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Evaluation of Tools and Models for Assessing Occupational and Consumer Exposure to Manufactured Nanomaterials – Part II: Performance testing results of tools/models for occupational exposure

Project: Assessing the Global Readiness of Regulatory and Non-regulatory Models for Assessing Occupational Exposure to Manufactured Nanomaterials

**Series on Testing and Assessment,
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SERIES ON TESTING AND ASSESSMENT

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INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
Paris 2021

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Objective

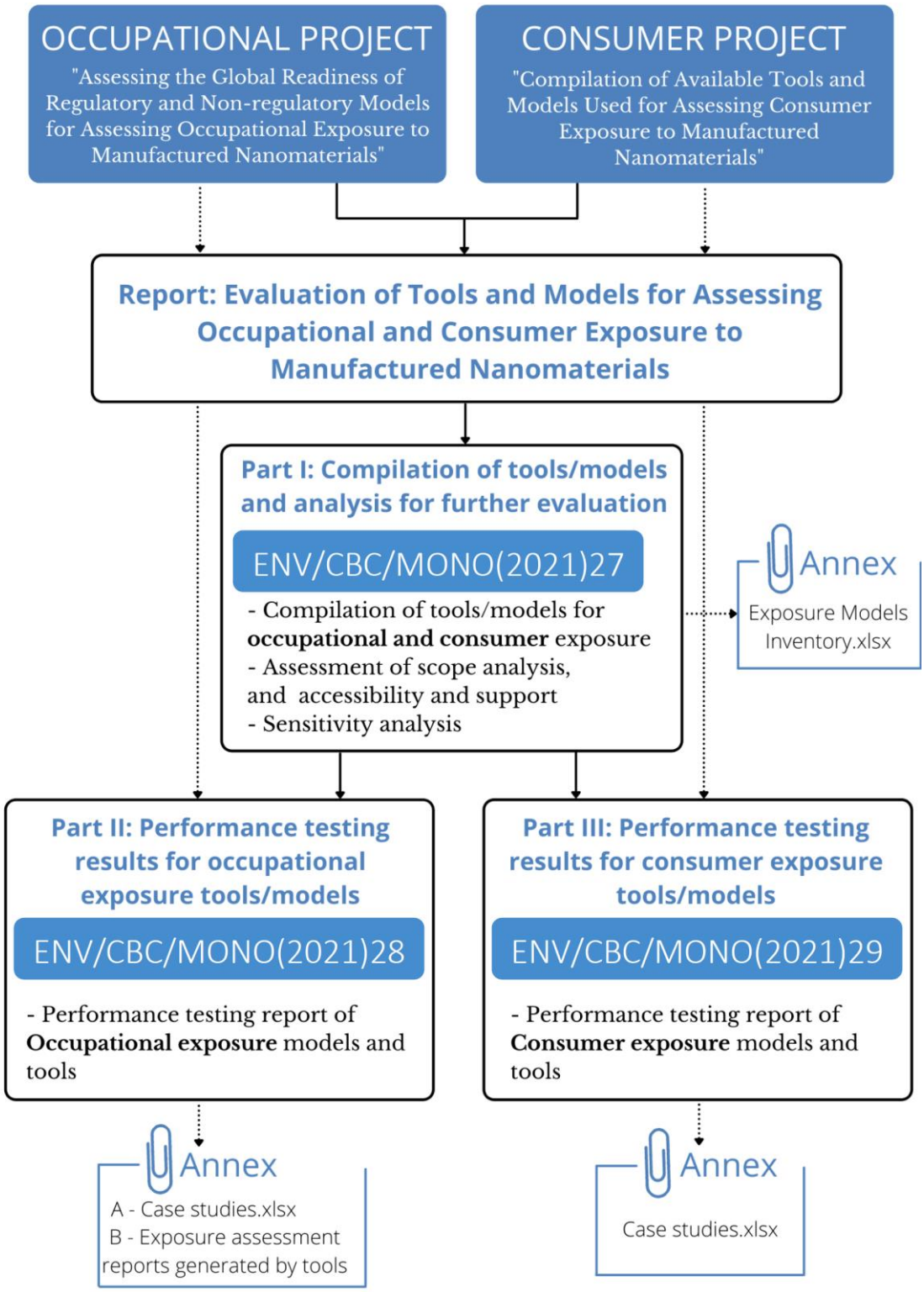
1. The objective of this report is to conduct a performance testing assessment of the occupational exposure assessment tools selected in the ENV/CBC/MONO(2021)27 report for its application to manufactured nanomaterials.

Design

2. The report assess the performance testing of a total of 15 tools (10 nanospecific and 5 conventional chemical tools ECHA recommended) for its use for exposure assessment of nanomaterials in occupational environments. First, measurement data on occupational exposure to nanomaterials suitable for performance testing was collected. A total of 126 cases were collected. A score (0-1) regarding the quality of the data was calculated for each case in order to use the cases with a highest score for performance testing. The performance testing consisted in comparing the tools output with experimentally measured exposure levels. For each tool, a minimum of 25 comparisons were conducted when possible. The general strategy for the assessment of the performance testing was to look at the Spearman correlation between output and measured exposure as well as quantify the percentage of underestimation. The tools were considered adequate for the assessment of nanomaterials in occupational environments when Spearman correlation was higher than 0.6 and the real measurement concentrations do not exceed the model estimates for more than 10% of the total comparisons.

Report description

3. This report contains the performance testing results of the selected tools after assessment of scope, accessibility and support, and sensitivity analysis (data reported in the ENV/CBC/MONO(2021)27 report). From the first initial list, which included 23 occupational exposure assessment tools (13 nanospecific and 10 conventional chemical tools), 15 were assessed for performance testing (10 nanospecific and 5 conventional tools for chemicals mentioned in ECHA guidance; hereafter denoted ECHA recommended). This report includes 1) results from the performance testing, 2) scenario-specific measurement data inventory named “Annex A – Case studies.xlsx”, and 3) original reports containing exposure assessment results for each of the assessed tools (Annex B).


OCCUPATIONAL PROJECT
"Assessing the Global Readiness of Regulatory and Non-regulatory Models for Assessing Occupational Exposure to Manufactured Nanomaterials"
CONSUMER PROJECT
"Compilation of Available Tools and Models Used for Assessing Consumer Exposure to Manufactured Nanomaterials"
Report: Evaluation of Tools and Models for Assessing Occupational and Consumer Exposure to Manufactured Nanomaterials
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ENV/CBC/MONO(2021)27
- Compilation of tools/models for occupational and consumer exposure
- Assessment of scope analysis, and accessibility and support
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Exposure Models Inventory.xlsx
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Case studies.xlsx

Executive summary

4. This report contains the results of the performance testing of 15 exposure assessment tools (10 nanospecific and 5 conventional chemical tools ECHA recommended) for its use for exposure assessment of nanomaterials in occupational environments. The selection of the 15 tools was based in the assessment of scope, accessibility and support, and sensitivity analysis (data reported in the ENV/CBC/MONO(2021)27 report). From the initial list of 23 tools/models assessed for scope, accessibility and support, and sensitivity analysis, and reported in the Joint report, 15 tools were selected for further performance testing assessment. The tools are: ISO/TS 12901-2:2014 CB nanotool v1.0 (Part 2), BIORIMA Occupational exposure section, RISKOFDERM, MEASE2 2.0, EMKG Expo tool 2.0, Stoffenmanager 8.3, Stoffenmanager nano v1.0, ENAE-CPSC model v1.0, LiCARA nanoSCAN v1.0, NanoSafer v1.1β, GUIDEnano, SUNDS, Swiss Precautionary matrix v3.0, ConsExpo nano 2.0 and Advanced REACH tool v1.5. The tools assessed are categorized as control banding, risk management, risk-benefit, risk assessment, risk categorization and quantitative exposure assessment.

5. For performance testing, the tool's outputs were compared to real measurement data. Thus, measurement data on occupational exposure to nanomaterials suitable for performance testing was collected through literature review, generated in EU projects as well as from an OECD call. A total of 126 cases were collected described in detail in "*Annex A* – Case studies.xlsx". The measurement data were graded for quality, and a score ranging from 0 to 1 was assigned to each case according to different parameters related to the relevance, reliability (quality of the exposure assessment) and completeness of the parameters required for the tools/models. A summary of the parameters used can be found in Appendix II-Table II.1. Detailed description of the parameters used as well as grading of the tools are provided in "*Annex A* – Case studies.xlsx". For the performance testing, cases with what was considered and acceptable quality scores were prioritized (≥ 0.7). The cases used for performance testing were aligned to the possible extent. However, due to the models having different input requirements a complete alignment of the cases used was not possible. The performance testing consisted in comparing the tools output with the experimentally measured exposure levels. For each tool, a minimum of 25 comparisons were conducted with the exception of RISKOFDERM, ConsExpo and LiCARA nanoSCAN due to the lack of case studies available on the tool specific domain and/or the tools characteristics. The general strategy for the assessment of the performance testing was to look at the Spearman correlation between output and measured exposure as well as quantify the percentage of underestimation. The tools were considered adequate for the assessment of nanomaterials in occupation environments when Spearman correlation was higher than 0.6 and they did not underestimate measured exposure in more than 10% of the comparisons (hereafter denoted underprediction).

6. From the 15 assessed tools, 8 of the nanospecific tools complied with the two main criteria established in this work (Spearman correlation > 0.6 and underprediction < 10% of the total comparisons). These tools are BIORIMA, Stoffenmamanger nano, ENAE-CPSC, LiCARA nanoSCAN, NanoSafer, GUIDEnano, Swiss Precautionary matrix and ConsExpo nano. However, it is important to note that for most of the tools, even though considered suitable, there are several aspects that need to be considered when using them. On the other hand, the 5 conventional chemical ECHA recommended tools did not fully comply with the established requirements.

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TABLES

1. Introduction

7. The aim of the OECD WPMN Project "Assessing the global readiness of regulatory and non-regulatory models for assessing occupational exposure to manufactured nanomaterials" is to assess the global readiness of existing regulatory tools (tools that recommended and included in accepted guidelines by regulatory authorities), and nanospecific non-regulatory models for assessing occupational exposure to manufactured nanomaterials (MNMs) in occupational environments. The ultimate objective is to understand to what extent different existing models are applicable and suitable for exposure assessment of MNMs in occupational environments. Currently, at European level, only tools which were not designed taking into consideration MNMs specificities, not tested, and nor calibrated and validated are recommended in guidance documents by the European Chemicals Agency (ECHA). In Liguori et al., (2016[1]) three main differences were identified between conventional and NOAA exposure and risk assessment tools: 1) the use of nano-specific Occupational Exposure Limits (OELs) or No Observed (Adverse) Effect Levels (NO(A)ELs), 2) chemical and physical characteristics of nanoparticles and released fragments and, 3) exposure scenarios and emission classes for nanomaterials and nano-enabled products (NEPs). Thus, the assessment of the performance of both types of models (nano-specific and conventional chemical) for exposure assessment of MNMs in occupational environments is paramount.

8. The performance testing results of the 15 tools (10 nanospecific and 5 existing conventional chemical tools – ECHA recommended) presented in this report are the culmination of several steps, which are detailed below:

i. Extensive compilation of tools and models for further evaluation through literature review, outcomes from recent international projects and inventories and consultation with WPMN member countries. The inventory is provided in the Excel file "*Annex – Exposure Models Inventory.xlsx"* of the ENV/CBC/MONO(2021)27 report.
ii. Identification of requirements and criteria for the assessment of risk- and exposure assessment tools/models for their readiness and potential use for occupational exposure assessment of MNMs.
iii. Creation of an inventory with high quality scenario-specific measurement data of occupational exposure to MNMs. The inventory is provided in the Annex A – Excel file *"Case studies.xlsx*".
iv. Evaluation of scope analysis, application domains, user-friendliness and sensitivity testing of the models, and selection of tools for performance testing. This evaluation is reported in the document ENV/CBC/MONO(2021)27.
v. Performance testing: evaluation of the predictive capability of the selected models/tools by comparing the modelling results with observations (real data) made in actual exposure scenarios.
vi. Final recommendation of tools for qualitative (Tier 1), semi-quantitative (Tier 2) and quantitative (Tier 3) assessment of MNM in occupational environments considering scope, application domain and output format required for purposes ranging from industrial risk management to regulatory exposure assessment.

9. These activities had direct collaboration with the EU H2020 caLIBRAte Project in regards to mapping of input/output parameters, sensitivity and performance testing of human risk assessment (HRA) models designed for MNMs.

2. Performance testing methods

10. The quality of a model simulation usually depends on two aspects: i) the appropriateness of the model describing release and transport of the generated aerosol (aim of the performance test), and ii) the precision of the input values that are derived from the exposure scenario descriptions. The second aspect enters as parameter uncertainty and has to be accounted for in order to be able to evaluate the degree of correspondence between model and exposure scenario.

11. A model accuracy and precision can be assessed by modelling measured exposure scenarios and comparing the model outcomes with the measurement data (Lamb et al., 2015[2]; Landberg et al., 2015[3]; Landberg et al., 2017[4]; Spinazzè et al., 2017[5]; van Tongeren et al., 2017[6]; Dunn et al., 2018[7]). The resulting model output values in form of exposure concentration can be compared to the experimental results and see how well the model performs in relation to real situation. Therefore, performance testing requires high quality measurement data with comprehensive contextual information suitable to cover the parameters requested by the occupational exposure models (see e.g. (Koivisto et al., 2018[8]; Ribalta et al., 2019[9])).

12. The aim of this section is to present an overview of the requirements and methodology behind the performance testing implemented in this OECD WPMN project. The approach used to assess the measurement data quality, testing criteria and procedure for performance testing used will be described.

2.1. Performance testing criteria and procedure

13. The tools and models considered form a very heterogeneous group (Table 1). Therefore, obtaining a unified dataset and performance testing procedure cannot be achieved with the currently available scientific data corpus. In the course of the work it was agreed that the testing procedure would be conducted with the following principles:

- Testing shall be done with the intended purpose of each tool.
- Modelled output (respirable dust, number concentration predictive values etc.) vs. real data.
- The data grading for confidence in performance testing of “HRA” should follow:
    1. Personal exposure measurement data (substance-specific respirable dust, particle number concentration).
    2. Personal exposure measurement data (non-substance-specific respirable dust, particle number concentration).
    3. Stationary exposure measurement data in NF (substance-specific respirable dust, particle number concentration).
    4. Stationary exposure measurement data in NF (non-substance-specific respirable dust, particle number concentration).
    5. Stationary calculated respirable dust concentrations in NF.
- Follow (if possible) the existing minimum criteria to assess the model/tool prediction (adapted from (Fransman, Marquart and le Feber, 2009[10])):

a A minimum of 25 exposure measurements are conducted and compared to the model outcome.

b Definitions of application domains. The application domain is known as well as which processes and substances, the model is suitable for (and which processes and substances, the model is not suitable for).

c The exposure situations, for which exposure measurements are conducted, are widely spread over the applicability domain of the model.

d The spearman correlation coefficient, which measures the rank correlation between model/tool estimates and measured exposure values is at least 0.6.

e Exposure measurements are not clearly and consistently higher than the model estimates in any domain.

f The tool estimates a reasonable worst case, which represents the upper side of occurring exposure values.

g Real measurements do not exceed the model estimates for more than 10% of the total comparisons.

h Evaluation is done separately for solids, liquids and/or gases/fumes whenever possible.

14. The performance testing procedure included parameterization of input values, running the models, recording the model outputs, and analysing the output data. Whenever it was possible, each tool was evaluated by one expert and afterwards, randomly selected cases were assessed for model parametrisation agreement with a second expert. If no issues were encountered, performance testing of the tool was considered acceptable. Conversely, if major disagreements occurred between experts a consensus was reached and if necessary a third expert was consulted.

15. The general strategy for performance testing consisted in comparing output with experimentally measured exposure levels in particle mass or number concentrations preferably background (BG) corrected, substance-specific respirable dust mass concentrations, and representative to the breathing zone of the person/worker. In case such data is not available in a particular scenario, measured respirable mass concentrations not background corrected, non-substance-specific and taken in near field (NF) by using stationary equipment were also considered but more careful interpretation of results should be taken. The model results (e.g. exposure band, or quantitative particle concentrations) were afterwards correlated with the real data (exposure: mass and/or number - preferably mass since most of the occupational exposure tools and models address this particle metric). The Spearman correlation coefficient to determine whether and to what extent the model estimations correlates with real measurement/test values were calculated. Finally, the overall performance of the assessed tool according to the minimum criteria to evaluate the model/tool prediction was discussed. If there are cautions to be provided for specific application domains or conditions that could not be tested, which may be of importance in regards to the reliability of the modeled outcome, were clearly noted.

16. For BIORIMA, ENAE-CPSC and NanoSafer tools a multiplier for the control measures used in all the exposure scenarios was applied to the tool output. This was done by following the Exposure Control Efficacy Library ECEL v3.0 and by applying the provided effectiveness median of high quality studies. Values used for each case scenario are fully described in "*Annex A* – Case studies.xlsx". ENAE-CPSC and NanoSafer do not have the option to introduce reduction due to local controls (LC). BIORIMA does have a separate option, which is based on the ECEL v3.0 library, thus in order to align the LC applied for the three models, the reductions due to the LCs in place in the BIORIMA were also conducted outside of the tool.

17. The work conducted for this OECD WPMN project is the result of a collaboration with EU H2020 caLIBRAte Project (https://cordis.europa.eu/project/id/686239). Work was conducted as summarized in Table 1.

Table 1. List of tested models. Category 1 (nanospecific), category 2 (conventional chemical ECHA recommended tools).

Nº	Model	Model type	Project
1	ISO/TS 12901-2:2014 CB nanotool v1.0 (Part 2)	Category 1	caLIBRAte
2	BIORIMA Risk assessment and risk control module (Occupational exposure section)	Category 1	OECD
3	Stoffenmanager nano v1.0	Category 1	caLIBRAte
4	Engineered Nanoparticle Airborne Exposure (CPSC ENP Model) v1.0	Category 1	OECD
5	LiCARA nanoSCAN v1.0	Category 1	caLIBRAte
6	NanoSafer v1.1β	Category 1	caLIBRAte + OECD
7	GUIDEnano	Category 1	caLIBRAte
8	The SUN Decision Support System (SUNDS)	Category 1	caLIBRAte
9	Swiss Precautionary Matrix v3.0	Category 1	caLIBRAte
10	ConsExpo nano 2.0	Category 1	caLIBRAte
11	RISKOFDERM	Category 2	caLIBRAte
12	MEASE2 2.0	Category 2	OECD
13	EMKG Expo tool 2.0	Category 2	OECD
14	Stoffenmanager 8.3	Category 2	OECD
15	Advanced REACH Tool v1.5	Category 2	OECD

18. Regarding SUNDS, the partners decided under the caLIBRAte project to not carry out the performance testing because it was covered sufficiently from the sensitivity analysis. In addition, SUNDS is based on other tools already assessed by caLIBRAte (e.g., a cloud solution with the basic exposure assessment model in NanoSafer).

2.2. Collection of exposure scenarios measurement data

19. Measurement data on occupational exposure to MNM suitable for performance testing was collected through an extensive literature review of peer-reviewed publications and data generated in EU Projects (e.g. caLIBRAte, GUIDEnano, SUN, NANoREG and NANOFASE). In addition to this, the project leaders and co-leaders elaborated a call through the WPMN in April 2019 to collect data from occupational and consumer nanomaterial exposure scenarios considering inhalation, dermal, and oral exposure. A document and an excel spreadsheet with the data requirements (see Appendix I-Table I.1) have been circulated to be filled and facilitate the performance test task. The required exposure data included material identifiers and information, safety data, detailed information regarding the activity and exposure situation as well as contextual information.

20. From the data call, the OECD Projects gathered 57 exposure scenarios:

- Database with 41 case studies focus on exposure to consumer products (Health Canada).
- Data from Health Canada regarding two exposure scenarios: 1) synthesis of MWCNTs and 2) handling MWCNTs.
- Two exposure scenarios from South Korea: 1) Ag, Cu nanoparticles synthesis and 2) handling TiO_2.
- Data from NIOSH regarding 11 exposure scenarios during manufacturing, handling, processing, spraying and cleaning of different MNMs.
- Measurement data regarding one case scenario of aerosols produced by spraying of consumer products (Public Health England, UK).

21. An exposure data library with 126 case studies containing information about MNM release and occupational exposure became available for models performance testing from the OECD call and liaison

with the completed EU H2020 caLIBRAte and at this time ongoing H2020 Gov4Nano Project (exposure scenarios generated or collected from scientific literature, and exposure databases such as NECID, and GUIDEnano library). In addition to these data sources, data libraries were identified and used if specific input parameters were missing in the studies (e.g. a dustiness library hosted by NRCWE, PROC-USE: Process and Product Use - release data library (Koivisto et al., 2017[11]; Mackevica and Foss Hansen, 2016[12]), and ECEL: The Exposure Control Efficacy Library (ECEL v3.0).

22. A high level of information and data is available for occupational exposure assessment for "raw" MNMs. However, limited information is available for exposure assessment of nanocomposite materials and the various nano-containing consumer products, unless they are based on experimental data (emission libraries; (Koivisto et al., 2017[11]). In addition, measured data is required in order to develop and apply tools and models for both MNMs and other nano-containing products.

23. Following the collection of occupational exposure scenarios, an evaluation of data quality of 120 exposure scenarios (out of 126) was carried out (see "*Annex A – Case studies.xlsx"* for details on the evaluation). To make up for this, an approach was elaborated. Each exposure case study was defined as a research conducted in a given workplace, targeting a specific material or a mixture of materials during a given task or group of tasks and given individual and/or collective risk management measures. Thus, a single case study could describe several exposure scenarios. For example, a study conducted on one material during four different working tasks performed in the same workplace and under the same control measure conditions were counted as three or four exposure situations (see e.g. (Koivisto et al., 2018[8]; Fonseca et al., 2015[13]; Ribalta et al., 2019[9])). In case of a mixture of materials, the total number of exposure scenarios was the product of the number of exposure situations and the number of materials involved (see e.g. (Fonseca et al., 2018[14]; Fonseca et al., 2021[15]; Koivisto et al., 2015[16]; Bressot et al., 2018[17])).

24. The overall criterion to assess the quality of different exposures studies was focused on three aspects: "*relevance"* (according to the source domain and whether or not there are MNM involved), "*reliability"* (quality of the exposure assessment) and "*completeness"* of the parameters required by the HRA models. All these aspects contain information/parameters that are expected to have an impact on exposure and are therefore deemed relevant for the gathering and evaluation of the case study. It should be noted that the quality approach was developed to be 'as complete' as possible. However, the amount and type of parameters requested from models is different and one exposure data set may be suitable for certain models but not for others which require more detailed contextual information.

25. The first aspect "*relevance*" consisted in identifying exposure situations that belongs to a specific source domain (release of primary particles during actual synthesis; handling of bulk aggregated/agglomerated nanopowders; spraying or dispersion of ready-to-use nanoproducts) and that reports potential occupational exposure to a given MNM.

26. The second aspect "*reliability*" consisted in grouping those confirmed exposure situations according to the study design, substance and activity information. All the included studies had to be conducted in the field and had to have high methodological strength following the harmonized 3-tier approach for particle exposure assessment published by the Organization for Economic Co-operation and Development (OECD, 2015[18]). It should include real-time particle monitoring combined with collection of samples for gravimetric, morphological analysis during working and non-working periods simultaneously at near field (NF), far field (FF), and breathing zone. However, we considered some methods more relevant than others for evaluating workers' exposure to MNM by attributing different weighing factor in the quality rank equation. For example, breathing zone sampling using personal mass samplers will lead to more relevant results than a NF and FF sampling using static samplers. This is because the NF respirable mass concentrations have been seen to underestimate the personal exposure measured at the breathing zone (Koponen, Koivisto and Jensen, 2015[19]; Koivisto et al., 2015[16]) although this is not always the case as found by Janssen *et al.* (1998[20]). This is likely due to the fact that the worker is on one hand often closer

to the activity than the stationary measurement position and on the other hand, may be exposed to particles outside of the NF volume. Such relevant other FF exposures may occur for example when empty bags are folded outside of the NF volume. For the NF and FF measurements, the use of instruments that provide exclusively total particle number concentrations, lead to less relevant results (in regard to exposure limit values usually set in mass/volume) than the use of mass samplers. Regarding the contextual information about the substance, at least information regarding the material identity, concentration of the nanomaterial in the product, the morphology of the nanoparticles and the chemical composition of the nanomaterial should be provided. Furthermore, sufficient information regarding the process should be reported in the study such as a comprehensive description of the task performed, risk management measures in use (e.g. local controls), secondary sources, production volume/ use rate, work area information such as whether the activity takes place indoors or outdoors, etc.

27. The third aspect "*completeness*" consisted in describing parameters that are not commonly reported in the studies but are considered sensitive input parameters. This is for example the case of the dustiness of a powder material which is the propensity of a powder to form airborne dust by a prescribed mechanical stimulus (EN 15051; and EN 17199), the size of the working area, presence of mechanical ventilation, the air ventilation rate, etc. A summary of the criteria used to qualitatively evaluate the strength of the exposure assessment of each study is presented Appendix II-Table II.1. The calculation of the quality score (Q) of the exposure studies consisted in an inclusion/exclusion criteria regarding the requirements (R; if present in study=1 and if not =0):

$$\text{Quality score (Q)} = \frac{\text{weighing factor}_1 \text{R}_1 + \text{weiging factor} \text{R}_2 + \cdots + \text{weighing factor}_\text{n} \text{R}_\text{n}}{\text{weighing factor}_1 + \text{weighing factor}_2 + \cdots + \text{weighing factor}_\text{n}}$$

28. Using the approach described above, the quality of the 120 occupational exposure scenarios mentioned in "*Annex A – Case studies.xlsx"* were evaluated and ranked from zero to one. Assuming an acceptable quality score ≥ 0.7, 112 exposure scenarios have been classified as fairly good to be used for the HRA model performance testing. Parameterizations of 99 of these exposure scenarios are currently available for models performance testing in "*Annex A – Case studies.xlsx".*

29. The exposure library was used to conduct performance testing of ISO/TS 12901-2:2014 nanotool, BIORIMA, MEASE, EMKG, Stoffenmanager, Stoffenmanager nano, ENAE-CPSC tool, NanoSafer, GUIDEnano, Swiss Precautionary Matrix, and the Advanced REACH Tool. The data set of exposure cases used for the performance testing of the tools was aligned to the extent possible across the tools. However, due to different requirements on input parameters of the tools, a unified set of cases could not be used for all the tools. For RISKOFDERM, LiCARA nanoSCAN and ConsExpo nano the exposure scenarios available in the library were not suitable to conduct performance testing. Therefore, for these models, specific cases were used. For all the tools, total number of cases used as well as a detailed description or identification code is provided in the corresponding subsection of section 3.

