Japan NANO 2007 *February 20, 2007*

Our Research Activities on Risk Assessment & Risk Management of Nanotechnology

Junko Nakanishi

Research Center for Chemical Risk Management (CRM)

National Institute of Advanced Industrial

Science and Technology (AIST)

Presentation Overview

- **Emphasize that risk assessment is critical for a new technology. The key is how to manage risk, not to determine whether the new technology is safe or dangerous. (Chapter 1)**
- **Explain in detail about our project to evaluate risks of nanomaterials (NMs). (Chapter 2-4)**
- **Stress the importance of having a bird's-view risk perspective across nanotechnology, not limited to risks caused by NMs. (Chapter 5)**
- **Ensure to make risk management policies around nanotechnology visible to the public. (Chapter 6 and 7)**

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Risk evaluation is needed for the new technology

1. **If nanotechnology has something new in terms of technology involved, it potentially contains a new kind of risk.**
2. **Any new technology or product should have risk evaluation results in its specifications.**
3. **The superiority of technology alone no longer justifies everything.**

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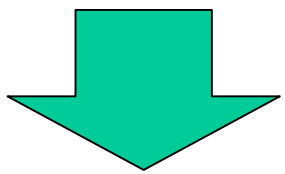
Key Advantage of AIST

1. **Owns a division dedicated to nanotechnology manufacturing research.**
2. **Owns a strong, advanced metrology research division that is critical for nanotechnology risks-related researches.**
3. **Is the only institution that has a research unit specialized in risk evaluation.**
4. **Is a pioneer in public acceptance study of nanotechnology.**



AIST should play a leading role in carrying out the risk evaluation of manufactured nanomaterials in cooperation with other research institutions and universities.

Basic stance for controlling new technology

1. **Assess the amount of risk and manage it, rather than deciding whether it is safe or not. We assess risk not safety.**

2. **Risk is a multiplication of toxicity and exposure. It is therefore important to look at exposure as well.**

$$\text{(RISK)} = \text{(TOXICITY)} \times \text{(EXPOSURE)}$$

3. **Nothing is totally risk-free.**

4. **Benefit of nanotechnology, if large enough, could justify its risk to a certain extent.**

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NEDO Project

EVALUATING risks associated with manufactured nanomaterials

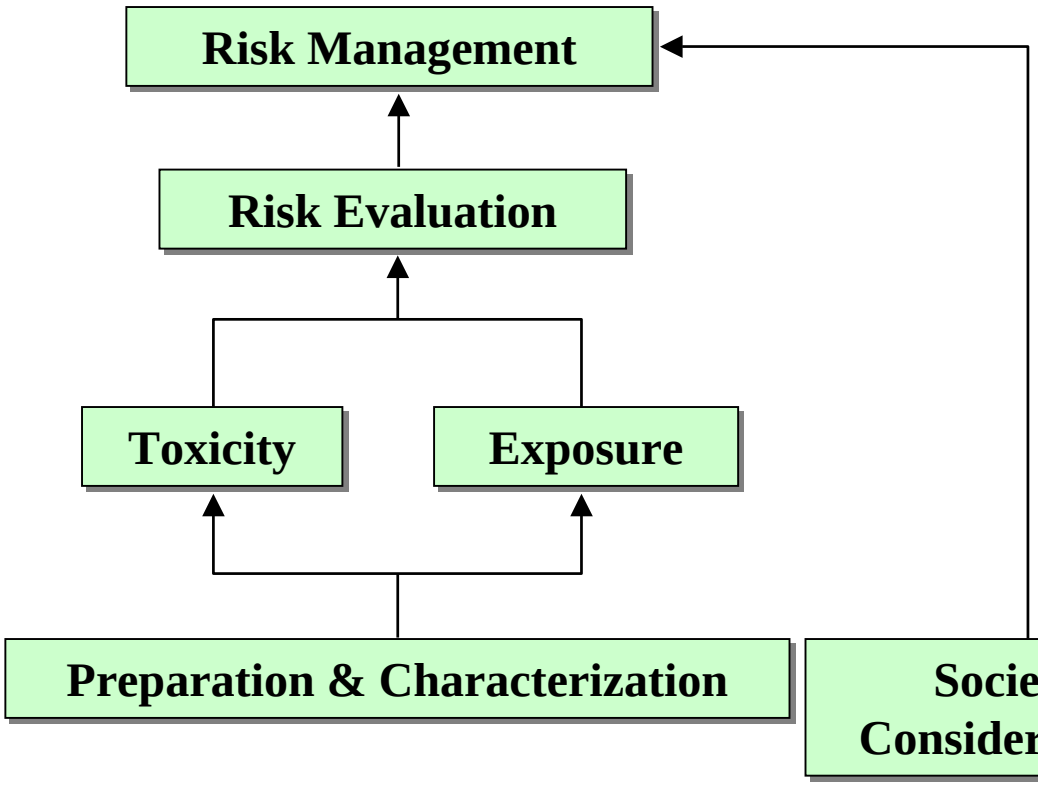
Project leader : Junko Nakanishi

NEDO:

New Energy and Industrial Technology Development Organization, Japan's largest public R&D management and funding organization

Major Components of the Research Project

Framework



Output

- **Guidance for the development of regulatory framework**
- **Risk assessment document of Fullerens , CNTs and TiO_2 (mainly human health risks)**
- **Protocol for toxicity tests**
- **Manual for sample preparations**
- **Standardized methods for characterization (measurement)**

Period: June, 2006 through March 31, 2010 (five years)

Amount: Approx. $ 17,000,000 for five years

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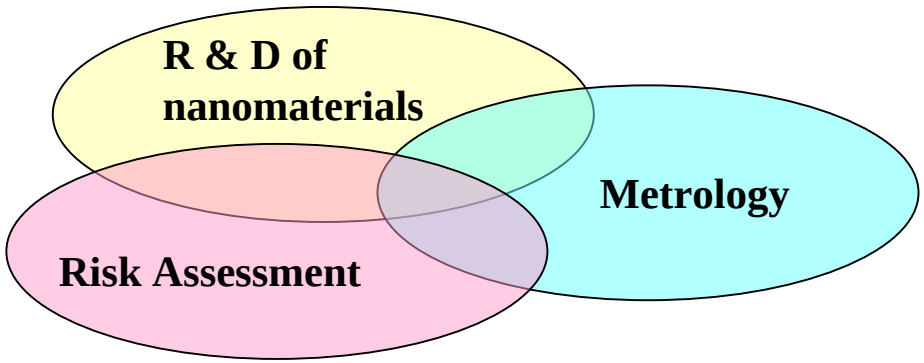
Research Institutions

AIST



- Research Center for Chemical Risk Management (CRM)
- Metrology Institute of Japan (MIJ)
- Advanced Manufacturing Research Institute (AMRI)
- Research Institute of Instrumentation Frontier (RIIF)
- Research Institute for Environmental Management Technology (EMTECH)
- Human Stress Signal Research Center (HSS)

University of Occupational and Environmental Health

Universities

- Graduate School of Engineering, Hiroshima University
- Faculty of Medicine, Tottori University
- Graduate School of Natural Science & Technology, Kanazawa University

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Key Strategy of the Project

- **To integrate metrology, toxicity and exposure evaluation into risk assessment**
- **To integrate the *in vitro* tests and continuous inhalation tests of rat into toxicity evaluation**
- **To develop the methods of**
  - **the measurement of the size and shape of non-spherical NMs in various media**
  - **the sample preparation for the toxicity tests and exposure analysis**
  - **the chemical analysis to know the translocation and fate of NMs in rat**
  - **the inhalation animal test for long days of NMs**

NMs: Nanomaterials

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Sections of the the Chapter 3

3 Toxicity evaluation methodology

- **§ 3-1 Dispersion of NMs for the toxicity tests**
- **§ 3-2 Biaxial Approach**
- **§ 3-3 Characterization and sample preparation**

§ 3-1

Dispersion of NMs for the toxicity test

Is dispersion of NMs necessary for the toxicity test?

