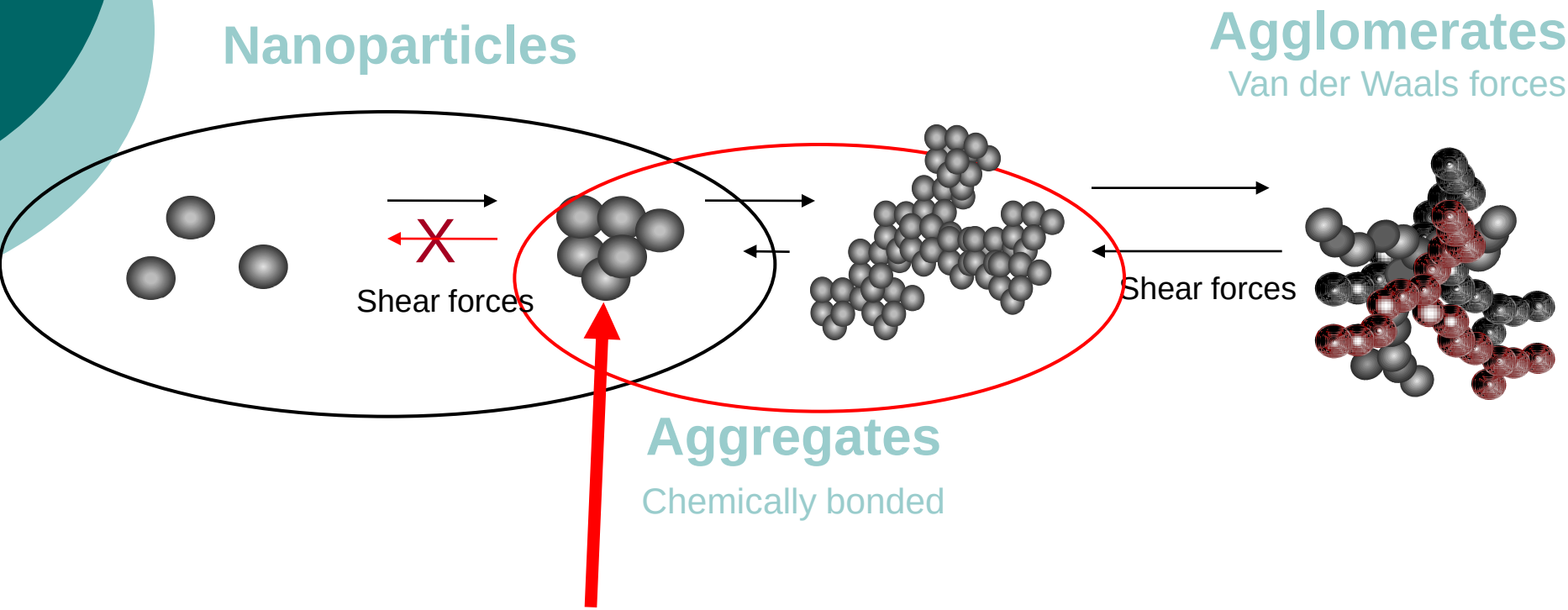
- Nanoparticle (1-100 nm)
  - Particle with all three external dimensions at the nanoscale. [Alternative descriptions: Crystal Size, Primary Particle Size]
- Aggregate (30-150 nm)
  - Particle comprising strongly bonded or fused particles where the resulting external surface area is significantly smaller than the sum of calculated surface areas of the individual components. [Alternative descriptions: Particle Size, Primary Particle Size]
- Agglomerate (1-100 µm)
  - Collection of loosely bound particles or aggregates or mixtures of the two where the resulting external surface area is similar to the sum of surface areas of the individual components.



