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A NOVEL APPROACH TOWARDS EFFECTIVELY ASSESSING THE RISK OF NANOMATERIALS IN BIOMEDICAL RESEARCH

Martine Orosco, Jacques Simons, Corinne Schiltz
Bureau de Coordination de la Prévention des Risques
Inserm, 101 rue de Tolbiac
75654 Paris Cedex 13 FRANCE

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The French National Institute of Health and Medical Research (Inserm)

An Institute entirely dedicated to biomedical research for human health

- 2016: 72 Research Units out of around 300 involved in activities with nanomaterials

➢ **Main applications**

- Nanovectors used as diagnostic and therapeutic tools
- Toxicological studies

Characteristics

- Large range of locally produced, often not characterized materials
  - Main materials: synthetic polymers and biopolymers, lipoproteins and liposomes
- Small amounts: laboratory-scale production

« As nanomaterials have therapeutic purposes, why should safety precautions be required? »

« what benefits patients cannot be harmful for researchers »

Aim of the study: Select a risk evaluation method

- Easy to apply
- Relevant to the specificities of academic research

Several methods could fit

- Control banding methods

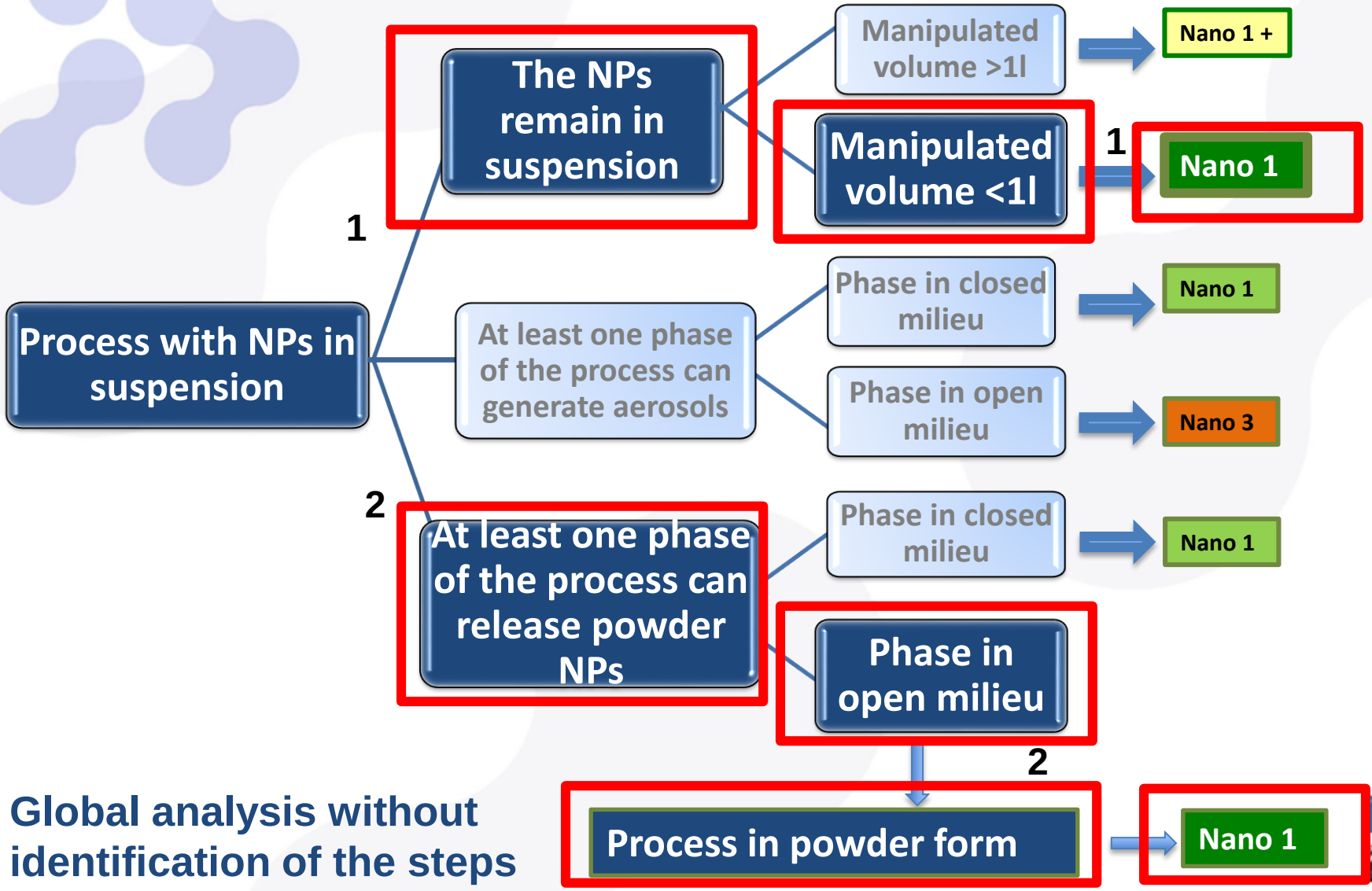
ANSES method: *Development of a specific Control Banding Tool for Nanomaterials, 2010*

