

Assessing the dose of nanomaterials in toxicological studies: Advanced approaches utilizing experimentation and modelling



Final ANNOUNCEMENT

- Chairs : Flemming R. Cassee & Philip Demokritou
- Venue : Tallinn, Estonia, National Institute of Chemical Physics and Biophysics, Akadeemia tee 23. Local host: Anne Kahru
- Dates : 4-5 May 2016
- Number of participants : 36 people altogether

Introduction

In vitro high throughput screening platforms based on mechanistic injury pathways are being used for hazard assessment of nanomaterials (NM). Toxicity screening and other in vitro nanotoxicology assessment efforts in essence compare and rank nanomaterials relative to each other. It has been shown that this ranking of NM is susceptible to dispersion and dosimetry protocols and particle kinetics taking place in the in-vitro system, which continue to be poorly standardized. In addition, and this applies both to in vitro studies with submerged cell cultures as well as inhalation studies in rodents, extrapolation to human becomes more reliable when dose and dose rate at the site of deposition is determined accurately.

Mixed experimental/computational approaches to cellular dosimetry can be used by nanoparticle toxicologists to accurately calculate the delivered to cell dose metrics for various NMs and in vitro conditions as a function of exposure time. In addition, in vivo dosimetry models will allow researchers to estimate the delivered dose in any region of the respiratory system and to study the implications of particle properties and lung function parameters. More importantly, it enables nanoparticle toxicologists to bring to the same level in-vitro and in-vivo doses and help in the development of validated in-vitro cellular screening assays.

The objective of the workshop is to promote the use of emerging particle dosimetry approaches for (inhaled) nanomaterial in-vitro and in-vivo toxicological assessment. The workshop will include lectures, demonstration activities and exercises. Presenters are ready to interact with the participants so be prepared for some challenges.

Programme

DAY 1		
8:30 – 9:00	Registration	
9:00 – 9:10	Welcome and general notice	Anne Kahru (NICPB, Tallinn, Estonia)
9:10 – 9:20	Introduction	Flemming Cassee (RIVM, Bilthoven, NL)
9:20 – 9:45	Needs and requirements for risk assessment	Lang Tran (IOM, Edinburgh, UK)
9:45 – 10:15	Linking real world exposures of nanomaterials to toxicology and adverse health effects?	Phil Demokritou (Harvard School of Public Health, MA, USA)
	Coffee/tea	
10:45 – 11:30	Evidence from rodent studies on the most relevant dose metric for nanotoxicology studies	Otmar Schmid (HMGU, München, DE)
11:30- 12:00	Experimental data from in vitro studies	Andrea Haase (BfR, Berlin, DE)
12:00 – 12:30	Emerging tools and approaches for in vitro dosimetry of engineered nanomaterials	Phil Demokritou (Harvard School of Public Health, MA, USA)
12:30 – 13:30	LUNCH	
13:30 – 15:00	<p>Overview of hands on training on Harvard, multi-step <i>in vitro</i> dosimetry (Deloid) (15 mins)</p> <ul style="list-style-type: none"> • STEP 1: Suspension preparation and characterization (Cohen) (15 mins) • STEP2: Particle Suspension Characterization (Pirela) (20 mins) • STEP 3: DG fate and transport modeling (Deloid) (25 mins) • Questions and Answers (15 mins) 	Phil Demokritou, G. DeLoid, S. Pirela, J. Cohen (Harvard School of Public Health, MA, USA <i>via</i> SKYPE)
	Coffee/tea	
15:30 – 17:00	<p>Case study (Fe₂O₃) applying concepts from the Integrated <i>in vitro</i> dosimetry approach from Harvard (via Skype with Harvard)</p> <ul style="list-style-type: none"> • Data on Fe₂O₃ powder characterization • Preparation of the Fe₂O₃ suspension • Characterization of the prepared suspension using Dynamic Light Scattering (DLS) • Measurement of effective density using Harvard Volumetric Centrifugation method (VCM) • Perform Fate and Transport modeling for dosimetry using Harvard DG motel (MATLAB software is required) <p>Data analysis</p>	G. DeLoid, S. Pirela, J. Cohen (<i>via</i> skype w/Harvard School of Public Health, MA, USA)

