A common European approach to the regulatory testing of nanomaterials

NANoREG

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Improved and validated occupational exposure models of release, exposure, dispersion and transfer

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1 Description of task

Inhalation exposure modelling is extensively used in regulatory exposure assessment for chemical agents. A number of exposure tools have been developed and recommended for use under REACH, including screening tools such as ECETOC TRA[1], MEASE[2], and EMKG-EXPO[3] and higher tier tools such as Stoffenmanager[4] and the Advanced REACH Tool[5] (ART) (ECHA, 2016) In addition, tools are becoming available that focus specifically on exposure to manufactured nanomaterials (MNMs). These cover relatively crude control banding tools such as the CB NanoTool as well as more advanced exposure/risk assessment tools such as Nanosafer and Stoffenmanager -NANO for occupational exposures and ConsExpo-nano for consumer exposure. However, most of these tools do not provide quantitative estimates of exposure.

It is important that quantitative models become available to assist with quantitative risk assessment. In addition, it is critical that all models used for predicting exposure have a sound scientific basis, are reliable and are validated and/or calibrated with high quality measurement results.

To address some of these issues the objectives of Task 3.4 of the NANoREG project were defined initially in the description of work (DOW) as follows:

a. To evaluate and compare existing exposure models and tools using data already collected as well as data collected as part of the NANoREG project

b. To modify and adapt existing models and develop new models and tools as necessary

c. To re-evaluate and promulgate these new models

d. To use these models to develop effective control banding approaches

After the start of the NANoREG project, a number of regulatory questions were defined to identify the priorities within the project. Task 3.4 focussed predominantly on the regulatory questions 11 and 12, although to some extent also provided input into addressing Q13.

> *"Q11: What are the main determinants for occupational and consumer exposure to MNM and what are the duration and type of exposure?*
>
> *Q12: How should human and environmental exposure be assessed in practice (determining exposure scenario, quantify input parameters for models, assumptions and use of proxy indicators, background and uncertainty estimation)? Consider both measuring and specific modelling for nanomaterials and evaluate the needs for standardisation and validation.*
>
> *Q13: Which scenarios could denote potential exposure and what information do we have on them? Can we develop standardized and efficient testing procedures for estimating release of nanoparticles (NP) from powders and NPs in matrices? What are situations in which MNM exposure is expected to be negligible / high? Are the amount and the nature of releases of MNM similar to regular chemicals, when common recycling and end-of-pipe techniques are used?"*

Subsequently, two main objectives were defined for Task 3.4:

1) Evaluate existing qualitative and semi- quantitative tools (such as control banding tools), and
2) Evaluate existing and develop new/modify existing quantitative tools.

The work to meet the first objective was addressed in the following sub-tasks:

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[11] http://www.ecetoc.org/tra
[2] http://www.ebrc.de/industrial-chemicals-reach/projects-and-references/mease.php
[3] http://www.reach-clp-biozid-helpdesk.de/en/Downloads/EMKG-EXPO-TOOL.xls?__blob
[4] https://stoffenmanager.nl/
[5] https://www.advancedreachtool.com/

1.1 Summarise the different tools available, in terms of their applicability domain, assumptions made, inputs required and outputs provided,
1.2 Compare the tools for selected exposure scenarios,
1.3 Compare the ranking of selected exposure scenarios by selected tools with actual exposure measurements, and
1.4 Conduct an inter-user exercise to evaluate the potential variability in the exposure outputs obtained from the tools.

To meet the second objective (evaluate existing and develop new/modify existing quantitative tools) the following sub-tasks were carried out:

2.1 Summarise quantitative tools and models,
2.2 Generate and collect measurement data to allow for a comprehensive evaluation of the quantitative models during a large-scale experiment under controlled laboratory conditions (detailed in D3.4),
2.3 Evaluation of the data collected via appropriate data analysis, and
2.4 Development and testing of a proposed new quantitative exposure model.

2 Description of work & main achievements

2.1 Summary

In this deliverable we have reviewed semi-quantitative and quantitative tools used for the assessment of inhalation exposure to MNMs. When possible the outputs of the tools have been compared with measurement data. The current deliverable provides information for addressing questions 11 and 12, advice on the main issues to consider on using the tools and recommendations for the tools developers.

The results from the review of control banding tools for MNMs showed there is a lack of literature on their performance. The available data show that the tools are useful for screening of risk but results for ranking of exposure scenarios in terms of exposure should be interpreted with caution. In addition to the tools performance, the inter-user variability study showed that there is a high variability in the results obtained by different users.

Under controlled laboratory conditions the two box quantitative model was shown to compare well with the measurement data and therefore quantitative tools may become available for predicting the exposure concentration over time. The two-box nano specific exposure model has been implemented into a friendly tool (I-Nano) that will be made available in early 2017. However, tools rely on detailed input data (in terms of rate of particulate release from the source as well as the particle size distribution) which is not always available and therefore default assumptions may need to be made to generate the assessment. Further work is needed to test the performance of the I-Nano tool in the field.

2.2 Background of the task

The innovative and economic potential of MNMs is threatened by a limited understanding of the related EHS (Environmental Health and Safety) issues. While toxicity data is continuously becoming available, the relevance to regulators is often unclear or unproven. The shrinking time to market of new MNMs drives the need for urgent action by regulators. NANoREG is the first FP7 project to deliver the answers needed by regulators and legislators on EHS by linking them to a scientific evaluation of data and test methods.

As previously highlighted in Section I, regulatory questions 11, 12 and 13 defined at the start of the NANoREG project are associated with WP3:

The work on Task 3.4 has contributed to answer questions 11 and 12, and in some extent also provided input into addressing Q13. State of the art tools for qualitative and semi-quantitative assessment of release/exposure were reviewed (ART, Stoffenamanager-Nano). These tools are currently being used by the nanosafety community; however, they have not been evaluated or demonstrated and therefore their applicability and appropriateness for regulatory purposes is hampered and unknown. The task has gone beyond the state of the art by developing and demonstrating a two-box quantitative model for exposure assessment of NMs and implementing this into a web-based tool.

2.3 Description of the work carried out

The report is structured in two parts that reflect the work carried out towards the two different objectives.

Part 1 includes the work carried out to fulfil Objective One: Evaluate existing qualitative and semi- quantitative tools (such as control banding tools). In Section 2.3.1, a summary of the different available tools is provided, in terms of their applicability domain, assumptions made, inputs required and outputs provided is required.

Section 2.3.2 includes a literature review on the performance of control banding tools, a comparison of the outputs of ART and Stoffenmanager-Nano with measurement data and an inter-user study to evaluate the potential variability in the answers obtained from different users when using the same tool for the same scenario.
Part 2 includes the work carried out to fulfil Objective Two: Develop and evaluate quantitative exposure models and tools.

In Section 2.3.3, a summary of the different quantitative tools, in terms of their applicability domain, assumptions made, inputs required and outputs provided. Section 2.3.4 describes the data collection for testing and evaluation of quantitative exposure models. Section 2.3.5, describes the evaluation of the data collected in Section 2.3. 4 and finally Section 2.3.6 describes the evaluation of the I-Nano tool developed as part of NANoREG.

PART ONE QUALITATIVE AND SEMI-QUANTITATIVE TOOLS

2.3.1 Objective 1.1 Qualitative and semi-quantitative tools

Table 1 lists the tools considered, whether they are control banding or risk level tools and their source domains. The majority of the tools considered here are control-banding (CB) tools. They differ in the assumptions made and the calculations undertaken but essentially they take the information provided by the user and generate some estimate (usually a category) of hazard, exposure and combine these into a risk score. A number of the tools also recommend control measures (if necessary) for the scenario being considered.

Table 1 Overview of activities covered by the Control Banding Tools. Modified from Brouwer (2012)

CB tool	Source Domain				Emission potential	Exposure potential	Control banding (CB)/ Risk Level (RL) and number of bands
	Synthesis	Powder handling	Ready to use product	Abrasion			
ANSES[1]	Y	Y	Y	Y	Y	N	CB (5)
Precautionary Matrix[2]	Y	Y	Y	Y	Y	N	CB (2)
CB NanoTool[3]	Y	Y	N	N	Y	N	CB (4)
Stoffenmanager-nano[4]	Y	Y	Y	N	N	Y	RL (3)

1: https://www.anses.fr

2 http://www.bag.admin.ch/nanotechnologie/12171/12174/12175/index.html?lang=en

3 http://controlbanding.net/Services.html

4: https://nano.stoffenmanager.nl/

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2.3.1.1 ANSES

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) developed a tool to assess emission potential of MNMs. The tool uses a hazard classification that is based on few fundamental physicochemical and toxicological properties of MNMs and groups materials by hazard and emission potential. It is designed to be part of an overall control strategy. The matrix proposes control bands adapted to the risk potential levels and helps define an action plan (Riediker et al., 2012). Figure 1 shows the flow diagram to allocate the hazard to one of five bands. .The highest hazard band is used for biopersistent fibres, for other MNMs the tool uses the hazard band based on the classification of the bulk material using the COSHH-Essentials methodology (Control of Substances Hazardous to Health[6]).

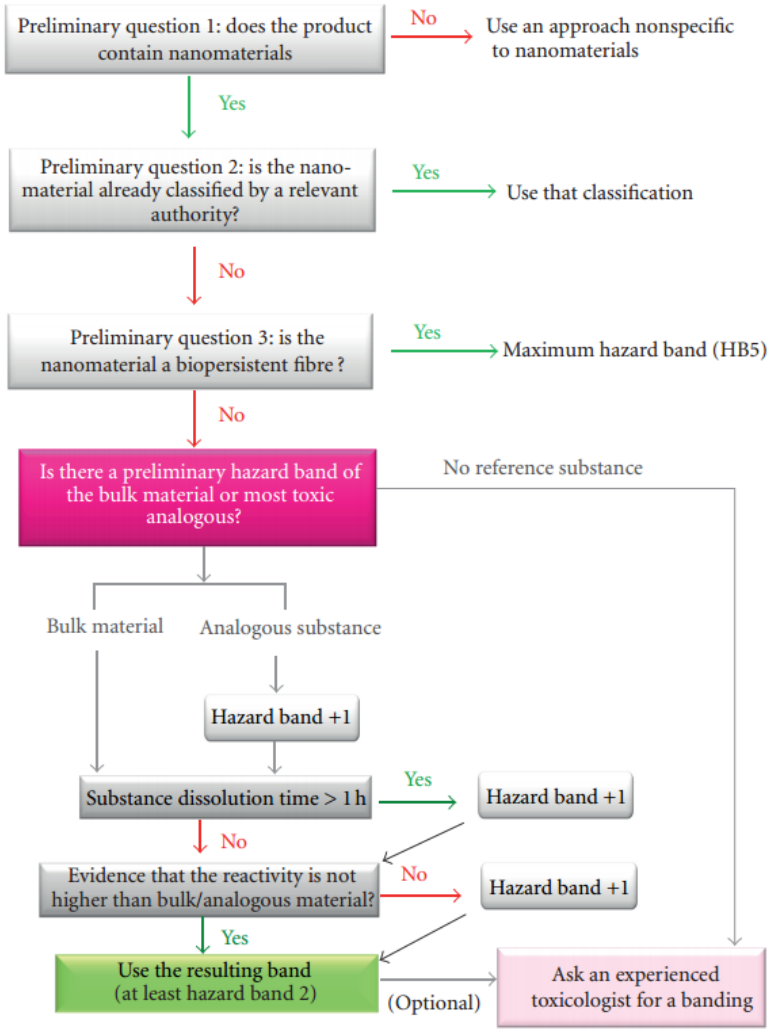

Figure 1 Flow diagram to allocate a MNM to a hazard band according to the level of knowledge on the nanomaterial (Riediker et al., 2012)

The emission potential comprises four bands and is determined by a mix of the physical form of the substance (solid, liquid, powder and aerosol) plus a further modification according to the

[6] http://www.hse.gov.uk/coshh/essentials/

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process (friable solids, NMs dispersed in highly volatile liquids, high or moderate dusty powders; generation of dust; melting and dispersion of a solid in a liquid; powder generation; spraying).

The combination of the hazard and emission bands is subsequently linked to five control bands (Table 2).

Table 2 ANSES control banding matrix (Riediker et al., 2012)

		Emission potential bands			
		EP1	EP2	EP3	EP4
Hazard bands	HB1	CB 1	CB 1	CB 2	CB 3
	HB2	CB 1	CB 1	CB 2	CB 3
	HB3	CB 1	CB 1	CB 3	CB 4
	HB4	CB 2	CB 2	CB 4	CB 5
	HB5	CB 5	CB 5	CB 5	CB 5

CB 1: natural or mechanical general ventilation.
CB 2: local ventilation: extractor hood, slot hood, arm hood, table hood, and so forth.
CB 3: enclosed ventilation: ventilated booth, fumehood, closed reactor with regular opening.
CB 4: full containment: continuously closed systems.
CB 5: full containment and review by a specialist required: seek expert advice.

2.3.1.2 The Swiss Precautionary Matrix

The Swiss Precautionary Matrix was developed by TEMAS in Switzerland (Höck et al., 2008, 2010, 2011, 2013) for the Swiss Federal Council (FOEN) to assess health and environmental risks of nanoproducts. The tool provides advice on whether a precautionary approach is required under normal working conditions, worst case scenario and for the environment. A score is determined for each scenario which is a function of the scores assigned for 'Nano-Relevance' (N), 'Potential Effect' (W), 'Potential Human Exposure/Potential Input into Environment' (E), 'Available Information on Life Cycle' (I).

The Precautionary Matrix contains two criteria for assessing nano-relevance. The first criterion is based on the EU proposed definition 2011/696/EU:

> *"Manufactured materials are considered as nano-relevant if they comprise particles in the unbound state, as an aggregate or agglomerate and in which at least 50% of the particles in the number size distribution have one or more external dimensions in the range 1 to 100 nm. In the case that the number size distribution is unknown, specifically manufactured materials are considered nano-relevant if they have a specific surface/volume greater than 60 m. Fullerenes, graphene flakes and single wall carbon nanotubes are considered to be nanomaterials even when they exhibit dimensions of less than 1 nm."*

The second being that nanospecific effects cannot be excluded even for particles > 100 nm as particles of up to ca. 300 nm can be taken up by organisms and cells (Hock et al., 2013).

The Precautionary Approach definition is as follows:

> *"Specifically manufactured materials are considered as nano-relevant which comprise particles in the unbound state, as an aggregate or agglomerate and in which one or more external dimensions are between 1 and 500 nm. Respirable materials up to 10 µm with nanoscale side branches can likewise trigger nanospecific effects and are likewise considered to be nano-relevant"*

The potential for causing health effects is determined based on the redox activity, catalytic activity and/or ROS (Reactive Oxygen Species)-formation (scored as 1 for those where the hazard is low, 5 for medium and 9 for high). This is then combined with the stability in the body or in the environment (assigned 1 for a short half-life (hours), 5 for a medium half-life (days/weeks) and 9 for a long half-life (months)) to derive an effect score for human or environment, respectively.

Potential for exposure is determined by the amount of the material being handled, the frequency of handling for both workers and consumers, and the form of the exposure and expressed as a score.

To estimate the precautionary need (V), the values determined for potential effect (W) and potential human exposure / input into the environment (E) are multiplied by each other. Then I as a measure of the available information is added and the result is multiplied by the nanorelevance (N). All of these scores are then combined:

$$V = N * (W * E + I)$$

Based on the result for V for the need for a precautionary approach is determined for:

Employees (normal production and worst case)

Consumers

Environment (disposal step of production waste, during use with specific waste disposal, disposal step of a utility product, use without specific waste disposal).

The scores are split into two classes. Table 3 highlighting how the classes are determined;

A – A low need for any specific nanomaterial action, and

B – Nanospecific action is needed.

A V score of higher than 20 is classed as B, and indicates the need for a precautionary approach It should be noted that the result of the evaluation does not say anything about actual risks. Establishing the precautionary need should motivate the user to think about whether existing protective measures meet this precautionary need or whether further measures are required.

Table 3 Precautionary Matrix risk matrix (Höck et al., 2008)

		Potential effect		
		Low **Low** reactivity and **low** stability	**Medium** **Medium** reactivity and **low** stability or vice versa	**High** **Medium or high** reactivity and **medium or high** stability
Potential e exposure of humans	**Low** **Low** amount of nanomaterial handled by a consumer/employee per day and **low** frequency of consumer product use /exposure of nanomaterial to an employee	**Class A**	**Class A**	**Class B**
	Medium **Medium** amount of nanomaterial handled by a consumer/employee per day and **low** frequency of consumer product use/exposure of nanomaterial to an employee or vice versa	**Class A**	**Class B**	**Class B**
	High **High** amount of nanomaterial handled by a consumer/employee per day and **high** frequency of consumer product use/exposure of nanomaterial to an employee	**Class B**	**Class B**	**Class B**

2.3.1.3 Control Banding NanoTool

The CB NanoTool[7] was developed at the Lawrence Livermore National Laboratory in the United States by Paik et al. (2008) and Zalk et al. (2009). The tool estimates an emission probability (without considering exposure controls), and a severity (hazard) score and provides advice on what engineering controls to use. It includes nine exposure domains covering handling of liquids, powders and abrasion of solids.