3. Performance testing results

30. In this section, performance testing results are presented individually for each tool assessed. For each tool, selected measured exposure data, input parameters and procedure used is specified. Finally, obtained performance testing results are described. Overall, the performance testing conducted was standardized as much as possible across the different tools in terms of the case studies used and treatment of the results. However, due to differences in inputs requirements as well as outputs obtained, there are some slight differences in both, the cases used and the data treatment conducted for each tool. The assessment of the total tools assessed, 15 in total, is divided in two groups: 1) nanospecific tools (10 tools), and 2) conventional chemical ECHA recommended tools (5 tools).

Nanospecific tools

3.1. ISO/TS 12901-2:2014 CB nanotool v1.0 (Part 2)

3.1.1. Introduction

31. The ISO/TS 12901-2:2014(E) CB nanotool is a decision tree type in which questions are answered one after the other. Most of the questions have yes/no answers but some have multiple choices. The tool is divided into two parts 1) hazard banding and 2) exposure banding. The hazard band (values A-E) and exposure band (values EB1-EB4) are used to generate value for the control band, which can reach values from CB1 to CB5. The tool was implemented in Python code and in a Web interface as part of the EU H2020 caLIBRAte project to easily use and test it. The full document can be purchased through https://www.iso.org/standard/53375.html.

3.1.2. Methods

Selection of measured exposure data

32. The ISO control banding tool was run for 44 case studies of which 28 studies were used to compare the ISO tool results (exposure, hazard and control bands) to measured respirable mass concentration (background corrected data separately) and measured number concentration (background corrected data separately).

33. The 28 case studies that allowed comparison were namely A1-A4, C1-C7, E1-E4, G1, S2, T1-T2, T4, U1, V1-V2, Z3, and B1- B4. The full list of case studies is available in "*Annex A – Case studies.xlsx"*.

34. As the ISO tool requires in most cases a hazard score for an analogous or bulk material, the methodology for determining a hazard classification based on the methodology described in ISO/TS 12901-2:2014(E) was applied. The data from all the case studies was entered to the programmed tool manually by a single person. User variability was not tested.

Input parameters (data entered into the tool)

35. The ISO tool has a total of 23 inputs/questions, which are specified below. Input parameters required by the tool are:

1. Is it a fiber paradigm driven toxicity NOAA?
2. Are there toxicological data on the NOAA?
3. Assign to hazard band according to toxicological data
4. Is there a HB for a bulk or analogous substance?
5. Choose the process/material matrix to define the EB
6. Manufacturing/Production process
7. Mechanical reduction type
8. Wet chemistry type
9. NOAA dispersed in a solid matrix
10. Unbound or weakly unbound to a solid matrix NOAA
11. Strongly bound to a solid matrix NOAA
12. NOAA in suspension or in a liquid matrix

13. Liquid: Manufacturing use and handling
14. Amount of NOAA > 1 g or amount of liquid > 1 l
15. Amount of NOAA < 1 g or amount of liquid < 1 l
16. NOAA in the form of a powder
17. Powder: Manufacturing use and handling
18. Amount of NOAA > 1 kg
19. Amount of NOAA > 0.1 g
20. Amount of NOAA < 0.1 g
21. Is the NOAA already classified for hazards? (Yes/No)
22. Is the NOAA highly soluble in water? (Yes/No)
23. Choose the process/material matrix to define the EB

36. Values entered for each case study are available in "*Annex A – Case studies.xlsx".*

Comparison of model estimates with measured concentrations

37. Performance testing was conducted for all the suitable data and the results discriminated between different data set qualities (all data, background corrected data, data without background correction). The model results (exposure band) were correlated with the real data (exposure: respirable mass and number concentrations) separately for all data, background corrected data and data without background correction. The classification range of measured exposure data (statistic parameters: geometric median, min, max) for each data set was determined. The Spearman correlation coefficient was calculated to determine whether and to what extent the model estimations correlates with real measurement/test values. In addition, the measured exposure data was plotted versus the respective predicted (modelled) values. Ratios (modeled/measured) versus the predicted (modelled) values could not be plotted since the ISO tool output values are unitless values that are not in the same unit as measured.

3.1.3. Results and discussion

38. The ISO control banding tool was used to estimate the hazard, exposure and control bands from 44 case studies. The results are presented in Figure 1. The hazard bands in the tool (A, B, C, D, and E) have been converted here to numbers from 1 to 5. Note that in many cases, the band values are the same, and, hence, the data points are on top of one another. The hazard bands vary from C to E, while the exposure band has larger variance from EB1 to EB4. The control band values range from CB2 to CB5 having the most counts towards the higher values. Lower control band values are not reached since low hazard band values are not represented.

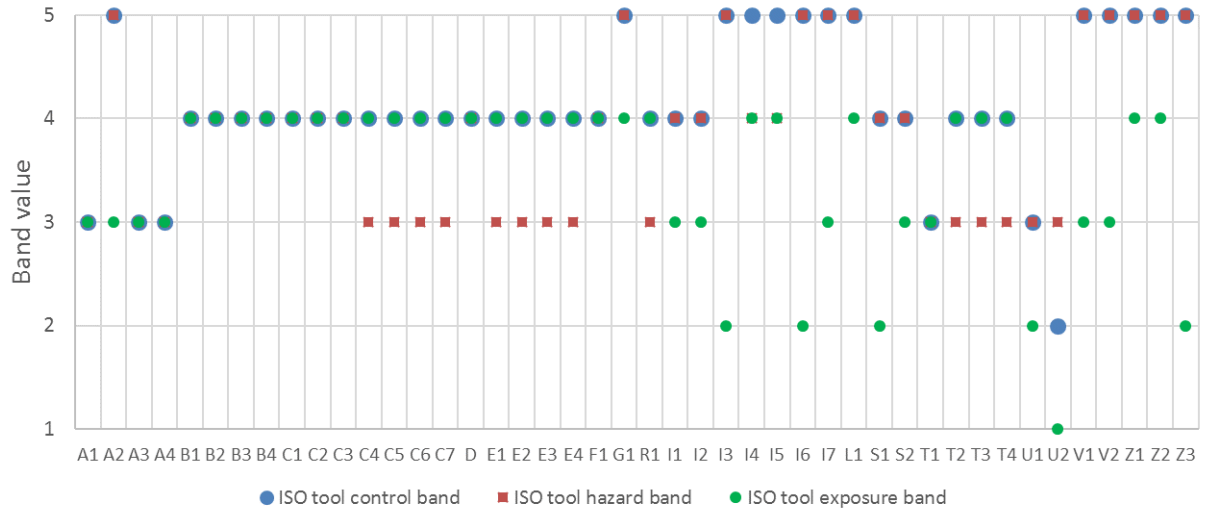


Figure 1. ISO tool hazard, exposure and control band values for case studies.

Comparison of exposure bands with measured respirable mass

39. The ISO exposure bands can be compared to the measured respirable mass from the case studies. For this comparison, we used a dataset of 28 case studies. We can see from Figure 2 that the ISO exposure band varies only slightly yielding mostly bands of EB3 or EB4. However, it seems that higher EB values are attained when the actual measured concentrations are higher. To clarify the differences, data was plotted in bar plots (Figure 3, Figure 4 and Figure 5).

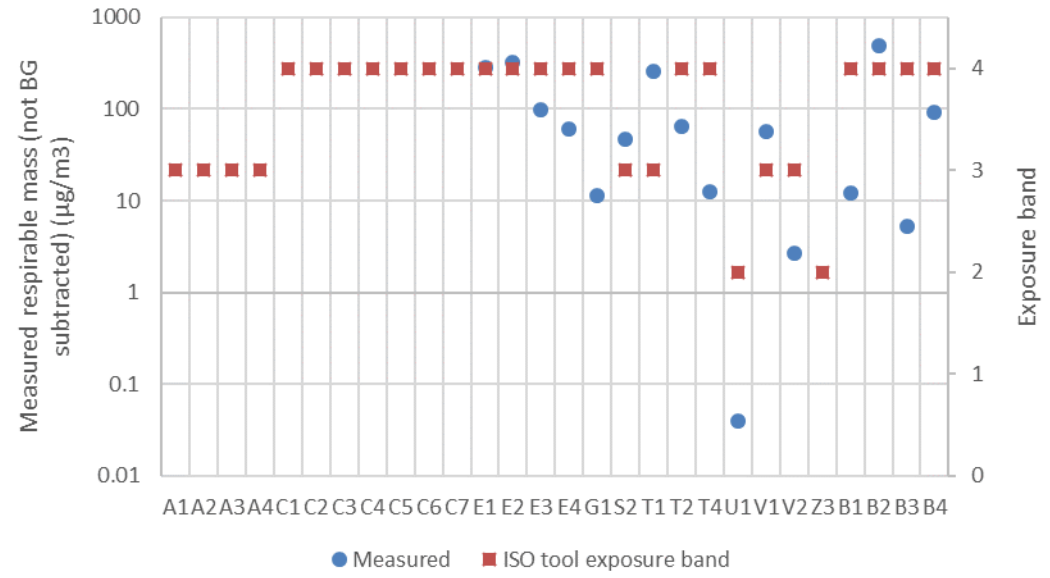


Figure 2. ISO exposure band versus measured not BG corrected respirable mass.

40. In Figure 3 the ISO exposure bands are compared to the background corrected data. This yields to an increasing band value from EB2 to EB3, but for the EB4, the variance in the measurement data is so high that clear conclusion cannot be made. Conversely, when compared to the data without background correction (Figure 4), we can see an increasing trend in the band values with increasing respirable mass.

Finally, when considering all of the data (Figure 5), the mean of the measured values in EB3 and EB4 are relatively similar. However, the values in EB4 have larger variance toward higher concentrations, especially having multiply outliers in the high concentration region. Therefore, it can be concluded that the ISO tool seems to yield higher exposure bands with higher concentrations having in same cases difficulties differentiating between EB3 and EB4. However, the measured dataset from the case studies has a large variance, and therefore, even larger dataset would be beneficial to confirm these conclusions.

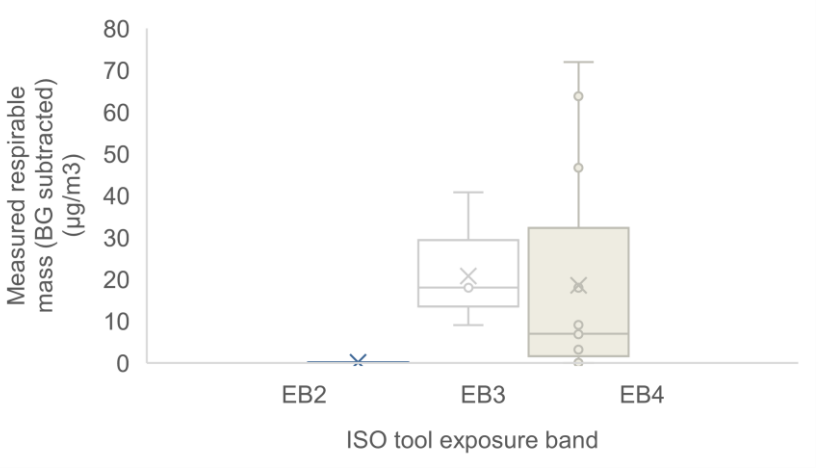


Figure 3. Measured BG corrected respirable mass for the different exposure bands.

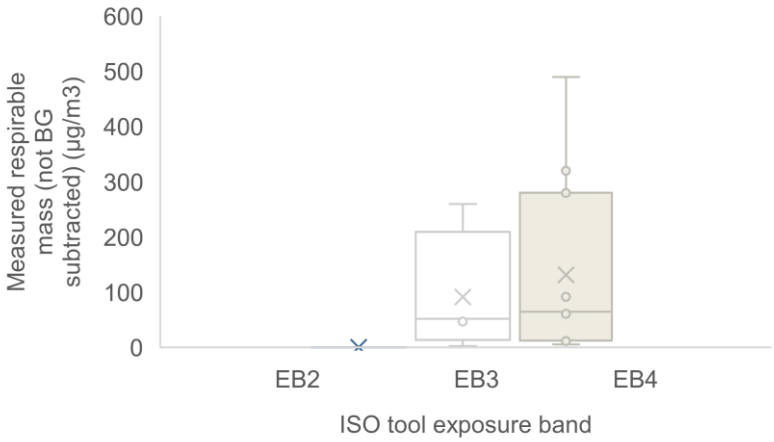


Figure 4. Measured not BG corrected respirable mass for the different exposure bands.

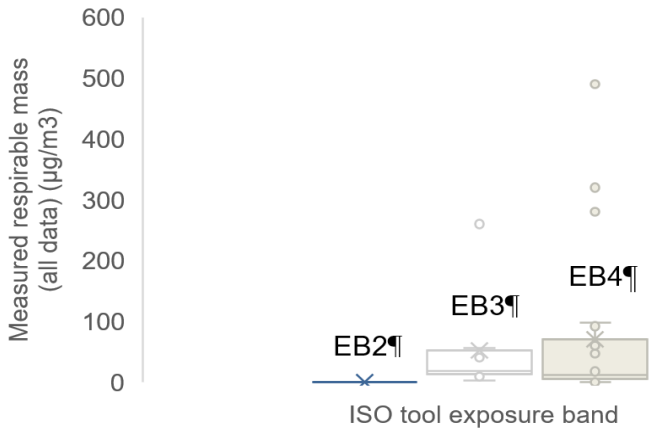


Figure 5. Measured respirable mass (all data) for the different exposure bands.

Comparison of exposure bands with measured particle number concentration

41. As for the measured respirable mass, the ISO exposure bands were compared to the measured number concentrations. These have been distinguished to background corrected data (Figure 6) and the data without background correction (Figure 7). The correlation between these two can be seen from Figure 8. The higher measured number concentration values correlate to higher exposure band. The difference between bands EB3 and EB4 is especially clear.

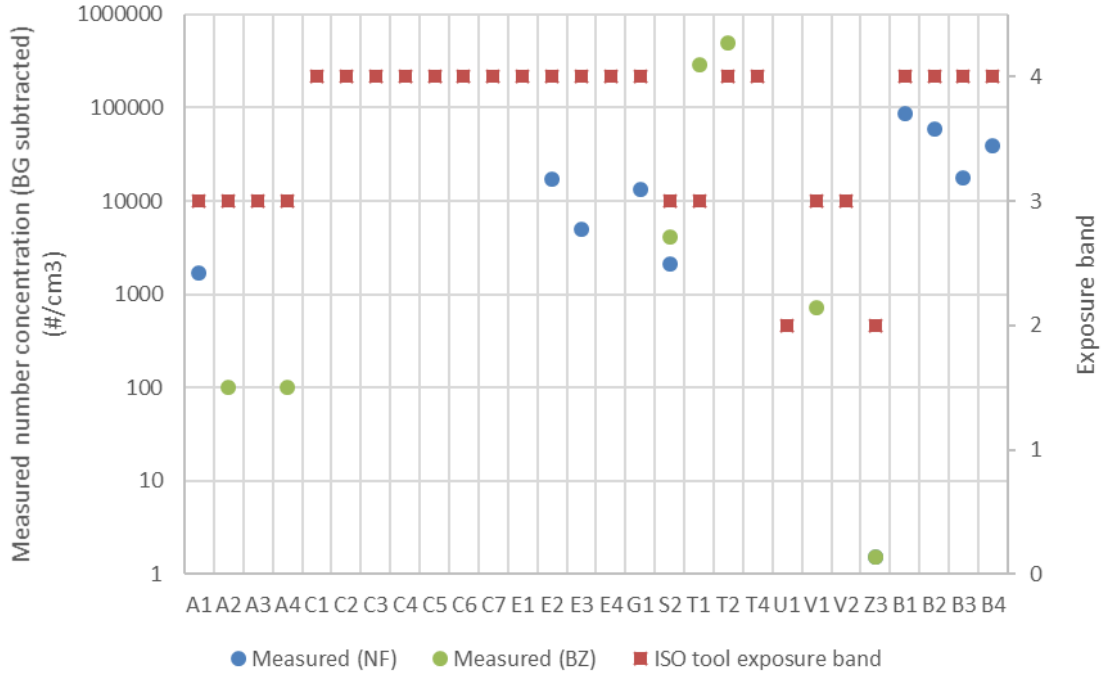


Figure 6. ISO exposure band versus the measured BG corrected number concentration.

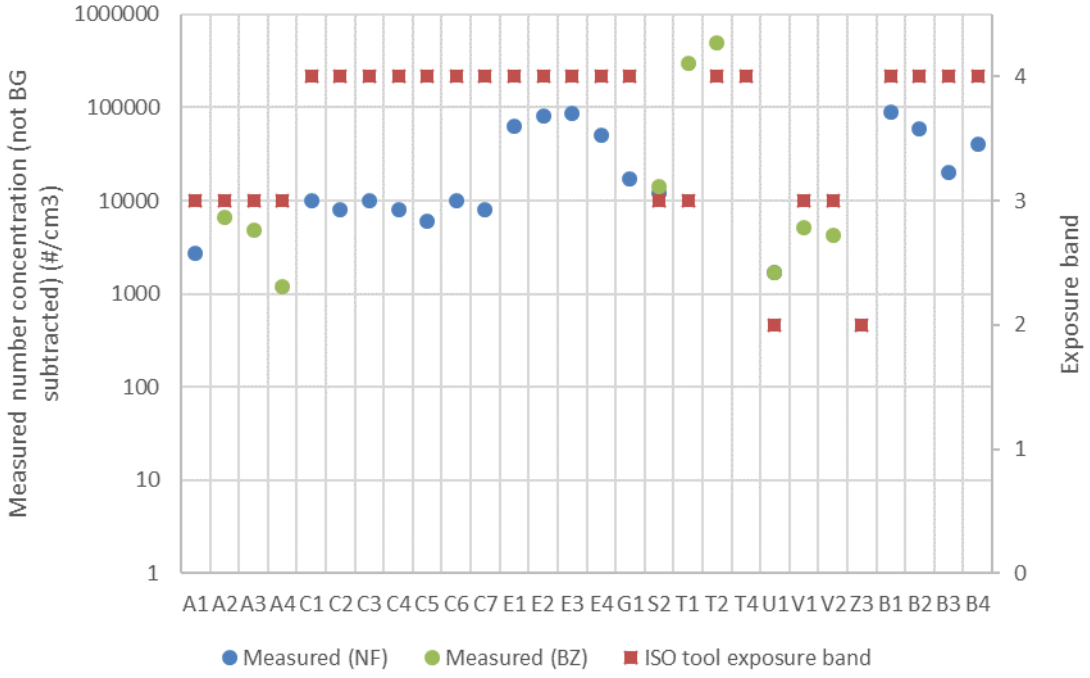


Figure 7. ISO exposure band versus the measured not BG corrected number concentration.

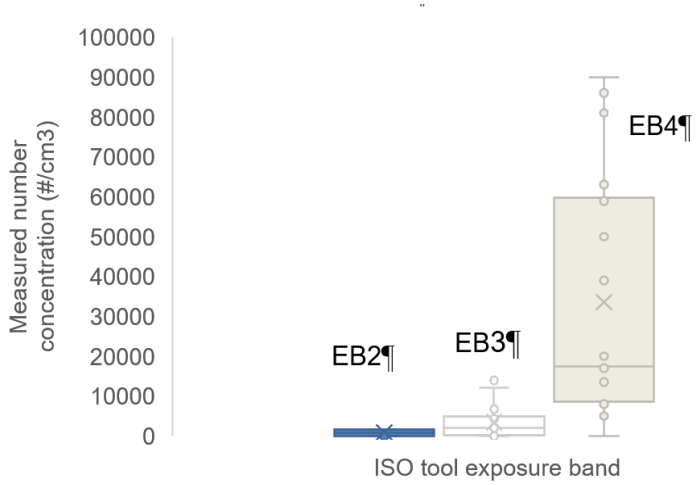


Figure 8. ISO exposure band for all the measured number concentration data.

Spearman correlation factor – measurements versus exposure band

42. The data in Figure 3, Figure 4, Figure 5 and Figure 8 was used to calculate the Spearman correlation factor between the measured values and the ISO exposure band. In addition, Table 2 presents the median, minimum and maximum values for the measured concentration data. As a performance criterion, Spearman correlation should be at least 0.6 between model estimates and measured exposure values. For the ISO tool, this criterion was fulfilled only for the number concentration data (0.63), whereas the respirable mass data had lower correlation factors. As discussed earlier, the low correlation might be due to high variance in the measured data between the studies. Other possible conclusion is that the ISO tool assigns higher exposure band for situations that could result in lower exposure and read EB4 instead

of EB3. This is a favourable behaviour for control banding tools that operate based on the precautionary principle.

Table 2. Correlation factors between the ISO exposure band and the measured concentrations.

	Measured number concentrations (all data, #/cm³)	Measured respirable mass (BG corrected data, µg/m³)	Measured respirable mass (not BG corrected data, µg/m³)	Measured respirable mass (all data, µg/m³)
Spearman correlation	0.63	-0.2	0.4	0.1
Median	8000	9.1	58.8	18
Min	0	0	0.04	0
Max	500000.0	72	490	490

3.1.4. Conclusions

43. The ISO control banding tool was run with 44 case studies and the consequent hazard, exposure and control bands were compared to measured respirable mass and number concentrations in 28 cases. The hazard bands vary from C to E, while the exposure band has larger variance from EB1 to EB4. The control band values range from CB2 to CB5 having the most counts towards the higher values. Lower control band values are not reached since low hazard band values are not represented.

44. The performance of the exposure estimation of the ISO tool was studied. The ISO tool seems to yield higher exposure bands with higher concentrations (more prominent from the number concentration data than respirable mass comparison). In other words, the higher measured number concentration values correlate to higher exposure band, which is a desired result. However, Spearman correlation was only >0.6 for particle number concentration.

3.2. BIORIMA Risk assessment and risk control module (Occupational exposure section)

3.2.1. Introduction

45. BIORIMA is a web based Integrated Risk Management framework that helps to assess the potential exposure, hazard and risk posed by MNM and nano-biomaterials to humans in occupational environments and to the environment. The framework consists of two modules 1) the Integrated Approaches to Testing and Assessment (IATA) module and 2) the risk assessment and risk control module, which conducts assessment of occupational and environmental risk during different life stages. For the human exposure part, the tool can estimate inhalation, dermal, inadvertent oral and ocular exposure. The performance testing of this framework focuses only in the occupational inhalation exposure part of the risk assessment and risk control module, which is designed to estimate occupational inhalation exposure to MNM in the form of solids or liquids. The tool can be accessed from https://sunds.gd/biorima/biorimaSelection.

3.2.2. Methods

Selection of measured exposure data

46. For the BIORIMA occupational inhalation exposure tool performance testing, a total of 53 cases, 44 for powder handling and for 9 spraying domains were used. Modelled mass concentrations were compared with real measured respirable and inhalable mass concentrations. The case studies that allowed comparison to the measurement data were namely A1-A4, C1-C7, E1-E4, F1, G1, J1-J2, L1, S1-S8, T1-

T4, V1-V2, Z1-Z3, FF1-FF7 for powder handling domain, and B1-B4, D1, GG1-GG4 for spraying domain with an average (min-max) quality score of 0.92 (0.70-1.0), and 0.82 (0.59-1.0), respectively. The full list of case studies is available in "*Annex A – Case studies.xlsx".* Input and output parameters entered in the tool for each case scenario are reported in *"Annex B1 – BIORIMA reports.pdf"* which contains the original tool reports.

47. For higher confidence in the performance testing, a selection of high quality (HQ) cases (quality score ≥0.7) and cases which did not present any limitation (measured concentration under detection limit and interferences of secondary processes) was used for assessment. In the HQ dataset, case studies included were C1-C7, E1-E4, F1, G1, J1-J2, S1-S8, V2, T4, Z1-Z3, FF1-FF7 for powder handling domain, and B1-B4, D1, for spraying domain.

Input parameters (data entered into the tool)

48. The BIORIMA occupational inhalation exposure tool only requires 10 input parameters in order to calculate inhalation exposure. Input data required is fully described in Table 3.

Table 3. Input data required by BIORIMA occupational inhalation exposure section.

Input	Options	Units
Particle diameter	Free numerical characters	[nm]
Specific density	Free numerical characters	[g/cm^3]
Percentage of pure NM	Free numerical characters	[%]
Used mass	Free numerical characters	[g]
Task duration	Free numerical characters	[min]
Duration of the generation phase	Free numerical characters	[min]
Number of repetitions	Free numerical characters	[-]
Room volume	Free numerical characters	[m^3]
Air changes per hour	Free numerical characters	[h^{-1}]
Activity generating the release rate	Drop down menu with more than 100 options	[-]

49. A single person entered the data from all the case studies to the tool manually and afterwards randomly selected cases were assessed for model parametrisation agreement with a second expert. User variability was not tested.

Comparison of model estimates with measured exposure

50. The performance of the tool was assessed by comparing the tool NF mass concentration output converted to 8h time-weighted average (TWA) and with the LC multiplier applied to, the real measured 8h TWA respirable and inhalable concentrations. For higher confidence on the performance testing comparisons, the preferences described in section 2.1 were followed.

51. To determine the extent to which modelled and measured mass concentrations correlated, the Spearman correlation factor for all the data set and for the individual application domains was calculated. In addition, Pearson correlation and the percentage of underestimation were also determined.

3.2.3. Results

52. Relevant information corresponding to 53 case studies used for performance testing (for powder handling and spraying domains separately) were retrieved and complied in Table 4.

53. Measured respirable and inhalable BG subtracted mass concentrations ranged from 0.021-193.1 and 19.0-1209.6 µg/m^3 for powder handling, and from 0.063-2.9 and 14.0-670.0 µg/m^3 for spraying domain.

Modelled mass concentrations were clearly and consistently higher than measured concentrations for the powder handling domain, with a ranged of 0.163-230,985,000,000 µg/m³. For spraying domain, modelled mass concentrations ranged between 0.00000000000041-1512.5 µg/m³. The statistical parameters of the measured and modelled exposure mass concentrations in all the cases considered in each application domain are shown in Figure 9 and Figure 10.

Table 4. Relevant information on data graduation, measurement data used for performance testing and BIORIMA tool estimated values.