DAY 2		
9:00	Comparing in vitro and in vivo data using dosimetry – Hedwig Braakhuis (RIVM)	Hedwig Braakhuis (RIVM, Bilthoven, NL)
9:40- 10:10	Modelling the dose (rate) in rodents and humans	Owen Price (ARA, Research Triangle Park, NC, USA)
	Coffee/tea	
10:30 – 12:00	Case studies and using the MPPD model	Owen Price (ARA, Research Triangle Park, NC, USA)
12:00 – 13:00	General Q&A and discuss overarching issues raised during the workshop.	Flemming Cassee (RIVM, Bilthoven, NL) + speakers
12:30	Lunch and adjourn	

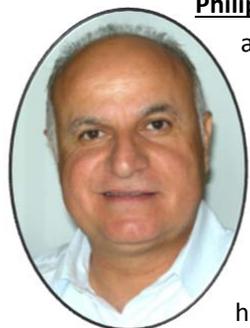
Guidance:

- Please bring a laptop to the meeting
- Make sure that you arrive on time as we have a small group and a full interactive programme
- Food and drinks are included
- All the events will take place in one building. No transport needed except between hotel and venue. The city centre is 8 km from venue, ca €10 by taxi and €3 by trolley bus.

Presenters:



Flemming R. Cassee is an inhalation toxicologist at the National Institute for Public Health and the Environment (RIVM) of the Netherlands and professor at the Institute for Risk Assessment Studies at the Utrecht University, the Netherlands. He is involved in the research on the adverse health effects of ambient particulate matter, nanomaterials and gaseous components. He supports government authorities at all levels, from the local to the international by coordinating and conducting research and providing support for policy. He was one of the initiators of the development of user friendly software to perform dosimetry calculations, now known as the Multiple-Path Particle Dosimetry (MPPD) model.



Philip Demokritou, Director of the Center of Nanotechnology and Nanotoxicology at Harvard University and has a focus on aerosol science and technology with emphasis on the elucidation of particulate matter (PM) health effects and environmental health and safety implications of engineered nanomaterials (ENMs). His particle research has involved the development of personal PM monitoring systems for use in exposure assessment and epidemiological studies and methods for the physicochemical and in-vitro/in-vivo toxicological characterization of particles. Dr Demokritou is currently the. He has published on the effective density as a crucial parameters to be measured in in vitro studies and his team developed the most advanced in vitro dosimetry model. Dr Demokritou is currently an Associate Professor at Harvard School of Public and a co-Editor in Chief of NanoImpact journal.



Anne Kahru is a Research Professor of the Estonian Academy of Sciences and Head of Laboratory of Environmental Toxicology of National Institute of Chemical Physics and Biophysics, Tallinn, Estonia. She belongs to the top 1% most cited scientists worldwide in the area Environment/Ecology and Pharmacology and Toxicology (data from Thomson Reuters ISI-ESI). Her group in NICPB was among the first ones in nanoecotoxicological studies of metal oxide nanoparticles. In 2011, she received the Estonian State Science Award for her research “Ecotoxicology of synthetic nanoparticles and their toxicity mechanisms”. She is also a founder (1997) and the President of the Estonian Society of Toxicology.



Lang Tran is Director of Quantitative Toxicology for the IOM, and is a computational toxicologist and mathematical modeller with extensive knowledge in PBPK and QSAR modelling and related fields. Lang is an active researcher in the field of particle toxicity, including publishing seminal studies on the potential toxicity of Poorly Soluble Low Toxicity (PSLT) particles which provided evidence on the role of particle surface area in the observed pulmonary inflammation and 'Overload'. Lang also the chairman of the COST Action TD1204 MODENA: Modelling Nanoparticle Toxicity.



Andrea Haase works at the German Federal Institute for Risk Assessment (BfR) at the department of Chemicals and Product Safety. Andrea Haase's research interests are mainly focused on nanotoxicology. To that end different cell lines, primary cells or 3D models are used. Nanoparticle mediated effects are analysed by standard assays, e.g. cytotoxicity or genotoxicity assays. In addition proteomic techniques are applied. Several current projects use proteomic approaches to understand interactions of nanoparticles with biomolecules, in particular proteins (i.e. protein corona) or to analyse changes in cellular proteins (i.e. protein oxidation) after nanoparticle treatment.