- The decision tree according to Groso et al., *Management of nanomaterials safety in research environment, Particle and Fibre Toxicology, 2010, 7:40*

Application of the method to pilot research units

- Decision tree
  - Firstly based on the physical state of the nanomaterials
  - Secondly based on quantities and use
- Approach
  - Identification of three pilot research units with different activities
  - Application of the decision tree to their process
  - Attribution of a hazard level ranging from 1 to 3
    - 1 = lowest hazard **Nano 1**
    - 2 = medium hazard **Nano 2**
    - 3 = highest hazard **Nano 3**

Production of polysaccharide nanovectors



Global analysis without identification of the steps

Production of polysaccharide nanovectors
Global analysis: conclusion

- Whereas powder form processes are known to be the most dangerous, how could we only find Nano 1?

- This method is not accurate enough

→ What shall we do?

↓ Adaptation of the method

1. Analyze the processes by identifying the experimental steps containing potential nano and associated risks

2. Attribute 1 out of 3 hazard levels TO EACH STEP of the process

Production of lipid nanovectors for anticancer drugs

Weighing water + oil+ surfactant + cytostatic molecules → Temperature cycles under stirring → Addition of water to the emulsion → Lyophilization

Weighing water + oil+ surfactant + cytostatic molecules → Carcinogenic, mutagenic and toxic to reproduction (CMR) hazards

Addition of water to the emulsion → Forming of nanovectors in suspension → The NPs remain in suspension → volume <1L → Nano 1

Lyophilization → This phase of the process releases powder NPs → Process in powder form → 1-100 mg/batch → NPs agglomerate → Nano 1