Within the CB NanoTool tool the hazard band is determined by the severity score. The severity score is based on a number of factors; surface reactivity, particle shape, particle diameter, solubility, and the carcinogenicity, mutagenicity, dermal toxicity, asthmagenicity of both the NM and the parent material.

The exposure (probability) band is based on 5 factors; estimated amount of chemical used in the task, dustiness and moistness, number of employees with similar exposure, frequency of operation and duration of operation. The scores associated with the responses to each question are given in Table 4

[7] http://www.controlbanding.net/Home.html

Table 4 CB NanoTool tool exposure scores (Paik et al., 2008)

Factor	Level	Score
Amount (25% of score)	>100 mg	25
	11-100 mg	12.5
	0-10 mg	6.25
	Unknown	18.75
Dustiness (30% of score)	High	30
	Medium	15
	Low	7.5
	None	0
	Unknown	22.5
Number employees with similar exposure (15% of score)	>15	15
	11-15	10
	6-10	5
	1-5	0
	Unknown	11.25
Frequency (15% of score)	Daily	15
	Weekly	10
	Monthly	5
	<Monthly	0
	Unknown	11.25
Duration (15% of score)	>4 Hours	15
	1-4 Hours	10
	30-60 Mins	5
	<30 Mins	0
	Unknown	11.25

These scores are then added to reach an overall hazard score (sum of all hazard input variables scores) and an overall exposure score (sum of all exposure factors scores).

These exposure (probability) and hazard (severity) scores are then combined to obtain the assessed risk level (RL) (Table 5).

Table 5 CB NanoTool tool risk levels (Paik et al., 2008)

		Probability			
		Extremely Unlikely (0-25)	Less Likely (26-50)	Likely (51-75)	Probable (76-100)
Severity	Very High (76-100)	RL3	RL3	RL4	RL4
	High (51-75)	RL2	RL2	RL3	RL4
	Medium (26-50)	RL1	RL1	RL2	RL3
	Very High (76-100)	RL1	RL1	RL1	RL2

The CB NanoTool also provides recommendations on the risk management measures (RMMs) that should be employed and/or whether the existing control measures need to be updated. The recommendations are based on the risk level estimated:

RL1: General Ventilation
RL2: Fume hoods or local exhaust ventilation (LEV)
RL3: Containment
RL4: Seek specialist advice

2.3.1.4 Stoffenmanager-Nano

Stoffenmanager-Nano[8] provides a risk assessment based on inhalation exposure to Manufactured Nano Objects (MNO). It is designed for use by Small to Medium sized Enterprises to rank potential health risks and identify effective RMMs.

Four domains are considered: 1) synthesis of MNMs; 2) powder handling; 3) spray and dispersions of ready to use nanoproducts; and 4) fracturing and abrasion of MNO embedded in products (the user is referred to Stoffenmanager®, the version for conventional chemical agents, - for this last domain).

According to the documentation supporting Stoffenmanager-Nano the applicability domain of the tool is use of MNOs that meet all of the following criteria:

- Particles are not water soluble and;
- The particles are purposely (synthetically) produced and not released as unintentional by-product, such as the particle production as a result of incomplete combustion processes, and
- The size of the primary particle is smaller than 100 nm and / or the specific surface area of a nanopowder is larger than 60 m^2/g;
- It concerns single particles as well as agglomerates or aggregates.

The main input parameters are: substance emission potential, activity emission potential, localized control, dispersion, surface contamination factor, personal enclosure, personal protection equipment, duration and frequency of the handling. Stoffenmanager-Nano uses information provided on the physico-chemical and hazardous properties of the material in order to classify the hazard. The hazard band is estimated based on information such as solubility, presence of fibre-type MNO and the specific hazard information about the MNO.

To estimate exposure the tool makes use of the source-receptor approach of Cherrie et al. (1999), extended by Schneider et al. (2010) for use within the domain of NMs (Van Duuren-Stuurman et al., 2012). The determinants of the exposure include task, form of material, local control measures, general ventilation and product properties. A score is given for each determinant.

The exposure score is then determined using the following algorithm:

$B = (C_{nf} + C_{ff} + C_{ds}) * n_{imm} * nppe * t_h * f_h$

Where

$C_{nf} = E * H * nlc_{nf} * ngv_{nf}$

$C_{ff} = E * H * nlc_{ff} * ngv_{ff}$

$C_{ds} = E * a$

E = Emission potential = weight fraction * dustiness * moisture content

C_{nf}, C_{ff}, C_{ds} are the concentration scores due to near-field, far-field and background sources;

n_{imm} is the multiplier for the effect of control measures;

n_{ppe} is the multiplier for the effect of PPE;

t_h is the multiplier for handling duration;

f_h is the multiplier for frequency of handling; the Handling (or task) multiplier;

a is the multiplier for the influence of background sources;

ngv_{nf} and ngv_{ff} are the multipliers for effect of general ventilation in near-field and far-field; and

[8] https://nano.stoffenmanager.nl/

nlc_{nf} and nlc_{ff} are the multipliers for effect if local control measures in near-field and far-field.

The exposure band is then determined from this score using the groupings in Table 6.

Table 6 Exposure bands for Stoffenmanager-Nano (Van Duuren-Stuurman et al., 2012)

Exposure Band	Range Scores
1	0-0.002
2	0.002-0.2
3	0.2-20
4	20-2000.03

For each risk assessment carried out using Stoffenmanager-Nano the output consists of the hazard class, the time-weighted exposure class and the risk score. The hazard and exposure bands are essentially combined as in Table 7 but take account of the duration and frequency of the task (time-weighted risk class) or provide an estimate for the risk during the task (task-weighted).

Table 7 Risk Banding within Stoffenmanager-Nano (Van Duuren-Stuurman et al., 2012)

		Hazard				
		A	B	C	D	E
Exposure	1	III	III	III	II	I
	2	III	III	II	II	I
	3	III	II	II	I	I
	4	II	I	I	I	I

Stoffenmanager-Nano also allows for the evaluation of the effect that various control measures could have on the estimated risk level associated with a task, allowing for further insight into the most appropriate RMMs given the circumstances of the task and the properties of the material.

2.3.2 Objective 1.2-1.4: Comparison of qualitative and semi-quantitative exposure tools

2.3.2.1 Literature review on validation of nano control banding tools

The main objective of the literature review was to inform how the tools specifically developed for MNMs (Table 1) and described in the previous section compare with measurement data.

NIOSH carried out a literature review in 2013 (published in 2016) on control banding tools (Eastlake et al., 2016). Therefore our search included the peer-reviewed literature identified in the NIOSH review and those publications found in a new search covering the period 2013-2016.

The search strategy covered the following terms, found in the title or abstract:

- Control band/bands/banding and nanomaterials/NOAA
- Risk band/band/banding and nanomaterials/NOAA
- Risk prioritization band/bands/banding and nanomaterials/NOAA

The following databases were searched:

- PubMed: PubMed Central® (PMC) is a free archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM).
- Google Scholar: Google Scholar index includes most peer-reviewed online academic journals and books, conference papers, theses and dissertations, preprints, abstracts, technical reports, and other scholarly literature, including court opinions and patents

We included papers that:

- assessed the control banding tools outputs in real occupational exposure scenarios either by comparing them with exposure/release measured data or the company existing risk management methods.

We excluded papers that:

- described and/or compared the tools from a conceptual basis but did not include an assessment of the tools output
- papers that were not published in English.

Table 8 shows the number of papers retrieved in the searches.

Table 8 Papers retrieved for the literature review

	Google Scholar (anywhere in text)	PubMed (title/abstract)
Control band/bands/banding and nanomaterials/NOAA	259	4
Risk band/band/banding and nanomaterials/NOAA	1	0
Risk prioritization band/bands/banding and nanomaterials/NOAA	0	0

After applying the inclusion and exclusion criteria, 6 peer-reviewed papers were selected for the review which highlights a paucity of peer-reviewed literature in this area.

Five studies were retrieved, where the CB NanoTool was studied (Paik et al., 2008; Zalk et al., 2009; Liaou et al., 2014; Sánchez Jiménez et al., 2016), and Stoffenmanager-Nano (Verbist, 2012; Sánchez Jiménez et al., 2016) were studied.

No studies that met the inclusion criteria were identified concerning the Precautionary Matrix Approach and the ANSES tools.

Two studies compared the respective tool output with measurement data (Verbist, 2012; Sánchez Jiménez et al., 2016) and three compared the exposure control recommended by the tool with the opinion of experts in industrial hygiene (Paik et al., 2008; Zalk et al., 2009; Liaou et al., 2014).

In general tools were found to be conservative when compared with the exposure controls that were considered to suffice to control the emission by the occupational hygienist.

Eastlake et al. (2016) reviewed the two studies written by the developers of the CB NanoTool (Paik et al., 2008; Zalk et al., 2009) and identified that a total of 32 activities handling NMs were evaluated with the CB NanoTool in these papers. These activities were be grouped as: synthesis or growth of material, sample preparation, product mixing or manipulation, and waste handling activities. The exposure control employed was compared with those recommended by the tool. For 59.4 % of the activities (19 out of 32) the tool agreed with the control in place; for 28.1% of the activities (9 out of 32) the tool recommended a higher exposure control and for 12.5% (4 out of 32) the recommended exposure control was less stringent than what was recommended by the experts.

Sánchez Jiménez et al (2016) compared the hazard and exposure output of the NanoTool, Nanosafer and Stoffenmanager-Nano with measured data. The outputs did not compare well with the experimental hazard data and measurement release data. The authors concluded that for some of the tools the information required to estimate the hazard is not always available in the Safety Data Sheet and the input of such information requires expert judgement. It was recommended that further work should be done to improve their estimates, especially the inclusion of modifiers that account for the effectiveness of the ventilation and the effect of high temperatures during the process.

Liaou et al. (2014) undertook a study where the output of the CB NanoTool was compared with the evaluation carried out by an occupational hygienist and the prevalence of disease. Four of the five operations evaluated in the study were found to have implemented controls consistent with what was recommended by the CB Nanotool. No agreement was found between the exposure risk and the prevalence of disease.

Verbist (2012) found no correlation between measurement results and the exposure output scores of Stoffenmanager-Nano.

The studies used a single measurement metric for the comparison: the particle number concentration below a specific size range. The number of particles is not specific to the MNMs under investigation (which is what the tools output referred to) and this makes such comparisons difficult as the aerosol background has to be taken into account.

2.3.2.2 Evaluation of ART and Stoffenmanager Nano

Within the NANoREG project we compared the output of two of the tools: ART (described in section 2.3.3.1), which has not been designed specifically for NMs, and Stoffenmanager Nano with 24 field measurement studies (involving 167 activities) provided by the Swiss Accident Insurance Fund (SUVA). The activities were classified in the following domains:

- Welding (MIG-MAG, TIG, oxy-acetylene)
- Transfer of powders (vacuuming, transfer & mixing of powders, weighing, various MNMs)
- Coating (coating of SiO_2 on a polyethylene foil by propane burning)
- Other hot processes (compounding of plastics and MNMs), incineration)
- Spraying (car cleaning, laser printers, application of ENMs on shoes, spraying of metal sheets)
- Impaction (blasting of CO_2 for cleaning, cutting and nailing nanoporous insulating material)

The input values for ART and Stoffenmanager Nano to each exposure situation were firstly assigned independently by two persons, trying to match as closely as possible the definitions of the parameters available in the references for the two models. The choice of parameters' values was then discussed until a consensus was found. The major sources of disagreement were the attribution of activities, especially the ones outside the scope of the models (e.g. welding & other hot processes).

The statistical analysis performed comprises the analysis of the correlations between the obtained scores and the measurements, conducted by computing the (non-parametric) Spearman correlation coefficient (r_S).

Error! Reference source not found.2 and **Error! Reference source not found.** show box ots of the particle number concentration (PNC) collected with a CPC (upper size limit 1 µm) and geometric mean diameter (GMD) measured by category (whiskers represent the minimum and maximum values, the box the inter-quartile range and the red line the median). The number of exposure situations per activity is indicated in brackets. PNC reached values of up to 25×10^6 ($\#/cm^3$). The GMDs were between 20 and 100 nm for most exposure situations.

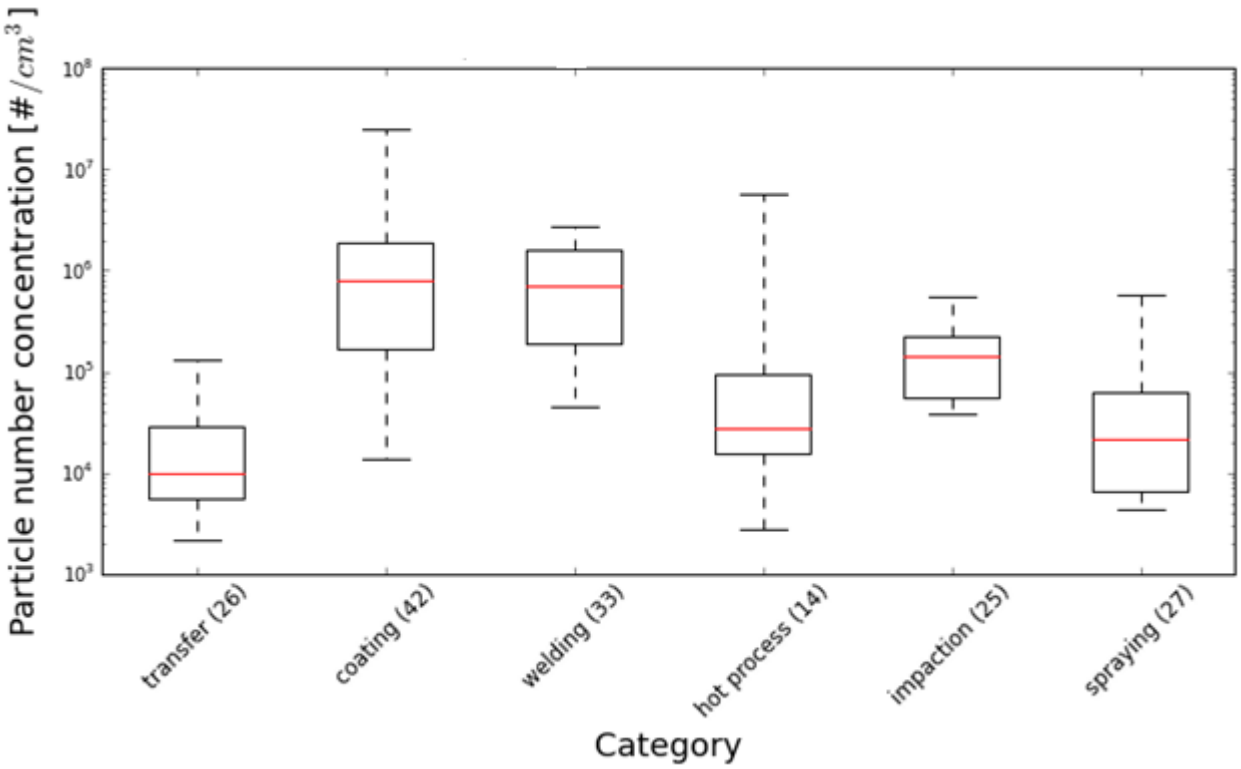


Figure 2 Average measured particle number concentrations (PNC) by activity

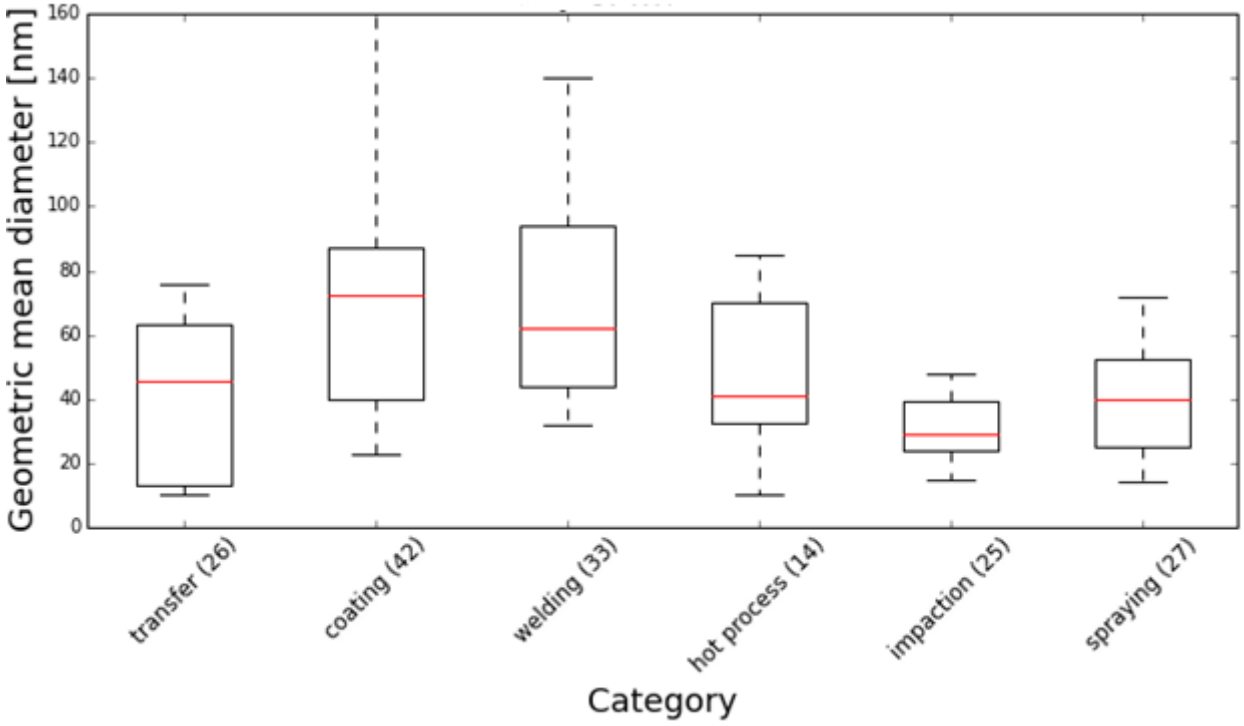


Figure 3 Average measured geometric mean diameters (GMD) by activity

Figures 4 and 5 show the comparison of model scores for ART and Stoffenmanager -Nano, respectively, and the measurement data.