*ISO CD of TS 27687 – Technical spec. August 2008

# Definitions of “Nano”

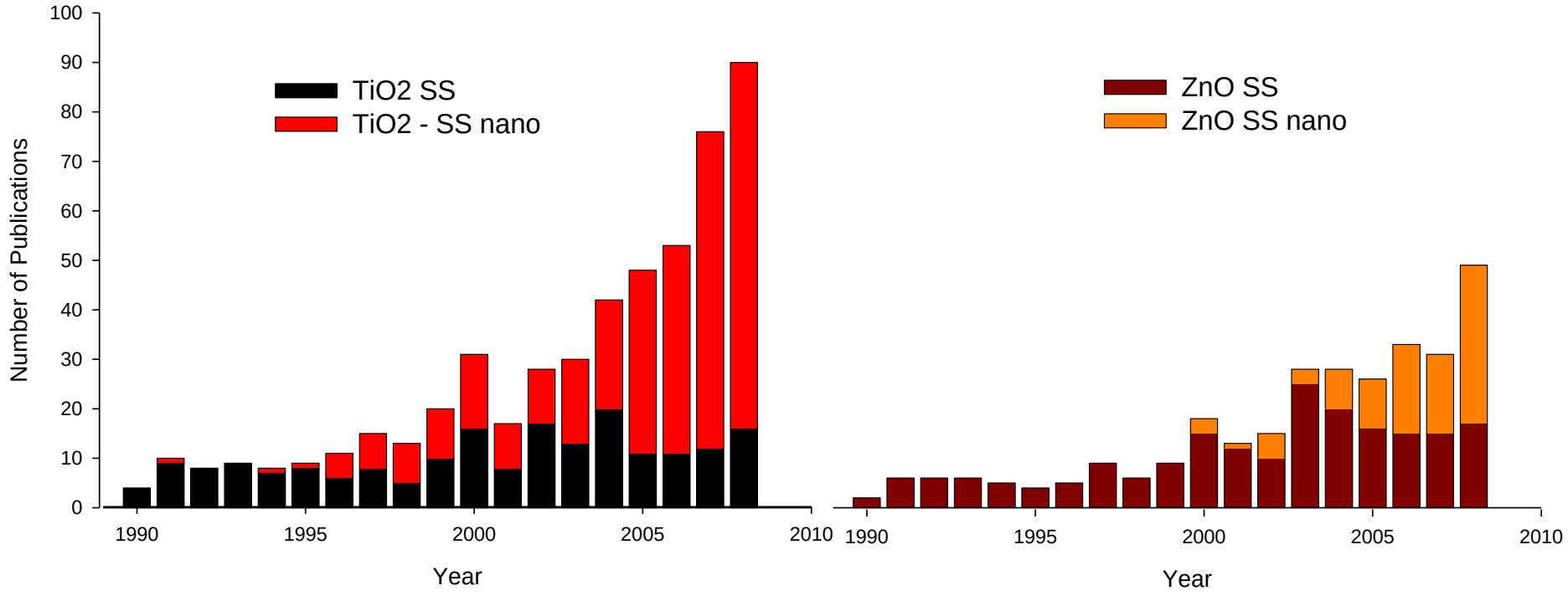
Nanoparticles form aggregates and agglomerates in practical systems