	Application domain	Powder Handling	Spraying
Report data from actual measurements	Number of studies considered	44	9
	Personal exposure data used	29	5
	Stationary exposure data NF used	15	4
	Stationary exposure data FF used	0	0
	Substance specific data	27	5
	Non-substance specific data	17	4
	Measured Respirable mass (BG sub) (µg/m³)	0.021-193.1	0.063-2.9
	Measured Respirable mass (not BG sub) (µg/m³)	0.043-360.9	0.129-92.0
	Measured Inhalable mass (BG sub) (µg/m³)	19.0-1209.6	14.0-670.0
	Measured Inhalable mass (not BG sub) (µg/m³)	35.5-2128.4	14.0-670.0
Report data from modelling	Range of NF exposure concentration (µg/m³)	0.163-230985000000.0	0.00000000000041-1512.5
	Range of FF exposure concentration (µg/m³)	0.008-3210300000.0	0.00000000000018-829.2
	Range of ratio NF modelled/measured Respirable	0.578-3414315789.5	0.00000000000321-1205
	Range of ratio NF modelled/measured Respirable (not BG sub)	1.78-438679245.3	0.00000000000321-991.8
	Range of ratio NF modelled/measured Inhalable	449315-1086448598.1	0.00000000000002-8.9
	Range of ratio NF modelled/measured Inhalable (not BG sub)	16.26-389010989.0	0.00000000000002-8.9

Note: 8h TWA (daily) concentration provided. LC multiplier applied to modelled concentrations, N/A: not available.

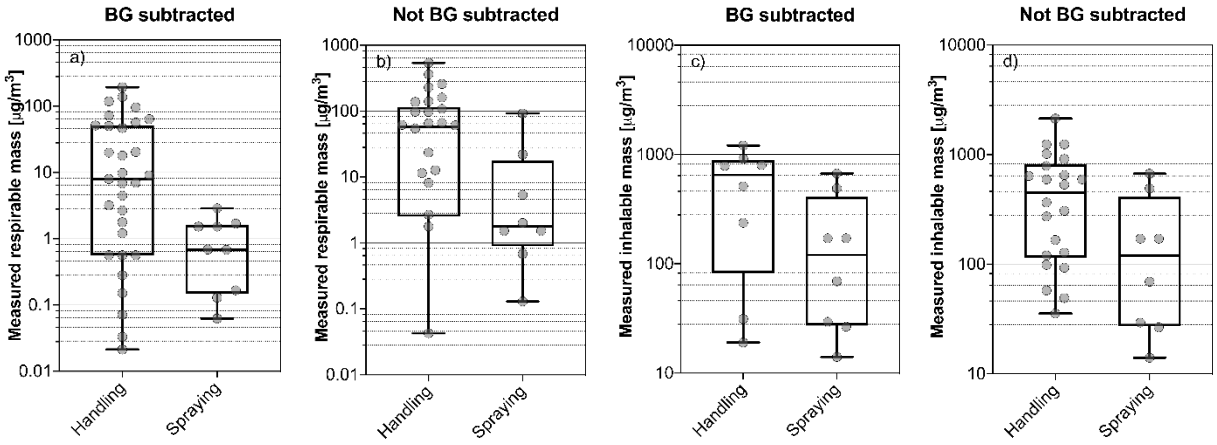


Figure 9. Vertical box plots for the measured daily respirable (a and b) and inhalable (c and d) mass concentrations for each application domain.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

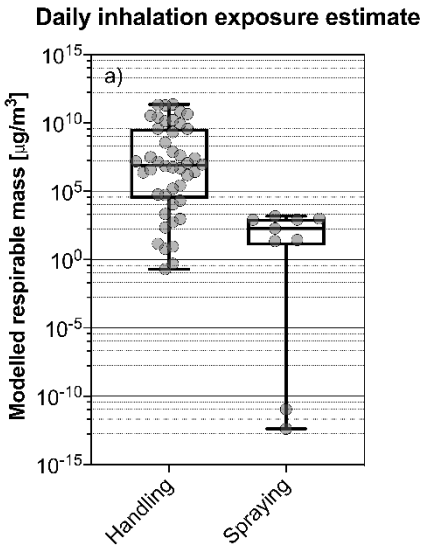


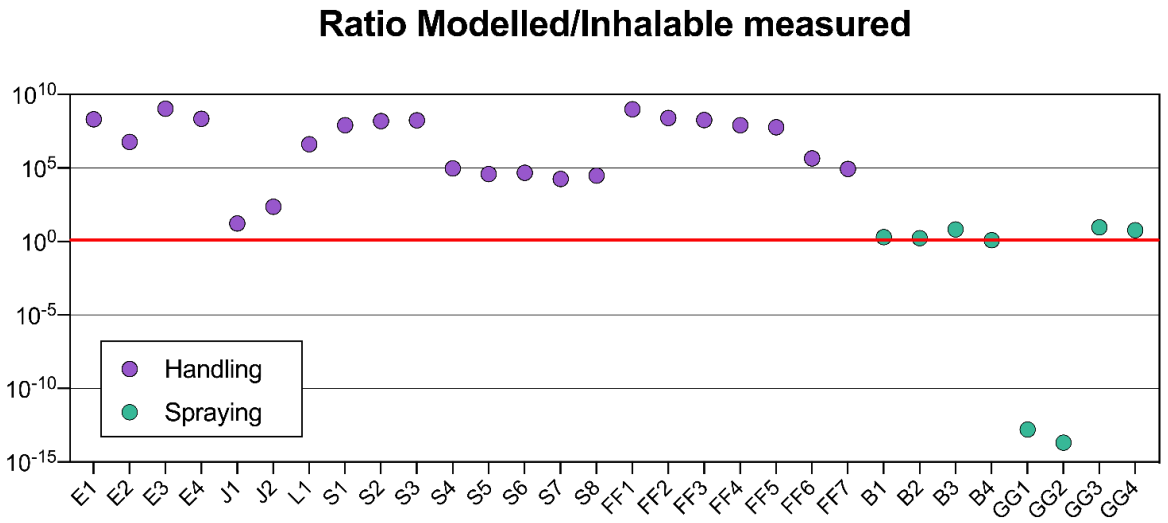
Figure 10. Vertical box plots for the modelled mass concentration for each application domain.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

Comparison of exposure score with measured mass concentrations

54. A total of 53 exposure scenarios, from which 41 were classified as HQ case studies, are used for comparison as detailed in section 3.2.2. The ratios of modelled inhalable mass concentration/measured respirable and inhalable mass concentrations are shown in Figure 11 and Figure 12, respectively together with the percentages of underestimation for each activity domain.

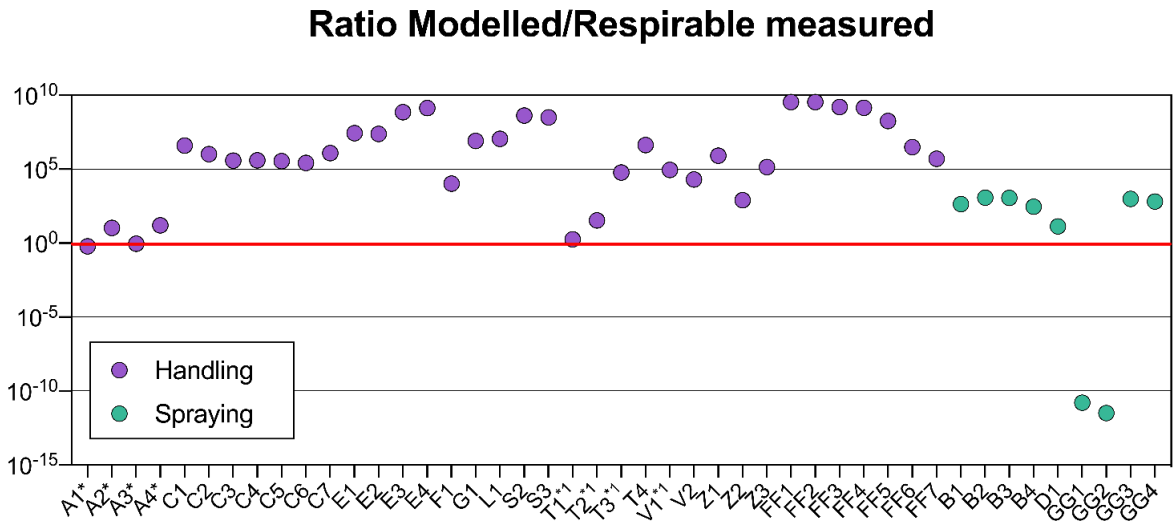
55. Measured inhalable mass concentrations were not underestimated (ratio <1) in any case for the powder handling domain. However, for spraying domain measured concentrations were underestimated in 25%, with an overall underestimation of 6.7% of the total cases. When considering only HQ case studies, total underestimations were 0. Similarly, respirable measured concentrations were underestimated in less than 10% of the total comparisons made for powder handling domain and when considering all cases (handling + spraying), whereas for spraying domain cases were underestimated in more than 10%. Considering only HQ case studies underestimations dropped to 0% in all domains. It is important to note that even though the model underestimated measured concentrations in less than 10% of the total cases, high overestimations (up to 10^{10} µg/m^3) were obtained for the powder handling domain.



All domains	All_HQ	Handling (H)	H_HQ	Spraying (S)	S_HQ
2/30 (6.7%)	0/26 (0%)	0/22 (0%)	0/22 (0%)	2/8 (25%)	0/4 (0%)

Figure 11. Ratio of modelled mass concentrations/measured inhalable BG subtracted mass concentrations.

Note: E2, E4, J1-J2, S1-S8, FF5, FF7 not BG subtracted values shown. The Table below the graph shows the percentage of underestimation for each activity domain.



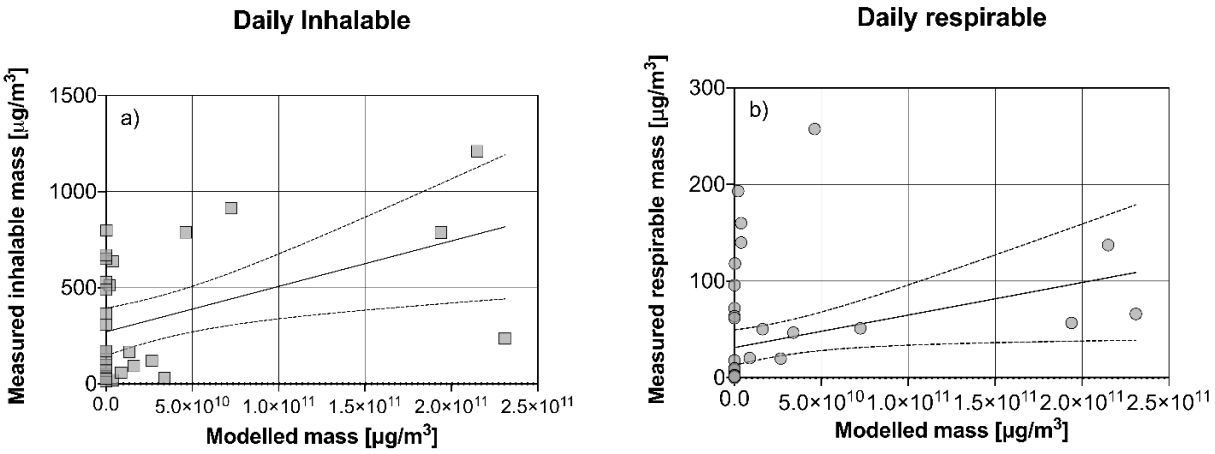
All domains	All_HQ	Handling	H_HQ	Spraying	S_HQ
4/45 (8.9%)	0/33 (0%)	2/36 (5.6%)	0/28 (0%)	2/9 (22.2%)	0/5 (0%)

Figure 12. Ratio of modelled mass concentrations/measured respirable BG subtracted mass concentrations.

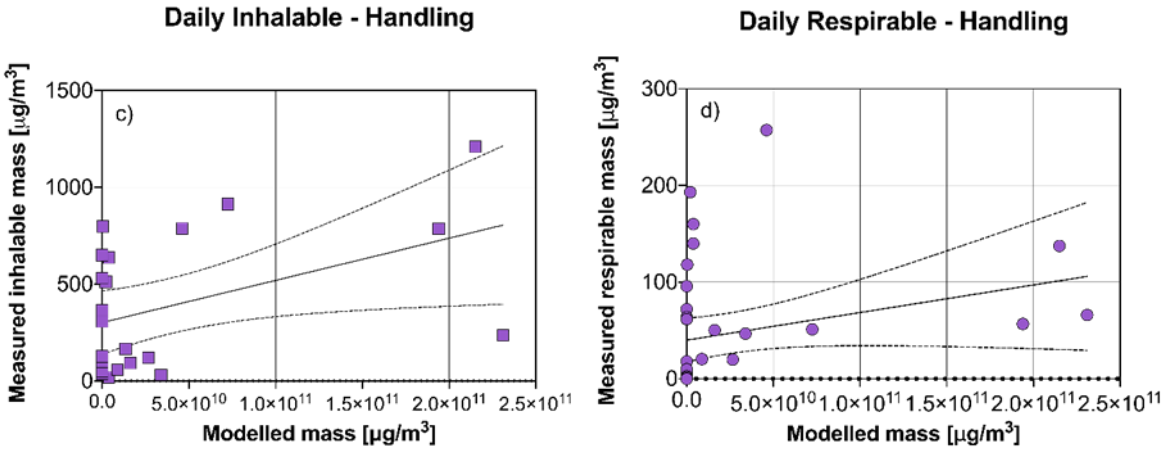
Note: E1-E2, FF1, FF5, FF7 not BG subtracted values shown. *measured concentration under detection limit and *1 considering other processes. The Table below the graph shows the percentage of underestimation for each activity domain.

Spearman correlation factor

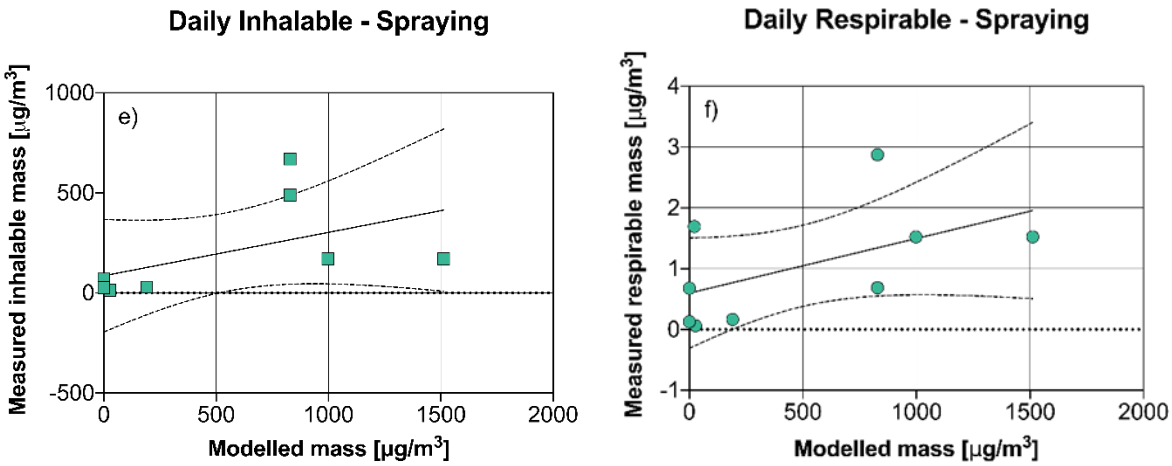
56. Modelled inhalable fraction correlation with measured respirable and inhalable fractions for all domains, handling and spraying are shown in Figure 13. Under each figure, number of cases used (n) for correlation, Pearson and Spearman correlation coefficients for all case studies as well as only HQ studies are provided.



All domains	Inhalable	Inh. HQ	Respirable	Resp. HQ
n	30	26	45	33
Pearson	0.460*	0.435*	0.307*	0.281
Spearman	0.452*	0.394*	**0.799****	**0.841****



Handling	Inhalable	Inh. HQ	Respirable	Resp. HQ
n	22	22	36	28
Pearson	0.453*	0.453*	0.270	0.243
Spearman	0.339	0.339	**0.763****	**0.797****



Spraying	Inhalable	Inh. HQ	Respirable	Resp. HQ
n	8	4	9	5
Pearson	0.508	0.965*	0.538	0.478
Spearman	**0.675**	**0.949**	0.496	0.308

Figure 13. Correlation of modelled mass concentrations with measured respirable and inhalable mass concentrations for a and b) all domains, c and d) powder handling, and e and f) spraying.

Note: For E1-E2, FF1, FF5, FF7 cases respirable not BG subtracted values shown. For E2, E4, J1-J2, S1-S8, FF5, FF7 cases inhalable not BG subtracted values shown.

57. Significant Spearman coefficients >0.6 were obtained for correlations between modelled mass fraction, and respirable measured mass concentrations when considering all case studies together as well as for powder handling domain. On the other hand, for spraying domain, a high degree of correlation (Spearman coefficient correlation of 0.54) was found for measured respirable mass concentration as well as for inhalable mass concentration, with a Spearman correlation between 0.68 and 0.95

3.2.4. Conclusion

58. The performance testing of the BIORIMA occupational exposure section was based on a total of 53 exposure scenarios, from which 41 were classified as HQ case studies. The total cases were divided in 44 and 9 cases scenarios for powder handling and spraying domains, respectively. When considering all case studies together, modelled concentrations Spearman correlation with measured respirable mass fraction was found to be significant with a coefficient of 0.80, and 0.84 when HQ cases were selected. Similarly, when considering only powder handling and spraying domain cases separately, spearman correlation coefficient was 0.76 (0.80 for HQ cases). These values are above the threshold set in this performance testing of 0.6. In addition, total underestimations were under the 10% limit set in this study. For the spraying domain, underestimations were only under the 10% when HQ cases were considered, and even though high spearman correlation for measured inhalable mass were obtained (0.66 and 0.95 for HQ), the data set is limited and reaching any conclusion would be hasty. It is also important to mention that, especially for powder handling, very high overestimations were obtained, with ratios up to 10^{10}, which is not ideal. The tool as assessed here is in its initial stages and probably modification and improvements will follow and more accurate predictions can be derived.

3.3. Stoffenmanager nano v1.0

3.3.1. Introduction

59. The Stoffenmanager nano model is a web-based control banding tool which is used to estimate worker inhalation exposure to manufactured nano-objects for risk assessment. In the present study, the performance of the model is tested by comparing its output with experimentally measured exposure levels in particle number concentrations. The tool can be accessed through https://nano.stoffenmanager.com/Default.aspx.

3.3.2. Methods

Selection of measured exposure data

60. A total of 10 adequate studies were used which consisted of 82 measurements.

Input parameters (data entered into the model)

61. The available information in the adequate studies was translated into input values for the model via an elicitation process. One person entered the values for model input parameters on the basis of exposure cases description and another person checked the input values for their consistency and correctness. If the entered value for a parameter was found consistent and correct by the second person, it was considered to be the consensus value and that value was used in the model estimations. If not, it was discussed by two persons to reach consensus on the inputs. For parameters with unknown values, it was decided to assume a value that would lead to the highest exposure estimate to make conservative estimates. Input parameters required are described in Table 5.

Table 5. Input parameters requested by Stoffenmanager nano.

Question	Options
Step 1: general	
Source domain	Release of primary particles during actual synthesis Handling of bulk aggregated/agglomerated nanopowders Spraying or dispersion of a ready-to-use nanoproduct (intermediate or ready-to-use) Fracturing and abrasion of MNOs-embedded end products
Step 2: Product characteristics	
Product, product name, Supplier, Date PIS, Date MSDS	[-]
Product appearance	Powder Granules / flakes Particles dispersed in liquid
Dustiness	Very high (> 500 mg/kg) High (> 150 – 500 mg/kg Medium (> 50 – 150 mg/kg) Unknown
Moisture content	Dry product (< 5%) 5 - 10% > 10%
Nano Component and name	[text]
Do you know exact concentration of the nanocomponent?	Yes / No If (Yes) then [%]
Does the product contain fibers/fiber like particles?	Yes / No If (Yes) then enter length as diameter or aspect ratio

Question	Options
Number of exposed employees	[n]
Production or usage-volume a year	[kg]
Startdate of period worked with the product	[dd-mm-yyyy]
Enddate of period worked with the product	[dd-mm-yyyy]
Last update date of additional registration	[dd-mm-yyyy]
Step 3: Handling / Process	
Characterize your task	Dependent on Source domain selected
Duration task	1 to 30 min 0.5 – 2 hours 2 – 4 hours 4 – 8 hours
Frequency task	Approx. 1 day a year Approx. 1 day a month Approx. 1 day per 2 weeks Approx. 1 day a week 2 – 3 days a week 4 – 5 days a week
Is the task being carried out in the breathing zone of an employee (distance head-product < 1 m)?	Yes / No If (yes) Is there more than one employee carrying out the same task simultaneously?
Step 4: Working area	
Is the working room being cleaned daily?	Yes / No
Are inspections and maintenance of machines/ancillary equipment being done at least monthly to ensure good condition and proper functioning and performance?	Yes / No
Volume of the working room	< 100 m3 100 – 1000 m^3 > 1000 m3 Outdoors
Ventilation of the working room	No general ventilation Mechanical or natural Spraying booth
Step 5: Local controls and personal protective equipment	
Local control measures	No control measures at the source Use of product that limits the emission Local exhaust ventilation Containment of the source Containment of the source with LEV Glove boxes/bags
Is the employee situated in a cabin?	The worker does not work in a cabin The worker works in cabin without specific ventilation system The worker works in a separated (control) room with independent clean air supply
Is personal protective equipment applied?	Filter mask FFP2 – FFP3 Half mask respirator with filter PL2 – PL3 Full face respirator with filter PL2 – PL3 Half/full face powered air respirator TMP1 – 3 Full face powered air respirator TMP3 Hood or helmet with supplied air system TH1 – 3

Comparison of model estimates with measured exposure

62. To assess the exposure at a situation, the Stoffenmanager Nano model estimates a qualitative score, which is classified in either of the four exposure bands: 1-low, 2-average, 3-high and 4-very high. The measured exposure in the selected studies were, however, quantified values in particle number concentration (#/cm^3). This disabled a direct comparison between the model estimate and measured

exposure. Therefore, the Spearman correlation coefficient was calculated to determine whether and to what extent the model estimated scores correlated with measured exposure values.

3.3.3. Results

63. In Figure 14 (a), the model scores (i.e. dimensionless output of the model) are shown to be positively correlated with their corresponding measured exposure concentrations. The Spearman correlation coefficient is equal to 0.78, which signifies a strong correlation. Compared to low measured exposure concentration ($<10^3$ #/cm^3), the model scores were observed to correlate better with higher measured exposure concentrations, which correspond to the exposure bands of 2-average and 3-high. The measured exposure concentration corresponding to the highest exposure band of 4-very high could not be found in the selected studies. The coefficient of fit of the best fit curve to all data points is equal to 0.68. The majority of data points within the exposure band of 1-low lie below the best fit curve which signifies that the model tends to overestimate the exposure at lower levels of exposure. Since the model estimate and measured exposure cannot be directly compared, it is not possible to directly determine the overestimation factor.

64. The measured exposure concentrations are classified in model estimated exposure bands in Figure Figure 14 (b). For 1-low exposure band, the respective median and geometric mean (GM) of the exposure concentrations are equal to 98 #/cm^3 and 113 #/cm^3. Both median and GM of the measured exposure concentrations in 2-average exposure band are greater than in case of 1-low exposure band. They are equal to 4948 #/cm^3 and 7177 #/cm^3, respectively. For 3-high exposure band, the respective median and GM exposure values are both further greater than in case of 2-average exposure band and are equal to 74376 #/cm^3 and 63061 #/cm^3. Clearly, the median and GM exposure values in each exposure band are distinct and distinguishable from one another. There is also no overlapping between respective interquartile ranges of measured exposure concentrations lying in 1-low and 2-average exposure bands. However, the measured exposure concentrations in 3-high exposure band are not completely distinct from those in 2-average exposure band as both median and GM exposure values of 3-high exposure band lie within the interquartile range of 2-average exposure band.

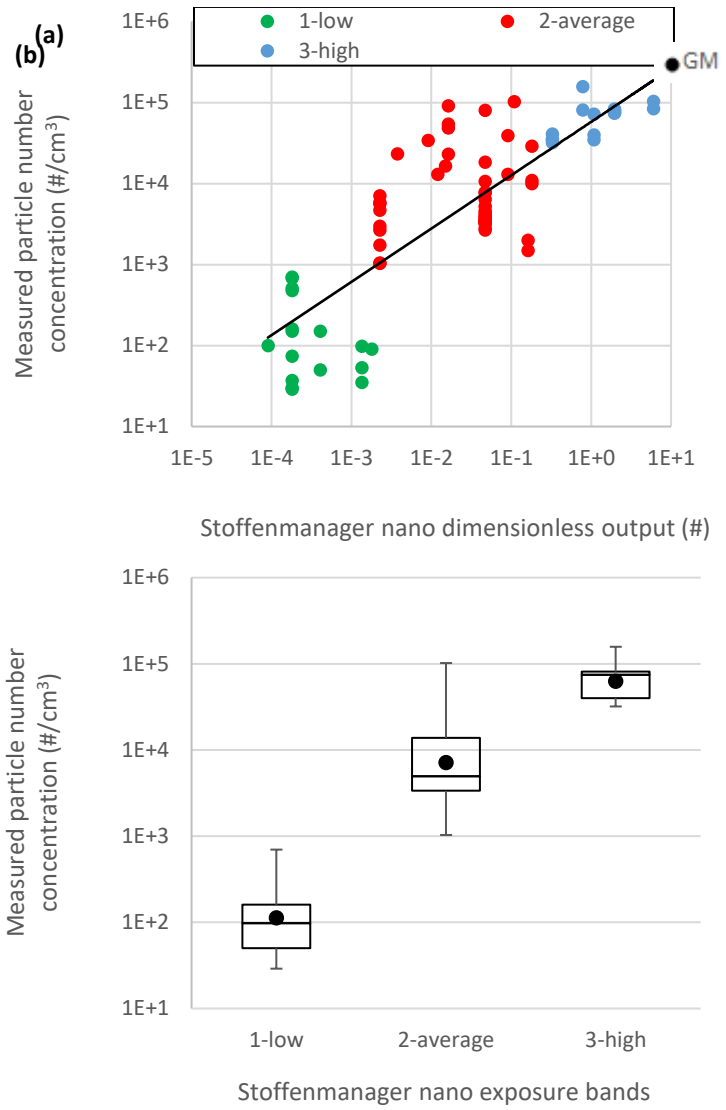


Figure 14. a) Correlation between model estimate and measured exposure for three exposure bands; b) classification of measured exposure in the model estimated exposure bands.