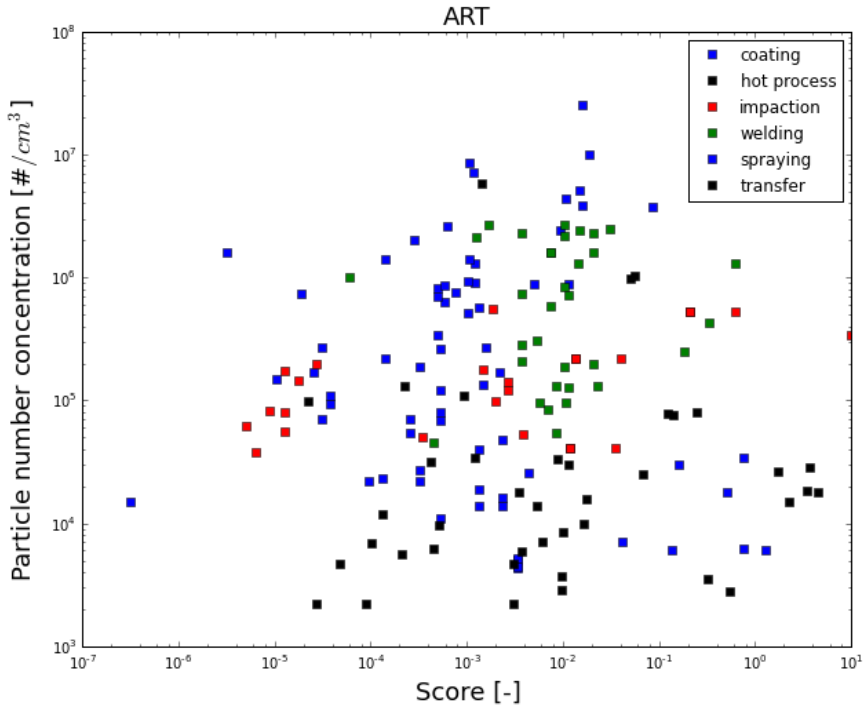


Figure 4 Normalized ART's scores & PNC measurements, by activity

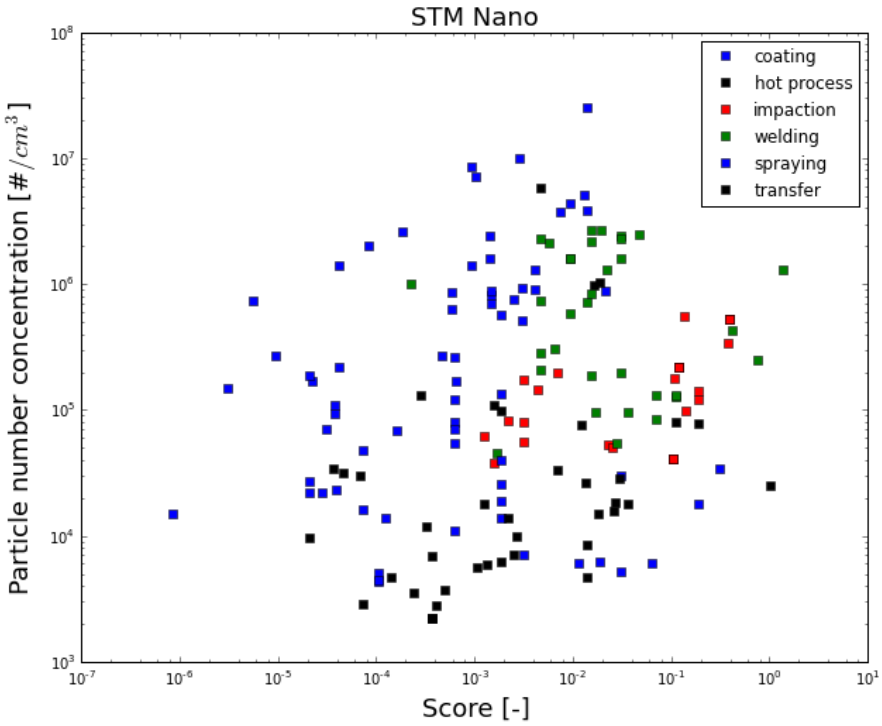


Figure 5 Normalized Stoffenmanager- Nano's scores & PNC measurements, by activity

Table 9 shows the Spearman correlation coefficients for each activity for both tools between their estimates and the particle number concentration measurements.

Table 9 Correlations between particle number concentrations and scores (p-values below 10% are in bold, for positive correlations)

Category\Statistic	*Spearman correlation*	*P-value*
ART		
Transfer	0.464	**0.017**

Coating	0.515	**0.000**
Spraying	-0.596	0.001
Welding	0.075	0.680
hot process	-0.473	0.088
Impaction	0.476	**0.016**
Stoffenmanager - Nano		
Transfer	0.195	0.340
Coating	0.590	**0.000**
spraying	-0.177	0.377
welding	-0.148	0.413
hot process	0.244	0.401
impaction	0.651	**0.000**

The overall correlation for all activities was closely to zero for both models (ART r_S = 0.03, StoffenmanagerNano r_S = 0.21). For ART, the activities of transfer, coating and impaction show a weak to moderate correlation at best, with values around 0.5. Welding exhibits almost no correlation, implying that the intrinsic variability of welding is larger than that explained by other factors (e.g. dispersion). The categories spraying and hot process are even negatively correlated. For Stoffenmanager-Nano, even the transfer category is not correlated significantly with the measurements, showing a significant correlation only for impaction and coating. The correlation coefficient for welding is again close to zero (although welding is not covered as the nanoparticles generated are not purposely synthesised, i.e. MNMs), while spraying and hot processes are not in accordance with the results from ART, which again shows that no reliable prediction can be made in these cases.

ART and Stoffenmanager-Nano show little correlation with PNC. In the case of ART the tool is not calibrated for MNMs, so this is perhaps not unexpected but in the case of Stoffenmanager-Nano (which has been calibrated for MNMs) a better correlation was expected.

Mass measurements were extrapolated from the results of the PNC measurements, assuming a log-normal size distribution of the MNMs and spherical particles. These estimated mass concentrations were also compared with the measurement data but again the results showed little correlation (results not shown). The assumptions made for the extrapolation possibly did not represent the real distribution and shape of the particles.

2.3.2.3 Inter-user variability when using nano control banding tools

Results from previous studies have shown considerable variability in results obtained by different users of risk/exposure assessment tools (BAUA, 2016). Lamb et al. (In Prep) studied the between user variability for lower tier screening tools (MEASE, Stoffenmanager, ECETOC TRA v3, RISKOFDERM, EMKG) recommended for use under REACH. Through a remote-completion exercise they identified and evaluated tool parameters and factors such as user demographics that may be potentially impact on the between-user variability. Participants (N=146) generated dermal and inhalation exposure estimates (N=4066) from specified workplace descriptions (n=20) and tool combinations. Exposure estimates ranging over several orders of magnitude were generated for the same situation by different tool users. Although variation was observed between choices made for the majority of input parameters, differing choices of PROC code/ activity descriptor and dustiness level impacted most on the resultant exposure estimates.

High levels of variation between users of the ART have also been observed (Schinkel et al., 2014). Schinkel et al. (2014), looking at the reliability of the ART, found extreme deviations from a gold standard estimate caused by assessors failing to include relevant exposure controls accurately. Errors in allocation of the LEV and local control parameters have a significant effect on the estimate obtained, and were a source of considerable variation.

Therefore, a small study was carried out to assess how different the exposure outputs from the nano control banding tools were when used by different users. The tools studied were qualitative

(CB NanoTool and Stoffenmanager-Nano, explained in section 2.3.1 and quantitative (Nanosafer, ConsExpo-nano and ART, although as mentioned earlier ART has not been calibrated for MNMs, described in section 2.3.3). Only the exposure assessment module of the tool was studied (and not the hazard assessment).

Five exposure scenario descriptions were selected from the MARINA library of exposure scenarios for nanomaterials[9] (Table 10).The criteria for selecting the scenarios was their completeness in terms of contextual information provided and quality of the information.

Table 10 Exposure scenarios used for the inter-user variability study

ES No.	ES Name	MNM
1	Spraying of nano Ag ink on to paper	Ag
2	Dispersion of TiO_2 and ZnO ENM into a paint matrix for testing	TiO_2 and ZnO
3	Dispersion of TiO_2 nanoparticles	TiO_2
4	Functionalization and dispersion of Zn nanoparticles	Zn
5	Synthesis of $CoAl_2O_4$ nanoparticles	$CoAl_2O_4$

The scenarios were provided by email in a Microsoft Excel template. An example of the scenario template is shown in Appendix 1.

The volunteers were recruited from a range of expertise areas, including:

- Research
- Industry
- Government
- Occupational Hygiene

Each volunteer was given a guide on how to use the tool and a feedback questionnaire at the end of the study

A total of 36 people participated in the study (only 28 completed the feedback questionnaire at the end of the study which the following results summarises). Figure 6 shows the percentage of respondents per area of expertise.

[9] http://marina.iom-world.co.uk/OccupationalGuidlines.aspx

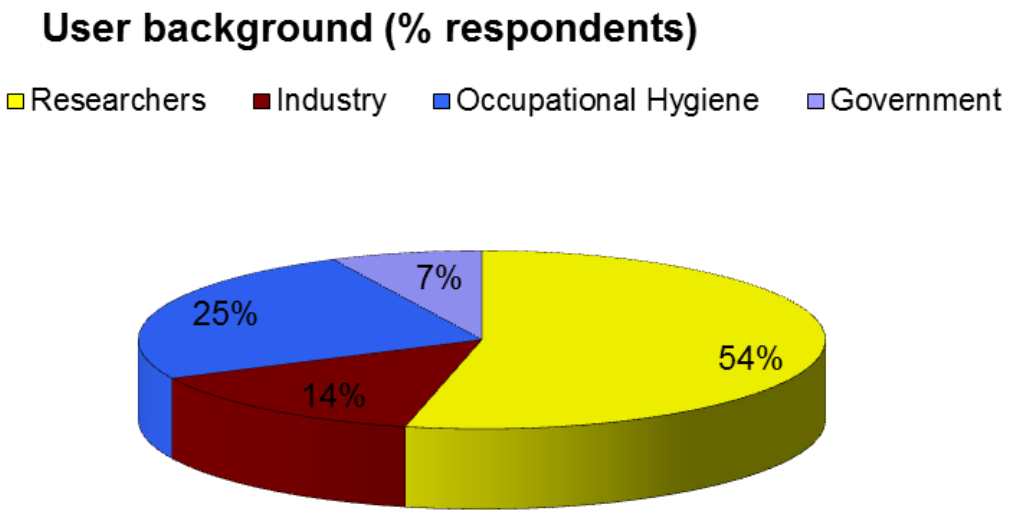


Figure 6 Percentage of respondents per area of expertise

Figure 7 shows the outputs for the CB Nanotool, Nanosafer and Stoffenmanager Nano as their output is a score and the three tools can be easily compared to each other. Figure 8 shows the output results for ART (median of inhaled concentration) and Figure 9 for ConsExpo-nano (mass inhaled).

For CB Nanotool, Nanosafer and Stoffenmanager-Nano to be able to compare their outputs the exposure score obtained (see section 2.3.1) was normalized to a scale of 1-100.

Results for ES1 (spraying) were only available for ConsExpo-nano.

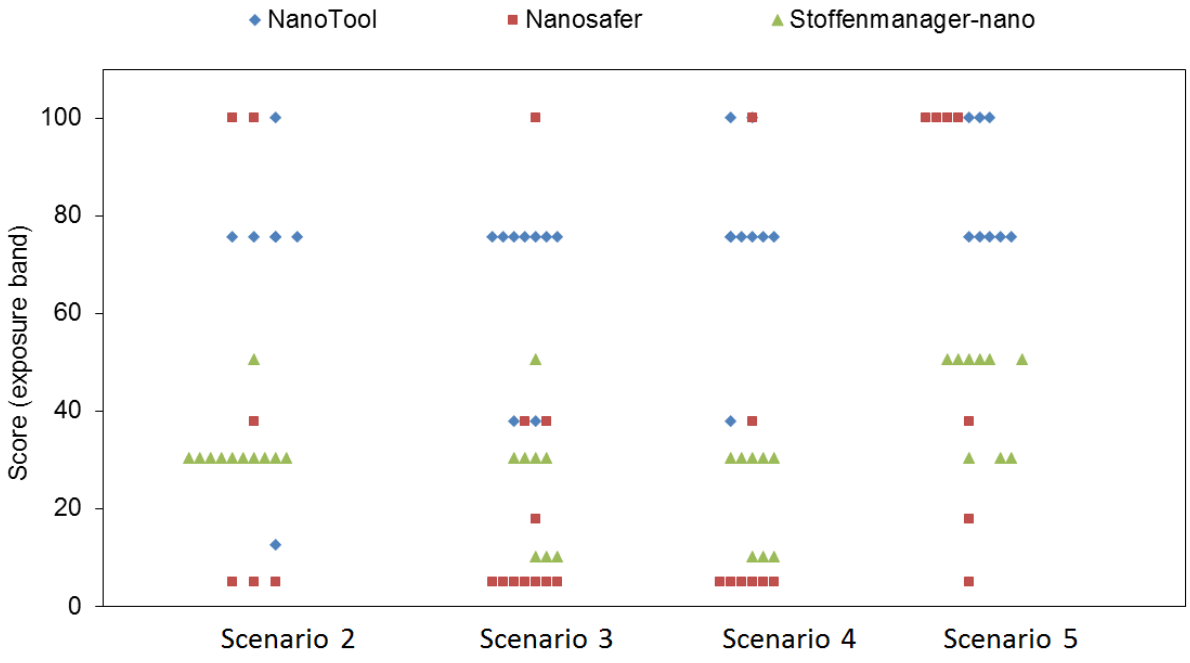


Figure 7 Tools' scores for each scenario

For all the tools a high inter-user variability was observed. For the same tool and the same scenario we would expect to see all data points aligned along the same exposure score, this would mean all users got the same output. However for all the scenarios the estimated exposure scores are spread along the Y axes. Nanosafer was the tool that resulted in the greatest range of estimates, with scores of 20, 75 and 100 for scenario 2 for example. Stoffenmanager-Nano

was the tool the resulted in less inter-user variability, with scores ranging between ~ 10-50 for all scenarios.

In addition to the between-user variability there also appears to be differences in exposure-score obtained by the different tools.