Yes, because…

1. **Possibility of dispersion, if small, cannot be overlooked in assessing risks.**
2. **In the applicaions process, NMs are dispersed in the organic solvent and surfactant, eventhough they are aggromerated as grown or as raw.**
3. **Interaction of NMs with biomolecules in the human body are more likely with decreasing particle size.**
4. **Various biosurfactants exist inside a living body and could disperse aggromerated nanoparticles.**
5. **Nano particples tend to disperse in the waste disposal.**

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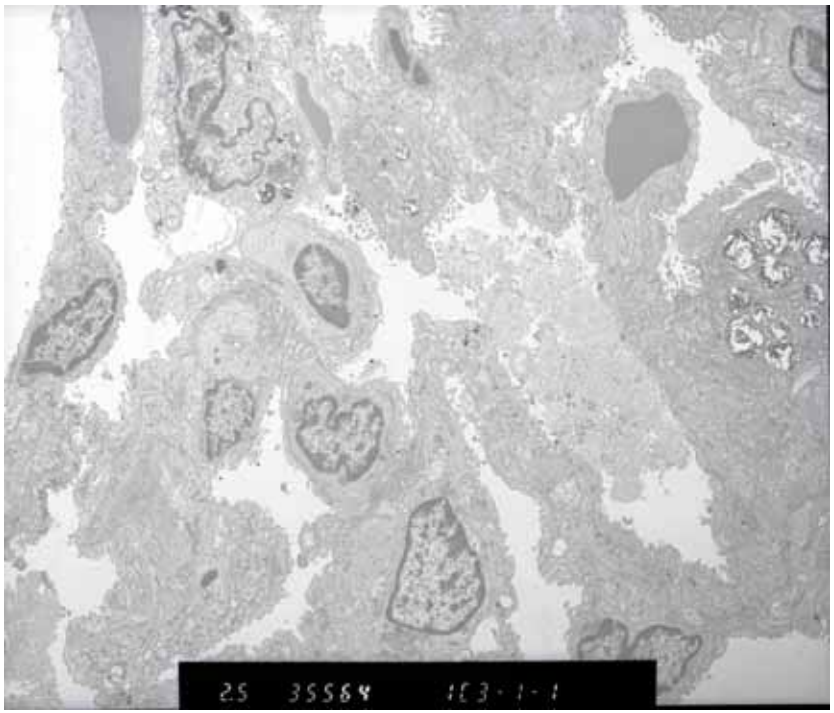
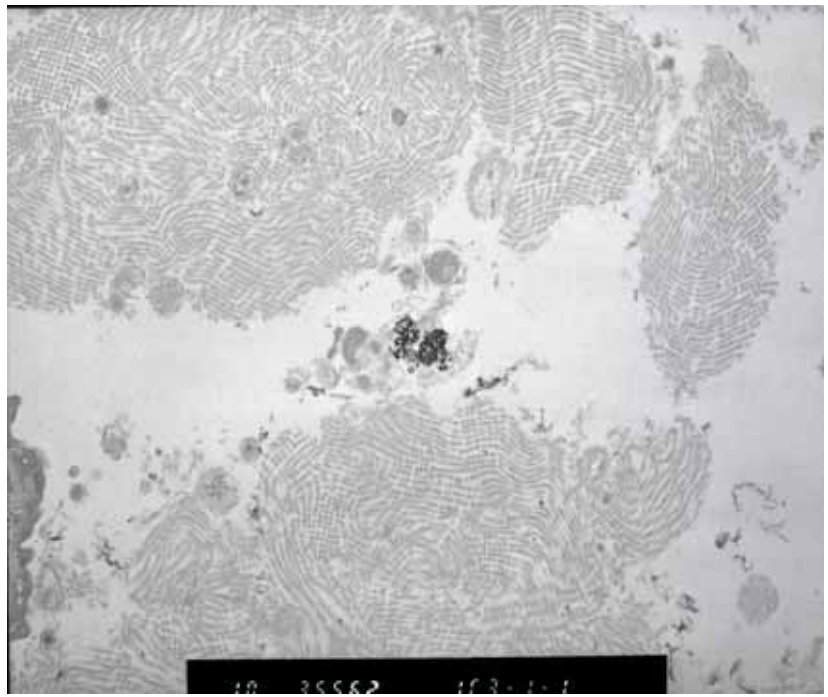
TEM Image of right lung of rat after intratracheal insillation of nano-NiO(intratracheal instillation)



10μm



2μm

NiO and biosurfactant

Kazuhiro Yamamoto, Yasuo Morimoto (2007)

How dispersed NMs should be used for the toxicity test?
− Fullerene −

Nakanishi proposed:

1. **Distinguish the sizes of test NMs between the *in vivo* tests and the *in vitro* tests**

2. **With the *in vitro* tests, disperse as much as possible (till the smallest size)**

3. **With the *in vivo* tests, disperse is necessary to such a degree that it does not impede inhalation test**

4. **The existing status of NMs in the environment should be into consideration**

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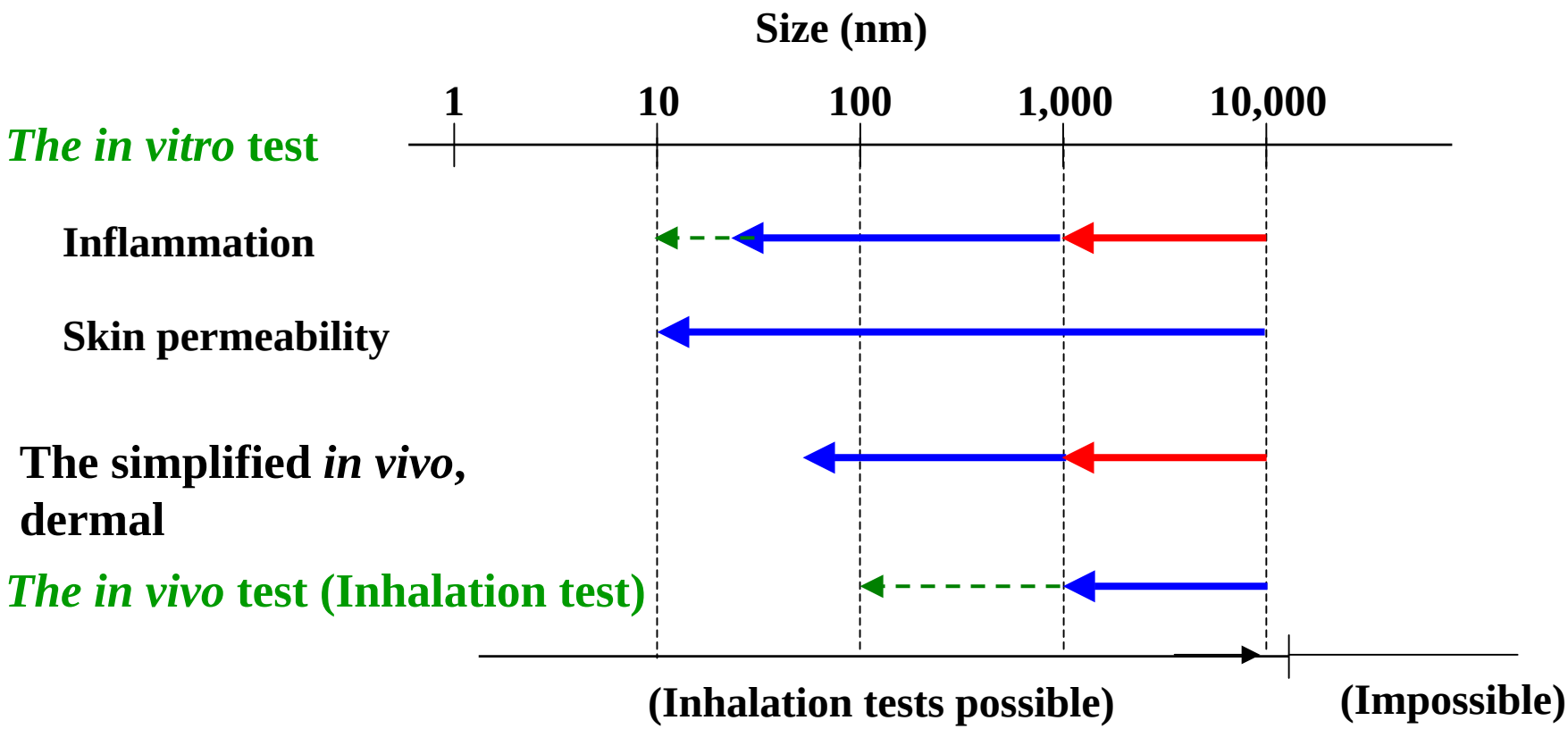
How dispersed NMs should be used for the toxicity test?
−Fullerene −



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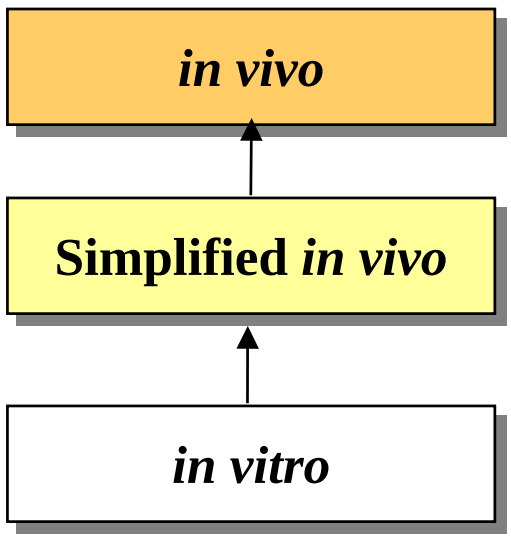
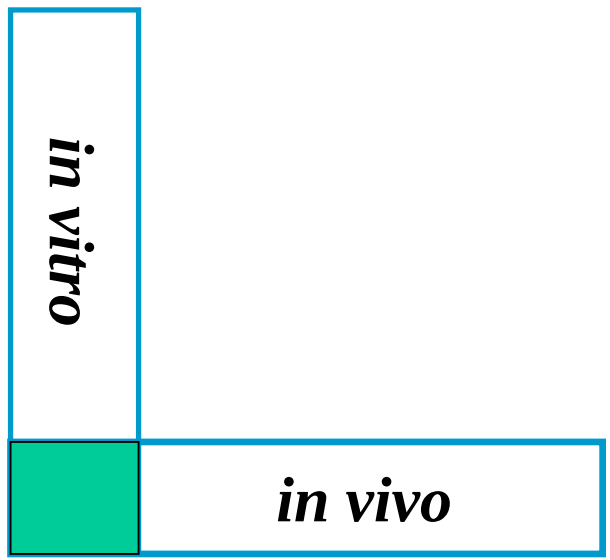
§3-2 Strategies for toxicity evaluation

－Biaxial Approach－

We applied the biaxial approach, but not the tiered one.