3.3.4. Conclusions

65. The overall estimated scores of Stoffenmanager Nano were found to be strongly correlating with the measured exposure concentrations (Spearman correlation coefficient= 0.78). The correlation improved from poor to strong with higher exposure concentrations (> 10^3 #/cm^3) or higher exposure bands (i.e. 2-average and 3-high). The measured exposure concentrations could also be distinctly classified in three estimated exposure bands of the model, however, with some overlap between 2-average and 3-high bands.

3.4. Engineered Nanoparticle Airborne Exposure (ENAE) Tool (CPSC ENP Model) v1.0

3.4.1. Introduction

66. The ENAE-CPSC is a web-based tool that provides inhalation and dermal exposure of consumers to nanoparticles. The tool is a single-zone model, based on the NIST multizone modelling software CONTAM. The model takes into account gravitational settling (i.e., particles settling to the floor), diffusion (i.e., particles settling on walls and surfaces) and dilution (i.e., effect of ventilation). The tool also assumes that nanoparticles remain unaltered in the process of exposure, and does not distinguish between nanomaterial types. The tool is available at https://pages.nist.gov/CONTAM-apps/webapps/NanoParticleTool/index.htm.

Selection of measured exposure data

67. For the ENAE-CPSC tool performance testing, a total of 39 exposure scenarios were used. The 39 exposure scenarios were divided in 34 cases for powder handling domain and 4 cases for spraying domain. Modelled mass concentrations were compared with real measured respirable mass concentrations or inhalable mass when respirable was not available.

68. The case studies that allowed comparison to the measurement data were namely A1-A4, C1-C7, E1-E4, G1, I1-I3, S1-S8, T1-T4, V1-V2, Z1-Z2 for powder handling domain, and B1-B4 for spraying domain with an average (min-max) quality score of 0.92 (0.74-1.0), and 1.0 respectively. The full list of case studies is available in "*Annex A – Case studies.xlsx*". Input and output parameters entered in the tool for each case scenario are reported in *"Annex B2 – ENAE-CPSC reports.pdf"* which contains the original tool reports.

69. All selected case scenarios had quality scores >0.7. For higher confidence in the performance testing, a HQ data set was used, removing all the cases that presented limitations (measured concentration under detection limit and interferences of secondary processes). In the HQ dataset, case studies included were C1-C7, E1-E4, G1, I1-I3, S1-S8, V2 and Z1-Z2 for powder handling domain, and B1-B4 for spraying domain.

Input parameters (data entered into the tool)

70. The tool requires a total of 39 input parameters for the exposure assessment. The entries are divided in 8 categories: zone geometry, ventilation system, particle properties, particle source, particle deposition velocities, particle resuspension, initial concentration and surface loadings and occupant exposure. Input data required is fully described in Table 6.

Table 6. Input data required by ENAE-CPSC. *auto-filled inputs.

Parameter	Units/Options
Zone Geometry	
Volume	[m^3; ft^3; in^3; mm^3; dm^3; μm^3]
Floor area	[m^2; ft^2; in^2; mm^2; dm^2; μm^2]
Wall area	[m^2; ft^2; in^2; mm^2; dm^2; μm^2]
Ceiling area	[m^2; ft^2; in^2; mm^2; dm^2; μm^2]
Envelope penetration factor	[-]
Ventilation System	
Supply airflow rate	[kg/s; scfm; sL/s; sm^3/; sm^3/h; lb/s; sft^3/h; sL/min; kg/h]
Return airflow rate	[kg/s; scfm; sL/s; sm^3/; sm^3/h; lb/s; sft^3/h; sL/min; kg/h]
Percent outdoor air	%
Air Change rate*	[1/s; 1/min; 1/h; 1/dy; 1/yr]
Outdoor airflow rate*	[kg/s; scfm; sL/s; sm^3/; sm^3/h; lb/s; sft^3/h; sL/min; kg/h]
Recirculation airflow rate*	[kg/s; scfm; sL/s; sm^3/; sm^3/h; lb/s; sft^3/h; sL/min; kg/h]
Exhaust airflow rate*	[kg/s; scfm; sL/s; sm^3/; sm^3/h; lb/s; sft^3/h; sL/min; kg/h]
Airflow imbalance*	[kg/s; scfm; sL/s; sm^3/; sm^3/h; lb/s; sft^3/h; sL/min; kg/h]
Zone air balance*	Balanced; Pressurized; Depressurized
Outdoor air filter	[MERV4-MERV16]
Recirculation air filter	[MERV4-MERV16]
Particle properties	
Diameter	[m; ft; cm; in; mm; dm; μm]
Density	[g/cm^3; kg/m^3; lb/ft^3]
Particle source	
Source type	[Constant; Burst]
Release rate	[kg; lb; g; mg; μg; ng; # / s; min; h]
Release amount*	[kg]
Source start time	[hh:mm:ss]
Source end time	[hh:mm:ss]
Particle deposition velocities	
Floor	[m/s; fpm; cm/s; mph;m/h; km/h; knots]
Walls	[m/s; fpm; cm/s; mph;m/h; km/h; knots]
Ceiling	[m/s; fpm; cm/s; mph;m/h; km/h; knots]
Particle resuspension	
Floor resuspension area	[m^2; ft^2; cm^2; in^2; mm^2; dm^2; μm^2]
Floor resuspension rate	[1/s; 1/min; 1/h; 1/dy; 1/yr]
Wall resuspension area	[m^2; ft^2; cm^2; in^2; mm^2; dm^2; μm^2]
Wall resuspension rate	[1/s; 1/min; 1/h; 1/dy; 1/yr]
Ceiling resuspension area	[m^2; ft^2; cm^2; in^2; mm^2; dm^2; μm^2]
Ceiling resuspension rate	[1/s; 1/min; 1/h; 1/dy; 1/yr]
Initial concentration and surface loadings	
Outdoor concentration	[kg; lb; g; mg; μg; ng; # / kg; m^3; lb; ft; L; cm^3]
Initial zone concentration	[kg; lb; g; mg; μg; ng; # / kg; m^3; lb; ft; L; cm^3]
Initial floor loading	[kg; g; mg; μg; #; lb / m^2; cm^2; ft^2; in^2]
Initial wall loading	[kg; g; mg; μg; #; lb / m^2; cm^2; ft^2; in^2]
Initial ceiling loading	[kg; g; mg; μg; #; lb / m^2; cm^2; ft^2; in^2]
Occupant exposure	
Exposure start time	[hh:mm:ss]
Exposure end time	[hh:mm:ss]

71. A single person entered the data from all the case studies to the tool manually and afterwards randomly selected cases were assessed for model parametrisation agreement with a second expert. User variability was not tested.

Comparison of model estimates with measured exposure

72. The performance of the tool was assessed by comparing the tool mass concentration output to the real measured task respirable mass concentration. When respirable mass concentration was not available inhalable was used. For higher confidence on the performance testing comparisons, the preferences described in section 2.1 were followed.

73. To determine the extent to which modelled and measured mass concentrations correlated, the Spearman correlation factor for all the data set and for the individual application domains was calculated. In addition, Pearson correlation and the percentage of underestimation were also determined.

3.4.2. Results

74. Relevant information corresponding to 39 case studies used for performance testing (for powder handling, and spraying separately) were retrieved and complied in Table 7.

75. Measured resiprable and inhalable BG subtracted mass concentrations ranged from 0.24-1276.0 and 30.0-460.0 µg/m^3 for powder handling and spraying domains, respectively. On the other hand, modelled mass concentrations for powder handling and spraying domain ranged between 0.535-152070 and 403.94-1913.5 µg/m^3, and 0.0032-38473.7 and 206.01-975.89 µg/m^3 when local controls reductions were applied. The statistical parameters of the measured and modelled exposure mass concentrations in all the cases considered in each application domain are shown in Figure 15 andFigure 16.

Table 7. Relevant information on data graduation, measurement data used for performance testing and MEASE tool estimated values.

	Application domain	Powder handling	Spraying
Report data from actual measurements	Number of case studies considered	35	4
	Number of personal exposure data used	26	4
	Number of stationary exposure data NF used	6	0
	Number of stationary exposure data FF used	0	0
	Number of substance-specific data	27	4
	Number of non-substance-specific	6	0
	Range of measured respirable mass (BG subtracted) (µg/m^3)	0.24-1276.0	30.0-460.0
	Range of measured respirable mass (not BG subtracted) (µg/m^3)	71.0-4880.0	30.0-460.0
	Range of measured particle number (BG subtracted) (#/cm^3)	0-490000	18000-87000
	Range of measured particle number (not BG subtracted) (#/cm^3)	1200-500000	20000-90000
Report data from modelling	Range of mass concentration (µg/m^3)	0.535-152070	403.94-1913.5
	Range of mass concentration LC (µg/m^3)	0.0032-38473.7	206.01-975.89
	Range of measured particle number concertation (#/cm^3)	0.347-77445000000	1476300-6993500
	Range of measured particle number concertation LC (#/cm^3)	0.09-39496950000.0	752913-3566685
	Range of ratio modelled mass/respirable measured	0.004-62665.5	4.160-13.465
	Range of ratio modelled mass LC/respirable measured	0.00002-376.0	2.12-6.87
	Range of ratio modelled particle number/particle number measured	0.00002-14387500000	16.969-179.321
	Range of ratio modelled particle number LC/particle number measured	0.00001-86325000	8.65-91.45

Note: 8h TWA (daily) concentration provided, N/A: not available.

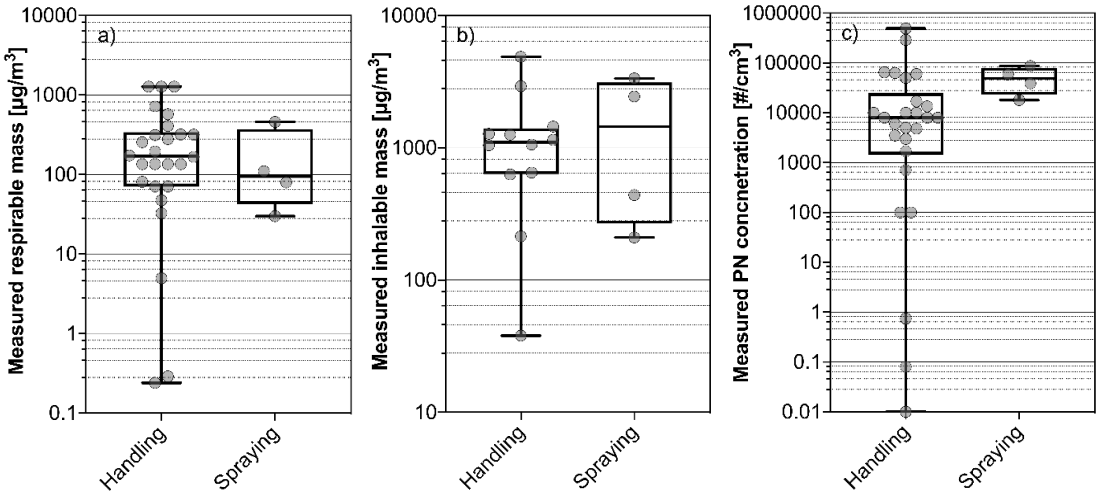


Figure 15. Vertical box plots for the measured task. a) Respirable b) Inhalable and c) Particle number concentration for application domain.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

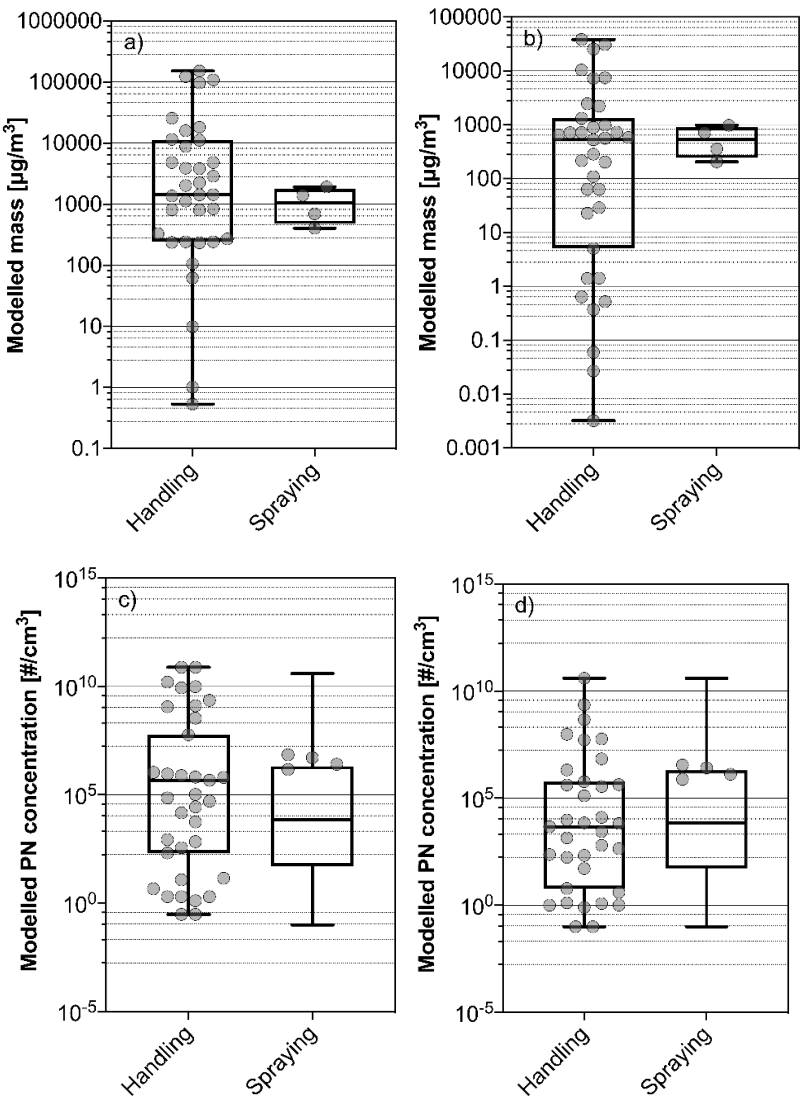


Figure 16. Vertical box plots for the task. a) Modelled mass, b) Modelled mass with LC, c) Modelled particle number, and d) Modelled particle number concentration with LC for each application domain.

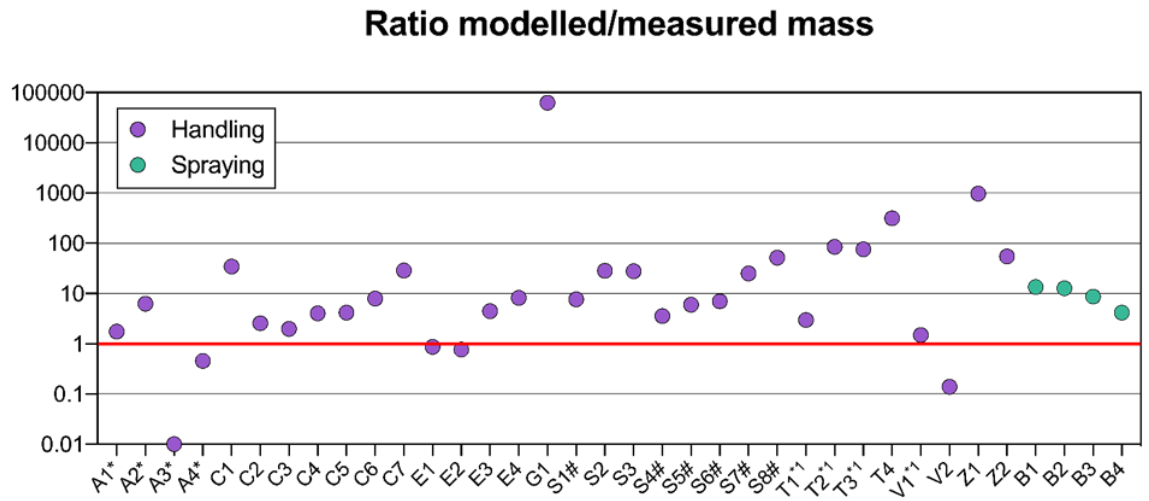
Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

Comparison of exposure score with measured mass concentrations

76. A total of 39 exposure scenarios, from which 31 were classified as HQ case studies, are used for comparison as detailed before. The ratios of modelled/measured mass concentrations and particle number are shown in Figure 17, Figure 18 and Figure 19 together with the percentages of underestimation for each activity domain.

77. Measured respirable mass concentrations were underestimated (ratio <1) in 14% of the total cases, 10.7% when only HQ cases studies were considered. All underestimated cases were powder

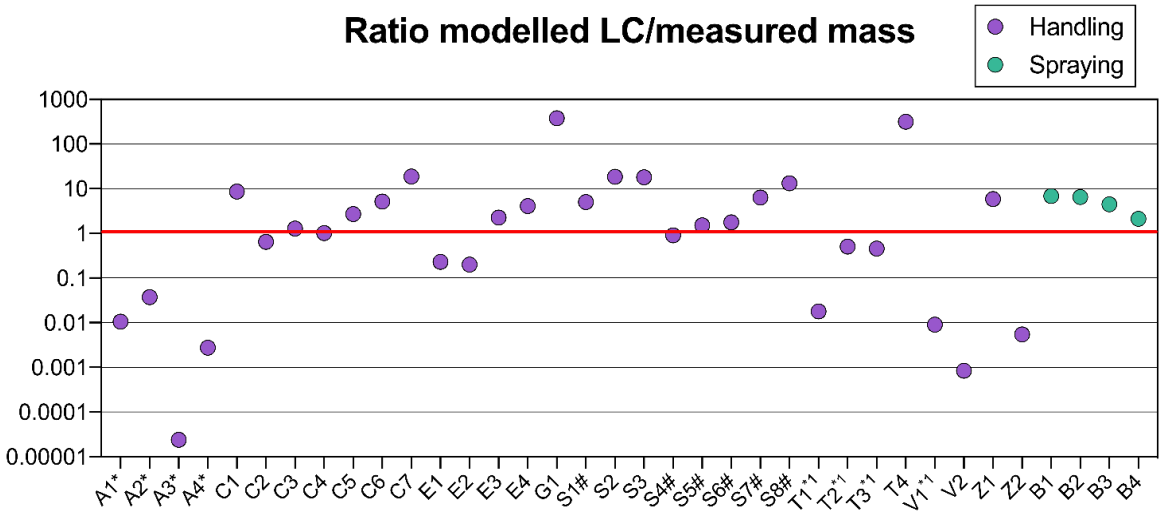
handling activities (underestimation of 15.6% of the cases, 12.5% when only HQ cases considered). Conversely, spraying activities were not underestimated in any case (Figure 17). When the LC multipliers were applied to modelled concentrations, HQ cases underestimations increased up to 18% and 21% for all domains and powder handling, respectively whereas for spraying domain measured concentrations were estimated with ratios between 1-10 (Figure 18). Similar results were obtained for modelled/measured particle number concentrations, but with higher underestimations of the powder handling activities (Figure 19).



All domains	All_HQ	Handling	H_HQ	Spraying	S_HQ
5/36 (13.9%)	3/28 (10.7%)	5/32 (15.6%)	3/24 (12.5%)	0/4 (0%)	0/4 (0%)

Figure 17. Ratio of modelled mass concentrations/measured respirable BG subtracted mass concentrations.

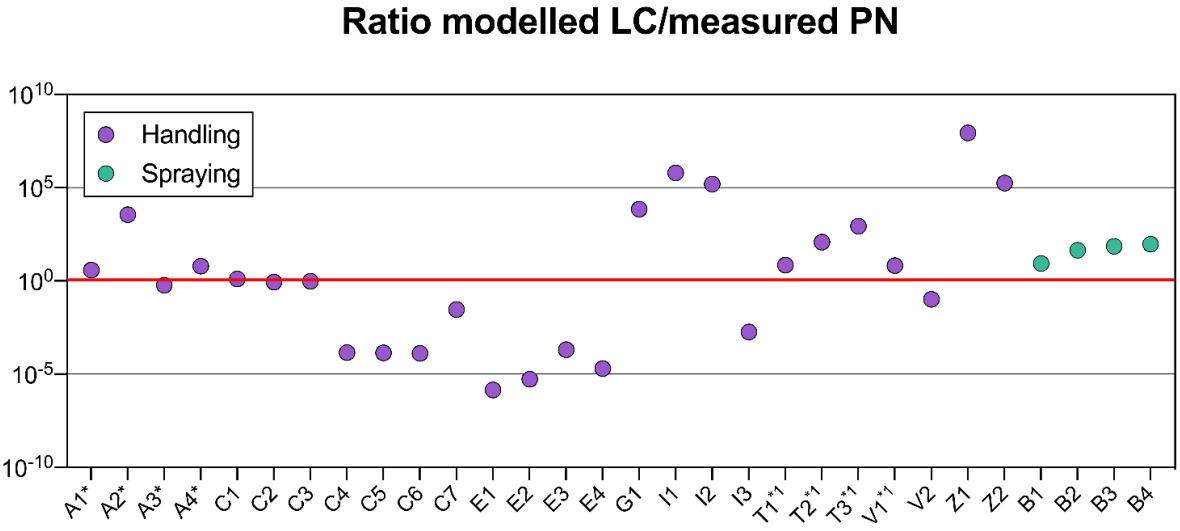
Note: For E1-E2 respirable not BG subtracted values are shown. For S1, S4, S5, S6, S7 and S8 (marked with #) inhalable not BG subtracted values shown. *measured concentration under detection limit, *1 considering other processes. The Table below the graph shows the percentage of underestimation for each activity domain.



All domains	All_HQ	Handling	H_HQ	Spraying	S_HQ
14/36 (39%)	5/28 (18%)	14/32 (44%)	5/24 (21%)	0/4 (0%)	0/4 (0%)

Figure 18. Ratio of modelled mass concentrations LC applied/measured respirable BG subtracted mass concentrations.

Note: For E1-E2 respirable not BG subtracted values are shown. For S1, S4, S5, S6, S7 and S8 (marked with #) inhalable not BG subtracted values shown. *measured concentration under detection limit, *1 considering other processes. The Table below the graph shows the percentage of underestimation for each activity domain.



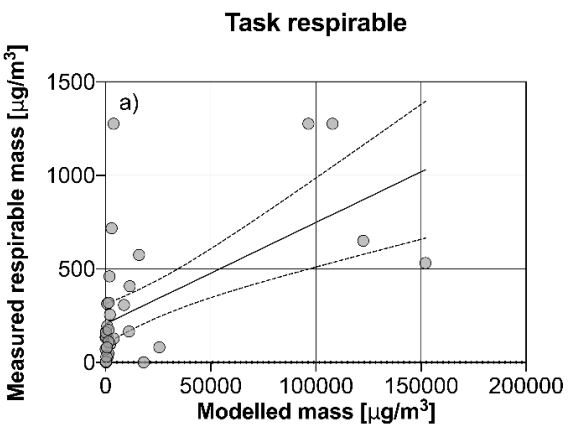
All domains	All_HQ	Handling	H_HQ	Spraying	S_HQ
12/30 (40%)	11/22 (50%)	12/26 (46%)	11/18 (61%)	0/4 (0%)	0/4 (0%)

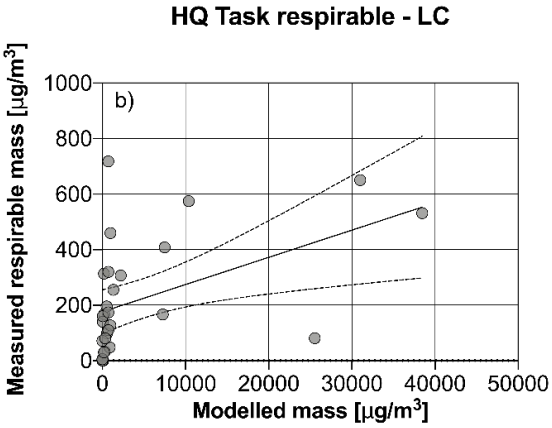
Figure 19. Ratio of modelled particle number concentrations/measured particle number BG subtracted concentrations.

Note: C1-C7, E4, I2-I3 and V2 not BG subtracted values shown. *measured concentration under detection limit, *1 considering other processes. The Table below the graph shows the percentage of underestimation for each activity domain.

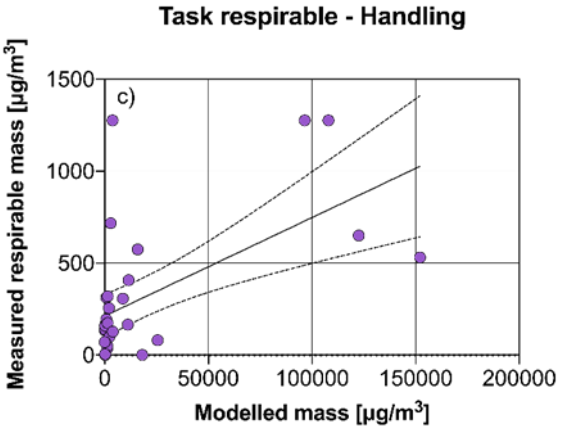
Spearman correlation factor

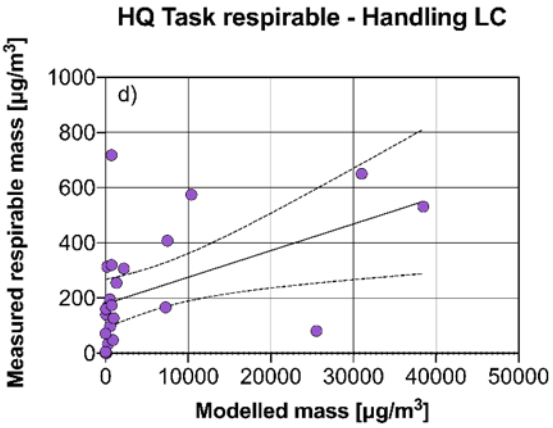
78. Modelled mass and particle number concentration correlation with measured respirable and particle number concentrations for all domains, handling and spraying are shown in Figure 20 and Figure 21. Under each figure, number of cases used (n) for correlation, Pearson and Spearman correlation coefficients for all case studies as well as only HQ studies are provided.