Production of lipid nanovectors for anticancer drugs: conclusion

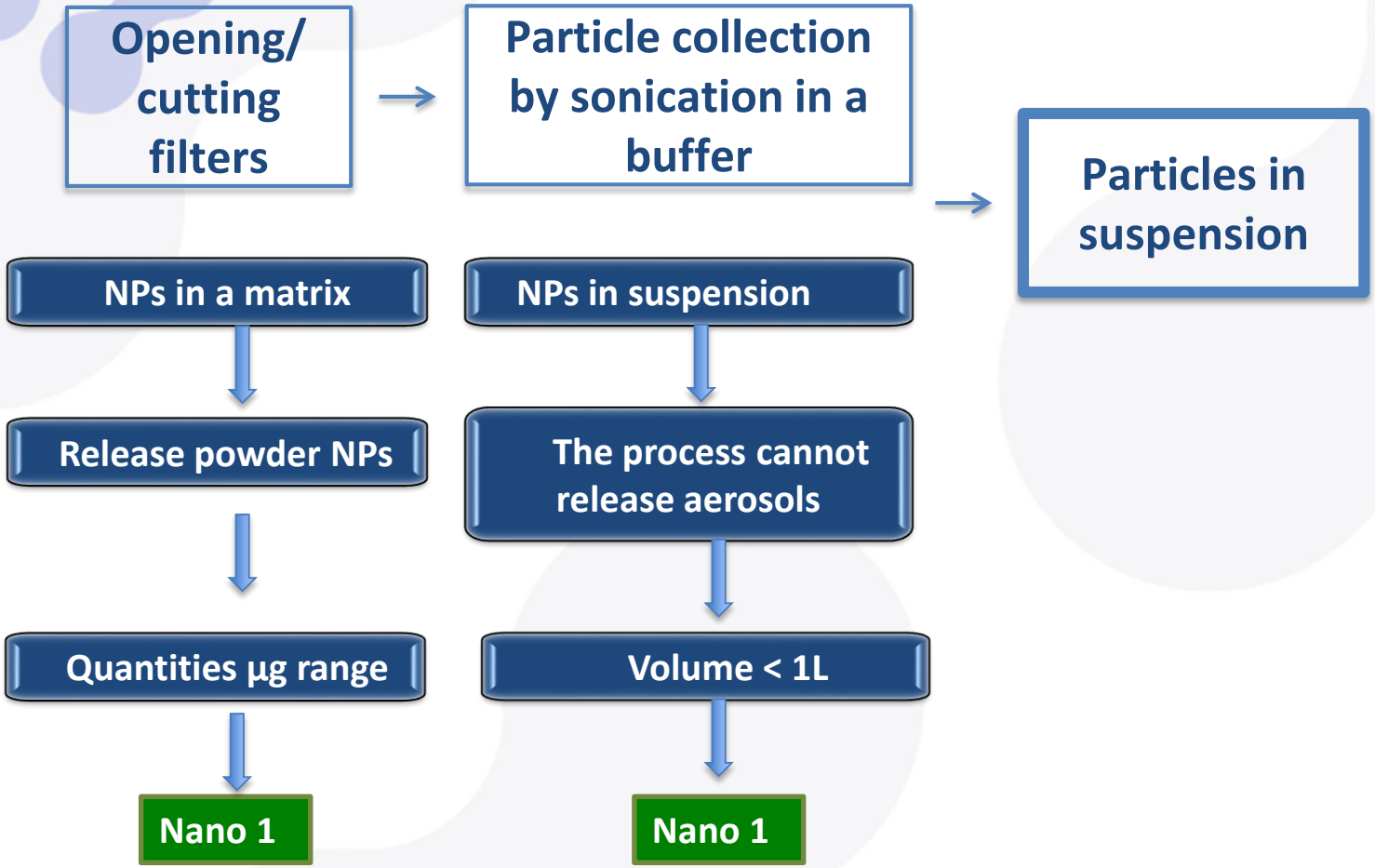
Dividing the process into separate steps allowed to:

- Locate precisely the nano hazards
- Dissociate from other hazards (here for instance, chemical)

This is essential to propose adequate safety measures at the right place and at the right time of the process.