Results obtained for ART (Figure 8) and ConsExpo-nano (Figure 9) also showed a high inter-user variability. In this case an exposure concentration value is reported for ART in Log-scale and a mass of the inhaled particles is reported for ConsExpo-nano

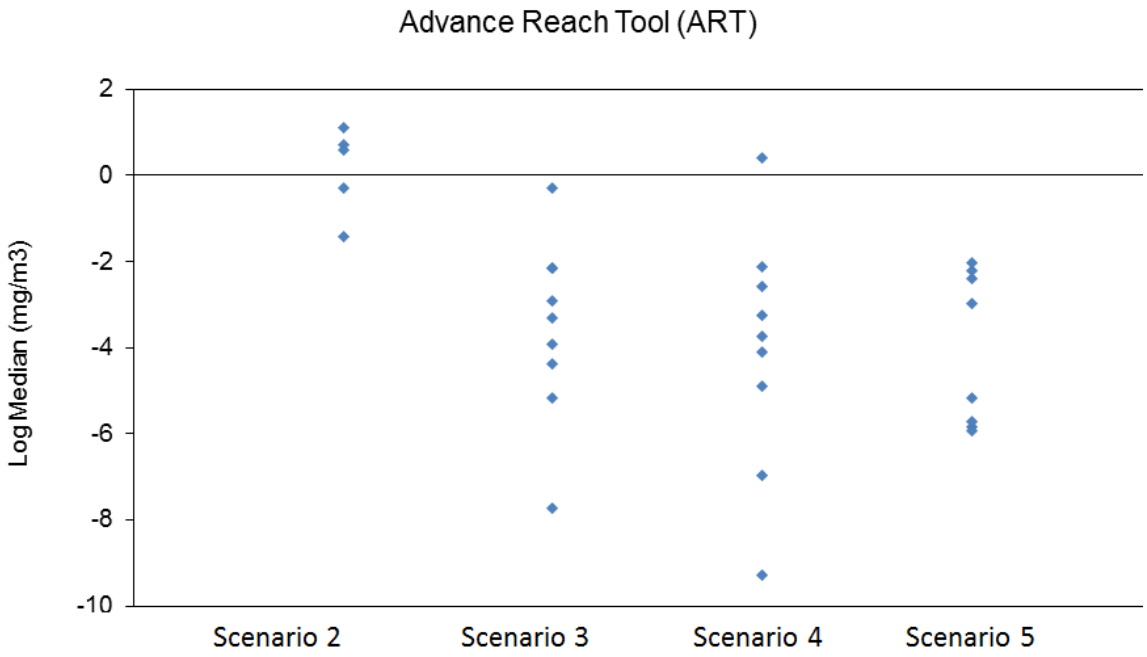


Figure 8 ART scores for each scenario

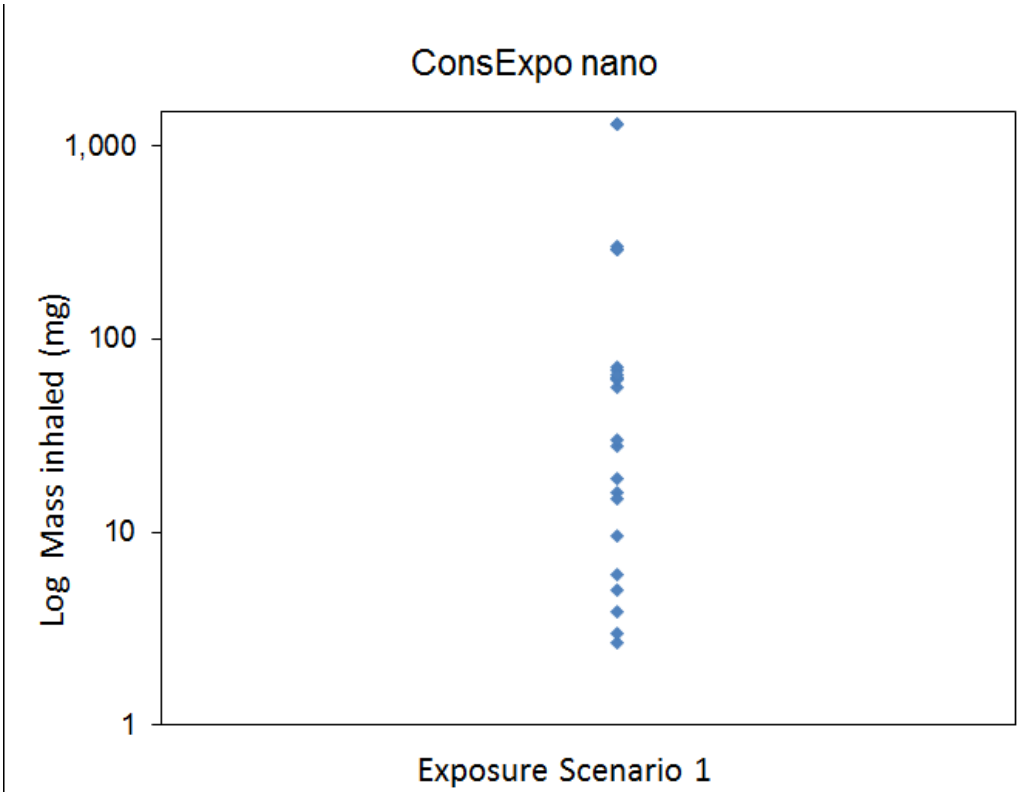
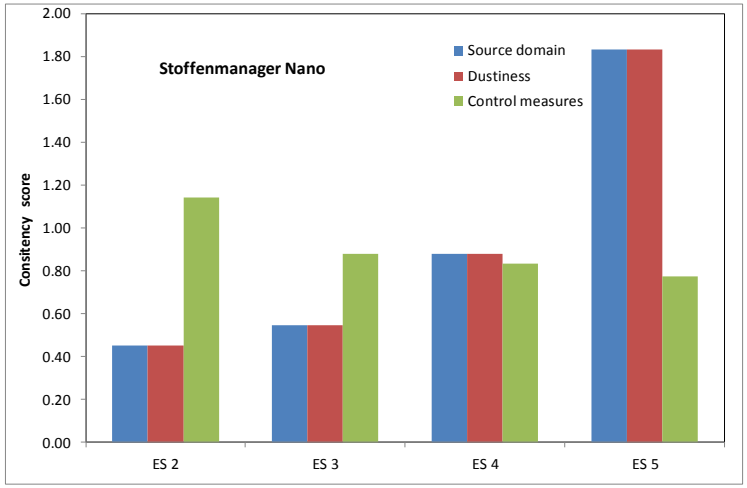


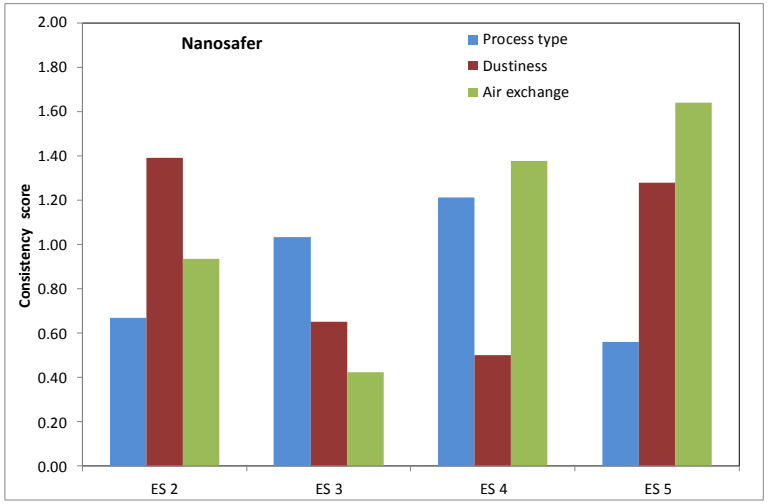
Figure 9 ConsExpo-nano scores for spraying (only scenario available in the tool)

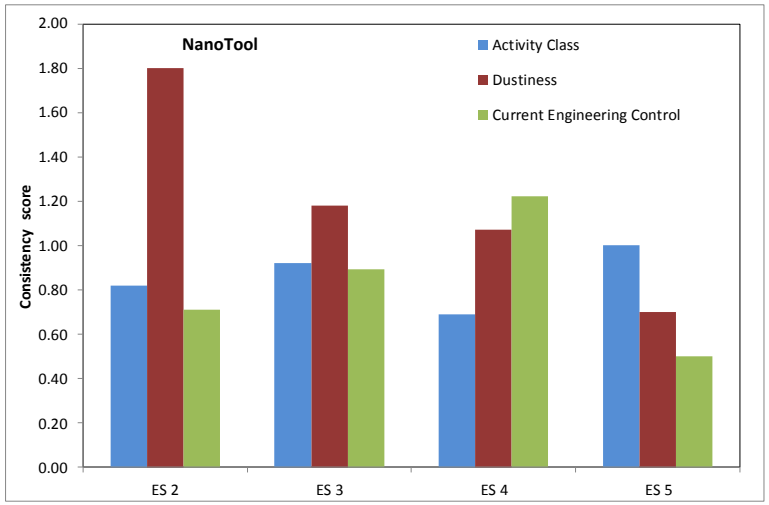
For each input parameter we determined the consistency with which different users scored the information and compared this across the different tools. Consistency scores were calculated taking account of the total number of categories for each input variable as follows:

- Calculate the proportion of categories not used for each variable so that a higher number means fewer categories were used (i.e. more consistency and less variability).
- Calculate the proportion of individuals in the largest category group (the most popular choice among users) as above so a higher number means more clustering of responses (i.e. more consistency and less variability).
- The total consistency score was estimated as the sum of the above two variables.

Figure 10 and Figure 11 show the consistency scores for the different tools and variables and allows for a relative comparison between –users for different input variables between tools. The variables shown are those that had input data in all scenarios.







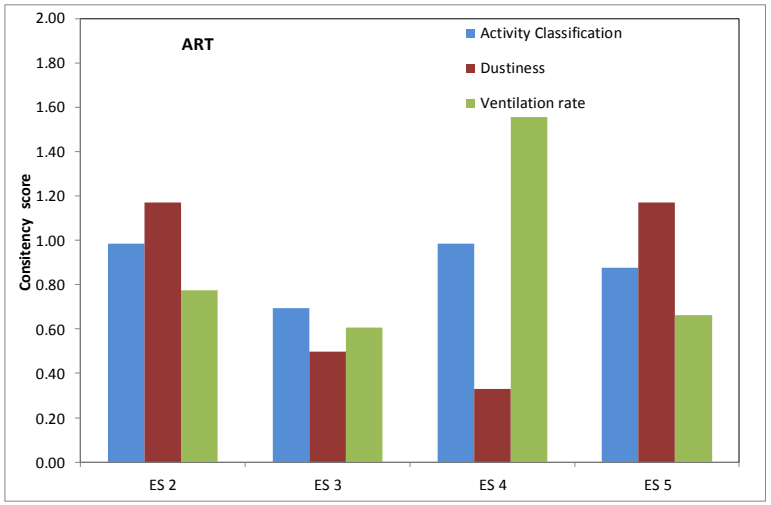


Figure 10 Consistency score for variables of Stoffenmanager-Nano, Nanosafer, CB NanoTool and ART.

This project has received funding from the European Union
Seventh Framework Programme (FP7/2007-2013)
under grant agreement no 310584

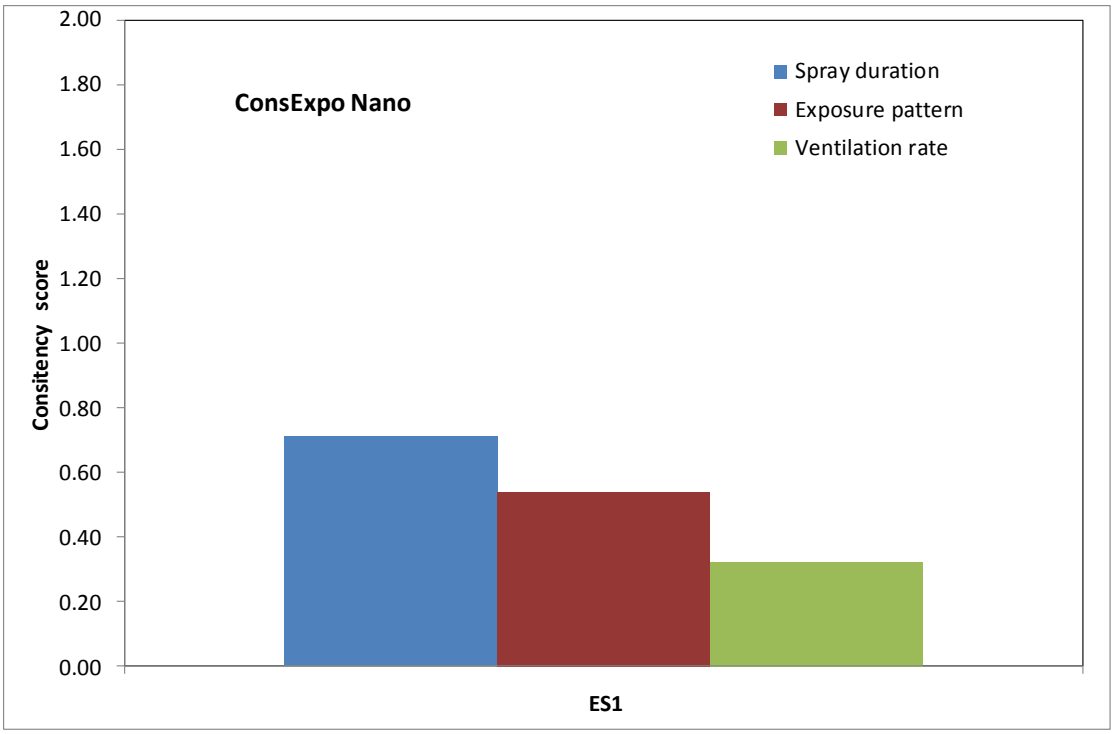


Figure 11 Consistency score for ConsExpo-nano (only ES1 available)

There was no pattern in the consistency found for the variables. The same variable showed a ranged of consistency scores across scenarios and tools. For example for dustiness a consistency score of only 0.4 was observed for exposure scenario 2 (ES2) in Stoffenmanager-Nano but a consistency score of 1.4 was observed for the same scenario when using Nanosafer, 1.8 when using the CB NanoTool and 1.2 when using ART. This means the agreement on this variable by the users was greater when using the CB NanoTool compared to the other tools.

Within Stoffenmanager-Nano the consistency score for the dustiness parameter ranged from 0.4 (ES2) to 1.8 (ES5). Similar results were found for the other tools.

The rest of the variables studied also showed similar results.

Figure 12 shows the responses from the feedback questionnaire.

This project has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no 310584

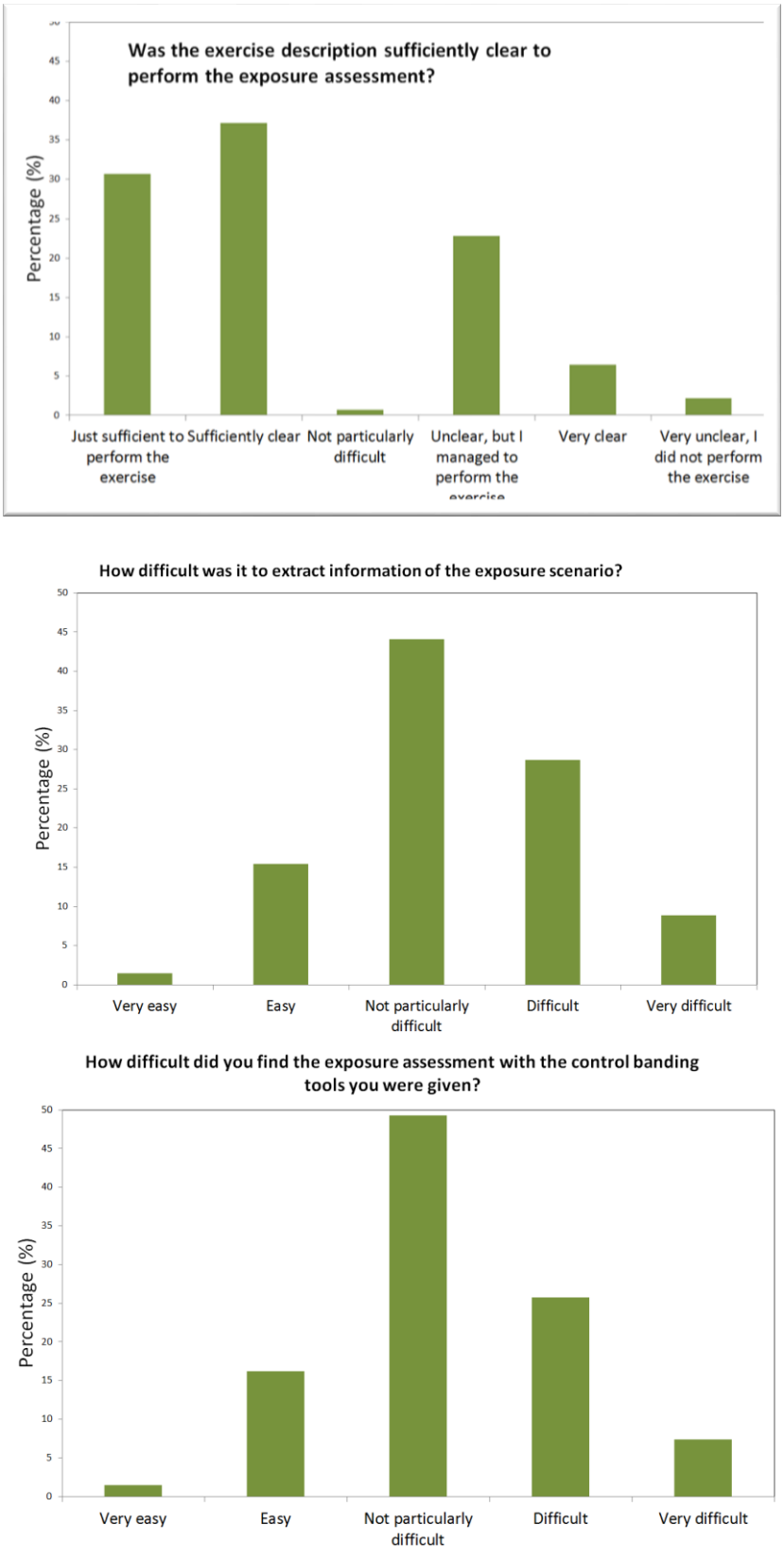


Figure 12 Users' responses to the feedback questionnaire.

Most of the participants found the instructions given were clear enough to carry out the exercise. Extraction of the data from the scenario templates provided was rated as not difficult by 45% of respondents whereas 30% found this task difficult. Most of the users did not find the tools difficult to use, although 25% found it difficult and 10% very difficult.

In summary, this study has confirmed that between user variation in interpretation of exposure scenario information and converting these into the input variables is an important source of uncertainty. In particular, input parameters for dustiness, exposure control and activity/process type are shown to be able to cause a high variability in the data input.