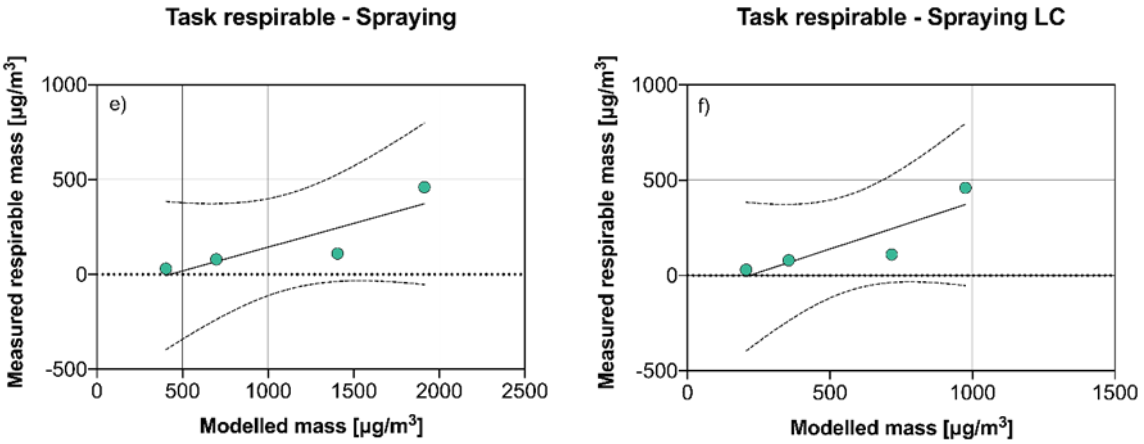


All domains	Task	HQ-Task LC
n	36	28
Pearson	0.587***	0.478*
Spearman	0.541***	**0.634*** **





Handling	Task	HQ-Task LC
n	32	24
Pearson	0.587***	0.492*
Spearman	0.530**	**0.612** **



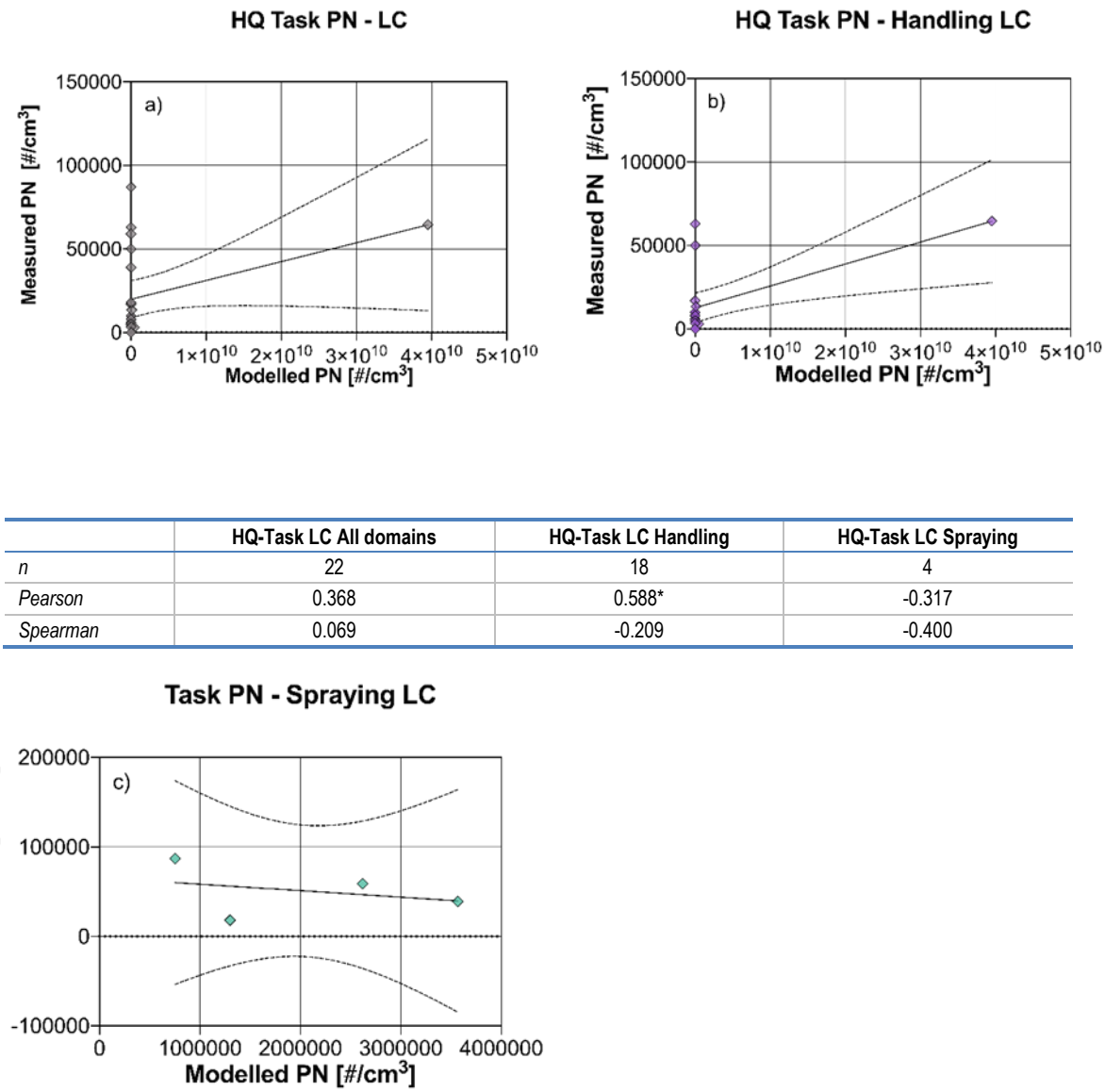
Spraying	Task	Task LC
n	4	4
Pearson	0.873	0.873
Spearman	**1.0**	**1.0**

Figure 20. Correlation of modelled mass concentrations with measured respirable BG subtracted mass concentrations for a) all domains, c) powder handling and e) spraying. HQ case studies with LC applied are shown for b) all domains, d) powder handling and f) spraying.

Note: For E1-E2 cases respirable not BG subtracted values shown. For S1, S4, S5, S6, S7 and S8 cases inhalable not BG subtracted values shown.

79. Significant Spearman correlation between modelled mass fraction and respirable measured mass concentrations were obtained with coefficients of 0.54, 0.53 and 1 for all domains, powder handling and spraying, respectively. When LC were applied and HQ case studies used, correlations coefficient for all domains and powder handling increased up to 0.63 and 0.61, respectively. Thus, overall, for mass concentrations spearman correlation coefficient obtained were over the 0.6 threshold values considered acceptable in this performance testing exercise. Conversely, only significant 0.59 spearman correlation coefficient were obtained for particle number concentrations and powder handling domain. It should be noted the high data clustering.

80.



	HQ-Task LC All domains	HQ-Task LC Handling	HQ-Task LC Spraying
n	22	18	4
Pearson	0.368	0.588*	-0.317
Spearman	0.069	-0.209	-0.400

Figure 21. Correlation of particle number modelled with measured BG subtracted particle number concentrations.

Note: a and b) all domains, b) powder handling, and c) spraying. Only HQ cases with LC applied shown. For C1-C7, E4, I2-I3 and V2 not BG subtracted values shown.

3.4.3. Conclusion

81. The performance testing of the ENAE-CPSC tool was based on a total of 39 exposure scenarios, from which 31 were classified as HQ case studies. The total cases were divided in 34 cases for powder handling domain and 4 cases for spraying domain. Overall, the correlation of modelled concentrations with measured respirable concentration was found to be significant, with coefficients that ranged between 0.61-1.0 (>0.6 threshold) when HQ cases were used and LC were applied. However, underestimations for powder handling and total cases were slightly higher than 10% with max underestimations percentages of

10.7 and 21% for the total comparisons and powder handling when using HQ case studies and with LC applied. For spraying domain, even though real measurements did not exceed the model estimates for more than 10% of the total comparisons and spearman correlation >0.6, only 4 data points were available, which is not sufficient to reach any solid conclusions.

3.5. LiCARA nanoSCAN v1.0

3.5.1. Introduction

82. LiCARA nanoSCAN is a web-based tool for life cycle and risk assessment. The performance of the tool was investigated using two life cycle scenarios especially generated under the caLIBRAte project for the tool testing purposes. The version available on the internet (https://acc-diamonds.tno.nl/licara) at 5th September 2019 was used in evaluations. The tool can also be accessed through the https://sunds.gd/ portal.

83. The LiCARA nanoSCAN is a tool devoted to small and medium enterprises (SMEs) to explore the benefits and the risks of the nanoproducts at an early stage of the innovation funnel (van Harmelen et al., 2016[21]). The tool is designed to serve as a screening level self-assessment. The LiCARA nanoSCAN tool guides through a decision-making processes and produces an overview of what the social, economic and environmental benefits of a new nano-product are compared to another, e.g. conventional product. The benefits are compared to the health risks for consumers, workers and the environment. The tool specifically consists of 6 different modules, namely environmental benefits, economic benefits, societal benefits, public health & environmental risks of nano, occupational health risks of nano and consumer health risks of nano. Depending on the specific aims of the screening, different modules may be relevant. After filling in the modules, a decision support is obtained.

3.5.2. Methods

Selection of measured exposure data

84. In the case of the LiCARA nanoSCAN tool the approach utilized for gathering input parameters for other models could not be used. Input parameters for benefits evaluation need very detailed information about the business case (e.g. reference material, material flows or market potential) which is not available in most of the case study descriptions. Therefore, two life cycle scenarios were created for testing of the model: 1) TiO_2 in façade coating system and 2) microfiber cloth treated with nAg or triclosan (based on (van Harmelen et al., 2016[21]) study).

85. In the first example the environmental performance of two different façade coating systems were compared. One system comprises of a layer of a traditional paint containing pigment grade TiO_2, covered then by a second layer, a transparent coating containing nano-TiO_2 (having a self-cleaning function, and thus a prolonged life-time), while the 2nd system represents a façade that is coated only with the traditional paint. In the second example cleaning cloths made from microfibers and treated with either nano-Ag or triclosan were compared.

Input parameters (data entered into the model)

86. The LiCARA nanoSCAN tool requires several input parameters related to the nanomaterial (7 questions), the environmental benefits (20 multiple choice questions), the economic benefits (5 multiple choice questions), the social benefits (3 questions), the public health and environmental risks (9 multiple choice questions) and the occupational health risks (applies Stoffenmanager nano). All the specific input parameters required in LiCARA nanoSCAN are listed in Table 8.

Table 8. Input parameters for LiCARA nanoSCAN tool.

Entry
0. Nanoproduct and legislation
Type of nanomaterial and application
Which nanomaterial will be used?
Please specify additional nano subtype or indications/properties:
In which type of application is the nanomaterial be used?
Is this a completely new product with a new functionality (which cannot easily be compared with a conventional product)?
If not, what conventional product is being replaced by the new nanoproduct? (this can also be 'doing nothing')
The product under evaluation is:
What is the main function that the nanomaterial provides in your application?
What is the appropriate unit to compare the nanoproduct with the conventional product? (It is fair to compare same functionality)
In case you have selected 'Other' please specify:
Nano-relevance
Approach 1 (precautionary approach): Ranges of sizes of primary particles contained in the materials (free, bound or as aggregates or agglomerates)?
Approach 2 (EU-proposed definition 2011/696/EU): Material containing primary particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the primary particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm or (if the number size distribution is unknown) Material where the specific surface area by volume is greater than 60m2/cm3 or Material consists of fullerenes, graphene flakes or single wall nanotubes.
Legislation
Are you aware of existing legislation (e.g. EU Nr. 1907/2006 (REACH), The EU Biocides Regulation 528/2012 (EU BPR), Regulation (EC) No 1223/2009 on cosmetic products …)
Is your nanomaterial approved or notified according to relevant EU-legislation (e.g. EU Nr. 1907/2006 (REACH), The EU Biocides Regulation 528/2012 (EU BPR), Regulation (EC) No 1223/2009 on cosmetic products …)
Do you use the nanomaterial below its specific concentration limits recommended in the legal framework (e.g. http://ec.europa.eu/environment/chemicals/biocides/active-substances/approved-substances_en.htm)
1. Environmental benefits
Manufacturing phase of the nanoproduct versus conventional product
Energy consumption of the manufacturing process of the product?
Materials consumption in this manufacturing process?
Amounts of hazardous substances used in the manufacture?
Efforts needed to produce the product using the nanomaterial?
Amount of solid waste from the manufacturing process?
Amount of waste water from the manufacturing process?
Emissions to the air or (waste) water from the manufacturing process itself?
Energy consumption of the manufacturing process of the product?
Use phase (only for final products and articles)
Product life time (use phase)?
Need for maintenance?
Amounts of hazardous substances used in maintenance?
Amount of solid waste from using the product?
Amount of waste water resulting from use of the product?
Emissions of hazardous substances to air, water and/or solid?
Efficiency of use?
Product life time (use phase)?
Need for maintenance?
End-of-life (only for final products and articles)
Volume of waste (due to e.g. longer lifetime, less weight, less material used)?
Amounts of other hazardous substances released from the waste water treatment?
Amounts of other hazardous substances released during incineration?
Established recycling systems (glass, PET, paper, carton, batteries, biowaste, electronic devices, etc.) exposed to the nanomaterial in the product?
Volume of waste (due to e.g. longer lifetime, less weight, less material used)?
Amounts of other hazardous substances released from the waste water treatment?
Can the waste water treatment facility eliminate the nanoproduct's emissions?

Can the waste incineration facility eliminate the nanoproduct's emissions?
2. Economic benefits
Market potential
Does the nanoproduct have increased marketability due to an improved functionality or a new functionality (for example: UV-protection, enhanced photolytical self-cleaning/ self-cleaning capacity/property, conductible, antimicrobial function), or a clear image advantage compared to the conventional product (e.g.: more resistant to environmental effects, prolonged lifetime/persistence, reduced weight or increased strength)?
What is the foreseen market potential of the nanoproduct or -application in Europe?
Profitability
What is the (expected) purchase price per unit of the nanobased product or material compared to the conventional one?
What are the operational costs (i.e. maintenance, energy use etc) during the use phase of the nanobased product or application compared to the conventional one? (Think of advantages due to nanoproperties in the manufacturing process)
Development stage
What is the time-to-market to manufacture the nanoproduct on a commercial scale?
3. Societal benefits
Technological breakthrough
Could the use or application of the nanoproduct be considered a technological breakthrough (in general, but particularly in energy systems and Information and Communication Technologies, ICT) compared to the conventional alternative?
Highly qualified labour force
Does the production of the application lead to a substantial improvement in the development of a highly qualified labour force compared to the conventional alternative?
Improving global health or food situation
Does the use or application of the nano-based product lead to improvements in feeding the world's population, a marked increase in food production and the nutritional value of food? OR Does the use or application of the nano-based product lead to improvements in people's health, particularly the direct user, e.g. by improvements in water purity, sanitation or medicines and pharmaceuticals?
4. Public health & environmental risks
System knowledge
Is the origin of the (nanoscale) starting materials known?
Are the next users of the nanomaterials under consideration known?
How accurately is the material system known or can disturbing factors (e.g. impurities) be estimated?
Potential effect
Do the nanomaterials cause redox activity, catalytic activity, have a potential for oxygen radical formation or to induce inflammation reactions?
What is the stability (half-life) of the nanoparticles present in the nanomaterial under ambient environmental conditions?
Potential input into the environment
What is the annual quantity of nanoparticles from the *manufacturing phase*that reaches the environment via wastewater, exhaust gases or solid waste?
What is the physical surrounding or carrier material of the nanoparticles in the product during the *use phase*?
What is the annual quantity of nanoparticles in products that reaches from production or use phase the environment via utility products, waste water, exhaust gases or solid waste?
What is the annual quantity of disposed nanomaterial (from the production or use phase)?
5. Occupational health risks
Hazard & exposure during manufacture of the nanomaterial
Hazard class and task weighted exposure class from Stoffenmanager® Nano module 1.0
Hazard & exposure during processing the nanomaterial
Hazard class and task weighted exposure class from Stoffenmanager® Nano module 1.0
Hazard & exposure during application of the nanoproduct
Hazard class and task weighted exposure class from Stoffenmanager® Nano module 1.0
6. Consumer health risks
Hazard & exposure by consumers during use phase
At what location is the nanoelement situated in the article or the product? The product…
What is the size of the consumer population using the nanoproduct and hence which may be exposed?

87. The information available in the scenario descriptions was translated into input values for the model. In this performance test, one person evaluated and entered the values for input parameters based on cases description. For parameters with unknown values, it was decided to assume a value that would

lead to the highest exposure estimate to make conservative estimates. Values entered for each case study are not available.

88. In the output screen, the benefits and risks are presented in relative scores for each of the three categories. The benefits are evaluated in comparison with a reference product ranging from score -1 (negative benefits, nanoproduct much worse than reference) to +1 (positive benefits, nanoproduct much better). The risks posed by nanoproducts are presented on a scale varying from 0 to 1. The following risk bands are formed: scores below 0.3 indicate 'low risks', scores between 0.33 and 0.67 indicate 'medium risks' and scores higher than 0.67 means a 'high risk' from nanomaterials.

89. In order to receive a positive assessment, sufficient data must show high potential benefits and low potential risks with a high confidence level. If some of the questions are not answered or unknown option has been selected, the ambiguity of the result is shown by error bars (large error bars).

Comparison of model estimates with measured concentrations

90. A comparison between the interpretation of input values and thus results given by LiCARA nanoSCAN was performed. Together with the case study descriptions a pre-filled input parameters for both case studies was achieved. The author of the tool assessment individually evaluated the input parameters based on the written description of the case studies. The outputs of the tool and the subsequent report were compared to the results of the case study owner.

3.5.3. Results and discussion

Case 1 – TiO_2 in façade coating

91. In the façade coating case study, the comparison between the results of the case study owner's and the author of the tools assessment report revealed the following disagreements (Figure 22).

- most of the differences were observed in the interpretation of the environmental benefits: case-study owner valued environmental benefits much more positive than the author of the tool assessment report.
- some disagreement with economic benefits: author of the tool assessment report valued the operational costs to be higher than the case study owner.
- some disagreement with the societal benefits: case study owner valued societal impacts to be higher than the author of the tool assessment report.
- in public and environmental risks discrepancies were observed with valuing in potential effect (redox and catalytic activity, radical formation etc.).
- in occupational risks the both appraisers got the same results.
- in consumer risks there were some differences in valuing the risks.

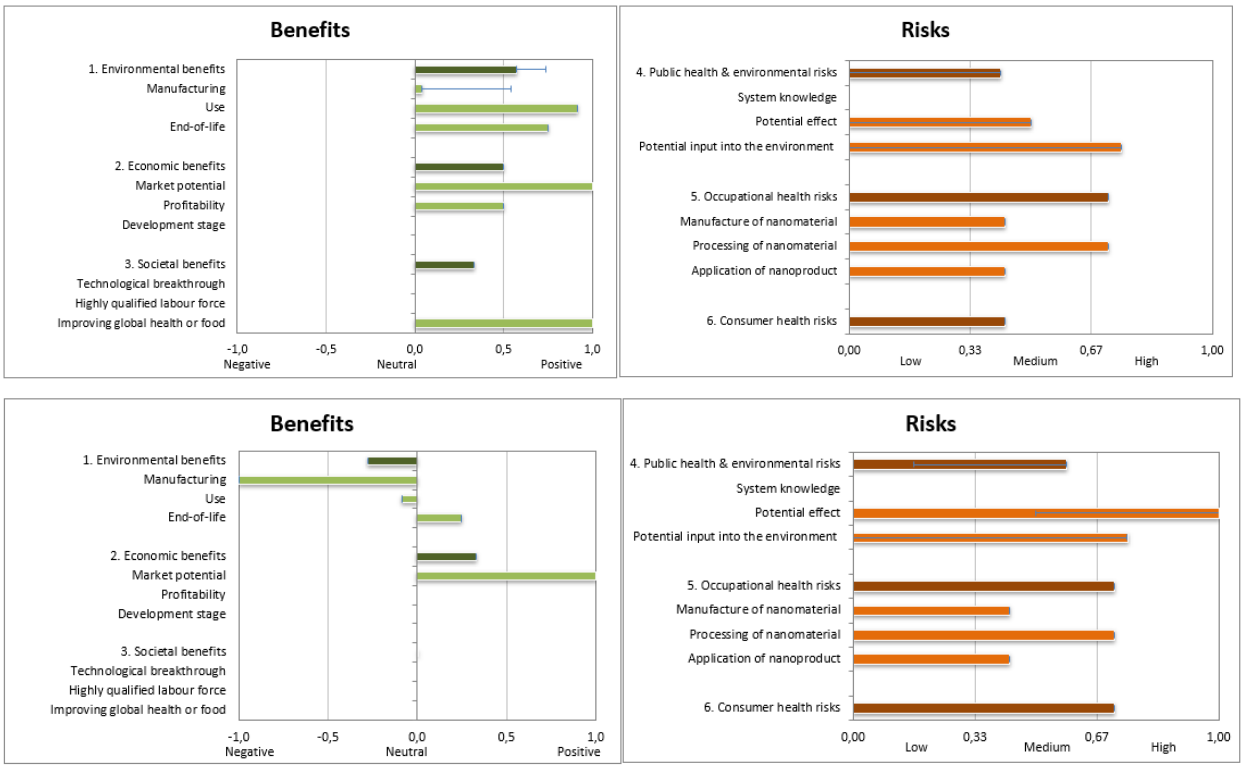


Figure 22. Comparison of separate presentation of benefits and risk. Upper figure: study owner's interpretation and lower figure: tool assessment author's interpretation.

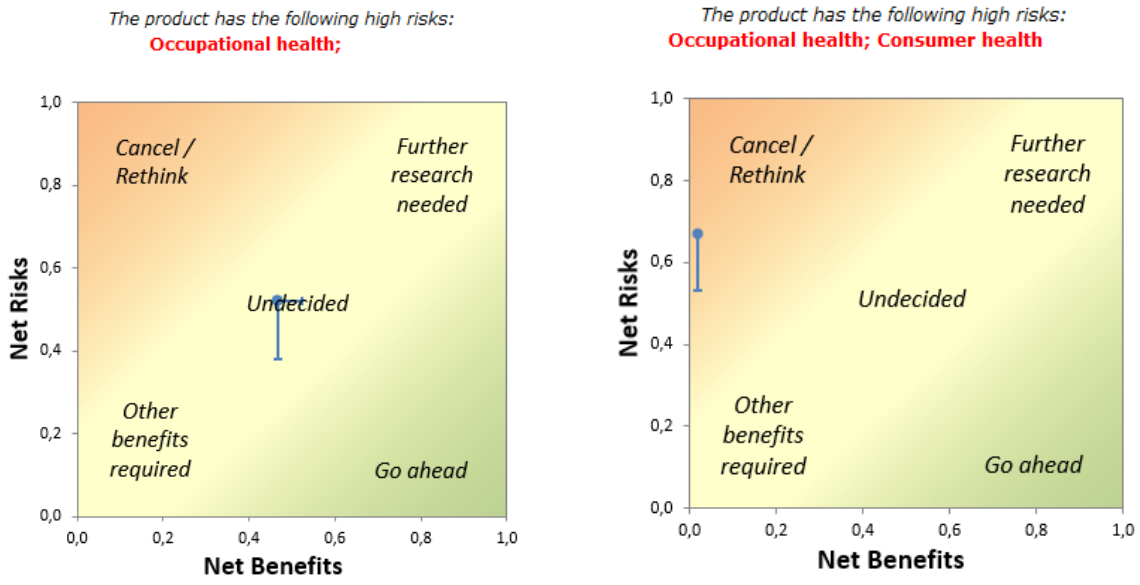


Figure 23. Comparison of the evaluation of benefits and risk. Left study owner's interpretation and right tool assessment author's interpretation.

92. As the opinions of the appraisers on the benefits of the new coating system disagreed significantly between the case owner and the tool assessment author, the decision support given by the LiCARA

nanoSCAN tool was different. The case study owner got “undecided” while the tool assessment author ended up advising to “cancel/rethink the case” (Figure 23).

Case 2 – Microfiber cloth treated with nano-Ag or triclosan

93. As in Case 1, the most differences between two appraisers were in valuation of the benefits. The case study owner considered the benefits much higher than the author of the tool assessment did. Again, the biggest difference was in evaluation of the potential effect. However, valuation of the risks were more similar in this case (Figure 24). Because the opinions of the benefits between two appraisers differed considerably, the outcome of the assessment was different as well. The case study owner decided to “Go ahead” while author of the tool assessment considered “Other benefits needed” (Figure 25).

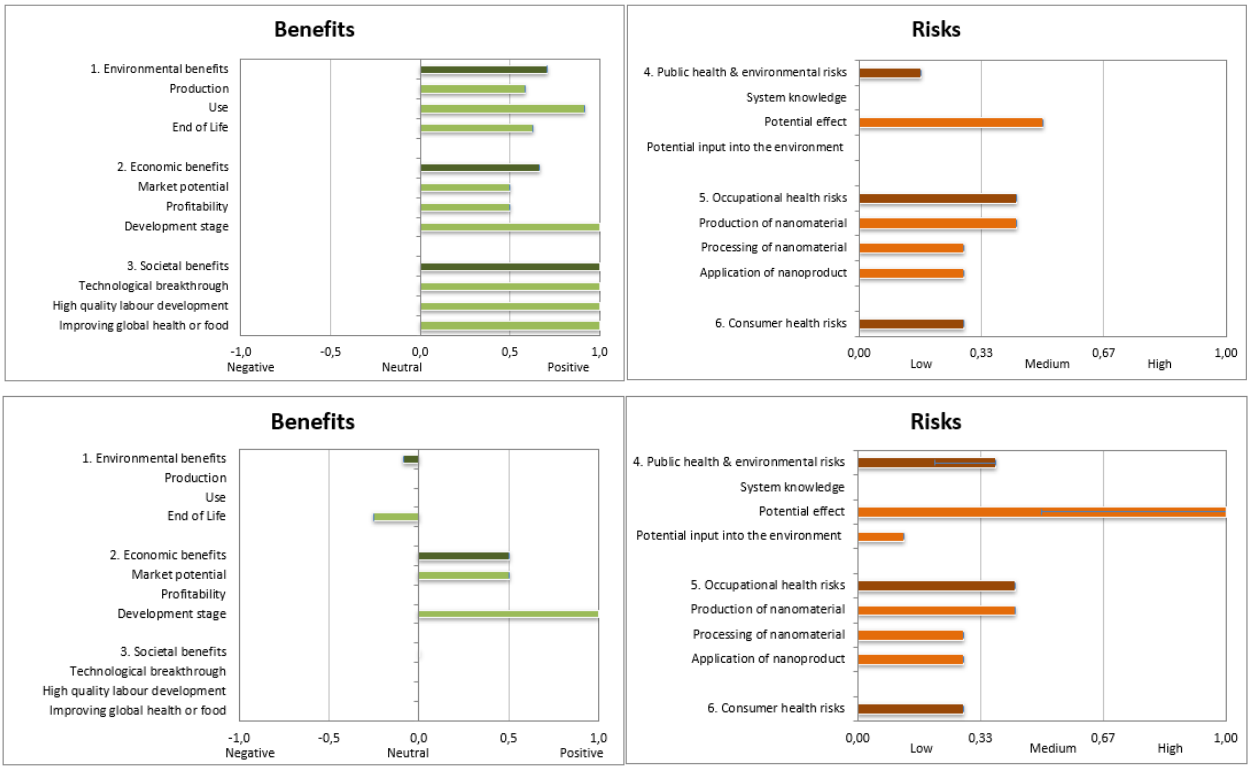


Figure 24. Comparison of separate presentation of benefits and risk. Upper figure: study owner’s interpretation and lower figure: tool assessment author’s interpretation.