The tiered approach

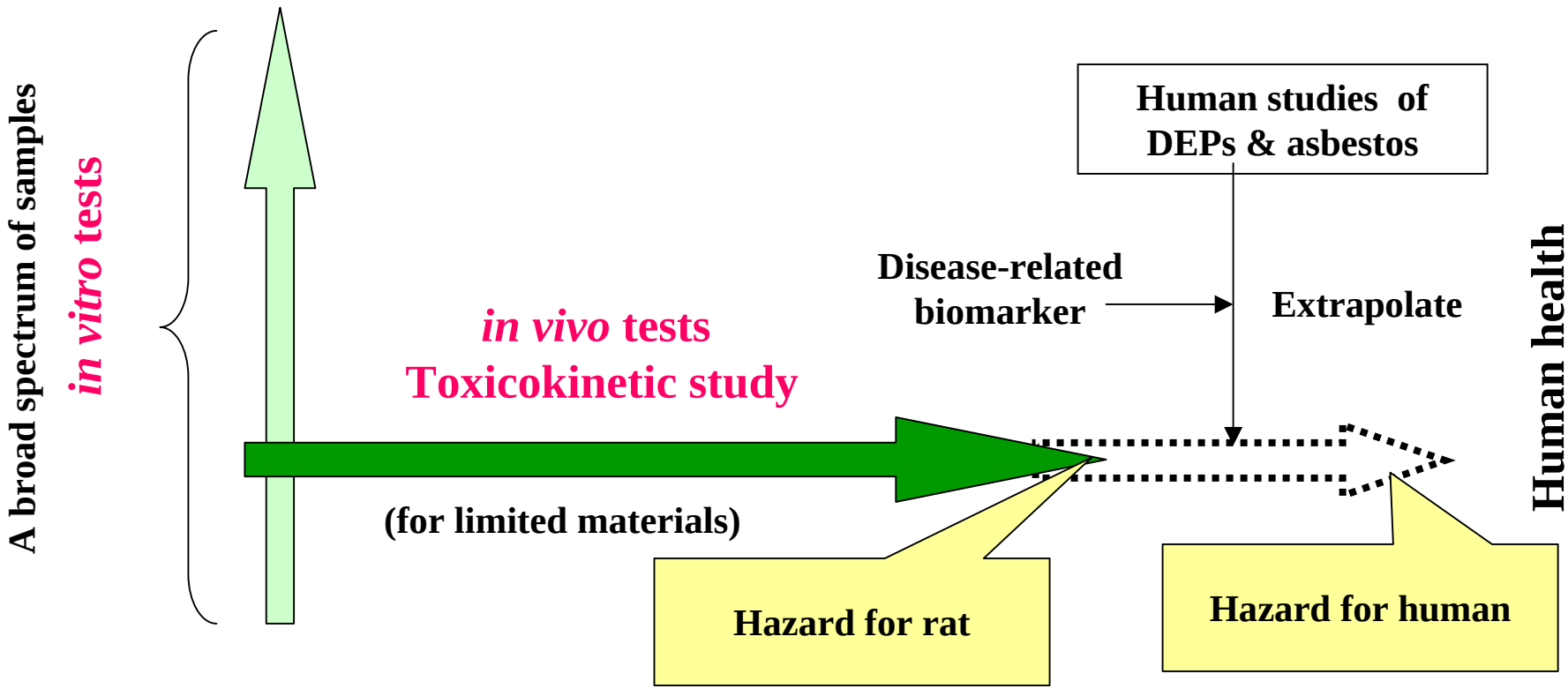


The biaxial approach

- Biaxial Approach -

The *in vitro* tests: to know the relative hazard potential of broad spectrum of substances, size and preparation methods

The in *vivo* tests: to know the target organ NOAEL for rat and extrapolate the effects for human, though for limited materials



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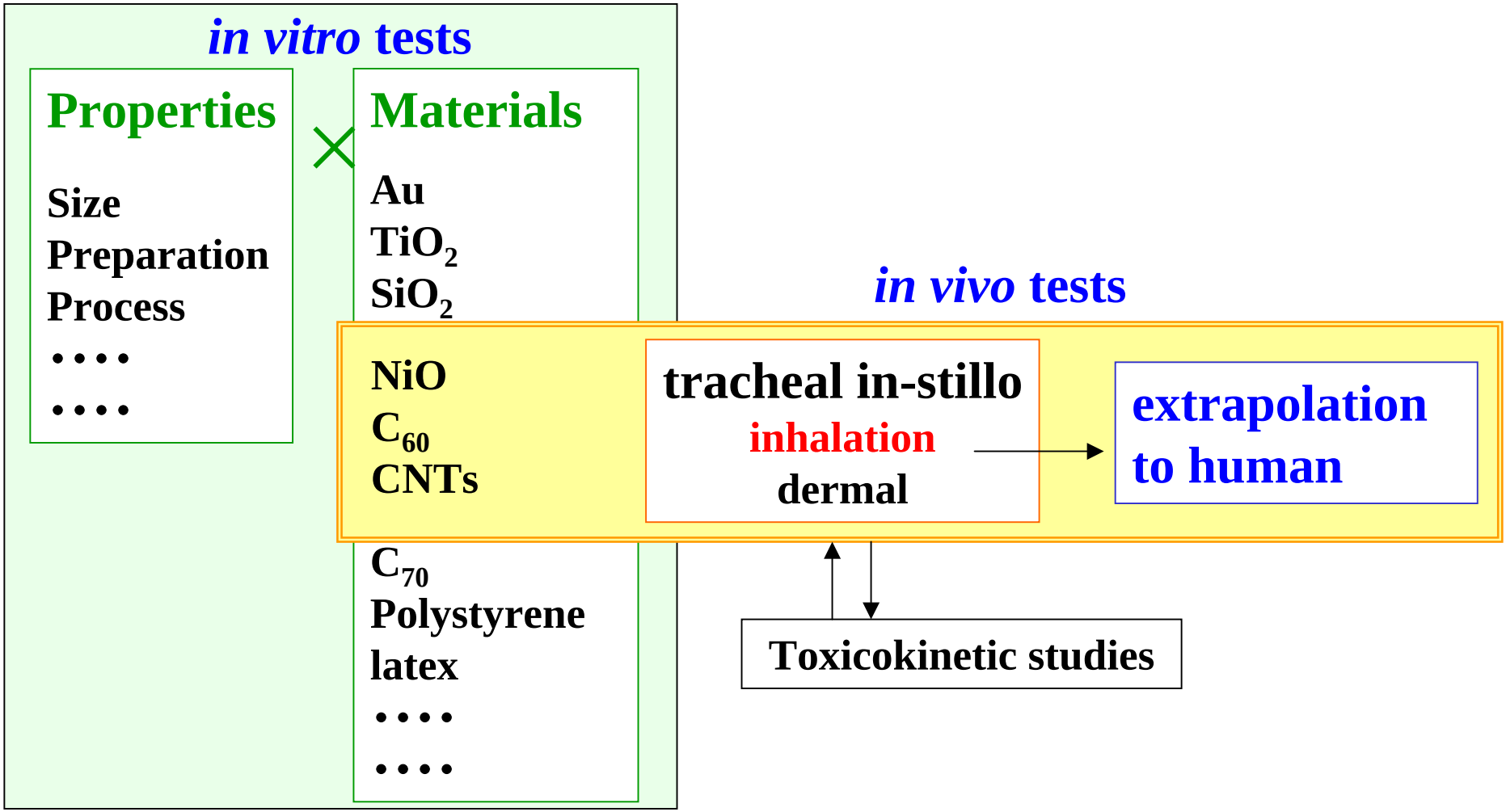
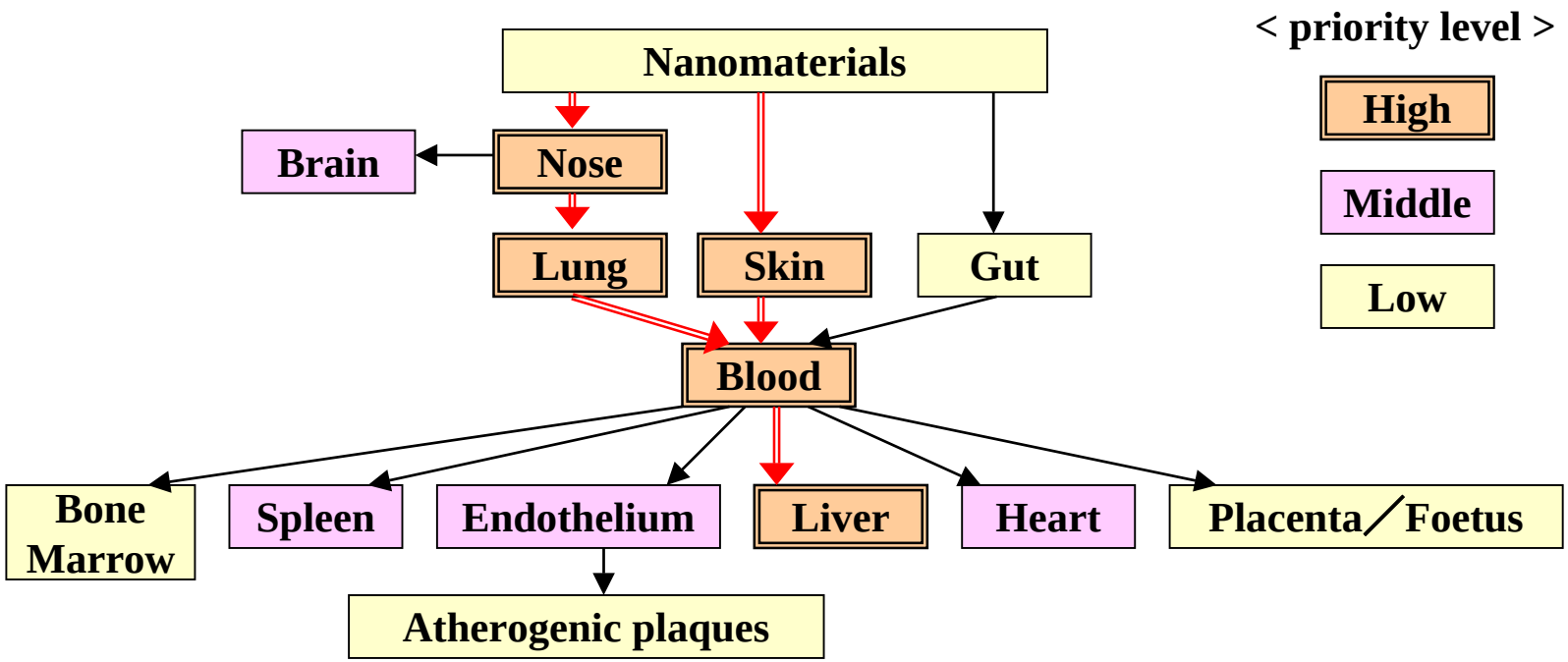
Target sample candidates for toxicity evaluation