This lack of consistency between users could lead to completely different conclusions being made based on exactly the same set of information. This uncertainty needs to be taken into account during the development of the tools and its supporting guidance documentation and also by users during the use of the tools.

On the basis of these results the following recommendations can be made:

- Guidance and help should be better communicated to users.
- Tool users should ideally be trained in the use of the exposure tools. It is probably not recommended that tools are used by people not trained in Occupational Hygiene or a related field. Appropriate quality control procedures should be developed for use and application of screening and higher tier tools (both for nano-specific and generic exposure tools), in addition to specific training, this could consist of:
    - Round -robin exercises between tool users based on standard exposure scenarios and feedback sessions.
    - Team assessments with consensus decisions.

PART TWO QUANTITATIVE TOOLS

2.3.3 Objective 2.1 Description of quantitative tools and models

2.3.3.1 The advance Reach Tool (ART)

The Advanced REACH Tool (ART) provides users with a quantitative estimate of exposure. Although ART has not been validated for NMs there is a potential to use ART for specific scenarios such as powder handling.

The ART model has two main components; a quantitative mechanistic two-box source-receptor model to estimate exposure and a Bayesian statistical framework to update exposure estimates from the mechanistic model with exposure measurement data. The two-box model (Tielemans et al., 2008; Cherrie and Schneider, 1999) describes the movement of contaminants from a source to the receptor (worker). The model allows for there to be emission in both the near and far-fields, where the near field is defined as the space around the workers, not the source (which means that a source can be in the near field or far field). Personal exposure from a near-field source (*Cnf*) is a multiplicative function of substance emission potential (*E*), activity emission potential (*H*), (primary) localized control (LC_1), secondary localized control (LC_2), and dispersion (*D*). The algorithm for a far-field source (*Cff*) also includes segregation (*Seg*) and personal enclosure / separation (*Sep*).

$$C_{nf} = (E_{nf} \cdot H_{nf} \cdot LC_{nf1} \cdot LC_{nf2}) \cdot D_{nf}$$

$$C_{ff} = (E_{ff} \cdot H_{ff} \cdot LC_{ff1} \cdot LC_{ff2} \cdot Seg_{ff}) \cdot D_{ff} \cdot Sep$$

The level of surface contamination (*Su*) for each activity depends on the location of the source, i.e. whether there is i) a near-field source only, ii) a far-field source only, or iii) both near- and far-field sources (in which case the surface contamination in the near-field is assumed to dominate that of the far-field:

$$Su_{nf} = Su_{factor} \cdot (E_{nf} \cdot H_{nf} \cdot LC_{nf1} \cdot LC_{nf2} \cdot D_{nf})$$

$$Su_{ff} = Su_{factor} \cdot (E_{ff} \cdot H_{ff} \cdot LC_{ff1} \cdot LC_{ff2} \cdot Seg_{ff} \cdot D_{nf} \cdot Sep_{ff})$$

Subsequently, the overall exposure score is estimated:

$$C_t = \frac{1}{t_{total}} \sum_{tasks} \left\{ t_{exposure} \cdot (C_{nf} + C_{ff} + Su) \right\} + t_{non-exposure} \cdot 0$$

The algorithm considers multiple activities (and exposure time ($t_{exposure}$)) within an 8 hr work shift (t_{total}) and also allows periods with assumingly zero exposure ($t_{non-exposure}$).

The semi-quantitative exposure score is subsequently converted into a quantitative estimate using a calibration curve, which has been developed based on large database of exposure measurements. The underlying mechanistic model produces an estimate of the median exposure value in an exposure scenario.

2.3.3.2 ConsExponano

ConsExpo-nano is a tool to investigate potential consumer inhaled dose and alveolar load of a NM in spray particles in consumer spray products. The model that simulates the external aerosol concentration in indoor air is equivalent to the ConsExpo 'exposure to spray model' described in (Delmaar et al., 2005).

The models used to simulate deposition and clearance from the alveoli is an implementation of the ICRP deposition model (ICRP, 1994). The reference provides different parameter sets depending on age, gender and activity level. ConsExpo-nano implements two models: the model for males and females performing light exercise.

The following assumptions are made in the model:

- The alveolar load varies in time and depends on the inhalation, deposition and clearance of particulate matter
- The NM is released as part of an aerosol. The NM is transported in the aerosol particles in indoor air and through the respiratory tract. I.e. the properties of the aerosol particle will ultimately determine inhalation and deposition of the NM.
- The aerosol particles are assumed to consist of the NM only. No other components are assumed to be present.
- The aerosol particles are assumed to remain unaltered in the process of inhalation and deposition. Only when deposited in the alveolar region, changes in aerosol due to dissolution (in lung lining fluid or alveolar macrophages) are considered.
- Dissolution of the NM in the alveoli (either in macrophage or lung lining fluid) is considered as a first order kinetic process, characterised by a single, constant dissolution rate. This rate is to be specified by the user.

In April 2016, the tool was updated according to comments and suggestions from users. In the new version of the tool, version 1.1, two major changes were implemented. First, apart from a spray scenario, the user is able to choose a custom scenario in which a known air concentration of aerosols (containing NMs) can be entered directly into the tool. This option enables the user to calculate an alveolar load in lungs from any inhalation exposure (outside spray exposure), which makes the tool applicable for scenarios other than spray scenarios, including those occurring at the workplace. The results provided in this report were estimated with the new version.

Furthermore, there is a possibility to enter exposure parameters of an animal hazard study with known adverse effects after inhalation exposure to a NM. In this way, it is possible to convert the external dose of NMs to which the animals are exposed, into an internal exposure dose i.e. the alveolar load. In this way, a comparison (indication of risk) can be based on comparison of the alveolar load.

2.3.3.3 Nanosafer

Nanosafer[10] was developed by the National Research Centre for the Working Environment (NRCWE) and the Danish Technological Institute (DTI) in Denmark, in collaboration with the Danish Industry, the Branch Organization for Industry Workers, and the Ministry for Science and Education (Kristensen et al., 2010). The tool provides a risk evaluation in the near and far-field for short (15 minutes) and long-term (8-hours) exposure for occupational exposures involving potential inhalation of MN as respirable dust, i.e. handling powders, releases from grinding which release dust with a known or assumed fraction of NM (NOAA) in the airborne fraction and in case of spills. In contrast to ART, the Nanosafer considers the near field to be the space around the source, rather than the worker (which means that a worker can be either in the near-field or the far-field).

The tool estimates whether the material is nano-relevant from the input parameters (i.e. particles ≤ 200 nm and/or products with a specific surface area (SA) ≥ 30 m^2 g^{-1}). The emission rate for a process is determined within the tool, based on either dustiness data (E_o) adjusted for the activity energy (h_i) and applied mass-flow (dM/dt) or a constant release rate ($E_{i,o}$). A first-order quantitative two-box aerosol dispersion model, as with most of the higher tier models, is then used to determine the near-field (NF) and far-field (FF) concentrations.

In addition to the dust transport between the two compartments, the aerosol decay rates are in principle considered as function of the ventilation rates, efficiencies of exposure control,

[10] http://Nanosafer.i-bar.dk/

ingression of particles from other sources, coagulation, and aerosol surface deposition by diffusion and sedimentation (Schneider et al., 2011). In the simplified Nanosafer model, only the calibrated aerosol transport and decay rates from the NF to the (FF ($NF_{NF\text{-}FF}$) and from the FF to the NF (Cherrie, 1999) are considered in the assessment as well as the residual concentration in the NF and FF.

$$NF_{FF\to NF} = \left[\frac{Q_{NF}\cdot C_{FF}}{\Delta t\cdot (Q_{NF})^2}\right]\cdot\left[Q_{NF}\cdot\Delta t + e^{(-Q_{NF}\cdot\Delta t)} - 1\right]$$

$$NF_{NF\to FF} = \left[\frac{Q_{NF}\cdot C_{NF}\cdot (E_i\cdot\Delta t)}{\Delta t\cdot (Q_{NF})^2}\right]\cdot\left[Q_{NF}\cdot\Delta t + e^{(-Q_{NF}\cdot\Delta t)} - 1\right]$$

$$NF_{residual} = \left[0.5\cdot\frac{(C_{NF,t-1} + C_{NF,t})}{(Q_{NF}\cdot dt)}\right]\cdot\left[1 - e^{(-Q_{NF}\cdot dt)}\right]$$

$$FF_{residual} = \left[0.5\cdot\frac{(C_{FF,t-1} + C_{FF,t})}{(Q_{FF}\cdot dt)}\right]\cdot\left[1 - e^{(-Q_{FF}\cdot dt)}\right]$$

The output from Nanosafer is an integrated risk assessment for short-term (15 min) and 8-hour NF and FF exposure. The risk scaling is based on compilation of hazard data and hazard indicators and the estimated potential exposure levels scaled according to a nanomaterial-specific theoretical occupational exposure limit calculated as the ratio between the volume-specific surface area of the nearest analogue bulk material (reference at 200 nm size) and the nanomaterial in question using the equation below (SSA: specific surface area; δ: relative material density; OEL: Occupational Exposure Limit for the nearest analogue bulk material):

$$OEL_{nano} = OEL\cdot\frac{30\cdot\frac{1}{\delta}}{SSA_{nano}}\text{, where } 30\cdot\frac{1}{\delta} = SSA_{200\,nm}$$

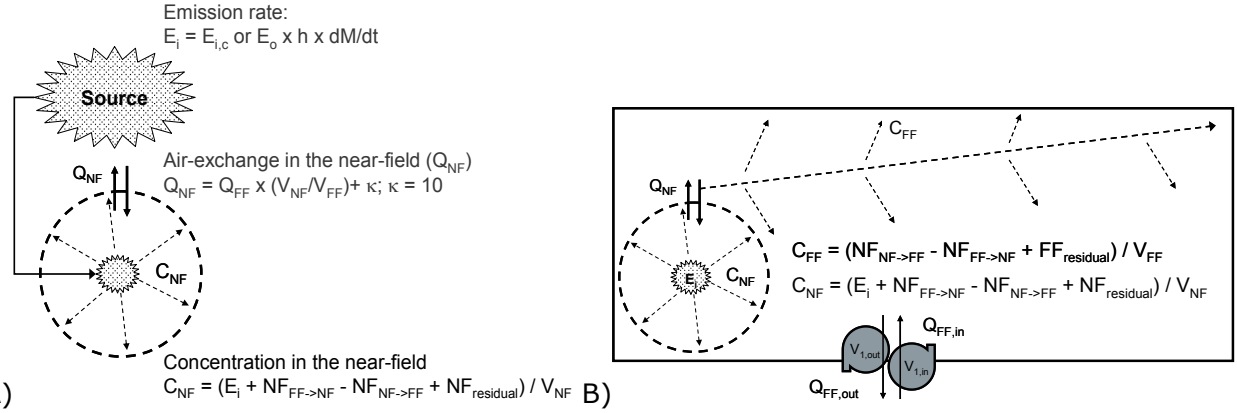


Figure 13 Calculation principles in Nanosafer 1.0 (Kristensen et al., 2010). A) Illustration of the release rate module, where the Emission rate (Ei) is given by a constant release rate (Ei,o) or the dustiness multiplied with mass-flow rate (kg/min) and a scenario-specific default handling energy factor (hi). B) Illustrates the two-box near-field (NF) and far-field (FF) instant mixing exposure model. The aerosol transfer and decay rates in the NF and FF volumes were calculation based on equations in Schneider et al. (2004). In this illustration the Ei, NF, FF values represent the total respirable aerosol mass transported or residing at the 1-minute time-resolution in the calculation.

2.3.3.4 I-NANO tool

During the NANoREG project, the I-Nano tool was developed by IOM and INRS, based on a two-box model and considering the singularities of NPs.

The two-box model is again based on the NF/FFFF source receptor model developed by Cherrie and Schneider (1999) and the algorithms developed by Maynard and Zimmer (2003) for estimating the time evolution PSD of NPs. To avoid confusion on the definitions of the N- and F-fields, within the I-Nano tool we defined the field around the source the Local Control Influencing Zone (LCIZ) and the NF as the box around the worker (Figure 14). Since the worker moves around the room, the concentration in the worker-NF can be estimated from the concentrations in the LCIZ and FF and the time he spends in each zone. In the nano-specific model, other size-dependent factors are taken into account such as coagulation and losses through gravitational settling (particles settling to the floor), diffusion (particles settling on walls and surfaces) and dilution (effect of ventilation).

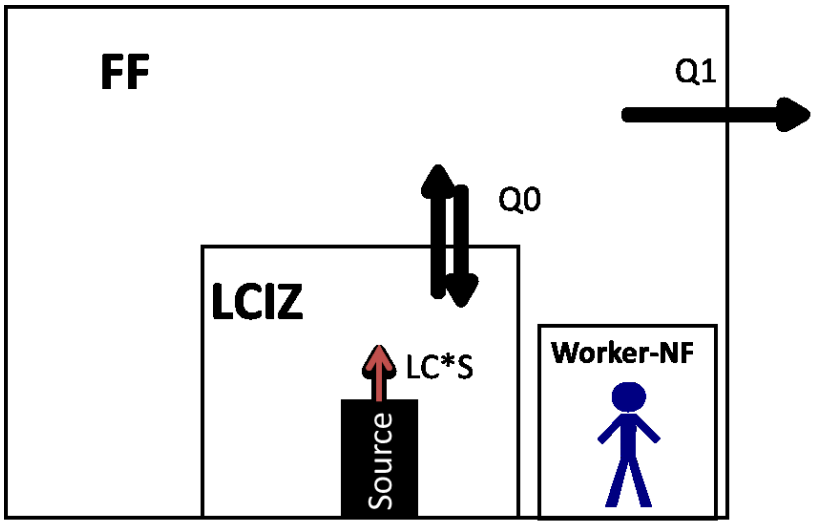


Figure 14 Illustration of the two-box -specific model; local control zone (LCIZ), far-field (FF). The picture shows the local control adjusted emission (LC*S), the air exchange between the two boxes (Q0) and the ventilation (Q1).

In order to estimate the PSD over time it is split into a number of bins of particles of size; $L_{1,}$,…..,L_j,……,L_N. The number of particles in each bin is then estimated over time, this is done separately for both LCIZ and FF.

The concentration in either zone is then a function of agglomeration, diffusion, dispersion, dilution and emission, with each particle size bin in each zone (LCIZ or FF) being described using the following equations (MacCalman et al., 2016):

$$\frac{dn(L_j)_{LCIZ}}{dt} = LC^{*}S_{LCIZ} - n(L_j)_{LCIZ}\frac{Q_{LCIZ}}{V_{LCIZ}} + n(L_j)_{FF}\frac{Q_{LCIZ}}{V_{LCIZ}} \quad + \quad \eta_{LCIZ}$$

$$\frac{dn(L_j)_{FF}}{dt} = LC^{*}S_{FF} + n(L_j)_{LCIZ}\frac{Q_{LCIZ}}{V_{FF}} - n(L_j)_{FF}\frac{Q_{LCIZ}}{V_{FF}} - n(L_j)_{FF}\frac{Q_{FF}}{V_{FF}} \quad + \quad \eta_{FF}$$

Where Q_{LCIZ} is the volume air flow between the LCIZ and FF (m^3/sec), Q_{FF} represents the ventilation (m^3/sec), S_{LCIZ} and S_{FF} represent the mass emission rate into the LCIZ and FF, respectively in particles/sec, LC represents the local control adjustment factor and η represents the size-specific factors (coagulation, diffusion and dispersion)

.

$$\eta \quad = \quad \frac{dn(L_j)}{dt} = \frac{1}{2}\int_{i=1}^{j} n(L_i)\,\beta(L_i, L_j - L_i)\,n(L_j - L_i)\,dL_i \quad - n(L_j)\int_{i=1}^{N} \beta(L_j, L_i)\,n(L_i)\,dL_i$$

$$- \quad \frac{n(L_j)v_{ts}}{h} \quad - \quad \frac{A\,n(L_i)\,D}{V\,\delta_{diff}}$$

The coagulation of particles is estimated using the continuous coagulation equation described by Smoluchowski (1997). In the continuum region the distribution of particles around the fixed absorbing particle can be described by a continuum diffusion equation where n (L, t) is the number concentration of particles of size L_i at time t. The first term of the equation represents the formation of particles of size L_i by the coagulation of smaller particles of sizes L_j-L_i. The factor ½ is introduced because collisions are counted twice in the integral. The second factor of the equation represents losses through the coagulation of particles of size L_j with all other particles.

$$\frac{dn(L_j)}{dt} = \frac{1}{2}\int_{i=1}^{j} n(L_i)\,\beta(L_i, L_j - L_i)\,n(L_j - L_i)\,dL_i \quad - n(L_j)\int_{i=1}^{N} \beta(L_j, L_i)\,n(L_i)\,dL_i$$

The equation assumes particles of any size can coagulate to form aggregates of N number of primary particles of size j. Collisions of three particles is ignored for now as they are only important for high concentrations. Considering only Brownian coagulation, the coagulation coefficient of particles in bin *j* with those in bin *i* reduces to:

$$\beta = f_{ij}\beta_{B0}^{coag}$$

where β_{B0}^{coag} is defined below (with $L{=}L_i$ and $L'{=}L_j$) and f_{ij} is the Fuchs correction factor.

$$\beta_{B0}^{coag} = 4\pi\sigma D_{ij}$$

It can be shown that the expression for β is very close to β_B^{coag} for pure Brownian coagulation. The coagulation coefficient for particles in the micro range has to be adjusted as in the nano-range not all the collisions will be successful, i.e. the coagulation rate does not equal the collision rate. We have used the Fuchs correction that assumes NPs move in a transition regime (between free molecular path and continuum regime) (Seinfield and Pandis, 1998).