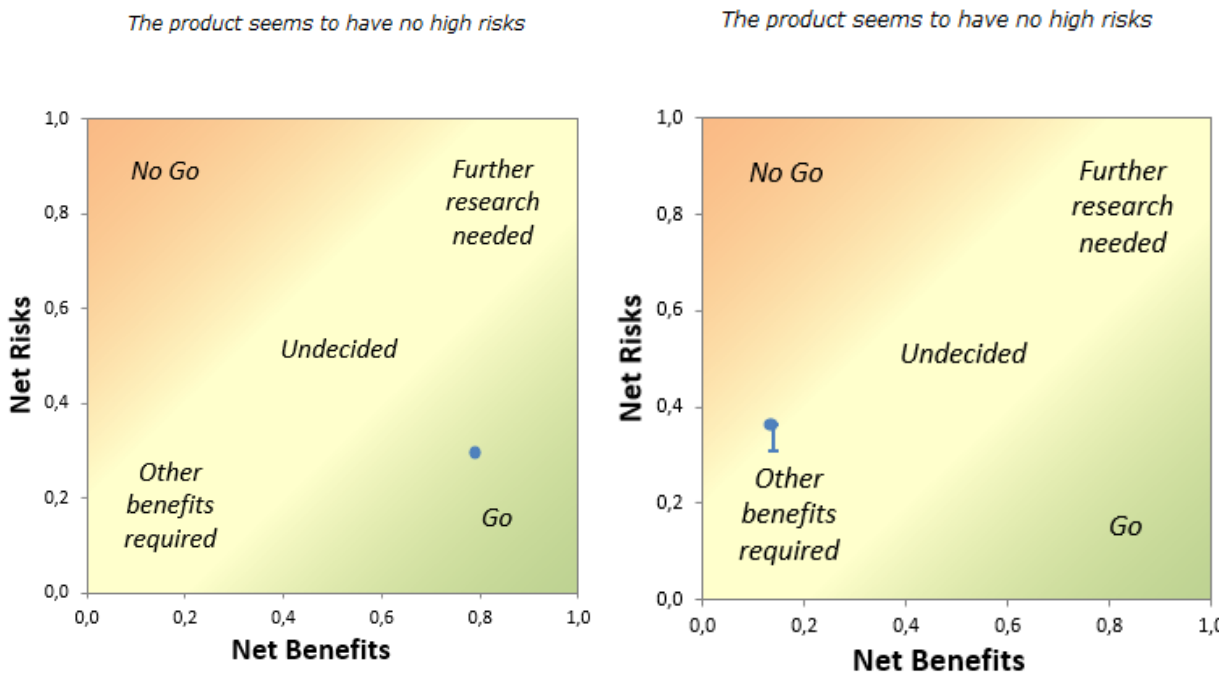


Figure 25. Comparison of the evaluation of benefits and risk. Left study owner's interpretation and right tool assessment author's interpretation.

3.5.4. Conclusions

94. According to the LiCARA guidelines (Som et al., 2014[22]) the original scope of the LiCARA nanoSCAN is to be an accompanying tool for the LiCARA product development concept helping SMEs to make decisions during the developing and producing of safe, sustainable nanoproducts. As indicated in the guidelines "the LiCARA nanoSCAN gives a first, inherently uncertain, indication of the pros and cons of a new nanoproduct".

95. During this testing period it was not possible to compare results with real-life values, especially for the benefits questions. Input parameters for benefits evaluation need very detailed information about the business case (reference material, environmental impacts such as energy and material flows, economic benefits such as market potential and profitability and societal effects). To fill in the LiCARA nanoSCAN profile in a sensible way, a multidisciplinary expertise is required as was pointed out also by Grieger *et al.* (2018[23]).

96. For the environmental benefits, the life cycle assessment reported in the case description gave a good basis for the input parameters. For economic and societal benefits, the input values were more or less expert judgements. For risk module the inputs parameters were more in the same line for both apprisers. The LiCARA nanoSCAN might benefit from the inter-assessor reliability study in which the ability of different assessors to reach the same conclusions about a specific case is investigated.

3.6. NanoSafer v1.1β

3.6.1. Introduction

97. The NanoSafer v1.1β is a combined control-banding and risk management tool (Kristensen et al., 2010[24]); Jensen et al., 2010 in preparation) that enables assessment of manufactured nanomaterials as well as products and articles containing nanomaterials (e.g., nanoparticles, nanoflakes, nanofibers, and nanotubes) in specific work scenarios (powder handling or leak/point source). Further developments in future aim to expand the application domains for an assessment of exposure for mechanical reduction and spraying processes and include assessment with risk management measures as part of caLIBRAte project (http://www.nanocalibrate.eu/home). The tool is currently intended for small and medium-size companies and laboratories with no or limited information on or experience in working with nanomaterials and/or insufficient resources to perform a full precautionary risk assessment. The tool is available at http://www.nanosafer.org/. At the moment for the performance testing assessment, two versions were available, the original v 1.1beta damped particle clearance model and a revision of it to full mass-balance version identified as "simplified". The performance of both versions were considered and examined.

3.6.2. Methods

Selection of measured exposure data

98. A total of 50 exposure measurement studies were used for performance testing of NanoSafer v1.1β (*Annex A – Case studies.xlsx)*. These studies were divided in two application domains: i) powder handling (41 exposure scenarios; A1-A4, C1-C7, E1-E4, F1, G1, S1-S9, T1-T4, U1, V1-V2, Z1-Z3, and FF1-FF5), and ii) leak/point source (9 exposure scenarios; B1-B4, GG1-GG4, and II1) with mean (min-max) quality scores of 0.94 (0.81-1.0) and 0.80 (0.59-1.0), respectively. The application domains tested depended on the availability of data in the exposure scenario rather than to the model applicability. The full list of case studies is available in "*Annex A –Case studies.xlsx*". Input and output parameters entered in the tool for each case scenario are reported in *"Annex B3 – NanoSafer Original reports.pdf"* and *"Annex B4 – NanoSafer Simplified reports.pdf"* which contain the original tool reports.

99. For higher confidence in the performance testing, a selection of high quality (HQ) cases (quality score ≥0.7) and cases which did not present any limitation (measured concentration under detection limit and interferences of secondary processes) was used for the performance testing assessment. In the HQ dataset, case studies included were C1-C7, E1-E4, F1, G1, S1-S9, T4, U1, V2, Z1-Z3, and FF1-FF5 for powder handling domain, and B1-B4 for spraying domain.

Input parameters (data entered into the model)

100. A total of 24 and 21 data entries are requested for powder handling and leak/point source, respectively. From these total data entries, 3 material identifiers are optional (manufacturer, CAS or EINICS number). Depending on the process domain, the number and type of requested parameters differ. Table 9 lists all of the selected input parameters with indication on in which modules the information is used.

101. The NanoSafer v1.1β control-banding tool includes four modules:

- Materials collects the information regarding the material information.
- Hazard information collects the information regarding safety data.
- Processes information collects the information regarding the process and contextual information.

– Risk Assessment evaluates the risk and predicts the hazard and exposure potential and the protection level that one should apply conducting the work described in the Process module with the selected materials.

Table 9. Data requested by NanoSafer v1.1β and indication of their application in specific modules of the risk evaluation system.

Input data	Type of Process		Unit	"Nano relevance"	Hazard	Exposure
	Powder	Leak/point source				
Material identifiers						
Material name	x	x	Text	-	-	-
Manufacturer	optional	optional	Text			
CAS number	optional	optional	Text	-	-	-
EINICS number	optional	optional	Text	-	-	-
Material information						
Is the nanomaterial labeled with a nano-specific word or term?	x	x	yes/no	x		-
Is the nanomaterial coated or surface modified	x	x	yes/no	x	x	-
Size of the primary nano-object ($a \leq b \leq c$)	x	x	nm	x	x	-
Relative density (specific gravity) density of the material	x	x	g/cm^3	x		x
Solubility of the material in water	x	x	binary	x	x	-
The specific surface area	x	x	m^2/g	x		-
Respirable dustiness of powder€	x	x	mg/kg	-		x
Safety data /Hazard						
Is there a nanospecific occupational exposure limit (OELnano) or target value?	x	x	yes/no	-	x	x
Respirable OEL for the nearest analogue material	x	x	mg/m^3	-	x	x
Hazard phrases / Risk sentences	x	x	decimal unit	-	x	-
Contextual information						
Emission rate if constant source emission or leak	-	x	mg/min	-	-	x
Activity handling energy factor£	x	-	decimal unit	-	-	x
Total mass of material handled in each work cycle	x	-	kg	-	-	x
Duration of the work cycle	x	x	min	-	-	x
Pause between work cycles	x	x	min	-	-	x
Number of work cycles per day	x	x	n	-	-	x
Amount of nanomaterial handled in each transfer	x	-	kg	-	-	x
Time required per task in cycle (spoon, bag, big-bag etc.)	x	-	min	-	-	x
Volume of the work room (width x length x height)	x	x	m^3	-	-	x
Air exchange rate	x	x	h^{-1}	-	-	x
Activity level in the room*	x	x	decimal unit	-	-	x

Note: € choose dustiness level if you do not have the test result
£ H0 "Zero energy" (e.g. Removal and handling of clean barrels and plastic containers)
H1 (e.g. Pouring of powders with up to 1 cm drop in free air; careful balancing)
H2 (e.g. Pouring of powders with 1-2 cm drop in free air; careful wet mixing)
H3 (e.g. Pouring of powders with 2-5 cm drop in free air; wet mixing)
H4 (e.g. Pouring of powders with 5-10 cm drop in free air; open conveying of powder)
H5 (e.g. Pouring of powders with 10-20 cm drop in free air; handling contaminated or leaking bags)
H6 (e.g. Pouring of powders with 20-40 cm drop in free air; filling of bags and big bags)
H7 (e.g. Pouring of powders with 40-60 cm drop in free air; careful dry mixing)
H8 (e.g. Pouring of powders with 60-80 cm drop in free air; dry mixing)
H9 (e.g. Pouring of powders with 80-100 cm drop in free air; vigorous handling, folding open bags)
H10 (e.g. drop heights > 1 m, dry mixing, cleaning with brusher or compressed air, accidents)
* this input parameter will be eliminated in the near future for control banding assessments

102. In NanoSafer, exposure levels are calculated using the potential emission rate (constant release or activity energy × dustiness index × mass-flow), duration and frequency of the activity, and information about the volume of the work area and its ventilation rate. The theoretical acute and 8-hour exposure level at NF and FF is scaled by normalization to a theoretical nanospecific OEL, which derived from the ratio between the specific surface area of the bulk OEL (using 200 nm sizes as the bulk particle reference) and the specific surface area of the nanomaterial in question.

103. The exposure score ranges from 0 to ∞ and the exposure risk level is defined in five scales separated at 0.1, 0.25, 0.5, and 1.0, where the surface-area derived estimated OEL_{nano} is exceeded when the exposure risk level is larger than 1. The hazard estimate is a finite four-step linear scale ranging from 0 to 1 with increase in hazard level at 0.25, 0.5 and 0.75 points.

104. Hazard assessment and case-specific exposure potentials are currently combined into an integrated assessment of risk levels expressed in control bands (RL1 to RL5) for the acute and daily NF and FF exposure in the scenario. Each control band (risk level) is associated with general recommendations for risk management such as use of local exhaust ventilation and personal protection. The output is a recommendation on the requirements to achieve a safe working environment.

105. The available information in each exposure scenario was gathered according the required input parameters for NanoSafer v1.1β and harmonized with other occupational exposure assessment tools (e.g. GUIDEnano and Stoffenmanager nano). The input information/values were entered manually by one person, and therefore, the user variability was not assessed. Other person checked the input parameters to validate the consistency and accuracy of the performance testing. If the data entered in the NanoSafer v1.1 varied from these two persons, a discussion was taken to reach consensus on the input parameters used in the model estimations. For unknown input parameters, it was decided to assume a value that would lead to the highest exposure estimate to make a precautionary assessment.

Comparison of model estimates with measured exposure

106. The performance of the tool NanoSafer v1.1β was tested by comparing its output for 8-hour exposure level at NF with experimentally measured exposure levels. The exposure level in NanoSafer is given in scores. The scores in NanoSafer v1.1β are classified in five exposure bands (EB): EB1-very low exposure potential, EB2-low exposure potential, EB3-moderate exposure potential, EB4-high exposure potential, and EB5-very high exposure potential. In order to compare the model output directly with the real measured values, the scores were converted in quantitative values of respirable particle mass concentrations (µg/m^3) with/without quantitative recommendations.

107. To determine whether and to what extent the model estimated scores correlated with measured exposure values, the Spearman correlation coefficient was calculated for each application domain as well as Pearson correlation and percentage of underestimation were also calculated.

108. For higher confidence on the performance testing, the output of NanoSafer v1.1β was compared to data preferably background corrected, substance-specific respirable dust concentration, and representative to the breathing zone of the person/worker. In case such data was not available in a particular scenario, measured respirable mass concentrations not background corrected, non-substance-specific and taken in NF by using stationary equipment were also considered but more careful interpretation of results was taken. It was decided, according to criteria described in section 2.1, that the exposure measurements should not be higher compared to the model estimates in any of the application domains of the model. Additionally, measurements should not exceed the model estimates for more than 10% of the total comparisons.

3.6.3. Results and discussion

109. For the purpose of performance testing, relevant information corresponding to 50 measurements (for powder handling and leak/point source domains separately) were retrieved and complied in Table 10. The statistical parameters of the measured and modelled (simplified and original version) exposure mass concentrations in all the cases considered in each application domain are shown in Figure 26 and Figure 27.

Table 10. Relevant information on data graduation, measurement data and tool estimated values.

	Application domain	Powder handling	Leak/point source
Report data from actual measurements	Number of case studies considered	41	9
	Number of personal exposure data used	30	5
	Number of stationary exposure data NF used	11	4
	Number of stationary exposure data FF used	0	0
	Number of substance-specific data	28	5
	Number of non-substance-specific	13	4
	Range of measured respirable mass (BG subtracted) (µg/m^3)	0.02-137.4	0.06-2.9
	Range of measured respirable mass (not BG subtracted) (µg/m^3)	0.04-539.2	N/A
Report data from NanoSafer simplified version	Range of NF daily exposure score (-)	0-175.8	0.02-9778.5
	Range of NF daily concentrations converted without considering the risk management measures (µg/m^3)	0.0-48150.0	99.9-52027.1
	Range of NF daily concentrations converted considering the risk management measures present in the case study, LC applied (µg/m^3)	0.0-8209.1	70.1-52027.1
	Range of ratio modelled/respirable measured	0.0-900793.9	77.1-34116.1
	Range of ratio modelled LC/respirable measured	0.0-5404.8	39.3-34116.1
Report data from NanoSafer original version	Range of NF daily exposure score (-)	0.0-351.6	0.04-9828.9
	Range of NF daily concentrations converted without considering the risk management measures (µg/m^3)	0.0-97320.0	198.6-52295.5
	Range of NF daily concentrations converted considering the risk management measures present in the case study, LC applied (µg/m^3)	0.0-16588.8	123.41-52295.5
	Range of ratio modelled/respirable measured	0.0-1564.9	171.0-153280.0
	Range of ratio modelled LC/respirable measured	0.0-153.2	171.0-78172.8

Note: N/A: not available

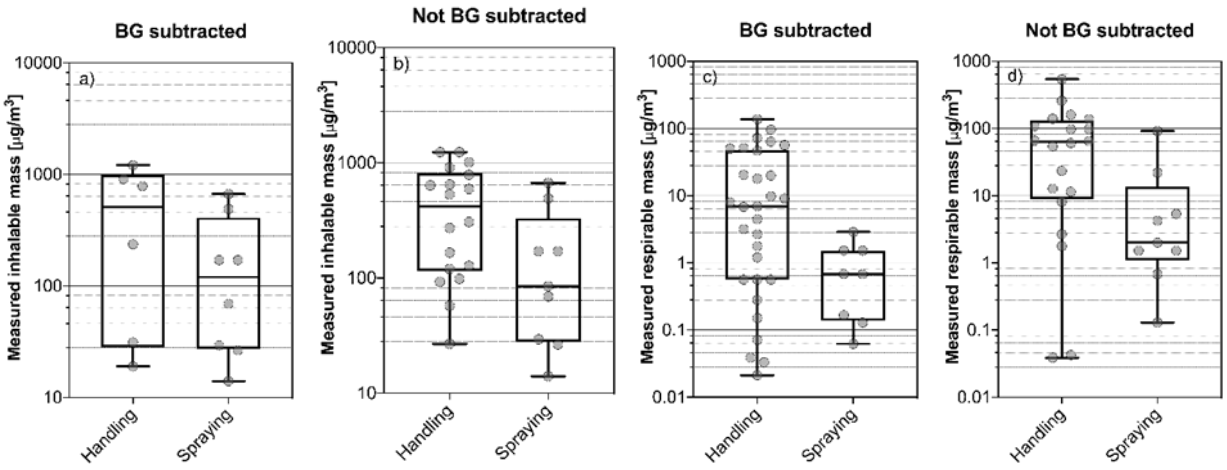


Figure 26. Vertical box plots for the measured exposure mass concentrations in each application domain of NanoSafer V1.1β a and b) original version, and c and d) simplified.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively.

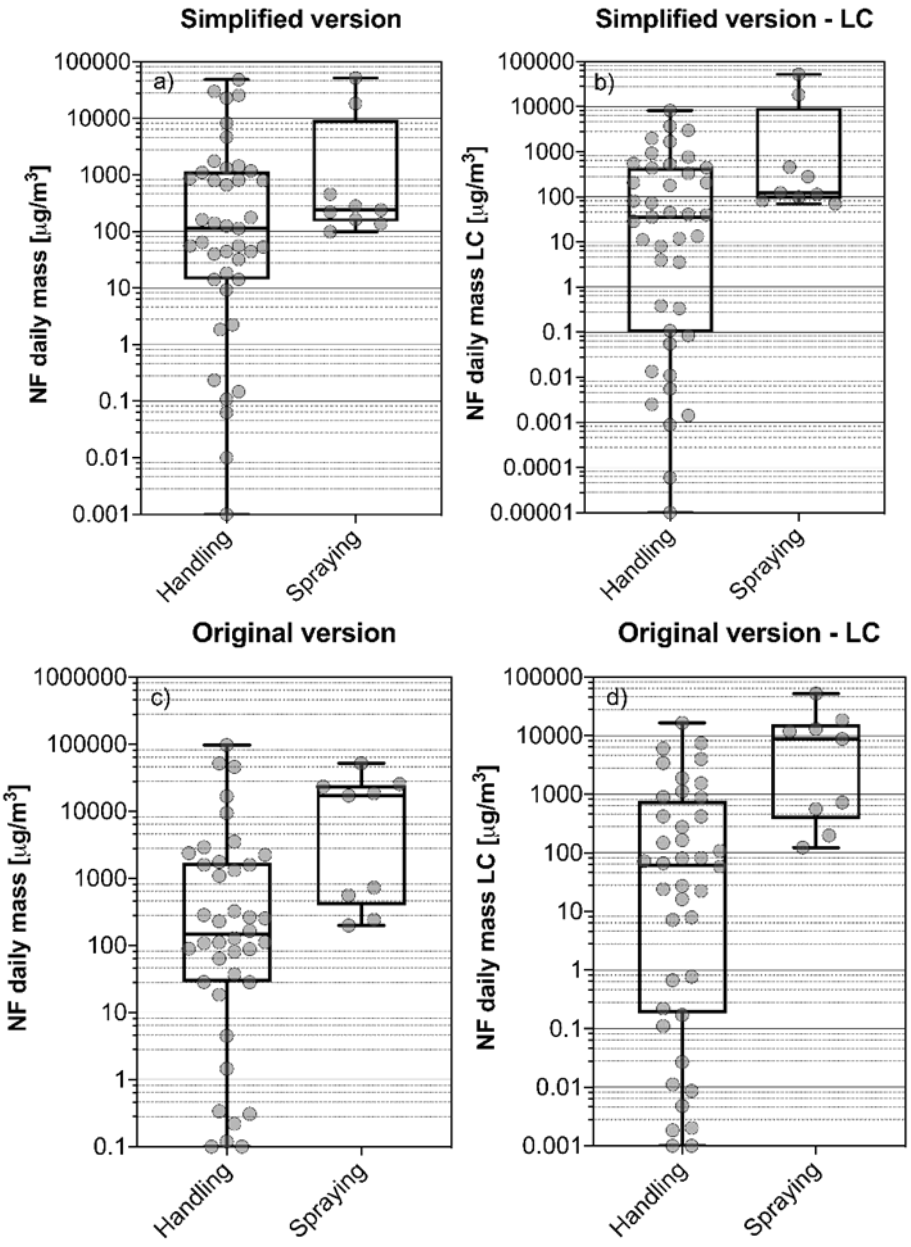


Figure 27. Vertical box plots for modelled exposure mass concentrations in each application domain of NanoSafer V1.1β when using the original (a) and simplified versions (c), and applying the corresponding LC factor (b and d, respectively).

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively.

Comparison of exposure score with measured respirable mass

110. The predicted scores (i.e. dimensionless output of the model from 0 to infinite), are shown to vary for the powder handling and spraying domains from 0-176 and 0.02-60133 for the simplified version, and 0-352 and 0.04-9829 for the original version (Table 10). These scores correspond to simplified version modelled concentrations varying from 0-48150 µg/m³ for powder handling and 100-52027 µg/m³ for

leak/point source domain, and original version modelled concentrations ranging from 0-97320 and 199-52296 µg/m^3 for powder handling and leak/point source domains. These converted modelled mass concentrations are without considering the reductions due to the local controls in place (LC). When applying the corresponding multiplier, simplified version modelled concentrations range from 0-8209 and 70-52027 µg/m^3 for powder handling and leak/point source domains, respectively. Similarly, for the original version modelled concentration with LC applied ranged were also reduced, and ranged from 0-16589 and 123-52296 52027 µg/m^3 for powder handling and leak/point source domains, respectively. In Figure 28, simplified and original version scores (Figure 28 a) are shown to correlate with a R^2 of 0.999 and a 95% confidence interval slope 0.988 to 1.00. On the other hand, converted mass concentration correlated for the two version with a R^2 of 0.899 and a 95% confidence interval slope of 0.542 to 0.619 (Figure 28 b). The small deviation observed are due to cases A3, A4, GG1 and GG3. Cases A3 and A4 are in the lower end of the concentration range with modelled exposure concentrations close to 0 in both cases, with nearly no variation on the modelled value between the versions. Similarly, cases GG1 and GG3 are in the higher end of the concentration range showing concentrations higher than 10000 µg/m^3. As occurred with the values in the lower end, modelled concentrations show very small differences between modelled versions as opposed to the behaviour of the tool in the rest of the range, where the simplified version concentrations are approximately double than in the original version. The deviations caused by these 4 cases are more evident after converting the scores provided by the tool to mass concentrations.

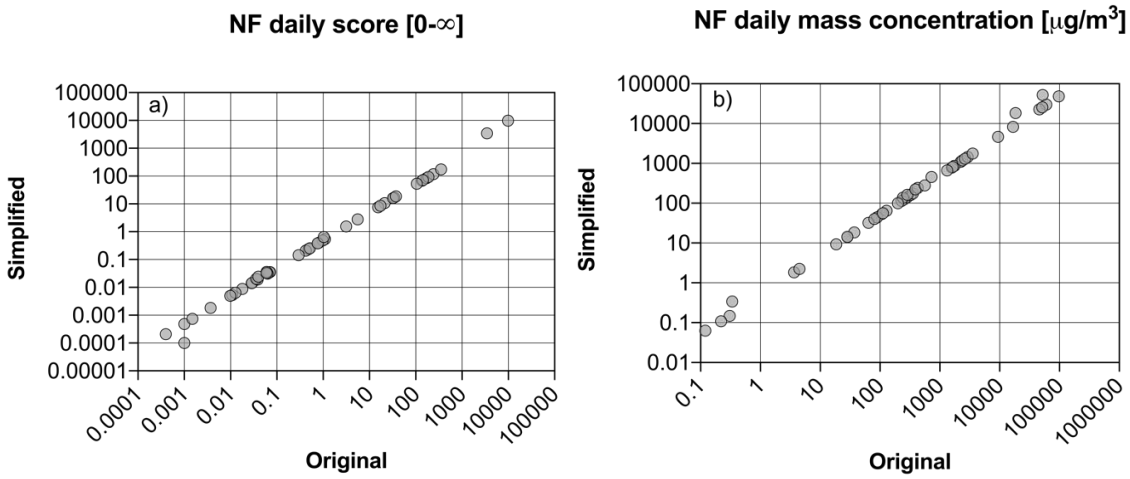


Figure 28. Correlation of NF daily score (a) and NF daily mass converted concentration (b) of simplified and original NanoSafer versions.

111. In Figure 29, correlation between NF daily score and the converted modelled mass concentration for the two NanoSafer versions (original and simplified) are shown. In both cases significant Pearson correlation were obtained, with values of 0.64 and 0.78 for the original and simplified version, respectively.