Dr. Otmar Schmid is head of the Pulmonary Aerosol Delivery Group at the Comprehensive Pneumology Center, Helmholtz Zentrum München (Munich, Germany) and Adjunct Assistant Professor at the Missouri University of Science and Technology (USA). For the past 15 years he has been working in the field of aerosol characterization, inhalation nanotoxicology, and dose-controlled aerosol delivery to in vitro and in vivo models of the lung. More recently, his research focus has widened to include therapeutic and diagnostic potentials of nanoparticles. He served on the board member of various aerosol societies (Association for Aerosol Research (GAeF), International Society of Aerosols in Medicine (ISAM)) trying to strengthen the interdisciplinary exchange between the aerosol science and biology, toxicology, health effects and medicine.



Hedwig Braakhuis is a toxicologist at the National Institute for Public Health and the Environment (RIVM) of the Netherlands. She recently finished her PhD research on the potential risks of nanomaterials after inhalation. The research was aimed at determining the dose metric which provides the best descriptor for dose-response relationships of nanomaterials after inhalation exposure. In addition, she worked on the development of *in vitro* lung models and their applicability to predict *in vivo* responses.



Owen Price is a senior scientist with Applied Research Associates, Inc. (ARA) in Arlington, VA, USA. Trained as an applied mathematician, he develops and implements mathematical models of biological systems for customers such as the US EPA, NIOSH, Office of Naval Research, and the Research Institute for Fragrance Materials. His chief responsibility at ARA is to continue to develop and maintain the Multiple-Path Particle Dosimetry Model (MPPD) which was created as part of a collaboration between the Chemical Industry Institute of Toxicology (CIIT) and the Netherlands National Institute for Public Health and the Environment (RIVM). MPPD is a free software tool used for a variety of inhalation dosimetry applications by thousands of users all around the world.

<i>Name</i>	<i>Institute</i>	<i>E-mail</i>
Phil Demokritou	Harvard School of Public Health, MA, USA	pdemokri@hsph.harvard.edu
Owen Price	ARA, Research Triangle Park, NC, USA	oprice@ara.com
Mariliis Sihtmäe	National Institute of Chemical Physics and Biophysics, Tallinn, Estonia	mariliis.sihtmae@kbfi.ee
Katre Juganson	National Institute of Chemical Physics and Biophysics, Tallinn, Estonia	katre.juganson@kbfi.ee
Anne Kahru	National Institute of Chemical Physics and Biophysics, Tallinn, Estonia	anne.kahru@kbfi.ee
Uko Maran	Tartu University, Estonia	uko@theor.chem.ut.ee
Flemming Cassee	RIVM, Bilthoven, NL	Flemming.cassee@rivm.nl
Lang Tran	IOM, Edinburgh, UK	lang.tran@iomhq.org.uk
Andrea Haase	BfR, Berlin, DE	Andrea.Haase@bfr.bund.de
Hedwig Braakhuis	RIVM, Bilthoven, NL	Hedwig.Braakhuis@RIVM.NL
Otmar Schmid	HMGU, München, DE	otmar.schmid@helmholtz-muenchen.de
Leigh-Anne Koekoemoer	Utrecht University and RIVM, NL	leigh.anne.koekemoer@rivm.nl
Chloé Puisney	Univ Paris Diderot-Paris 7	c.puisney@gmail.com
Steve Evans	Swansea University	323299@swansea.ac.uk
Marie Carriere	CEA Grenoble, F	marie.carriere@cea.fr
Vicki Stone and/or Helinor Jonston	Heriot Watt University, Edinburgh, UK	v.stone@hw.ac.uk/ H.Johnston@hw.ac.uk
Luisa Campognolo	Tor Vergata Univ, IT	campagno@uniroma2.it
Ivana Vinkovic Vrcek	Institute for Medical Research and Occupational Health Ksaverska cesta. Zagreb, Croatia	ivinkovic@imi.hr
Thomas Moore	Adolphe Merkle Institute	thomaslee.moore@unifr.ch
Thomas Kowoll	Karlsruhe Institute for Technology	Thomas.kowoll@kit.edu
Kunal Bhattacharya	Karolinksa, Stockholm	kunal.bhattacharya@ki.se
Chang Guo	Public Health England	Chang.Guo@phe.gov.uk
Søren Thor Larsen	NRCWE, Copehnagen	stl@arbejdsmiljoforskning.dk
Sandor Balog	Adolf Mercke/ Uni Fribourg	sandor.balog@unifr.ch
Nadia von Moos	Institute of Materials, Laussane	nadia.vonmoos@epfl.ch