The Fuchs correction factor is determined via:

$$f_{ij} = \left(\frac{L_i + L_j}{L_i + L_j + 2\delta_{i,j}} + \frac{8D_{B_{ij}}}{v_{i,j}(L_i + L_j)} \right)^{-1}$$

$$\delta_i = \left(\frac{1}{3L_i\lambda_{pi}} \left[(L_i + \lambda_{pi})^3 - (L_i^2 + \lambda_{pi}^2)^{(3/2)} \right] - L_i \right); \quad \delta_{i,j} = \sqrt{\delta_i^2 + \delta_j^2}$$

where $D_{B_{ij}}$ is $D_{Bi,j} = \frac{K_B T \tau_{i,j}}{\mathrm{m}}$ where $\tau_{i,j} = \tau_i m_j + \tau_j m_i$

with $L=L_i$ and $L'=L_j$ and where the particle mean free path (λ_{pi}) is:

$$\lambda_{pi} = \frac{8 D_b(L_i)}{\pi v_i}$$

In this equation, $D_b(L_i)$ is :

$$D_b(\mathrm{L}_i) = \frac{\mathrm{K}_B T \, Cu\,(L)}{3\pi\mu_f L}$$

The thermal velocity is:

$$v_i = \sqrt{\frac{8 k_b T}{\pi m_i}} \qquad\qquad v_{i,j} = \sqrt{v_i^2 + v_j^2}$$

where, assuming spherical particles the mass (m_i) of the agglomerate can be expressed as:

$$m_i = N \frac{\pi \rho_p L_m^{\,3}}{6}$$

Where:

ρ_p is the agglomerate elemental density, N is the number of particles in the agglomerate and L_m is the diameter of primary particle (monomers)

The mass of the agglomerate is the sum of the mass of all primary particles in the agglomerate:

$$N \frac{\pi \rho_p L_m^{\,3}}{6} = \frac{\pi \rho_p L_i^{\,3}}{6}$$

Therefore, the number of particles in the agglomerate is:

$$N = \left(\frac{L_i}{L_m} \right)^3$$

Where:

L_i = the diameter of the agglomerate (mid-point of the bin). For each bin the number of particles in the agglomerate does not change over time (as the two components, L_m and L_i do not change).

The rate of particle loss through gravitational settling assuming continuous mixing is estimated as described as follows (Maynard and Zimmer, 2003).

$$\frac{dn(L_j)}{dt} = - \frac{n(L_j) v_{ts}}{h}$$

Where h is the distance from the source to the deposition surface (m) and v_{ts} is the particle settling velocity (m.s^{-1}):

$$v_{ts} = \frac{\rho_p L_i^2 g Cu(lL)}{18 \mu_f}$$

ρ_p is the particle density (1000 kg m^{-3}), = air viscosity of air (1.807 10^{-5} Pa.s at 293.15 K and 1013 hPa) and g denotes gravity (9.81 m.s^{-2})

The rate of particle loss through diffusion is estimated as:

$$\frac{dn(L_j)}{dt} = - \frac{A\, n(L_j)\, D_b(L_j)}{V\, \delta_{diff}}$$

Where V is the room volume (m^3), A is the total surface area available for deposition (e.g. walls, ceilings, floors) (m^2) and δ_{diff} = diffusion boundary layer depth at the surfaces, which is a function of particle diameter and air movement at the boundary:

$$\delta_{diff} = c\, D_b(L)$$

Where c is an empirically determined constant that is dependent on the geometry and conditions being modelled and α is expected to lie between 1/2 and 1/3 (Maynard and Zimmer, 2003). In Maynard and Zimmer's study, the values that better adjusted to the experimental data were c=0.050±0.005 m$^{1/3}$ s$^{1/3}$.and α=1/2. We also used these values.

The approach used to resolve the differential equation for the coagulation rate does not conserve the mass (i.e. the mass of the agglomerate m_k formed by particles of mass m_i and m_j does not equal $m_i + m_j$). To conserve the mass the differential equation is multiplied by the following expression:

$$\frac{m_i + m_j}{m_k}$$

Table 11 outlines the model parameters, the majority of which are dependent on the experimental conditions or the environment of the workplace.

Table 11 Summary of parameters used in the model

Abbreviation	Full name	Unit	Value
A	Surface deposition area	m^2	
D	Stokes's diffusion coefficient	$m^2\ s^{-1}$	
L, L_i, L_j	Particle diameters assumed to be the mid-point of the bin	M	
Dm	Mobility diameter	M	
h	Distance from the source to the deposition surface	M	
k_B	Boltzmann's constant	$m^2.kg.s^{-2}.K^{-1}$	$1.381\ 10^{-23}$ N m K^{-1} at T= 293.15 K and P=101.3 Pa
h	Characteristic height of the model system	M	
P	Pressure	Pa	1013 hPa
S	Particle source	$Particles.m^{-3}.s^{-1}$	
V	Room volume	m^3	
L_m	Diameter of the primary particle	M	
T	Temperature	K	293.15 K
α	Empirically determined constant	Unitless	
δ_{diff}	Diffusion boundary layer depth at the surface	M	
μ_f	Viscosity of the air	Pa.s	$\mu_f = \mu_{f_0} + \left(\frac{T_r + S}{T + S}\right)\left(\frac{T}{T_0}\right)^{3/2}$ μ_{f_0} = reference viscosity at T_r (1.708 10^{-4} Pa s) T_0 = reference temperature (273.15K) T = temperature (293.15 K) S = Sutherland constant (110.4 K, at 293.15 K and 1013 hPa, as discussed in Allen and Raabe,1985)
ρ_p	Particle density	kg m^{-3}	Assumed to be 1000 kg m^{-3}
λ_{air}	Mean free path of the air	m	$\lambda_{air} = \lambda_\circ + \left(\frac{T}{T_\circ}\right)\left(\frac{P_0}{P}\right)\left(\frac{1+S/T_\circ}{1+S/T}\right)$ λo =reference free path (λ_{air} 0.0674 × 10^{-6} m) at T_0 and P_0 T_0 = reference temperature 273.15 K T = temperature (293.15 K) P_0 = reference pressure (1013 hPa) S = Sutherland constant (110.4 K, at 293.15 K and 1013 hPa, as discussed in Allen and Raabe,1985)

Evaluation of the effect of local controls can be incorporated by adjusting the emission appropriately. Local controls can include anything from the use of glove boxes to the use of fume hoods. A local control adjustment factor, LC, is applied to the number concentration at the point of emission to allow for these controls.

$$S = S^{*} LC$$

With a current lack of knowledge of the effect of local controls on the levels of nanomaterials, it was decided to base this adjustment factor on those used in the development of the ART model (Table 12).

Table 12 Modifying factors for local controls (Fransman et al., 2011)

Type	Classification	Multiplier
No localized control	No localized control	1.0
Suppression technique	Wetting at the point of release	0.1
	Knockdown suppression	0.7
Containment- not extraction	Low level containment (loose lid or cover, which is not air tight)	0.1
	Medium level of containment (sealed process)	0.01
	High level of containment (sealed with valves and enclosed)	0.001
Local ventilation systems- Receiving hoods	Canopy hoods	0.5
	Other receiving hoods	0.2
Local ventilation systems- Capturing hoods	Fixed capturing hoods	0.1
	Movable capturing hoods	0.5
	On tool extraction	0.1
Local ventilation systems- Enclosing hoods (enclosure + LEV)	Fume hood	0.01
	Horizontal downward laminar flow booth	0.1
	Other enclosing hoods	0.1
Local ventilation systems- Other LEV	Other LEV	0.5
Glove bags and glove boxes	Glove bag (non-ventilated)	0.01
	Glove bag (ventilated or kept under negative pressure)	0.001
	Low-specification glove box	0.001
	Medium-specification glove box	0.0003
	High-specification glove box	0.0001

The I-Nano tool developed during the NANoREG project has been implemented in an easy to use tool that will be implemented in a web-based user interface. The tool is coded in MatLab. A shot-screen of the interface is shown in Figure 15. The tool allows the estimation of the GM and GMD of the concentration based on input information on emission rate, room dimensions, ventilation and local controls.

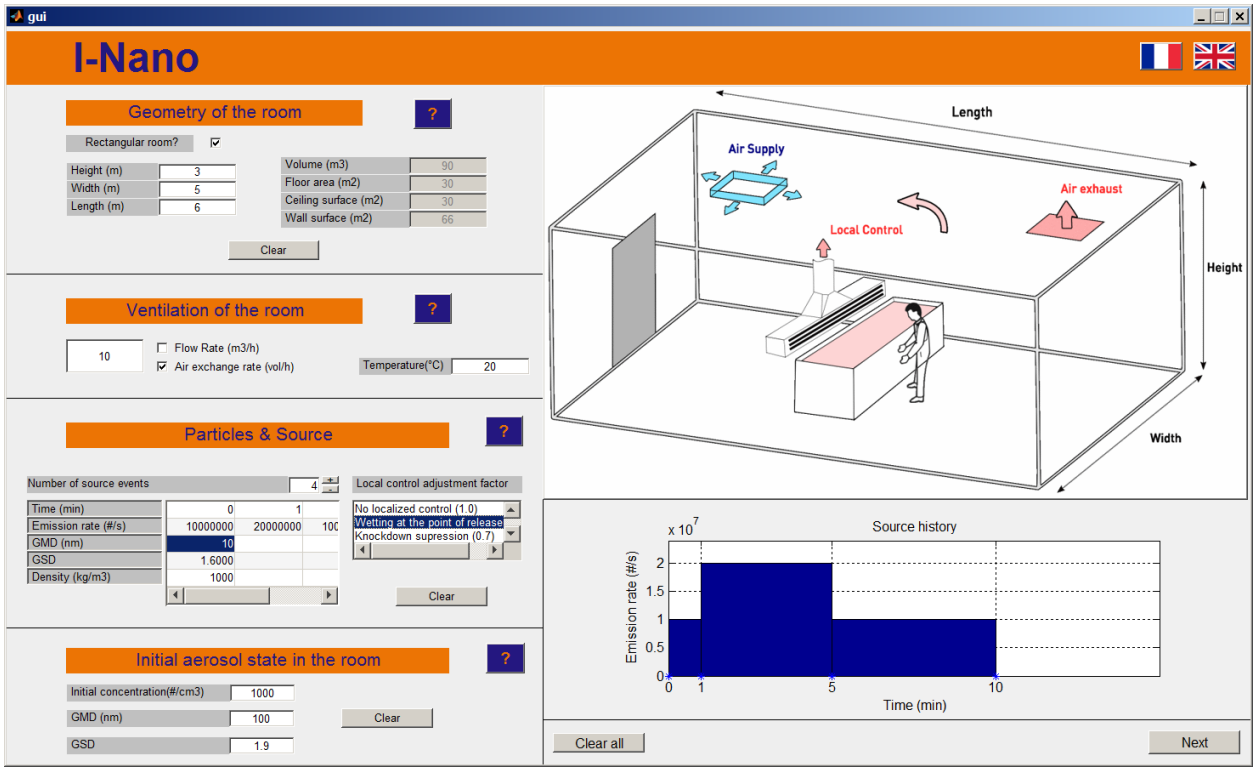


Figure 15 I-Nano tool interface incorporating the two-box nano-specific model

2.3.4 Objective 2.2 Data collection for testing and evaluation of quantitative exposure models

To test the two-box model in the I-Nano tool, a range of experiments were carried out in a large exposure chamber at DTU in Copenhagen, Denmark (March 2015). Full details of the setup of the experiment are provided in D3.4. In summary, NaCl and SiO_2 (NM-201) was aerosolised under different release conditions (constant release and burst or spikes release) in a climate-controlled room where a series of instruments (CPC, FMPS, SMPS, ELPI, NanoTracer and DiscMini) were located to capture the temporal and spatial variability of the generated aerosol. During each experiment equipment was set up at the source, NF and FF in the room, measurements were also taken at the inlet and outlet air. In this deliverable we compare the measured concentrations for the experiments (Table 13) with the modelled concentrations using the described tools. .

Table 13 Summary of the scenario characteristics

ID	Nanomaterial	ACH	Emission Type	Source rate (N/s^{-1})		Source GMD (nm)	
				Mean	SD	Mean	SD
ES3	NaCl	10	Constant Emission	3.73 E+09	3.55 E+07	29.3	0.57
ES4	NaCl	10	Constant Emission	3.73 E+09	3.55 E+07	29.3	0.57
ES6	NaCl	3.5	Constant Emission	3.73 E+09	3.55 E+07	29.3	0.57
ES7	NaCl	3.5	Constant Emission	3.73 E+09	3.55 E+07	29.3	0.57
ES8	Na-fluorescence	3.5	Constant Emission	1.59 E+09	2.13 E+07	35.3	0.37
ES9	NaCl	3.5	Seven spikes	3.73 E+09	3.55 E+07	29.3	0.57
ES10	NaCl	10	Seven spikes	3.73 E+09	3.55 E+07	29.3	0.57
ES11	NaCl + N_2O	10	Constant Emission	3.73 E+09	3.55 E+07	29.3	0.57
ES12	Na-fluorescence	3.5	Constant Emission	1.51 E+09	7.87 E+07	35.3	0.37
ES14	SiO_2 (NM-201)	3.5	Constant Emission	6.70 E+07	3.15 E+07	121.7	8.25

ACH: air exchanges per hour; GMD: Geometric Mean Diameter

2.3.5 Objective 2.3 Evaluation of the data

Tables 14 shows the mean concentrations and confidence intervals measured with the different instruments. The SD is shown in Table 15 and the GMD and GSD are shown in tables 16 and 17, respectively.

Figure 16 shows the different instrument positions.

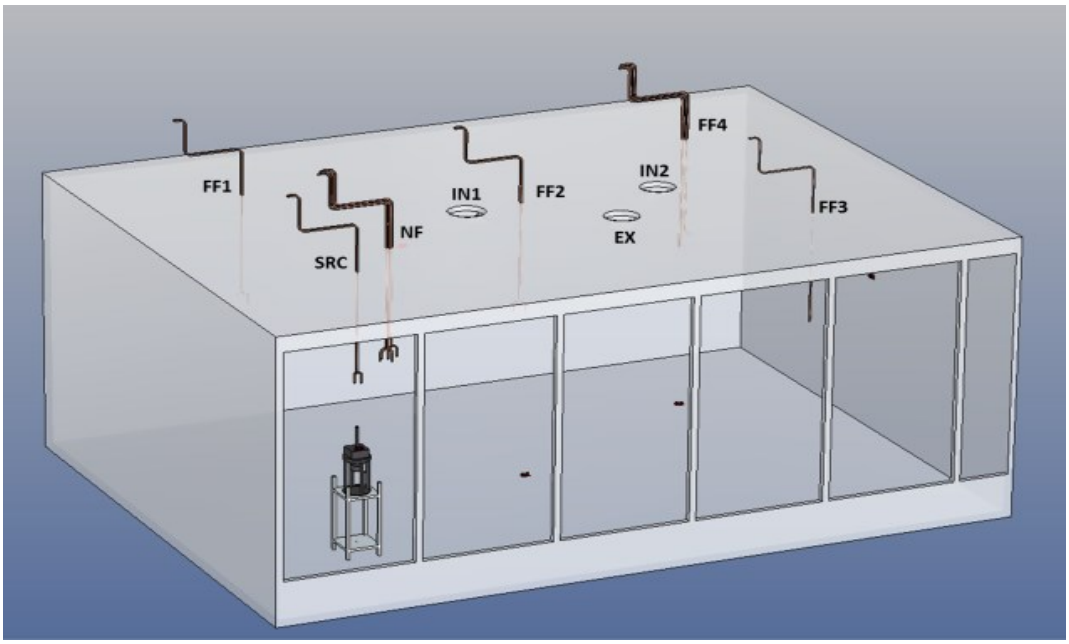


Figure 16 Schematic representation of the instrument positions. SRC : IN ; inlet (for the incoming air) source ; EX : exhaust; NF: near field exhaust; FF: far field.

Concentrations were on the range of E+04 particles cm^{-3} and which was not sufficiently high to cause coagulation between the particles. As a consequence the GMD is very similar in the NF and FF.

As expected the concentrations in the NF were higher than in the FF. FF1 showed the highest concentrations followed by FF2 (as these locations were relatively close to the source). Concentrations in FF3 and FF4 were similar and lower than those in FF1 and FF2 as they were located further away from the source.