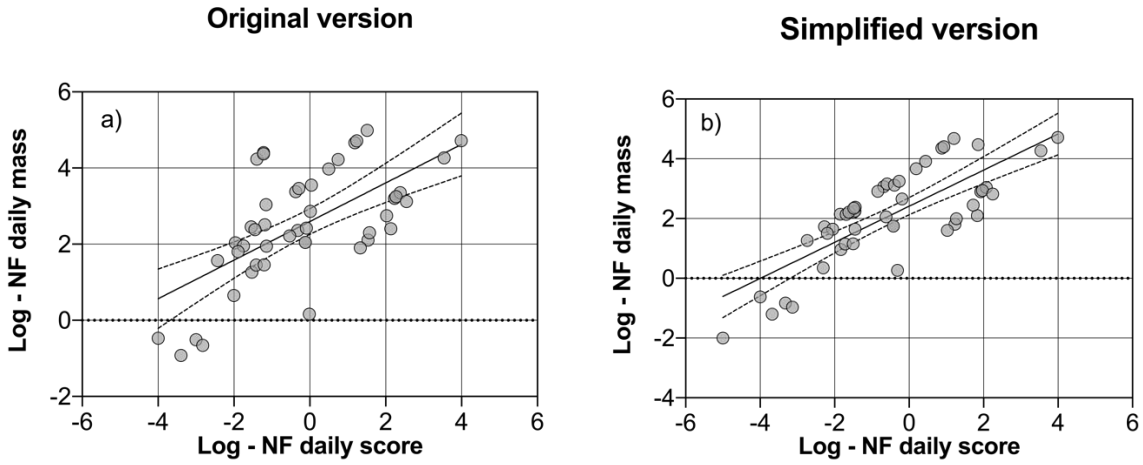
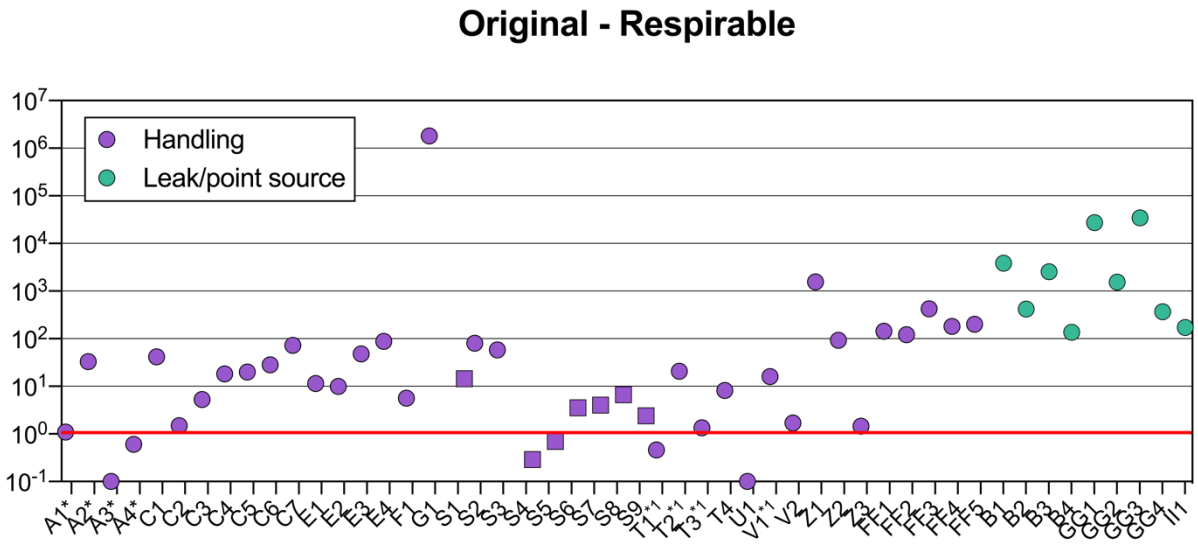
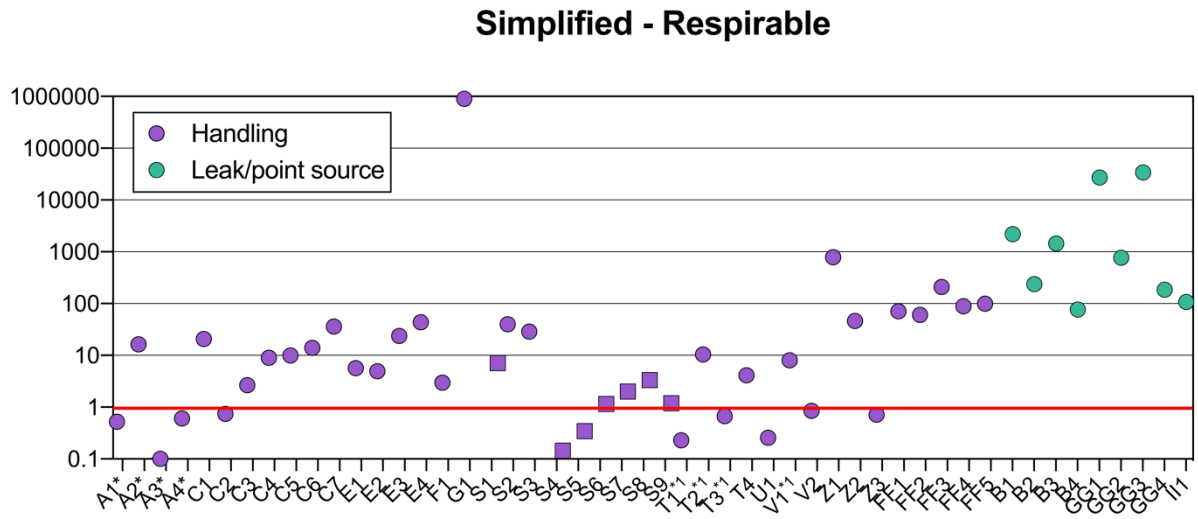


Figure 29. Modelled exposure in respirable mass concentration and corresponding predicted score correlation. Log-transformed values used.



All domains	All_HQ	Handling	H_HQ	Leak/point source	L_HQ
6/50 (12%)	1/30 (3.3%)	7/40 (17.5%)	1/21 (4.8%)	0/9 (0%)	0/4 (0%)



All domains	All_HQ	Handling	H_HQ	Leak/point source	L_HQ
11/50 (22%)	4/30 (13.3%)	11/41 (26.8%)	4/21 (19%)	0/9 (0%)	0/4 (0%)

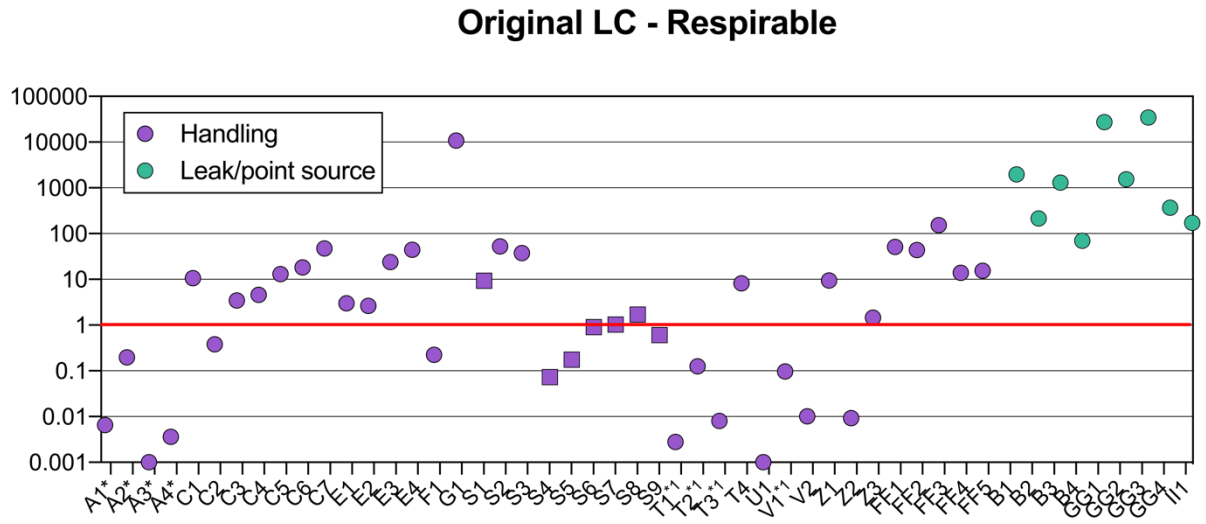
Figure 30. Ratios of predicted (modelled) mass concentrations at near field versus the real measured concentrations for original and simplified versions (without considering reductions due to local controls applied).

Note: * Marks exposure measurement values below the detection limit and consequently low validity; *1 Marks the exposure scenarios which other sources of particles were detected and therefore low validity. Squared shaped = inhalable not BG subtracted concentrations. The Tables below the graphs show the percentage of underestimation for each activity domain.

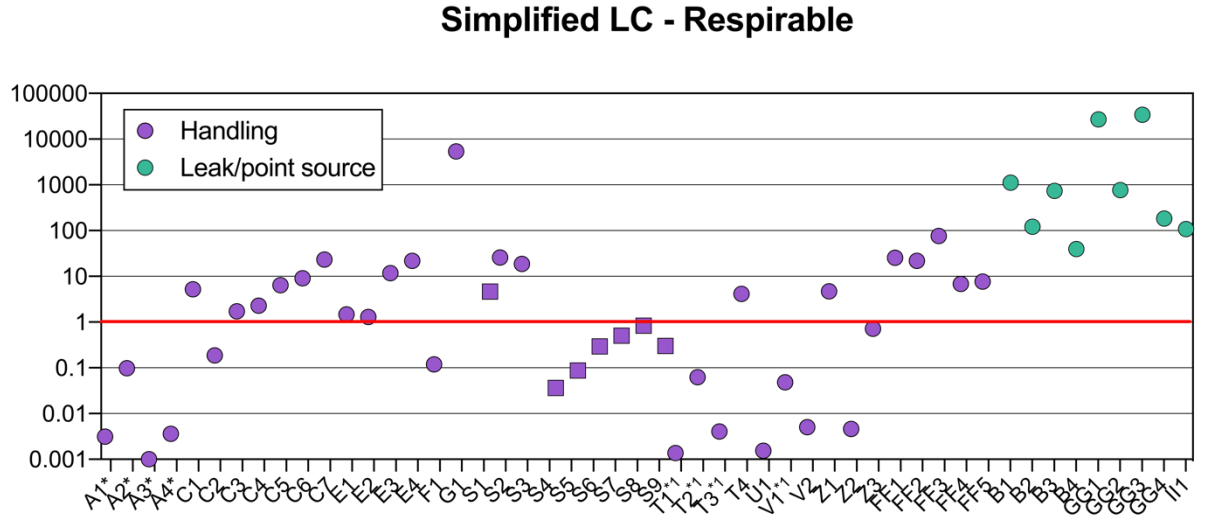
112. The ratios (modelled/measured mass concentrations at NF are shown in Figure 30. Most of all the studies considered in the performance testing, resulted in ratios >1 meaning that modelled concentrations were consistently overestimated. An explanation for ratios < 1 (e.g. cases A1, A3 and A4) is due to the measured respirable mass, which were below the detection limit of quantification. Thus, when considering only HQ cases, exposure underestimations were < 10% of the total comparisons for the original version, whereas for the simplified version, powder handling domain measured concentrations exceeded the model estimates for more than>10% of the total comparisons (13.3%). It is also important to take into consideration that modelled and measured mass concentrations cannot be directly compared because the risk management measures were not included in the NanoSafer v1.1β (e.g. emission control in place such as fume hood or containment by a discharge cone). In order to overcome this, a multiplier for each LC in place was used (the multipliers used are described in "*Annex A – Case studies.xlsx*". The multipliers were obtained from the ECEL library. Ratios obtained for both NanoSafer versions when applying the correspondent LC multipliers are represented in Figure 31. When the LC were applied the NanoSafer original version underestimated a 7.2% of the total HQ cases, which corresponded to a 23.8% underestimation of powder handling domain and 0% for the leak/point source domain. For the simplified version underestimation of the total HQ cases was up to 20%, which corresponded to a 28.6% of the powder handling cases, and 0% of the leak/point source. However, as the LC factors were applied outside the limits of the tool, these results should be treated with care.

113. It is important to note that even though in the HQ case studies dataset, studies where impacts on exposure concentrations due to secondary sources have been reported were not considered, there might still be some studies where influence of background or soot particles were detected but were not quantified. This is the case of for example case C and S for which the model slightly underestimates exposure.

Moroever, for some cases the information on secondary or background sources effect on measured concentration was not described or not know.



All domains	All_HQ	Handling	H_HQ	Leak/point source	L_HQ
17/50 (34%)	5/30 (7.2%)	17/41 (41.5%)	5/21 (23.8%)	0/9 (0%)	0/4 (0%)



All domains	All_HQ	Handling	H_HQ	Leak/point source	L_HQ
20/50 (40%)	6/30 (20%)	20/41 (49%)	6/21 (28.6%)	0/9 (0%)	0/4 (0%)

Figure 31. Ratios of predicted (modelled) mass concentrations at near field versus the real measured concentrations for original and simplified versions with local controls applied.

Note: * Marks exposure measurement values below the detection limit and consequently low validity; '1 Marks the exposure scenarios which other sources of particles were detected and therefore low validity. Squared shaped = inhalable not BG subtracted concentrations. The Tables below the graphs show the percentage of underestimation for each activity domain.

114. Additionally, all the modelled respirable mass concentrations considering the recommended protection factor by the tool were below the respirable OEL for the nearest analogue material (Figure 32) and the calculated or defined OEL nano (Figure 33). This confirms that the protection factors recommended

by NanoSafer v1.1 (original and simplified versions) seem to be acceptable for all the work situations analysed here.

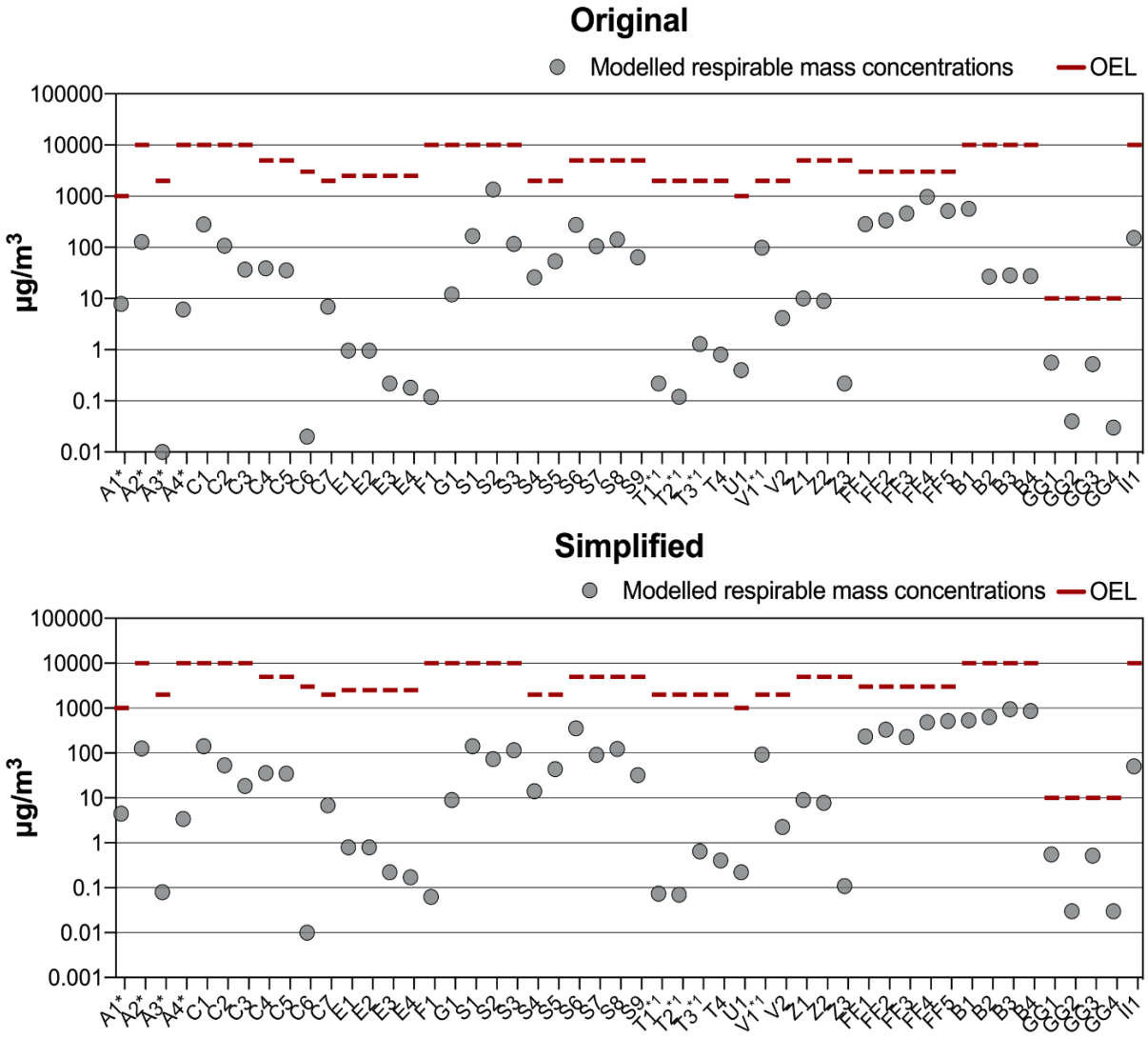


Figure 32. Comparison of respirable OEL for the analogue bulk material with the modelled respirable mass concentrations considering the recommended protection factor by the tool with the Original and Simplified versions.

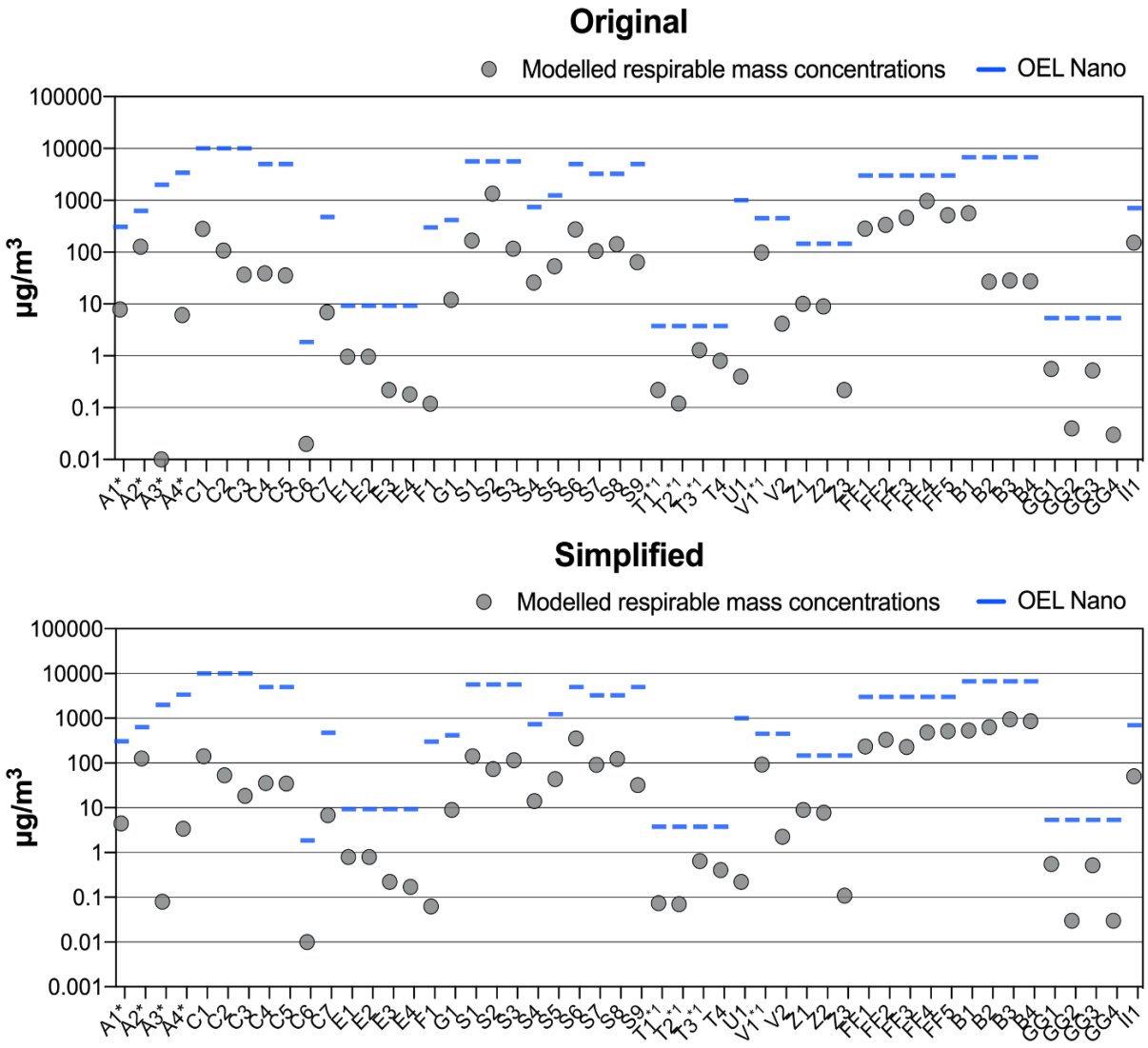
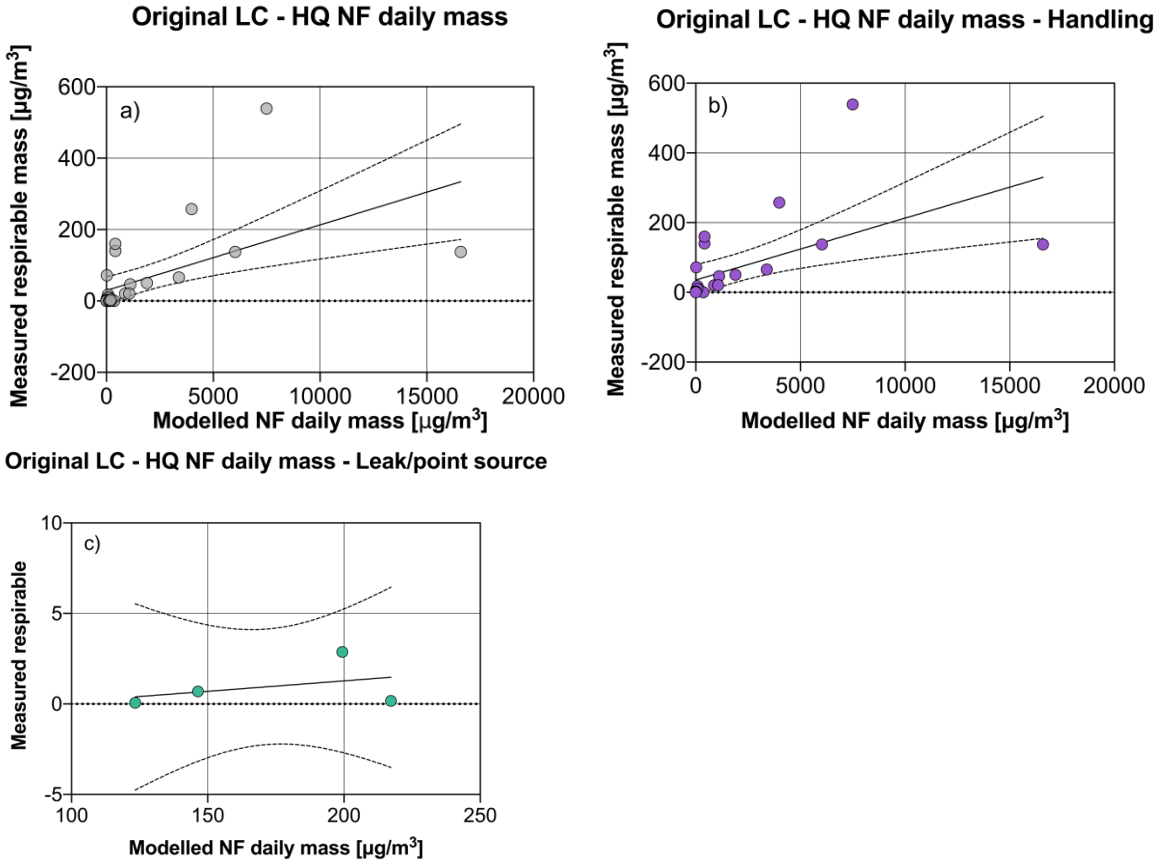


Figure 33. Comparison of respirable OEL derived for the nanomaterial by the tool with the modelled respirable mass concentrations considering the recommended protection factor by the tool with the Original and Simplified versions.

Spearman correlation factor

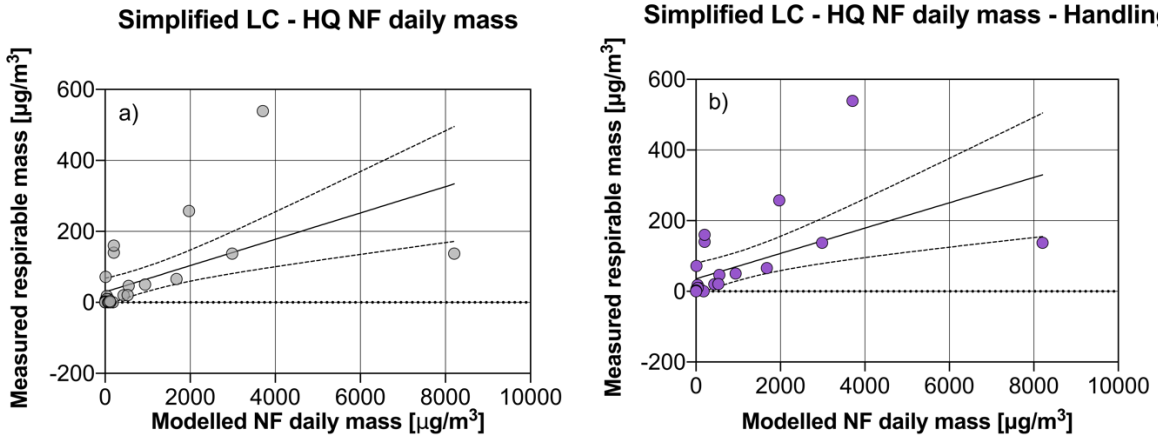
115. Significant Spearman correlation coefficient between the real measured mass concentrations and the converted modelled mass concentration were obtained when using HQ cases studies with applied LC (Figure 34 and Figure 35). Coefficients for all domains and powder handling were 0.72 and 0.80 for the simplified and original versions, respectively. Conversely, for leak/point source weaker correlations were obtained (0.40 for both versions). Spearman and Pearson correlations for the simplified and original versions, considering all case scenarios applying and without applying the LC multipliers, were calculated and are fully detailed in Table 11.