At the beginning, the tiered approach was considered which consists of the tier 1 of the *in vitro* test for a screening , the tier 2 of the tracheal instillation and the tier 3 of inhalation test. However, we knew that it would be hard to find the *in vitro* testing method intrinsic of nano scale.

Junko Nakanishi, modified (2007)

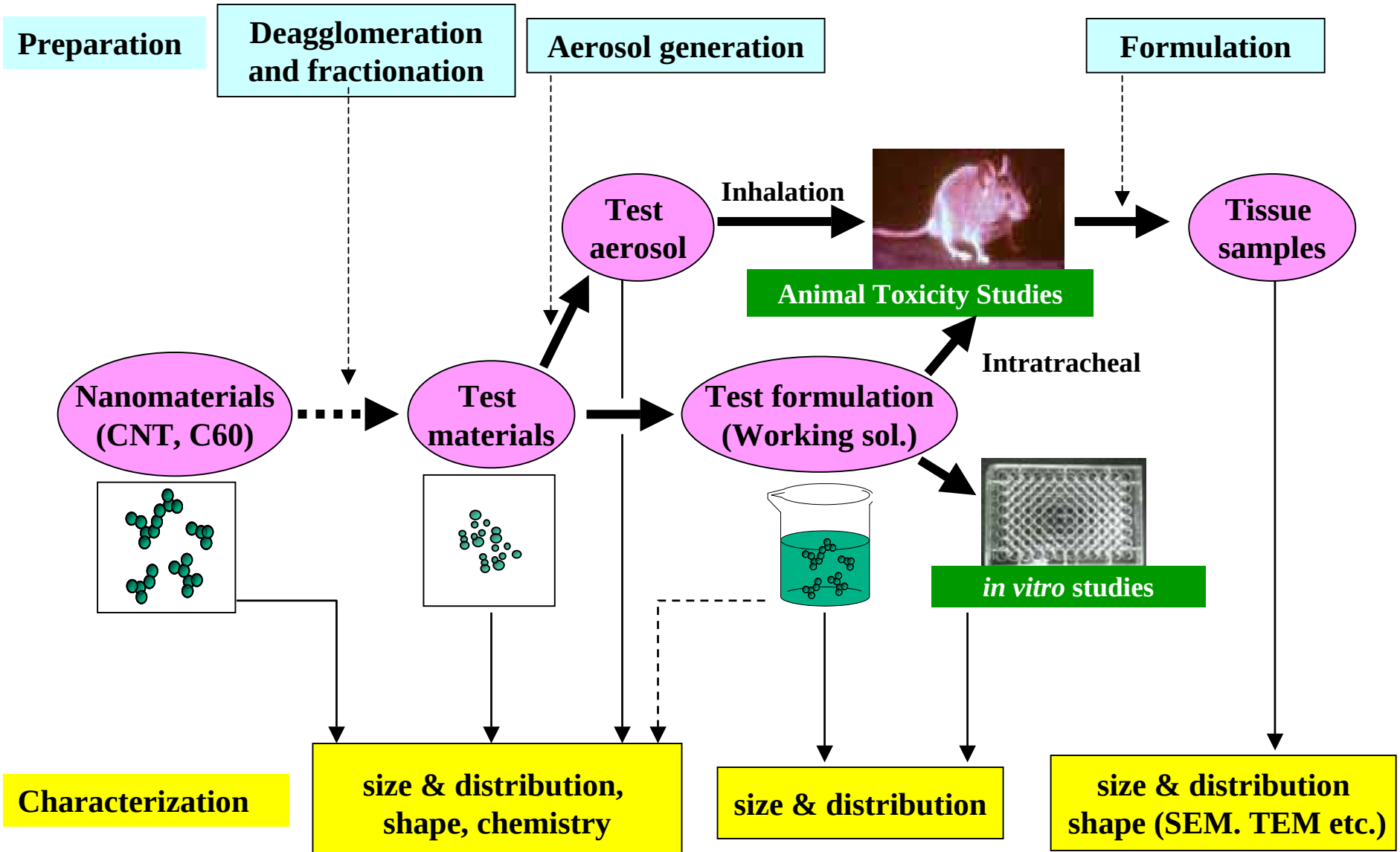
Hypothetical toxicokinetic pathway for NMs and priority for organs examined



To understand the absorption of NMs via the lung, skin and gut and their distribution in the body, identifying potential target organs for toxicity evaluation. For this purpose, the chemical analysis methods will be mainly used.

Junko Nakanishi, adapted from DEFRA

§ 3-3 Characterization & Sample Preparations



(Nakanishi 2005, adapted from Kawasaki's chart)

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Exposure assessment for NMs

<factors>

- population
- production volumes
- application

- exposure route & pathway
- working conditions
- environmental conditions
- lifestyles

- particle properties (size, shape, composition, etc.)
- environmental conditions

- particle properties (size, shape, composition, etc.)
- lifecycle (production, use, consumption, disposal)

exposure assessment and management

exposure scenarios (potential exposure)

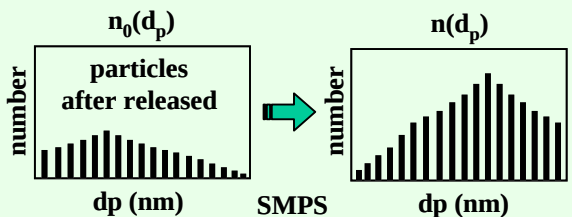
environmental behavior (modeling)

emission scenarios (potential release)