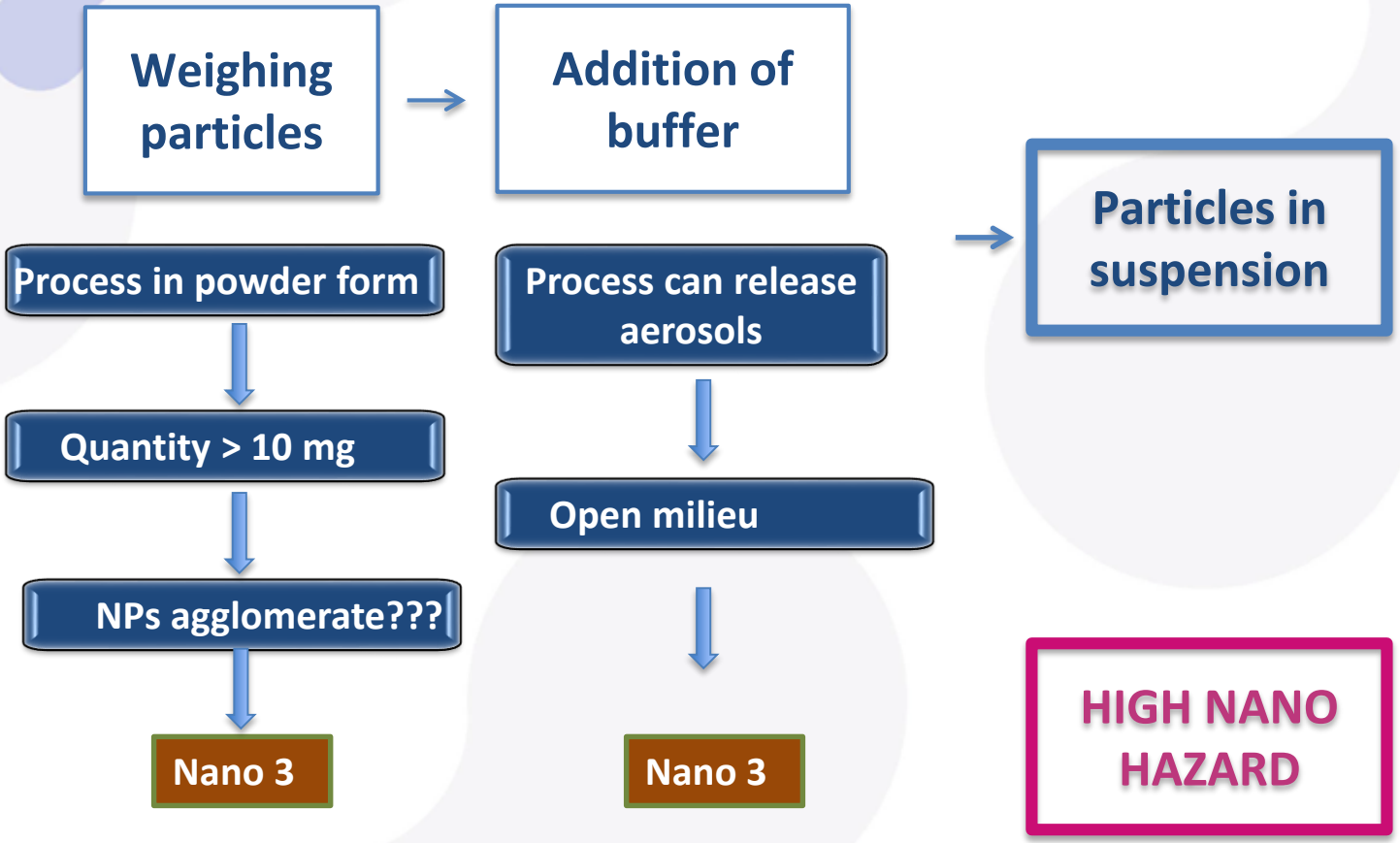
Toxicity of urban particulate matters

Obtention of particles from urban pollution



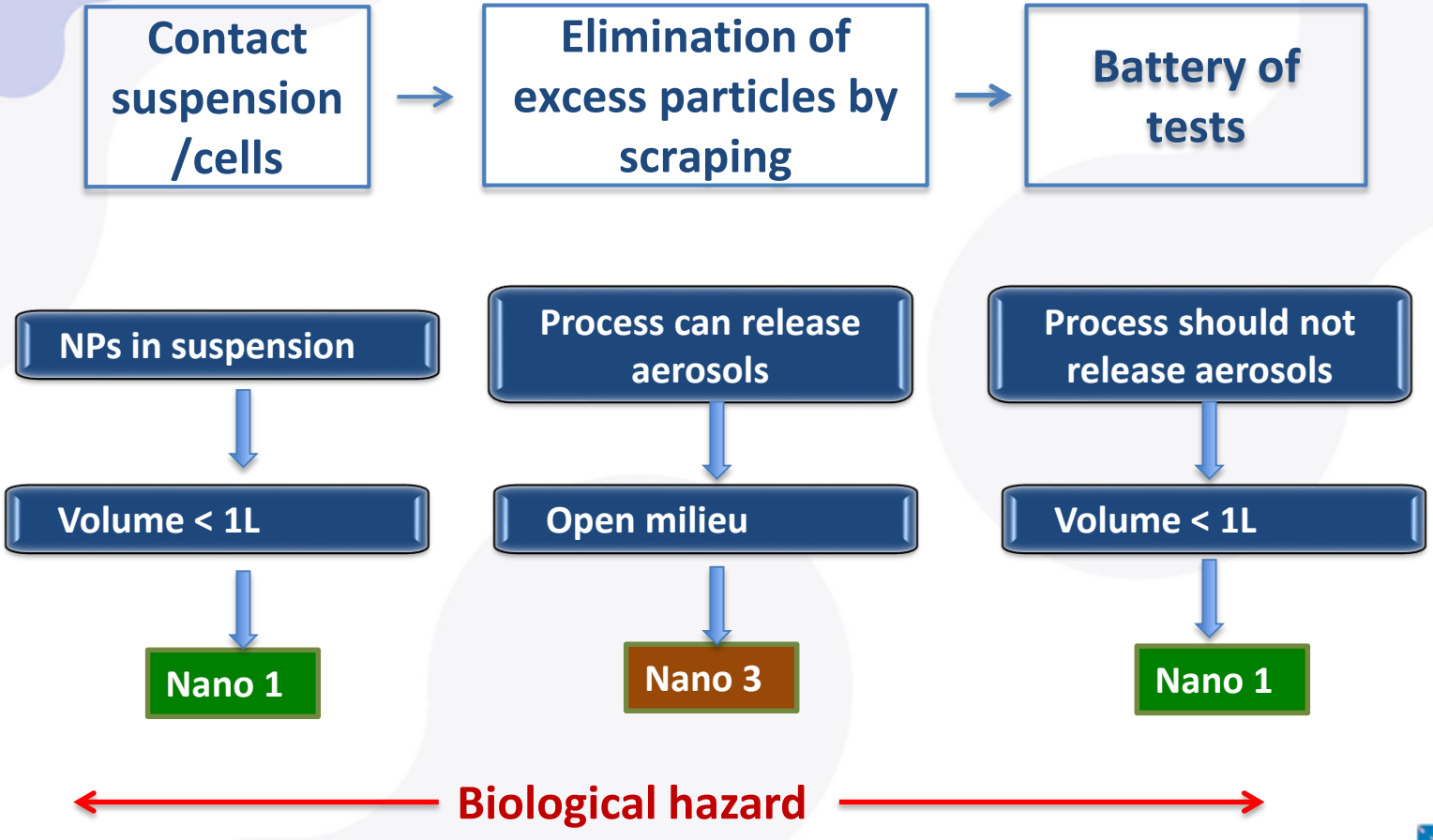
Toxicity of urban particulate matters

- Obtention of manufactured nanoparticles (carbon black, titanium dioxide, standard reference particule matter) in suspension



Toxicity of urban particulate matters

➢ Exposure of human bronchial epithelial cells to nanoparticles



Toxicity of urban particulate matters: conclusion

Dividing the process into separate steps also demonstrates that:

- It is possible to alternate different levels of nano hazards in a same process
- Another kind of hazard (biological for instance) may however exist all along the process

Both observations have to be considered in order to define and prioritize adequate safety measures

- for each step of the process
- for associated hazards

Conclusion 1

Decision tree by Groso et al.

- **Well adapted to research laboratories to define a class of nano hazard for each step of a process**
- **But does not allow to identify the associated risks which are always present in biomedical research laboratories**

Preventive measures, only established on nano hazards, are not necessarily the most adapted.

Conclusion 2

Our study

- By dividing the process in successive steps we could identify associated risks occurring simultaneously or not

- We could therefore supply case-by-case and step-by-step recommendations and protective measures depending on:

  - location of the hazardous steps
  - identification of the associated risks
  - recognition of the nature of the nanomaterials

- Lack of consideration of only one of these endpoints may lead to inappropriate prevention.

Conclusion 3

Additional advantages

- **It is easy to implement :**

The method has been applied in several other laboratories with the help of our local and regional health and safety correspondents.

⟹ **Researchers and technicians become actors of their prevention**

- **It allows to define prevention measures at targeted steps of the experimental process without useless over-protection.**

THANK YOU FOR YOUR ATTENTION