Smallest structure present in cosmetic formulations 30-150 nm

# Definitions of “Nano”:  consequences

## Publications on $TiO_2$ and ZnO in sunscreen and "nano"



# Toxicological Considerations: Dermal Penetration

| STUDY | MATERIAL | RESULTS |
|---|---|---|
| Tan *et al.*, 1996 | Microfine $TiO_2$ | Penetration into dermis claimed, but no statistically significant difference from controls |
| Dussert and Gooris, 1997 | $TiO_2$ (50-100 nm), ZnO (20-200 nm) | No penetration into epidermis/dermis (man) |
| Lademann, 1999 | Microfine $TiO_2$ | |
| Pflücker *et al.,* 2001 | $TiO_2$ , 10 and 100 nm | |
| Schulz *et al.,* 2002 | $TiO_2$ , 10-100 nm, different coatings and shapes | |
| Menzel *et al*, 2004, EU NANODERM project | Commercial sunscreens containing $TiO_2$ NPS | Penetration through SC into S granulosum, but not into S spinosum; porcine skin *in vivo* (no penetration in hair follicles) |
| Gontier *et al,* 2004 | $TiO_2$ NPs | No penetration into living skin (mouse, pig and human skin *in vitro)* |
| Popov *et al.,* 2005 | $TiO_2$ NPs | No penetration into epidermis/dermis most penetration within 3 µm; NB: SC is 15-20 µm thick (man, repeated application) |
| Gamer *et al*., 2006 | ZnO and $TiO_2$ (30-160 nm) | No penetration of Zn, ZnO, Ti or $TiO_2$, porcine skin *in vitro* |
| Cross *et al*., 2007 | ZnO, 15 and 30 nm | No penetration into epidermis or dermis, human skin *in vitro* |

# Toxicological Considerations: Dermal Penetration

| STUDY | MATERIAL | RESULTS |
|---|---|---|
| Mavon *et al*., 2007 | $TiO_2$, 20 nm | No penetration into epidermis or dermis; epidermal artefacts *in vitro;* human skin *in vitro* and *in vivo* |
| Lekki *et al*., 2007 (EU NANODERM project) | $TiO_2$ (20 nm) in sunscreen formulations (ion microscopy and autoradiography) | - No penetration into living skin (human and porcine skin *in vitro*)<br>- Presence of NPs in 3-5 first layers of SC and in follicles only (mechanical movement, no « diffusion » pathway) |
| Pinheiro *et al.* (2007), EU NANODERM project | $TiO_2$ NPs in sunscreen formulations (nuclear microscopy) | - No penetration into living skin, using human intact or psoriatic skin *in vivo*<br>- $TiO_2$ permeation profile similar in healthy and psoriatic skin |
| Japan Cosmetic Industry Association (2007) | $TiO_2$ (10-20 nm) and ZnO (20-30 nm) NPs in Water/D5 emulsions | No evidence of skin penetration of $TiO_2$/ZnO NPs beyond first layers of the SC, pig skin *in vitro* |
| Kiss *et al* (2008), EU NANODERM project | Commercial sunscreens containing nano $TiO_2$ | No penetration of $TiO_2$ into living skin ; human skin xenografts implanted onto mice |
| Sadrieh *et al* (SoT poster, March 2008) | Sunscreen formulations containing $TiO_2$ (nano or micro, coated or not) | No systemic distribution of $TiO_2$ (slightly increased Ti levels in dermis, but not in liver or lymph nodes in all groups, micro or nano); mini-pig, repeated application |

# Toxicological Considerations: Genotoxicity/photo-genotoxicity

- Example of genotoxicity/photogenotoxicity for nano $TiO_2$

| CRYSTALLINE FORM | Mean primary particle size (nm) | COATING | Ames / Photo-Ames | CHO / Photo-CHO |
|---|---|---|---|---|
| Rutile | 14 | $Al_2O_3$/Dimethicone | **negative** | **negative** |
| Anatase | 60 | $Al_2O_3/SiO_2$ | **negative** | **negative** |
| Anatase | 60 | Uncoated | **negative** | **negative** |
| Anatase | 200 µm | Uncoated | **negative** | **negative*** |
| Rutile | 20 | $Al_2O_3$/Dimethicone | **negative** | **negative** |
| Rutile | 17 | $Al_2O_3$/Stearic acid | **negative** | **negative** |
| Rutile | 20 | Uncoated | **negative** | **negative** |
| Rutile | 15 | $Al_2O_3$/Stearic acid | **negative** | **negative** |
| Rutile | 15 | Uncoated | **negative** | **negative** |
| Rutile | 11-28 | $Al_2O_3/SiO_2$ | **negative** | **negative** |

* Some inconclusive / positive results at high cytotoxic levels, but overall rated negative.