<methods>

- field monitoring (ex. around plant)
- laboratory exp. (in chamber)
- computational approach
- field monitoring (ex. work place)
- laboratory exp. (release potential)
- interview

chamber experiments on particle growth and interaction between particles and gas



required techniques:
NMs generation, measurement, chemical analysis

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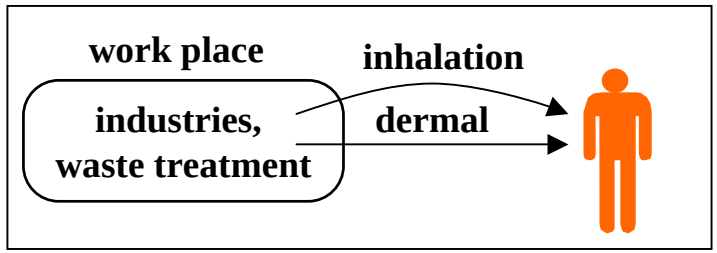
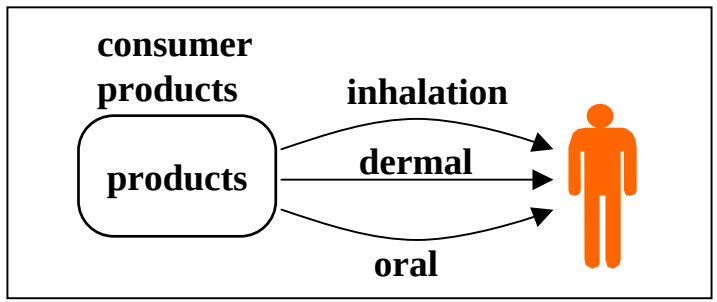
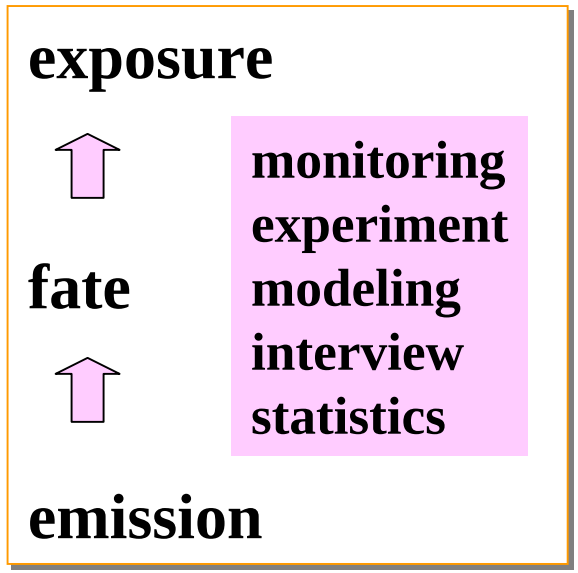
Exposure Assessment during the Lifecycle of NMs

at work place

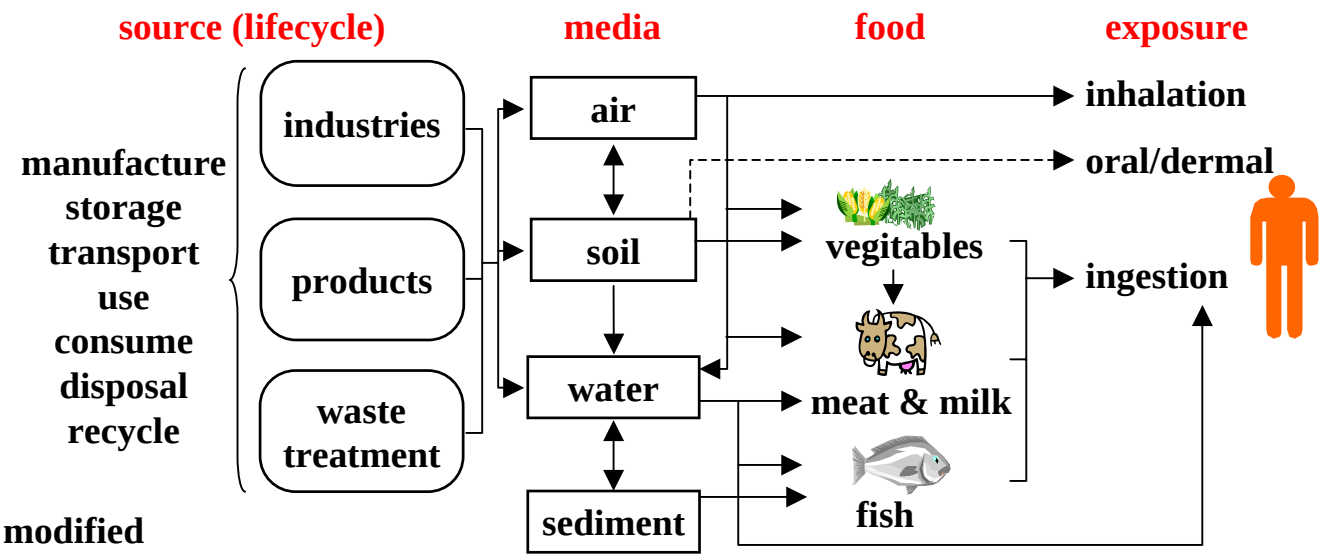


via consumer products





via environment



Isamu ogura(2006), modified

Risk Assessment and Assessment Document

(○: toxicity tests are carried out, EXT: extrapolated)

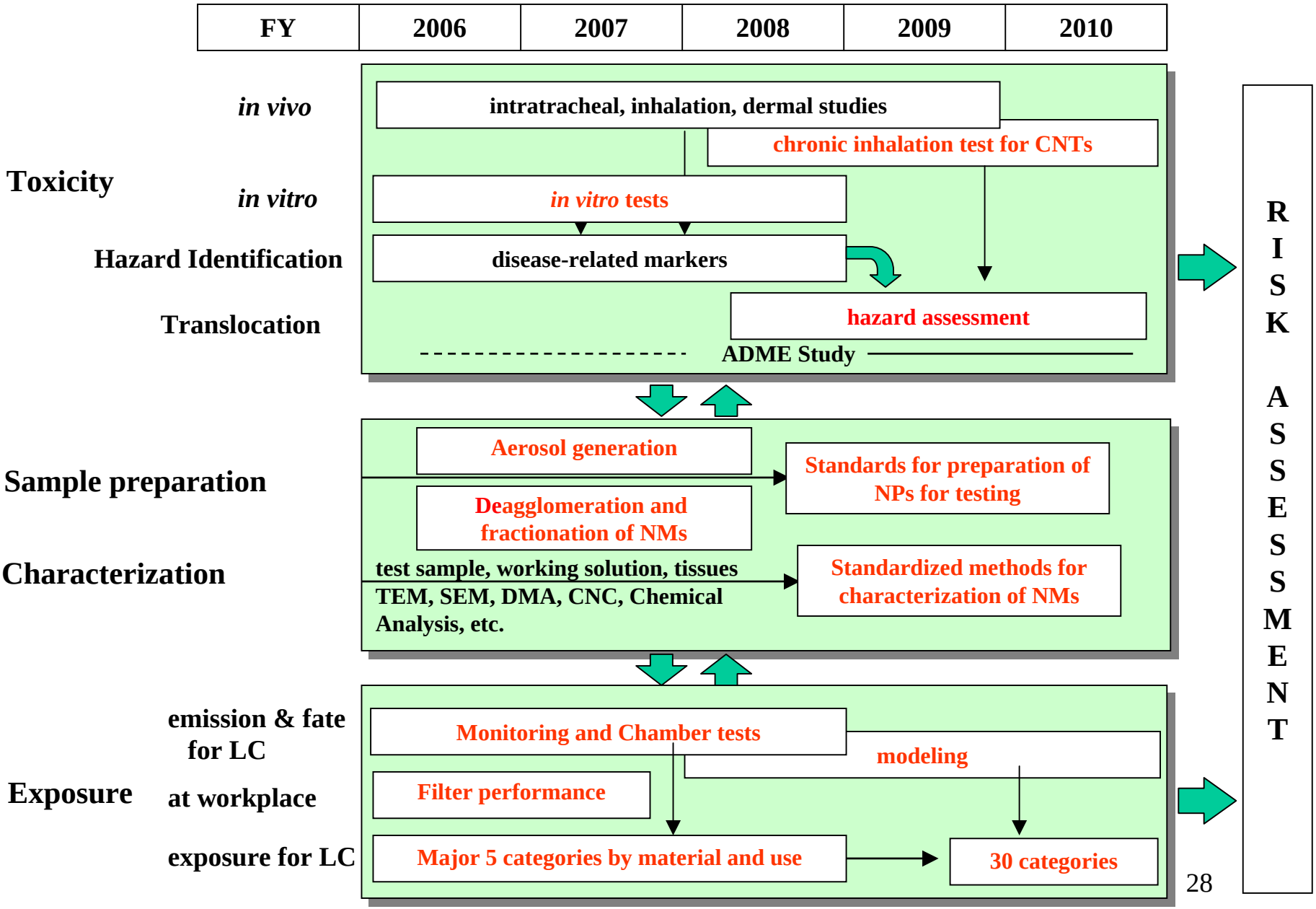
	Toxicity Test			Exposure Analysis	Risk Assessment	Assessment Document
	in vitro	*in vivo* Inhalation test	Biomarker			
Au Particle	○*	–	–	–	–	
Silica	○*	–	–	–	–	
⋮						
TiO2	○	Published data	○	○	○	Document on TiO2
C_{60}	○	○	○	○	○	Document on Fullerens
C_{70}	○	EXT				
SWCNT(1)	○	○	○	○	○	Documents on CNTs
SWCNT(2)	○	EXT	EXT			
SWCNT(3)	○	EXT	EXT			
MWCNT(1)	○	○	○	○	○	
MWCNT(2)	○	EXT	EXT			
MWCNT(3)	○	EXT	EXT			
⋮		–	–			
Carbon Black	○*			–	–	

* A spectrum of relative hazard potential of NMs clarifies the position of C60, for example, among other NMs.