Table 14 Mean steady-state concentrations for all stationary experiments and devices in #.cm^{-3}

	exh cpc		exh fmps		ff1 cpc		ff1 smps		ff2 cpc		ff2 fmps		ff3 cpc		ff4 cpc		ff4 discmini	
	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval
Experiment E3	-	-	1.69E+04	1.44%	-	-	2.52E+04	12.62%	1.19E+04	0.87%	1.76E+04	0.88%	1.92E+04	0.64%	1.06E+04	0.70%	1.49E+04	1.63%
Experiment E4	-	-	1.67E+04	0.91%	-	-	2.81E+04	14.43%	1.24E+04	0.73%	1.76E+04	0.64%	1.93E+04	0.53%	1.14E+04	0.43%	1.49E+04	1.38%
Experiment E6	3.81E+04	0.52%	3.45E+04	0.54%	2.37E+04	0.45%	3.36E+04	5.29%	2.51E+04	0.78%	3.54E+04	0.79%	4.83E+04	0.50%	2.48E+04	0.37%	2.59E+04	1.11%
Experiment E7	3.79E+04	0.84%	3.47E+04	0.73%	2.56E+04	0.73%	3.73E+04	8.56%	2.50E+04	1.15%	3.42E+04	1.02%	4.96E+04	0.71%	2.71E+04	0.46%	2.77E+04	1.28%
Experiment E8	9.74E+03	0.80%	9.79E+03	1.77%	1.14E+04	2.14%	-	-	6.58E+03	1.58%	1.06E+04	1.21%	9.85E+03	0.95%	6.61E+03	0.72%	8.60E+03	4.02%
Experiment E11	2.47E+04	2.73%	1.16E+04	1.82%	3.51E+03	0.81%	5.71E+03	26.25%	-	-	1.00E+04	4.12%	9.99E+03	2.89%	5.16E+03	1.26%	6.46E+03	3.30%
Experiment E12	2.34E+04	0.16%	2.21E+04	0.08%	-	-	3.09E+04	1.90%	-	-	2.95E+04	0.17%	1.79E+04	0.13%	-	-	2.11E+04	0.68%
Experiment E14	2.23E+03	0.77%	3.03E+03	0.53%	1296.236	0.41%	2.01E+03	2.72%	1568.911	0.87%	3.19E+03	0.85%	3.20E+03	0.66%	1113.941	0.83%	5.19E+02	1.29%

	ff4 elpi		ff4 fmps		in cpc		nf cpc		nf discmini		nf elpi		nf fmps		nf nsam		sf1 cpc	
	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval	Mean	Conf. Interval
Experiment E3	4.32E+04	0.29%	1.38E+04	0.45%	-	-	7.52E+04	4.69%	1.22E+05	15.88%	1.22E+05	7.49%	1.05E+05	6.12%	-	-	1.05E+05	1.55%
Experiment E4	4.35E+04	0.28%	1.38E+04	0.42%	-	-	7.00E+04	3.89%	9.74E+04	13.55%	1.01E+05	6.10%	9.29E+04	5.03%	-	-	-	-
Experiment E6	5.97E+04	0.30%	2.39E+04	0.34%	-	-	4.28E+04	0.65%	5.32E+04	2.36%	4.22E+04	0.72%	4.03E+04	0.64%	-	-	2.53E+05	0.04%
Experiment E7	6.39E+04	0.35%	2.60E+04	0.40%	-	-	4.49E+04	1.12%	5.47E+04	3.25%	4.27E+04	1.13%	4.23E+04	0.98%	-	-	2.43E+05	0.06%
Experiment E8	5.97E+04	0.44%	8.44E+03	0.70%	-	-	3.64E+04	11.28%	4.79E+04	24.12%	-	-	3.66E+04	10.53%	-	-	6.44E+04	11.90%
Experiment E11	2.49E+04	0.88%	7.73E+03	1.21%	-	-	5.08E+03	0.65%	5.62E+03	2.44%	1.91E+02	3.87%	4.38E+03	0.85%	-	-	4.07E+03	0.58%
Experiment E12	2.12E+05	0.18%	2.18E+04	0.18%	-	-	2.57E+04	0.14%	3.43E+04	0.33%	5.52E+04	0.08%	2.71E+04	0.10%	-	-	2.28E+04	0.27%
Experiment E14	2.03E+04	0.24%	2.32E+03	0.51%	-	-	2.28E+03	0.71%	7.42E+02	1.39%	5.79E+03	0.50%	3.47E+03	0.48%	-	-	2.18E+03	0.44%

Instrument positions: exh: nf: near field exhaust; ff: far field;

Type of instruments: cpc: Condensation Particle Counter; fmps: Fast Mobility Particle Sizer; smps: Scanning Mobility Particle Sizer;elpi: Electrical Low Pressure Impactor; nsam: lung-deposited Nanoparticle Surface Area Monitor;

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Table 15 Standard deviations of steady-state concentrations for all stationary experiments and devices in #.cm-3

	exh cpc		exh fmps		ff1 cpc		ff1 smps		ff2 cpc		ff2 fmps		ff3 cpc		ff4 cpc		ff4 discmini	
	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval
Experiment E3	-	-	5.27E+03	3.38%	-	-	2.00E+03	272.85%	2.16E+03	3.51%	3.35E+03	3.38%	2.47E+03	3.67%	1.51E+03	3.59%	1.61E+03	11.85%
Experiment E4	-	-	3.88E+03	2.85%	-	-	3.26E+03	187.36%	2.20E+03	2.98%	2.86E+03	2.84%	2.50E+03	2.98%	1.22E+03	2.94%	1.64E+03	9.71%
Experiment E6	7.76E+03	1.85%	7.34E+03	1.81%	4.06E+03	1.89%	3.07E+03	61.10%	7.69E+03	1.84%	1.10E+04	1.83%	9.57E+03	1.83%	3.53E+03	1.87%	3.51E+03	6.12%
Experiment E7	6.94E+03	3.35%	6.03E+03	3.05%	4.16E+03	3.27%	2.57E+03	187.36%	6.36E+03	3.29%	8.31E+03	3.04%	7.64E+03	3.34%	2.71E+03	3.36%	2.67E+03	10.31%
Experiment E8	9.40E+02	6.23%	2.37E+03	5.46%	2.68E+03	6.84%	-	-	1.09E+03	7.20%	1.75E+03	5.46%	1.10E+03	6.39%	5.50E+02	6.50%	1.47E+03	19.65%
Experiment E11	1.58E+04	3.10%	5.75E+03	2.65%	6.57E+02	3.15%	6.04E+02	528.47%	-	-	1.13E+04	2.65%	6.01E+03	3.52%	1.47E+03	3.21%	1.81E+03	9.05%
Experiment E12	2.01E+03	1.29%	1.77E+03	0.70%	-	-	2.90E+03	16.56%	-	-	5.15E+03	0.69%	1.95E+03	0.84%	-	-	4.65E+03	2.25%
Experiment E14	4.59E+02	2.70%	4.70E+02	2.46%	129.4139	2.97%	4.40E+01	187.36%	359.6129	2.75%	7.95E+02	2.46%	5.55E+02	2.76%	216.77	3.11%	6.02E+01	8.50%

	ff4 elpi		ff4 fmps		in cpc		nf cpc		nf discmini		nf elpi		nf fmps		nf nsam		sf1 cpc	
	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval	Std. Dev	Conf. Interval
Experiment E3	2.64E+03	3.45%	1.34E+03	3.38%	-	-	7.21E+04	3.58%	1.16E+05	13.21%	1.98E+05	3.39%	1.39E+05	3.38%	-	-	3.52E+04	3.38%
Experiment E4	3.09E+03	2.85%	1.49E+03	2.84%	-	-	6.77E+04	2.93%	9.80E+04	10.49%	1.57E+05	2.84%	1.19E+05	2.85%	-	-	-	-
Experiment E6	6.93E+03	1.86%	3.26E+03	1.81%	-	-	1.07E+04	1.87%	1.51E+04	6.22%	1.20E+04	1.82%	1.01E+04	1.83%	-	-	3.28E+03	1.96%
Experiment E7	5.29E+03	3.05%	2.48E+03	3.04%	-	-	1.10E+04	3.33%	1.29E+04	10.74%	1.16E+04	3.04%	9.96E+03	3.04%	-	-	3.02E+03	3.36%
Experiment E8	3.53E+03	5.53%	8.04E+02	5.47%	-	-	5.05E+04	6.11%	4.55E+04	21.53%	1.51E+02	5.45%	5.26E+04	5.45%	-	-	8.71E+04	6.62%
Experiment E11	6.00E+03	2.65%	2.56E+03	2.66%	-	-	7.74E+02	3.09%	1.16E+03	9.07%	2.02E+02	2.65%	1.02E+03	2.65%	-	-	5.48E+02	3.17%
Experiment E12	3.85E+04	0.69%	4.10E+03	0.69%	-	-	2.85E+03	0.89%	3.62E+03	2.24%	4.79E+03	0.70%	2.83E+03	0.69%	-	-	5.00E+03	0.88%
Experiment E14	1.46E+03	2.46%	3.50E+02	2.46%	-	-	4.29E+02	2.74%	9.41E+01	8.41%	8.55E+02	2.46%	4.92E+02	2.46%	-	-	2.54E+02	2.76%

Instrument positions: exh: nf: near field exhaust; ff: far field;

Type of instruments: cpc: Condensation Particle Counter; fmps: Fast Mobility Particle Sizer; smps: Scanning Mobility Particle Sizer; elpi: Electrical Low Pressure Impactor; nsam: lung-deposited Nanoparticle Surface Area Monitor.

Table 16 mean GMD (nm) measured by the various granulometers in steady-state for stationary experiments

	exh fmps		ff1 smps		ff2 fmps		ff4 elpi		ff4 fmps		nf elpi		nf fmps	
	mean	std. dev.	mean	std. dev.	mean	std. dev.	mean	std. dev.	mean	std. dev.	mean	std. dev.	mean	std. dev.
Experiment E3	36.5	0.7	36.3	1.7	-	-	29.0	1.1	37.4	0.6	30.0	1.5	35.0	3.5
Experiment E4	36.5	0.5	36.9	1.6	-	-	28.8	1.1	37.2	0.8	30.8	1.3	35.2	3.4
Experiment E6	42.0	0.6	43.0	1.5	40.6	0.9	38.3	1.3	43.0	0.6	39.4	1.1	41.5	0.9
Experiment E7	42.6	0.5	41.8	1.3	41.3	0.8	38.5	1.2	43.4	0.5	41.5	1.0	42.0	0.9
Experiment E8	51.7	1.0	-	-	49.6	1.6	20.8	0.6	52.0	1.2	-	-	50.4	5.6
Experiment E11	33.4	1.0	33.1	0.7	-	-	25.6	1.9	34.3	0.9	-	-	33.8	1.2
Experiment E12	57.6	1.1	59.9	1.6	-	-	17.1	1.1	57.6	1.8	28.3	0.5	55.9	1.0
Experiment E14	117.9	6.5	136.2	3.3	-	-	28.9	2.7	115.6	10.7	90.9	10.0	106.0	7.0

Table 17 mean GSD measured by the various granulometers in steady-state for stationary experiments

	exh fmps		ff1 smps		ff2 fmps		ff4 elpi		ff4 fmps		nf elpi		nf fmps	
	mean	std. dev.	mean	std. dev.	mean	std. dev.	mean	std. dev.	mean	std. dev.	mean	std. dev.	mean	std. dev.
Experiment E3	1.70	0.02	1.72	0.03	-	-	2.56	0.02	1.71	0.02	2.59	0.07	1.74	0.11
Experiment E4	1.69	0.01	1.70	0.01	-	-	2.56	0.02	1.71	0.04	2.67	0.07	1.73	0.11
Experiment E6	1.68	0.02	1.71	0.03	1.67	0.04	2.57	0.04	1.68	0.02	2.82	0.02	1.67	0.04
Experiment E7	1.68	0.02	1.72	0.01	1.66	0.03	2.59	0.03	1.68	0.02	2.85	0.02	1.67	0.03
Experiment E8	1.64	0.03	-	-	1.67	0.06	2.49	0.02	1.69	0.04	-	-	1.72	0.19
Experiment E11	1.71	0.03	1.71	0.02	-	-	2.55	0.02	1.70	0.03	-	-	1.70	0.04
Experiment E12	1.72	0.04	1.80	0.03	-	-	2.27	0.07	1.70	0.06	2.79	0.06	1.68	0.03
Experiment E14	1.82	0.16	2.02	0.03	-	-	3.02	0.03	1.98	0.27	2.50	0.29	1.86	0.18

Instrument positions: exh: nf: near field exhaust; ff: far field;

Type of instruments: cpc: Condensation Particle Counter; fmps: Fast Mobility Particle Sizer; smps: Scanning Mobility Particle Sizer; elpi: Electrical Low Pressure Impactor; nsam: lung-deposited Nanoparticle Surface Area Monitor.

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2.3.6 Objective 2.4 Evaluation of the I-Nano Tool

Figures 17 to 20 show the time series plot of the modelled and measured data collected with the condensation particle counter (CPC) size range 10 nm to 1 µm for ES3 (Figure 17); ES4 (Figure 18), ES6 (Figure 19) and ES7 (Figure 20). Note that the NF is called LCIZ as described in the model in section 2.3.7

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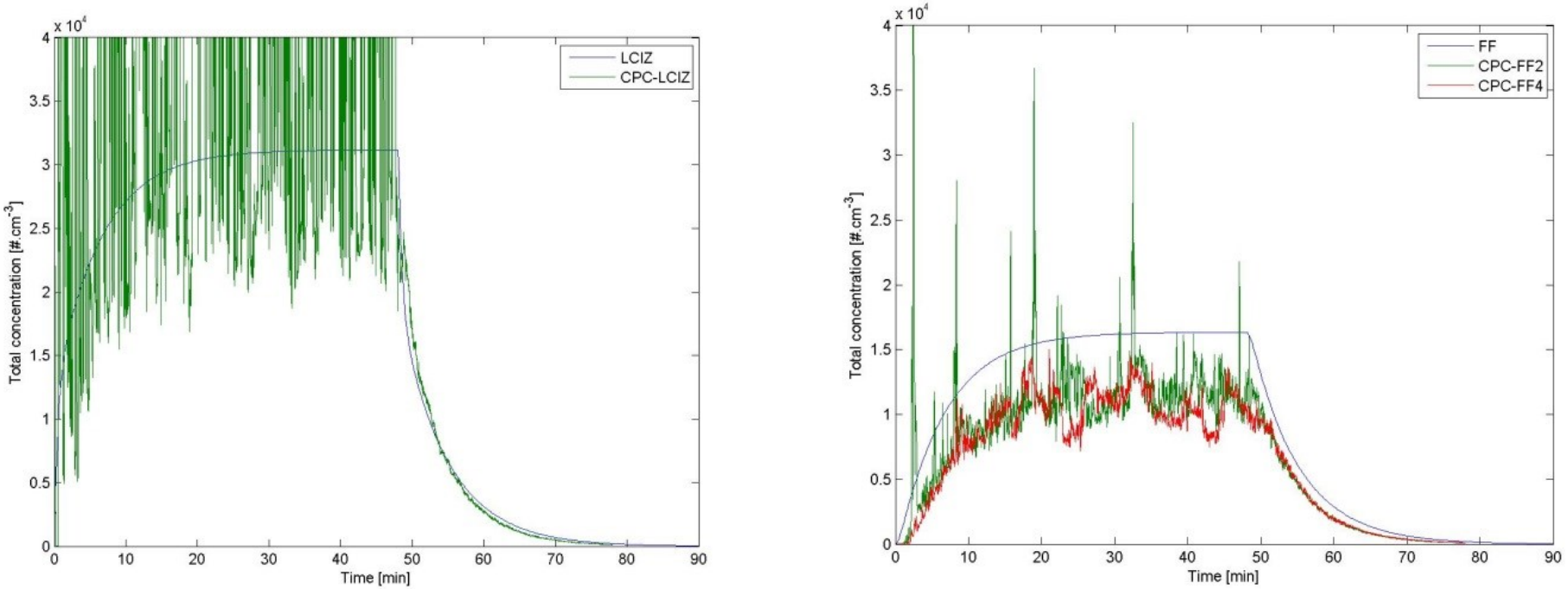

Figure 17 I-Nano modelled vs measured data for ES3 (Source nano NaCl; ACR:10)