Junko Nakanishi (2006)

Roadmap of Risk Assessment

NMs: nanomaterials



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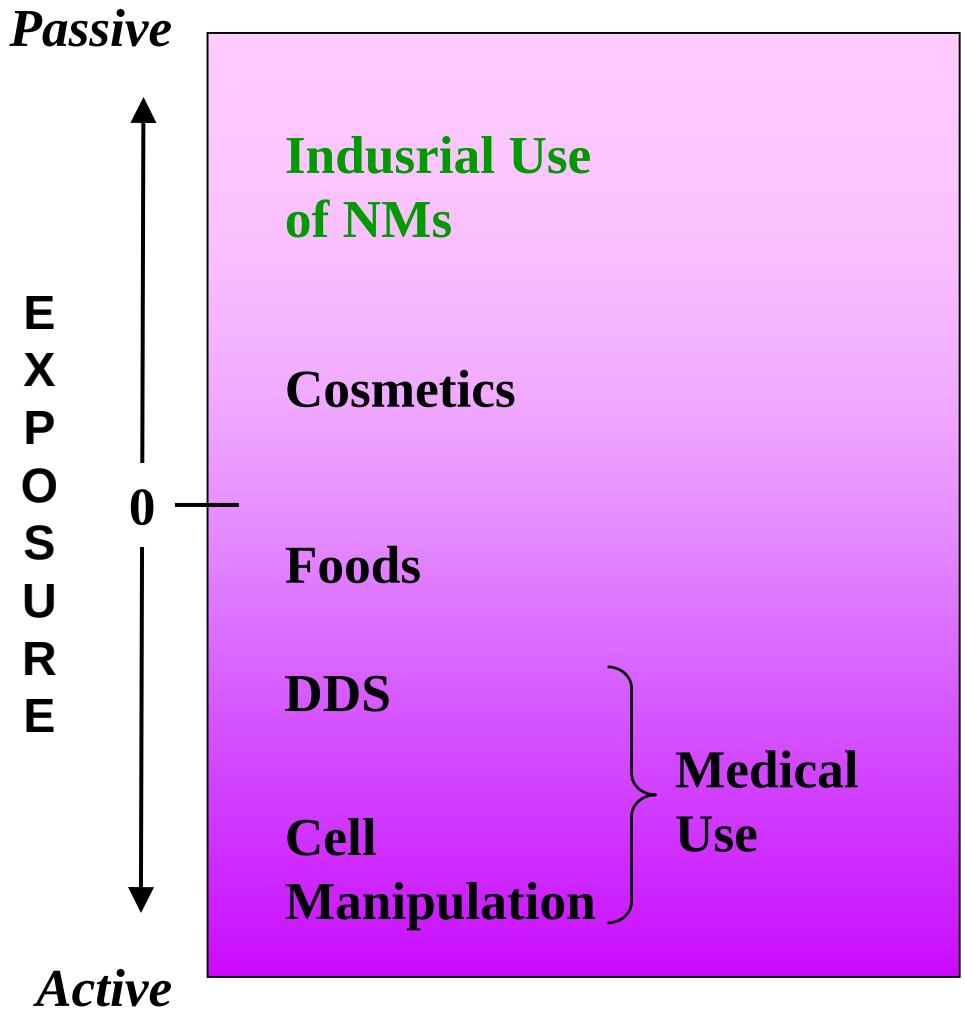
Expand our horizons to the risks from the general nanotechnology, not limiting to the risks from NMs

Overview of risks from across the nanotechnology

◆**Exposure type varies according to their use, from passive to active.**

Passive Exposure

Active Exposure



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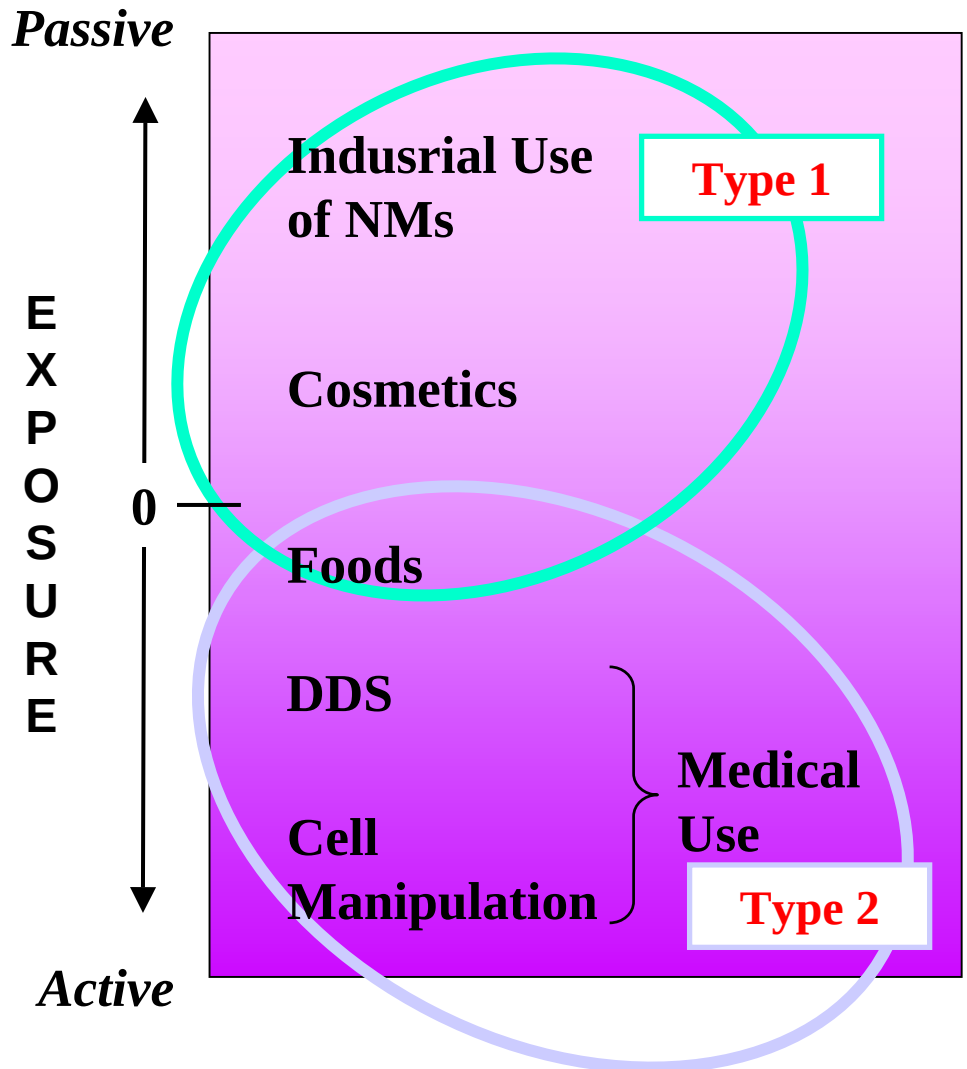
Two types of risks of nanotechnology

- **Type 1 is one of typical environmental problems.**
- **Type 2 is one of the product safety problems.**
- **The risks from nanotechnology consists of the two types of risks, different from each other.**



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Two kinds of Exposure

Type 1 (Passive Exposure)	Type 2 (Voluntary Exposure)
Release from the lifecycle of the manufactured NMs (production, use, consumption and disposal/recycle)	Voluntary use of NMs for enhancement of human capability
Industrial Use	Cosmetics Food Medical

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Two types of risks associated with nanotechnology

	Type 1	Type 2
Sources	**Release from the lifecycle of manufactured NMs**	**The medical use of NMs**
Effects on	**The ecology and human health**	**The human health and ethical issues**
Factors	**Nano scale size effects**	**Adverse effects**
Approaches	**The science – based risk evaluation**	**Various approaches according to usage** **Societal framework for ethical problems**

The type 2 risk should not be slighted, though they are entirely different in terms of risk perspectives.

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What is being done for regulating risks of NMs in the US?

< USEPA >

1. **Stewardship program**
2. **TSCA new chemicals approach**
3. **The Samsung 'Silver Wash" washing machine should be regulated under the FIFRA (US Federal Insecticide, fungicide and rodenticide act) , 22 November, 2006**

< The National Institute for Occupational Safety and Health (NIOSH) >

4. **The stricter occupational exposure limits for ultrafine TiO_2(nano scale) at the workplace by classifying TiO_2 as a potential occupational carcinogen**

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NIOSH PROPOSAL

Occupational exposure limits as time-weighted for up to 10hr/day during a 40-hour work week

For fine TiO_2	**1.5 mg/m^3**
For ultra fine TiO_2	**0.1 mg/m^3**

The limits for ultra fine particles (nano size) are 1/15 of those of fine particles (micron size)

Fine: all particle sizes that are collected by respirable particle sampling (50% collection efficiency for particles of 4 μm, with some collection of particles up to 10 μm.

Ultra fine: primary particle diameter <0.1_μm.