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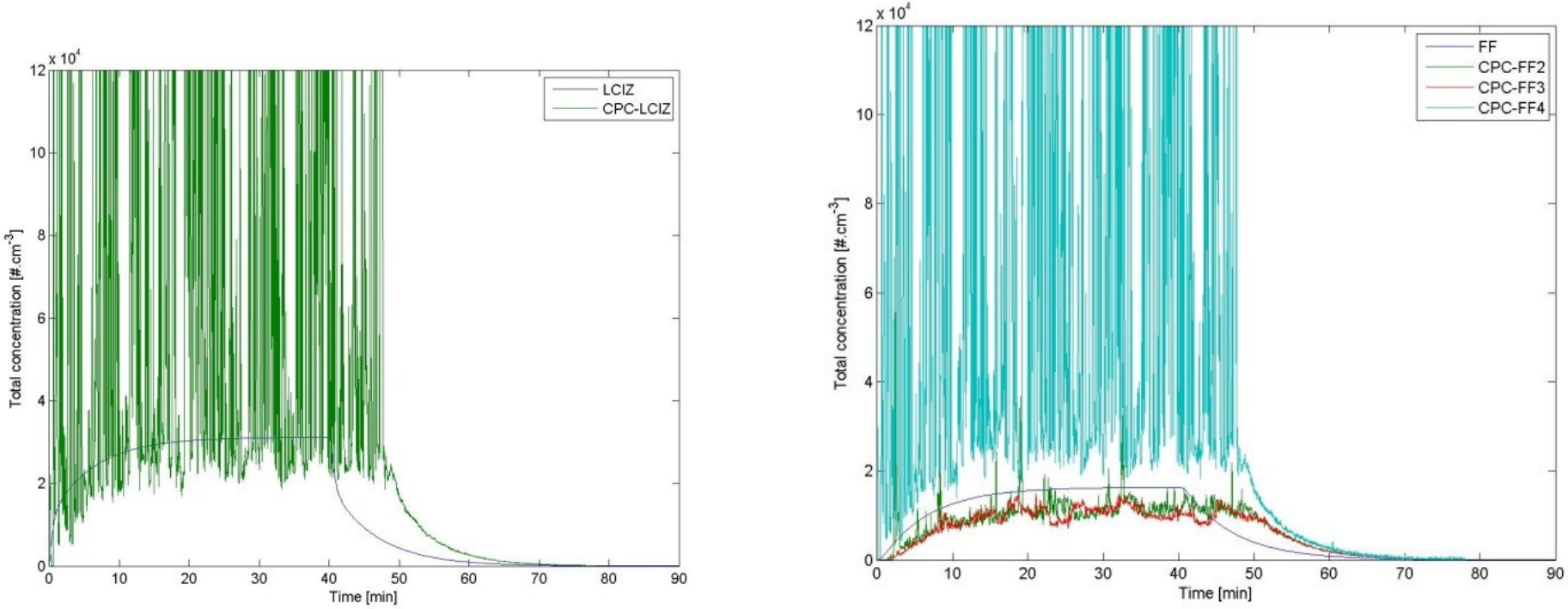

Figure 18 I-Nano modelled vs measured data for ES4 (Source nano NaCl; ACR:10)

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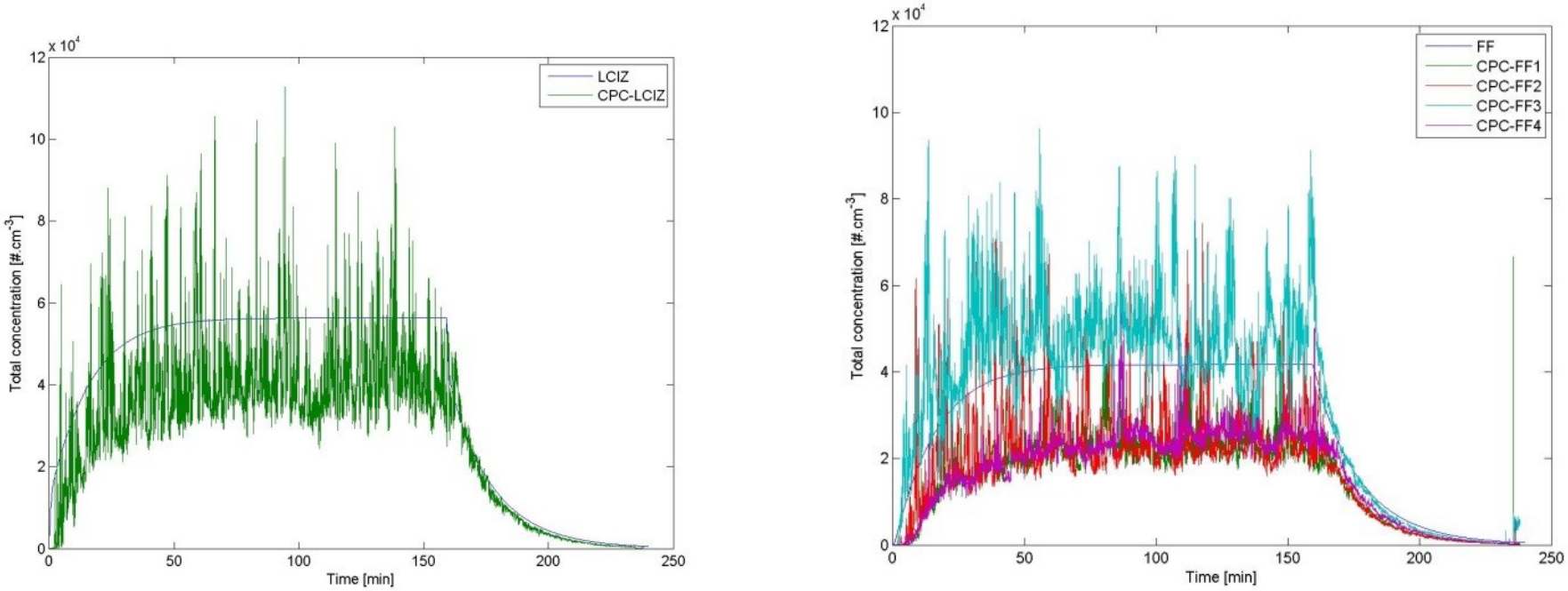

Figure 19 I-Nano modelled vs measured data for ES6 (Source nano NaCl; ACR:10)

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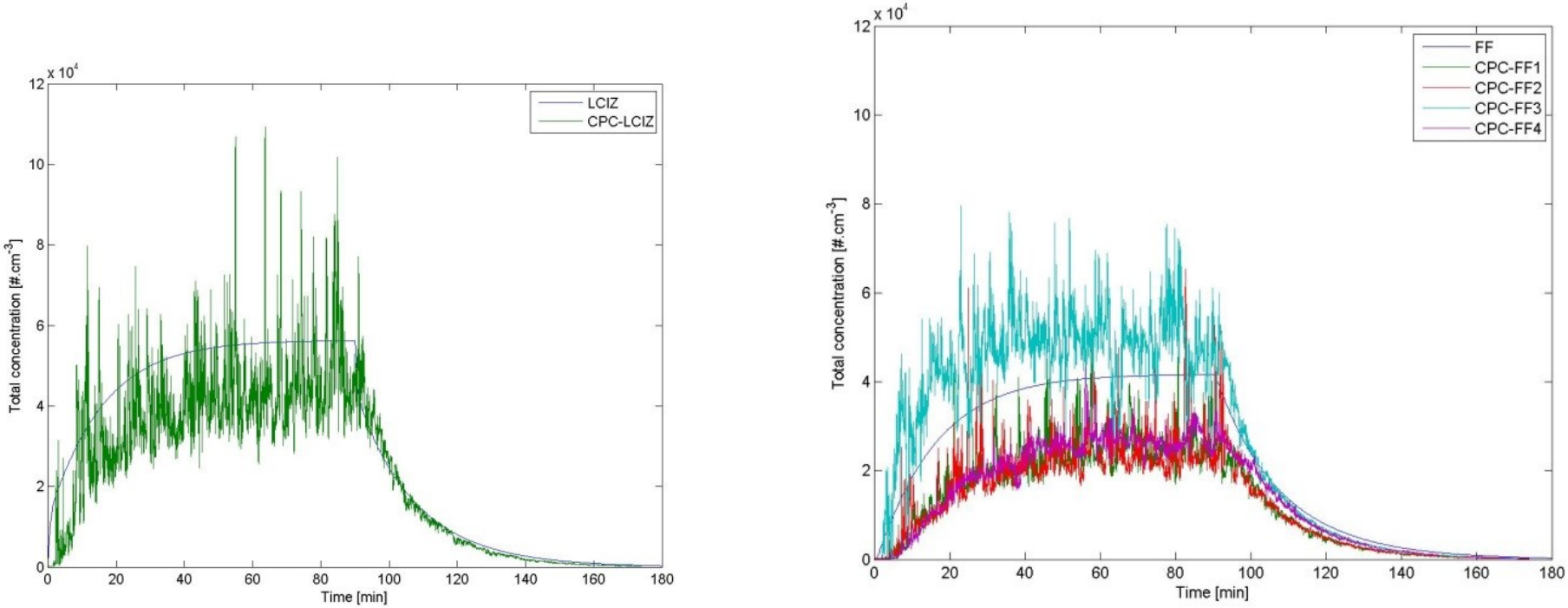

Figure 20 I-Nano modelled vs measured data for ES7 (Source nano NaCl; ACR:10)

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The model predicted reasonably well the time evolution of the concentrations in the LCIZ and FF for all the scenarios. In general concentrations were slightly overestimated which is the desirable model's performance for a conservative approach.

The variability on the measured data compared to the modelled data is partly due to the difference in the resolution between the measured and modelled concentration time-series; for the modelled concentrations we obtained an estimate every ten seconds while the resolution of the measured data is 1 second. In addition the source might have been less stable than originally thought as once the source stops (around 100 mins) the variability is considerably reduced.

Measured data for the LCIZ and FF4 in ES4 was very unstable and this is thought to be related to the instrument performance. The CPC contains a condensation tube where particles condense with the water and grow to a size that can be counted using optical methods. If the instrument runs out of water or the tube becomes dry the counting efficiency decreased.

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2.4 Evaluation and conclusions

Inhalation exposure assessment of MNM using measurements is challenging because of the temporal and spatial variations nanoparticles may undergo from emission until they reach the breathing zone of the worker. These changes affect the particle number and mass concentration as well as the PSD and the assessment requires the use or personal monitors. However, because of the different physical principles used to measure particles in the nano and micron rage there is not a single monitor that covers from the nano range up to the respirable fraction, which is the recommended health relevant fraction that should be covered for risk assessment. Exposure modelling, particularly when combined with exposure measurement data, can be a useful tool for risk assessment and risk management by enabling prediction of exposures using information about emission and the conditions of the workplace that affect particle dynamics.

This deliverable has reviewed and tested a number of the exposure models that can be used for MNM either for qualitative or quantitative risk assessment. The qualitative models are simple and straightforward to use and they have been made available through easy to use web tools. However, a literature of their performance revealed that the models have not actually been demonstrated with field data and the few studies that have looked at their performance acknowledge that the outputs have to be considered with care.

The dataset collected in a chamber room and presented in D3.4 have allowed us to investigate the performance of the new I-Nano tool in terms of temporal and spatial resolution (NF and various FF positions) under different source emission and ventilation conditions.

The measurements collected at multiple FF points have allowed us to estimate how different the FF concentrations at the different locations differed from each other and whether the single modelled FF concentration is justified for using in these scenarios.

The different source emission types (constant and burst/spike) as well as the different ventilation conditions allowed us to explore the sensitivity of these models to changes in those variables and adds information on Q11 on the determinants of occupational exposure and Q12 on the how data should be collected for model input.

The predictions from the I-Nano two box model compared well with the measured data collected in the 'purpose build' simulation study. Concentrations in some of the FF locations were overestimated for some scenarios but overall the model appeared to be reliable at least within this experimental set-up.

Unfortunately the concentrations achieved where not sufficiently high to cause coagulation between the released nanoparticles and therefore the model has not been demonstrated for their sensitivity to pick up changes in the PSD over time.

The two main input variables for the models are the ventilation and the source emission. Based on the results from the experiment and modelling, ventilation is an important determinant on the concentration. Therefore, information on the ventilation rates should always be recorded in occupational hygiene surveys.

The model has been demonstrated under controlled conditions, with aerosols largely based on spherical particles and therefore although initial correlation is good, the model would need to be further tested in real workplace environments and with different types of nanoparticles (e.g. fibres, platelets).The field measurements collected as part of NANoREG could not be used for such validation as they did not include data on the emission rates which the model required. Finally models are not easy to use as they required knowledge of the mathematical programs they have been coded in (usually MatLab or R). They have to be implemented in easy-to use web-based interfaces. The I-Nano two-box model has been implemented in a friendly web based interface which will be made available in early 2017.

2.5 Data management

The data collected as part of this task for the testing and evaluation of exposure models is stored in a database in MatLab. The data will be made publicly available as part of a set of peer-reviewed publications that will be prepared.

3 Deviations from the work plan

There are no deviations from the work plan.

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Annexes 1 Exposure Scenario Template for the inter-user variability study

Contributing Exposure Scenario for Uses Of Substances By Workers (CES-1)

PLEASE READ THE GUIDELINES BEFORE COMPLETING THIS FORM

Quality of the exposure scenario data	Description (free text)	Select from the drop down list
Contextual information		High
Measurement data		High
Description of the contributing scenario	**Description (free text)**	**Select from the drop down list**
Name of the contributing scenario	Generation of NanoCoAl2O4 particles by pyrolysis	**Other**
Description of tasks	Nano particles are created using pyrolysis in a closed system.	
Product characteristics	**Description (free text)**	**Select from the drop down list**
Type of product		Not apply (pure NM)
Product (brand) name		
Fraction or concentration of the NOAA in the product		
Substance characteristics	**Description (free text)**	**Select from the drop down list**
Type of substance		Not apply (pure NM)
Name of the NOAA(s) used	$CoAl_2O_4$	Other
CAS Registration number		
Physical state of the NOAA or the substance containing the NOAA that you are handling at 20 °C and 101,3 kPa		Powder
Primary particle size (nm) (crystallite size)	60	40-100 nm
Mean particle size of the bulk NOAA (nm)	30	11-40 nm
Shape of the NOAA		Spherical
Surface area of the NOAA (m^2 g^{-1})		
Density of the NOAA (kg m^{-3})	4200	
Type of density		
Substance emission potential of the NOAA or product-containing NOAA:		High
If a mixture is being used, or the NOAA is contained in a substance (i.e. suspension, paste) what concentration of NOAA is present in the mixture/substance?		
Activity emission potential	**Description (free text)**	**Select from the drop down list**
Describe the activity in terms of the energy applied to the process		Very high
Amount of NM or product-containing NM used during the CES?	ENM is generated in the process typically 1.4-2kghr^{-1}	1-5kg
Temperature at which the process is carried out	1000oC	
Presence of a secondary source of non-engineered nanomaterials (e.g release from the equipment used, or other substances used in the process)	Combustion by products (Fuel and solvent)	
Technical conditions and measures at process level (source) to prevent release	**Description (free text)**	**Select from the drop down list**
Process design aiming to prevent releases and hence exposure of workers: level of containment	Largely enclosed and ventilated unit during production and separation (from the air stream) and collection of the nanomaterial produced. Insulation at quenching zone and HEPA filter at harvesting zone. The unit is open during the removal of collected product at the harvesting zone.	**Semi-enclosed (e.g. fume cupboard)**
Effectiveness of containment to be specified (e.g. by quantification of residual losses or exposure)	High during operation and low during harvesting	
Is the workder located in a cabin?	No	
Automation level	The pyrolysis system is largely enclosed. The worker operates a control panel next to the plant furnace and manually removes the receptacle collecting the nanoparticles	Semi automatic

Technical conditions and measures to control dispersion from source towards the worker	Description (free text)	Select from the drop down list
Type of local ventilation (at the source)	Reactor is under negative pressure and exiting air is filtered	Enclosing hood
Efficiency of the local ventilation		High
Room conditions	**Description (free text)**	**Select from the drop down list**
Is the process carried out in the inodoor or outdoor environment?		Indoor
Room volume (m^3)	1008	> 1000 m3 (e.g. warehouse)
Room temperature (°C)	27	
Room pressure (Pa)	Unknown but negative	
Room relative humidity (%)	44	
Type of general ventilation		Mechanical dilution ventilation (incoming and outgoing air)
Air exchanges per hour (h^{-1})	10	
Other given operational conditions affecting workers exposure	**Description (free text)**	
For example technology or process techniques determining the initial release of substance from process into workers environment; (via air and waste water); dry or water based processes; (e.g. spray technique), machinery design (e.g. feeder type)	This is largely a dry process with a liquid feed syphonedd in to the furnace from an open bin. The unit is enclosed, under negative pressure and the quenching zone is covered with an insulating blanket. A reverse flow filtration system is used on the screens in the product recovery hopper and the product is filtered and collected in an enclosed drum. The drum is removed from the delivery spout to be emptied or closed and the spout can be sealed with a small jar during any product transfer	
Organisational measures to prevent /limit releases, dispersion and exposure	**Description (free text)**	
Frequency of the cleaning of the working area	Once per day (premises washed and pyrolysis unit is flushed after each production run). Wet Cleaning	
Frequency of the maintenance of the engineering controls and ventilation system.	As required	
Conditions and measures related to personal protection, hygiene and health evaluation	**Description (free text)**	**Select from the drop down list**
Type of personal protection equipment (PPE) e.g. type of gloves, face protection, type of coveralls, type of eye protection	Nitrile disposable gloves, lab coat, full face respirator (combination filter dust P3 and gases, disposable). E.g. full face respirator (3M 6099 with a combination filter for dusts and gases). Disposable masks (1730 Climax FFP3NR) are issued to factory visitors and worn by relief worker, when covering the plant.	
Level of effectiveness of the PPE		High
Were the workers wearing respiratory protection equipment (RPE)? If yes, explain what type.		Respirator / Full face mask, particle filter (P3)
Exposure	**Description (free text)**	**Select from the drop down list**
Duration of the activity/process		3-6 hrs
Time the worker spends in direct contact with the ENM or product-containing ENM (in the same room/working area)	The process is semi automatic the worker may only have direct contact when harvesting the material.	1-15 minutes
Exposure pattern		Intermittent
Frequency of the activity (e.g. number of times the task/activity is done a week/month/year)		1 day a week
Distance from the source to the breathing zone of the worker (m)	Two possible sources of inhalation exposure, leakage from the pyrolysis unit and during harvesting of the ENM.	1-2 m