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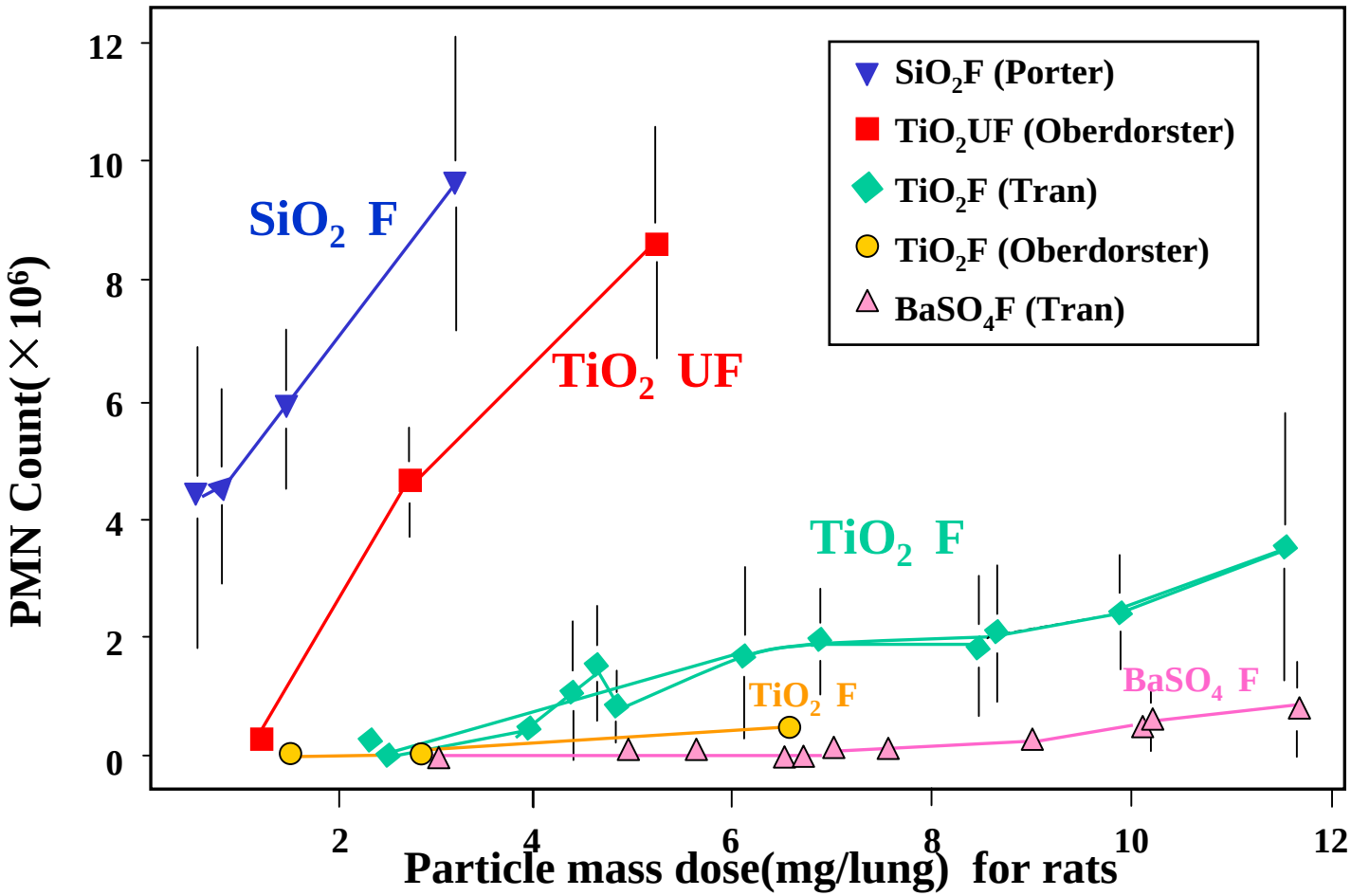
Pulmonary inflammation (PMN count) to subchronic inhalation based on particle mass dose in rat lungs



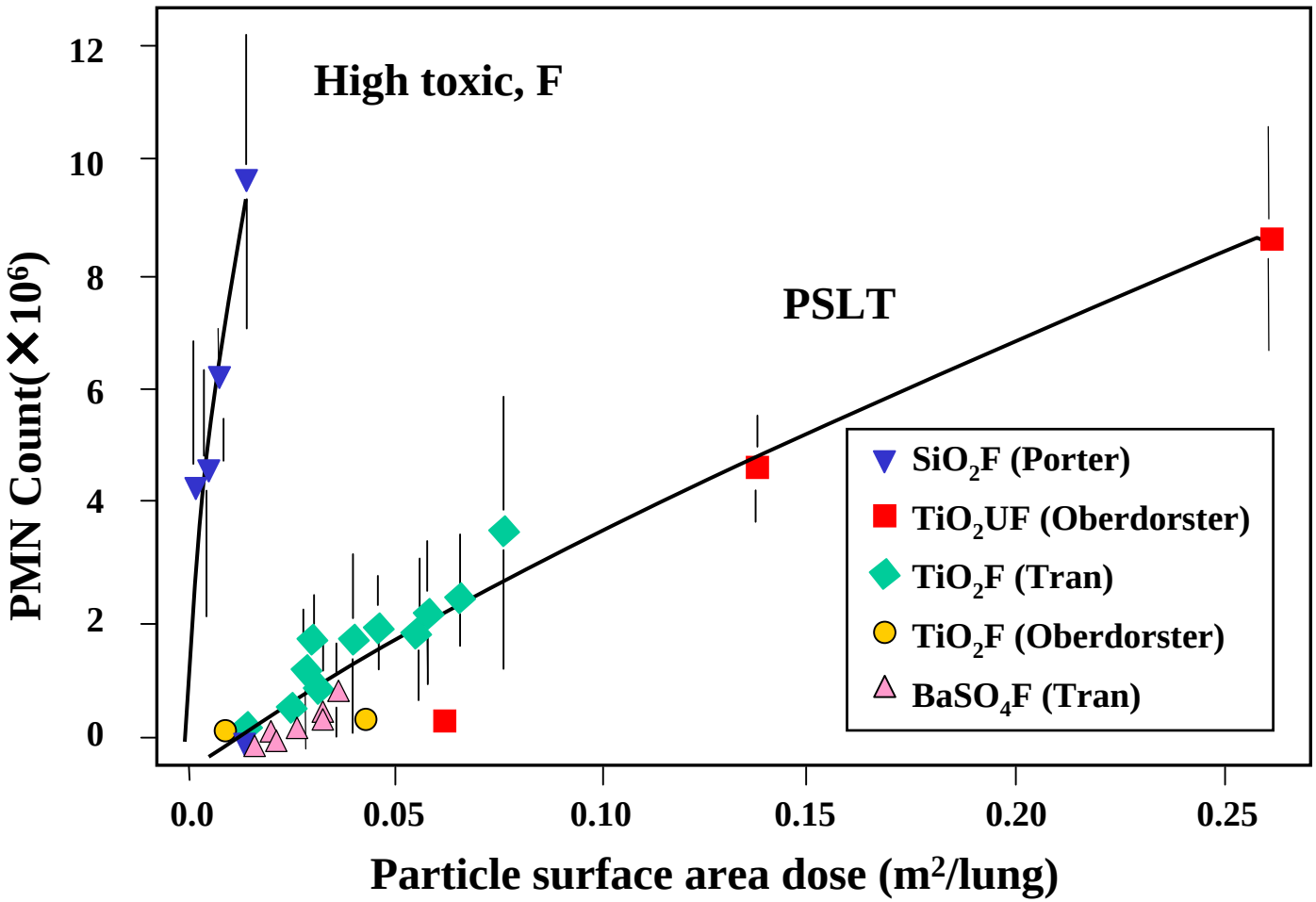
The data fall on different dose-response curves based on mass dose.

F: fine

UF: ultra fine

Data from: Porter et al. [2001]; Oberdörster et al. [1994]; Tran et al. [1999]. Adapted from NIOSH (2003)

Pulmonary inflammation (PMN count) to subchronic inhalation -- based on particle surface area dose in rat lungs.



The data for **PSLT(poorly soluble, low toxicity)** fit the same dose-response curve based on surface area dose.

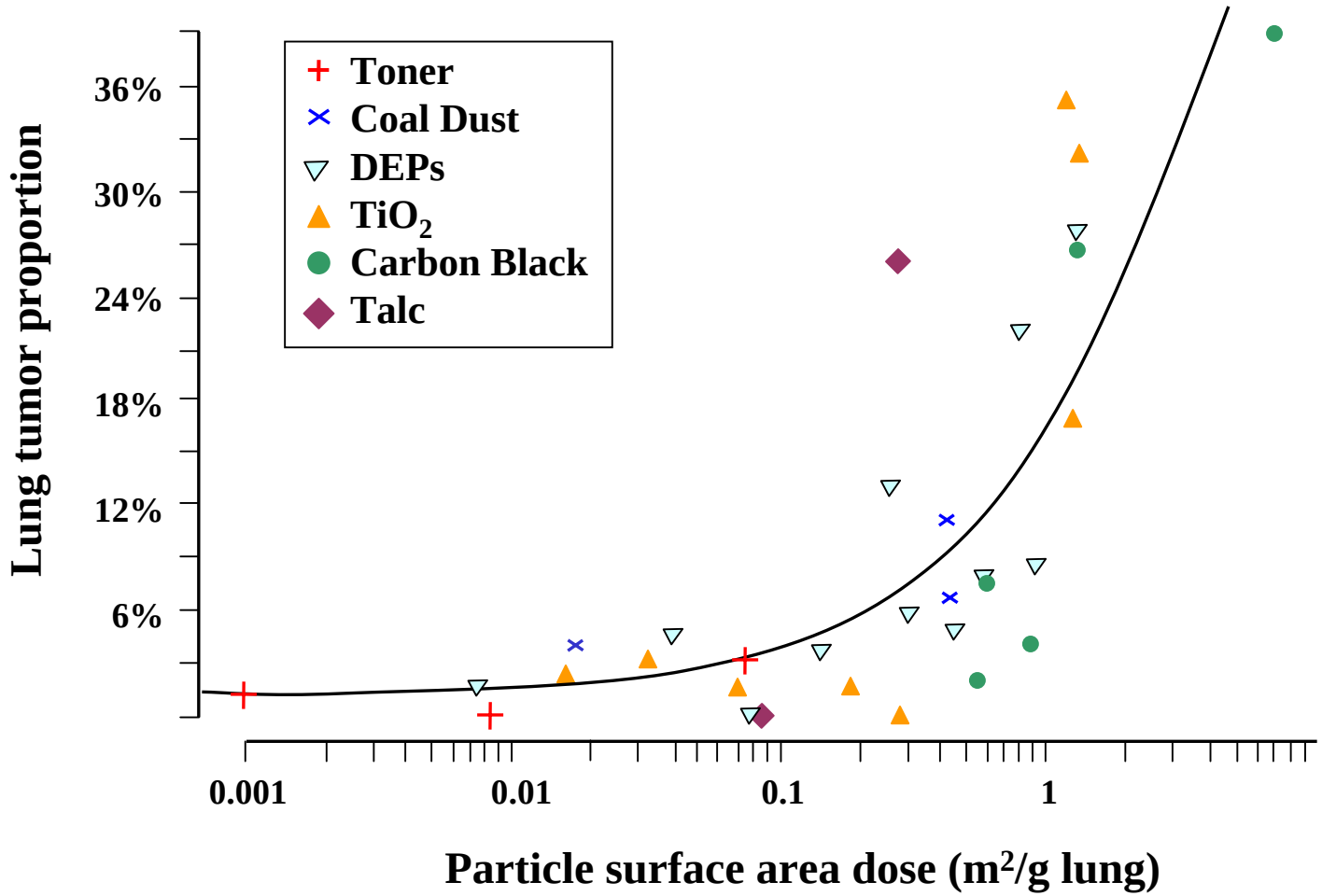
F: fine

UF: ultra fine

Data from: Porter et al. [2001]; Oberdörster et al. [1994]; Tran et al. [1999]. Adapted from NIOSH (2005)

Lung tumor proportion based on particle surface area dose(in the case of PSLT particles*)

*** Poorly soluble low toxicity particles**



NIOSH (2005)

NIOSH Concluded

1. **The tumorigenic effects of TiO2 exposure in rats appear not to be chemical-specific or a direct action of the chemical substance itself.**
2. **Rather these effects appear to be a function of particle size and surface area acting through the secondary genotoxic mechanism, associated with persistent inflammation.**
3. **Current evidence indicates that occupational exposures to low concentrations of TiO2 produce a negligible risk of lung cancer in workers.**
4. **It designates TiO2 as a "potential occupational carcinogen" , though with insufficient evidence.**
5. **This is a temporary and purudent health-protective measures for workers until a more complete understanding of the possible health risks.**

NIOSH (2005)

Implications of NIOSH Proposal

If the assumption regarding TiO2 is accepted,

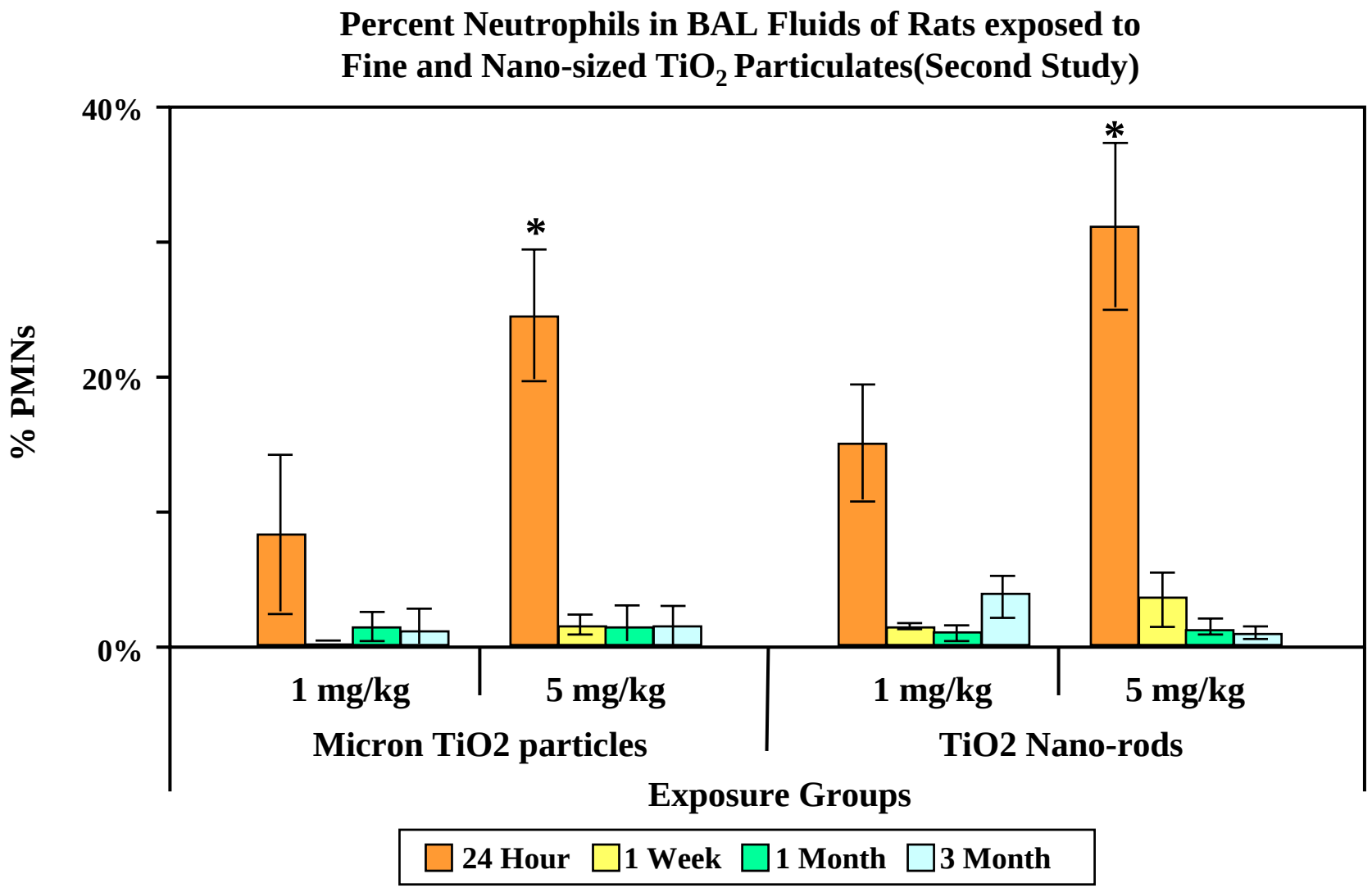
1. **''' there is some possibility that all inert and low soluble nanomaterials may be designated as possible carcinogen.**
2. **''' acceptable level will be proportional to the one dimensional size.**

However,

there are many problems regarding the NIOSH's analysis of TiO2 carcinogenicity, for instance, (1) rat overload, (2) assumed mechanism of the carcinogenicity, (3) the dose-response relationship, (4) measurement of surface area of NMs,

NIOSH (2005)

PULMONARY TOXICITY OF Nano- and Micron-sized TiO



Adapted from David B. Warheit et al (2006)

Many issues remain unsolved

1. **The test results on which the new proposal is based still have the following issues:**

   1. **Almost all tests lack sufficient measurement of material size, impurities and surface area**
   2. **Partly because of the above, the test results are contradictory to each other.**
   3. **It is crucial to perform safety tests with common, standardized test materials**

2. **The US government policy suggests that, if the public uneasiness over the risk of nanotechnology enlarges, a lot of regulation may be introduced without sufficient scientific proof.**

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Next steps

1. **Continue with our recently-started project that has already been highly appreciated and commended as such at**

the 1st Meeting of the Working Party on Manufactured Nanomaterials of OECD（October 26-27, 2006 in London):

“The Japanese research effort was recognized as a good starting point for consideration in the health effects area”

Next steps (continued)

2. Maintain the existing NMs risk assessment policy and keep our research as scientific as possible.

3. Contribute to various nanotechnology policy decisions through aggressively sending out messages both domestic and global institutions.

4. Take the Initiative in making the international rule on risk governance related to the nanotechnology.

5. Increase our involvement in the overall nanotechnology risk issues that are not necessarily covered by our current project, as risk issues are becoming more and more significant social problems.