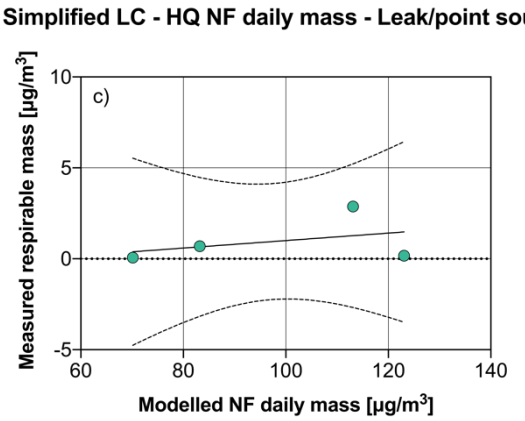


Original v.	All domains	Handling	Leak/point source
n / R^2	30	26	4
Pearson	0.5612**	0.5479**	0.3887
Spearman	**0.7157****	**0.8044****	0.4000

Figure 34. HQ cases correlation of NanoSafer original modelled mass concentrations (LC applied) with measured respirable BG subtracted mass concentrations.

Note: a) all domains, b) powder handling and c) leak/point source. For E1-E2, FF1 and FF5 cases respirable not BG subtracted values shown.





Original v.	All domains	Handling	Leak/point source
n	30	26	4
Pearson	0.5616**	0.5480**	0.3869
Spearman	**0.7213****	**0.8049****	0.4000

Figure 35. HQ cases correlation of NanoSafer simplified modelled mass concentrations (LC applied) with measured respirable BG subtracted mass concentrations.

Note: a) all domains, b) powder handling and c) leak/point source. For E1-E2, FF1 and FF5 cases respirable not BG subtracted values shown.

Table 11. Spearman and Pearson correlation coefficients for modelled/respirable measured for all case scenarios.

Version	Domain	Respirable		
		n	Pearson	Spearman
Original	*All*	42	0.7129****	0.5196***
	Handling	34	0.7871****	**0.7057****
	Leak/point source	8	0.1975	0.5509
Original LC	*All*	42	0.1026	0.5075***
	Handling	34	0.5588***	**0.7592****
	Leak/point source	8	0.1965	0.5030
Simplified	*All*	42	0.5622***	0.5105***
	Handling	34	0.7858****	**0.7039****
	Leak/point source	8	0.1958	0.5509
Simplified LC	*All*	42	0.00655	0.5036
	Handling	34	0.5588***	**0.7582****
	Leak/point source	8	0.1952	0.5030

Note: Values were calculated for simplified and original version of NanoSafer, and including LC multipliers.* statistical significance. Values in bold when Spearman correlation > 0.6.

3.6.4. Conclusion

116. The overall performance of the NanoSafer v1.1β exposure model was based on 50 exposure scenarios (41 powder handling domain and 9 leak/point source domain) with high quality data containing most of all the required parameters. The overall estimated exposure mass concentration for the HQ cases when applying the corresponding LC multipliers (Figures 34 and 35) were found to be well correlated with the measured respirable exposure mass concentrations with Spearman correlation coefficients of 0.72 for the simplified and original versions, respectively. For powder handling domain, correlations were stronger

for HQ data (0.80 for both the simplified and original versions, respectively) than for leak/point source domain (0.4) (Figure 34 and 35). However, it is important to note the limitation on data available for the leak/point source domain. Even though the good correlations obtained, especially for the simplified version, real measurements exceeded the model estimates for 20% of the total comparisons. Conversely, the original version kept underestimations under the 10% limit even when LC multipliers were applied.

117. Despite the good performance, some caution should be taken due to the sensitivity of the model regarding potential assumptions on the activity handling energy factor, emission rate, and correct material information on the shape, specific surface area and relative density. Overall, the results from the NanoSafer v1.1β performance testing shows that the exposure model in NanoSafer v1.1β work well. However, the limited number of exposure scenarios tested for both domains (especially the leak/point source) may be of importance in regards to the reliability of the modelled outcome.

3.7. GUIDEnano

3.7.1. Introduction

118. GUIDEnano is a web-based guidance tool, intended to guide the nano-enabled product developers (industry) into the design and application of the most appropriate risk assessment and mitigation strategy for a specific product. The tool can be accessed at https://tool.guidenano.eu/.

3.7.2. Methods

Selection of measured exposure data

119. GUIDEnano performance testing was conducted for different application domains: 1) Powder handling, 2) Spray and 3) Leak/Point source. The kind of application domain tested depended on the availability of data in the exposure scenario rather than to the model applicability. For GUIDEnano, the case studies were selected following an evaluation performed according to a set of "quality criteria" (> 0.7). A total of 25 cases belonging to three different application domains were tested in GUIDEnano: 17 were related to "Powder handling" activities (A1-A4, C1-C7, E3, G1, V1-V2, Z1-Z2), 5 were related to "spraying" activities (B1-B4, D1) and 3 were focusing on "Leak/Point source" situations (F1-F3).

Input parameters (data entered into the model)

120. For GUIDEnano performance test, entry data were harmonized (as much as possible) with those used in NanoSafer. Data were entered in GUIDEnano manually by one person and therefore no user variability were assessed. GUIDEnano requires information regarding material, hazard and scenario. Specific input parameters required are described bellow:

Material Identifiers

- Material name/definition
- CAS number

Material information

- Is the nanomaterial coated or surface modified?
- Product type (e.g. Ready to use)
- Appearance/Physical state (e.g. powder)
- Task powders
- Task liquids

Other information

- Ranges of sizes of primary particles
- Materials consumption in the production process
- Amount used in production
- Product life time (use phase)
- Product life time (use phase)
- Knowledge of material system

Material properties

- Morphology (NM)
- Dimensions of the primary nano-object (a £b£c) /Particle size distribution
- Median particle size
- Coefficient of variation for PSD
- Relative density (specific gravity) density of the nanomaterial
- Specific surface area of the nanomaterial
- Solubility of the material (dilution of MNM in water)
- Moisture content in powdered product
- Viscosity of liquid
- Concentration of ENM in product
- Weight fraction of substance
- Aggregation/Agglomeration [material/particle property]
- Crystal structure/Crystallinity [material/particle property]
- Surface charge [material/particle property]
- Dissolution rate [material/particle property]
- Enthalpy of formation [material/particle property]
- Hamaker constant [material/particle property]
- Purity [material/particle property]

Safety/Hazard data

- Is there a nano-specific occupational exposure limit (OELnano) or target value?
- Respirable OEL for the nearest analogue material
- Known hazards of analogue bulk material
- Hazard & exposure during manufacture of the nanomaterial (class)
- Hazard & exposure during processing the nanomaterial (class)
- Hazard & exposure during application of the nanoproduct (class)
- Location of the nanoelement in the article
- Size of the consumer population using the nanoproduct
- Depending on the focus of the risk assessment:
- Asthmagen/lung toxicity/Respiratory effects [Human Hazard information]
- Generation of reactive species. Biotic system [Human Hazard information]
- Immunotoxicity/inflammation [Human Hazard information]
- Carcinogenicity [Human Hazard information]

- Reproductive toxicity [Human Hazard information]
- Oral toxicity [Human Hazard information]
- Inhalation toxicity [Human Hazard information]
- Genotoxicity (mutagenicity) [Human Hazard information]
- Sensitization [Human Hazard information]
- Dermal toxicity [Human Hazard information]
- Corrosivity [Human Hazard information]
- Irritating potential (skin/eye) [Human Hazard information]
- Chronic NOEC [Environmental Hazard information]
- Acute endpoints - Fish (EC50/NOECs/LOECs) [Environmental Hazard information]
- Acute endpoints - Invertebrate (Daphnia) (EC50/NOECs/LOECs) [Environmental Hazard information]
- Acute endpoints - Algae (EC50/NOECs/LOECs) [Environmental Hazard information]
- Acute endpoints - Test species (EC50/NOECs/LOECs) [Environmental Hazard information]
- Acute endpoints - Duration (EC50/NOECs/LOECs) [Environmental Hazard information]

Scenario information

- Emission rate or Activity handling energy factor
- Dustiness of powder
- Dustiness for granules
- Pause between work cycles
- Number of work cycles per day/Frequency
- Amount of material handled in each transfer
- Time required per task in cycle (spoon, bag, big-bag etc.)
- Volume of the work room (width x length x height)
- Width of the room
- Length of the room
- Height of the room
- Surface of floor
- Volume Near Field (LCLZ)
- Air exchange rate
- Activity level in the room
- Task synthesis
- Breathing zone (Y/N)
- Is the employee situated in a cabin? (Y/N)
- Number of exposed workers
- Ventilation (mechanical, natural etc.)
- Ventilation rate
- Air flow between the NF and FF volumes
- Local control measures (incl. efficiency in %)
- Personal protection (Y/N)
- Activity

- Activity Input - Rate
- Activity release(s) - Relative release
- Activity release(s) - Rate / location
- Activity output(s) - Relative amount output
- Temperature
- Pressure
- Spray duration
- Mass generation rate
- Airborne fraction
- Density non volatile
- Aerosol particle size distribution
- Aerosol Median diameter
- Aerosol Arithmic coefficient of variation
- Spray duration
- Exposure duration
- OEL nano or the one of the bulk analogue material

Comparison of model estimates with measured exposure

121. GUIDEnano can provide different outputs depending on the specific risk assessment that user want to perform. The performance testing was focused on the occupational domain, for which the GUIDEnano outputs are the predicted MNM concentration in the NF and FF. The GUIDEnano particle concentration estimates (NF) were directly compared with the measurement data available in the literature papers selected for the occupational model testing. If a measurement of the background was available in the paper, then the value used for comparison in the model testing was corrected for background concentrations. However, also some cases without BG corrected data were considered. In GUIDEnano, the MNM concentration in the zone derived estimates is calculated in mass/volume concentration but it can be transformed in other units. For GUIDEnano testing, the particle mass concentration was the most commonly used metric, unless the measurement data in the paper were provided only in particle number concentration. When the comparison between measured and predicted data is performed using the particle number concentration, the user must use the most precise information on the MNM shape, size and density, because these values are used for the conversion between particle mass and particle number.

3.7.3. Results

122. For the purpose of performance testing, relevant information corresponding to the 25 measurements were retrieved and compiled in Table 12 in form of a summary for each application domain (Powder handling, Spray and Leak/Point source).

Table 12. Summary of key results for exposure assessment with GUIDEnano model.

	Application domain	Powder handling	Spraying	Leak/point source
Report data from actual measurements	Number of case studies considered (actual cases referred to in text)	17	5	3
	Number of personal exposure data used	0	0	0
	Number of stationary exposure data NF used	17	5	3
	Number of stationary exposure data FF used	0	0	0
	Number of substance-specific data	16	5	0
	Number of non-substance-specific	0	0	0
	Range of measured respirable mass (BG subtracted) (µg/m^3)	0-314	-	0.29-19.45
	Range of measured respirable mass (not BG subtracted) (µg/m^3)	83-768	210-3350	-
	Range of measured number concentration (BG subtracted) (#/cm^3)	1010-298700	15400 (just one)	-
	Range of measured number concentration (not BG subtracted) (#/cm^3)	3870-5130	-	-
	Statistical parameters of measured exposure (mass or number)	median; geometric mean; percentiles (15/17)	median; geometric mean; percentiles (4/5)	-
Report data from modellings	Quantitative recommendation (% of efficiency)	-	-	-
	Range of exposure score (-)	-	-	-
	Range of exposure band (-)	-	-	-
	Range of concentrations (µg/m^3 or #/cm^3)	Mass conc. µg/m3 0.33-1402; Number conc. #/cm^3 3043-241339	Mass conc. µg/m^3 0.25-28.50	Mass conc. µg/m^3 130,10-2468; Number conc. #/cm^3 15400 (just one)
	Statistical parameters of modelled exposures (exposure band, score, and/or concentrations)	median;	median;	median;
	Spearman correlation of model estimations vs. real measurement / test values	0.95	1	1
	Ratio of modelled concentration/measured concentration	0.54-5.26	0.59-0.74	0.51-1.47

123. Overall, the GUIDEnano estimate were correlating very well with the corresponding measured stationary NF measurements for all the application domains considered, providing a spearman coefficient of 0.97, meaning a strong correlation. The coefficient of fit of the best fit curve to all datapoints (R^2) is equal to 0.96 (Figure 36).

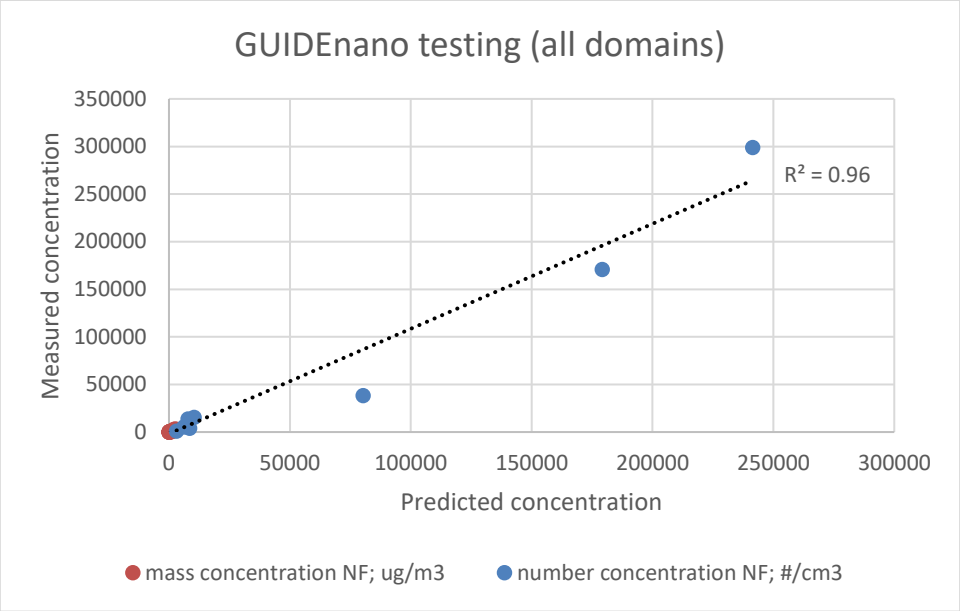


Figure 36. Correlation between GUIDEnano model estimate and stationary measurements for all application domain.

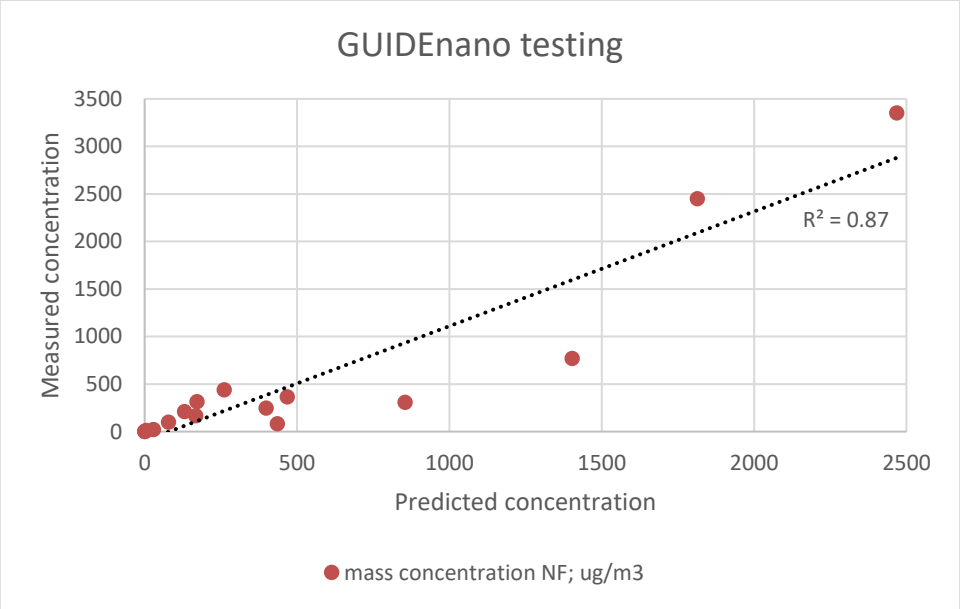


Figure 37. Correlation between GUIDEnano model estimate in mass concentration and stationary measurements for all application domain.

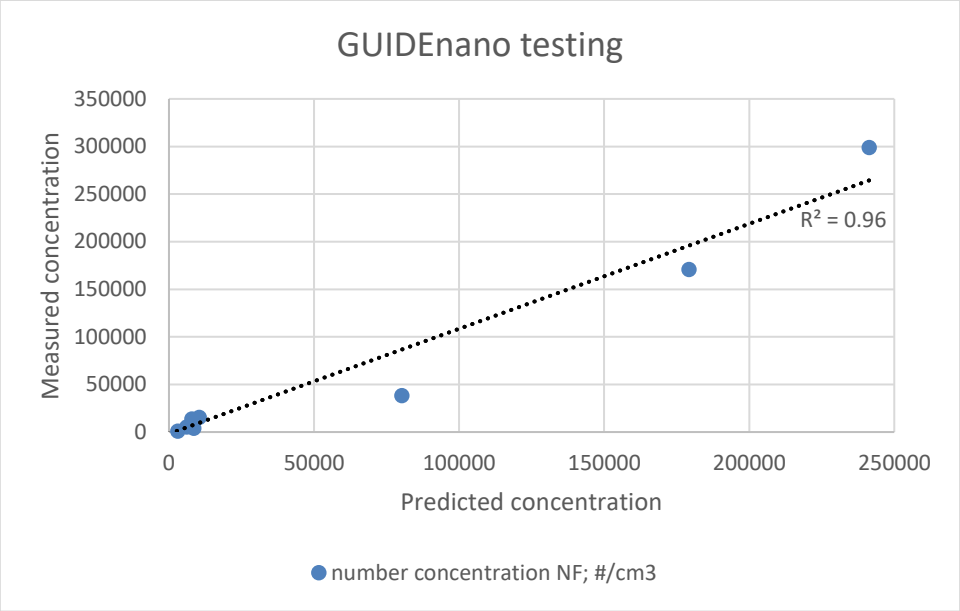


Figure 38. Correlation between GUIDEnano model estimate in number concentration and stationary measurements for all application domain.

124. The coefficient of fit of the best fit curve of data in particle mass concentration is equal to 0.87 (Figure 37) and the one in particle number concentration is 0.96 (Figure 38).

125. Focusing on each application domain, we observe the best correlation between measured and predicted data for "powder handling" (Figure 39) and "spraying" (Figure 40) activities (R^2=1 and 0.96, respectively), and a bit lower correlation (R2=0.89) for "leak/point source" (Figure 41). The Spearman correlation coefficients for data in each domain, "powder handling" "spraying" activities and "leak/point source" situation, were 0.95, 1 and 1, respectively.

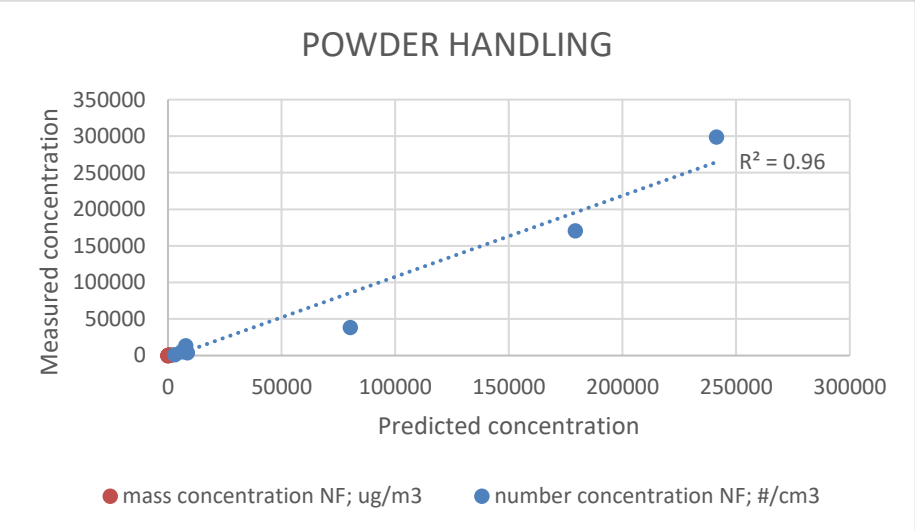


Figure 39. Correlation between GUIDEnano model estimate and stationary measurements in the "Powder handling" application domain.

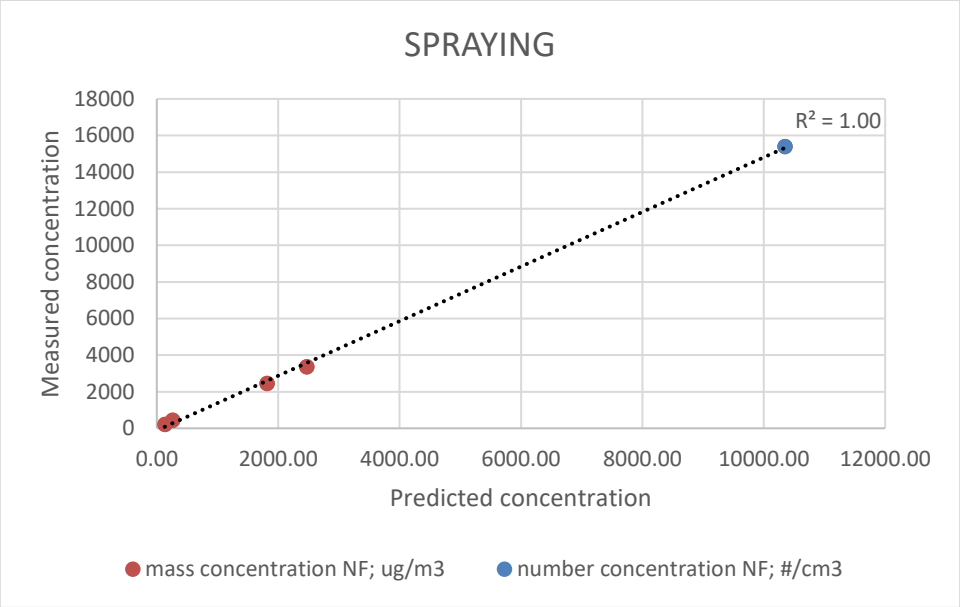


Figure 40. Correlation between GUIDEnano model estimate and stationary measurements in the "Spraying" application domain.

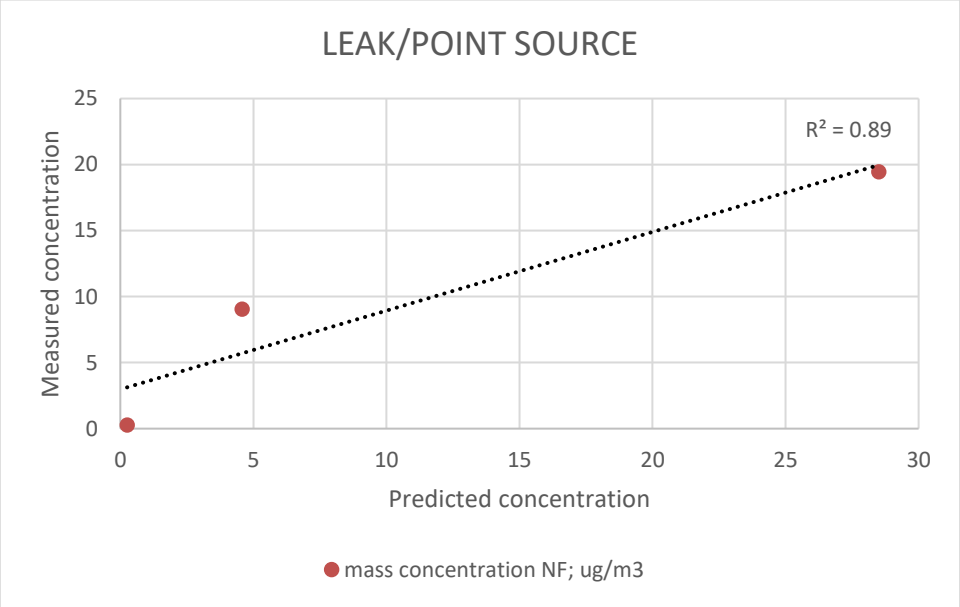


Figure 41. Correlation between GUIDEnano model estimate and stationary measurements in the "Leak/Point Source" application domain.

3.7.4. Conclusions

126. The assessment of GUIDEnano performance was based on 25 cases with very high-quality data and showed a strong correlation between the predicted and measured concentrations in stationary measurement (Spearman correlation coefficient = 0.96). The assumptions regarding the activity mass

balance are strongly influencing the model outcome and therefore we recommend to limit the use of assumptions or ask for an "expert" advice. Even considering this as a preliminary assessment due to the little number of cases tested, we conclude that GUIDEnano tool showed a great potential for modelling occupational exposure. However, future testing should also include personal exposure measurements to inform on the performance considering worker protection.

3.8. The SUN Decision Support System (SUNDS)

127. The performance testing of the SUNDS was not conducted as the sensitivity analysis provided in ENV/CBC/MONO(2021)27 was considered sufficiently complete. Furthermore, SUNDS is based on other tools which have been assessed under this Project.

3.9. Swiss Precautionary Matrix v3.0

3.9.1. Introduction

128. The Swiss Precautionary Matrix (SPM) is a risk-screening tool for synthetic nanomaterials. The tool is applicable in early stage-gates of innovation in which usually not many information or data are available. The SPM gears toward industry and trade and gives guidance for assessing potential nano-specific health and environmental risks of nano-enabled products for workers, consumers and environment, covering the complete product life cycle. The SPM is based on a web-application[1] or standalone software, which comprise a short questionnaire with several single and multiple choice answers. Different scores are attributed to the answers resulting into total eight different output results for worker, consumer or environmental related aspects including the likely disposal pathways during the life cycle. The resulting score indicates if additional information aspects are required (> 20 points). The tool is available from https://www.bag.admin.ch/bag/en/home/gesund-leben/umwelt-und-gesundheit/chemikalien/nanotechnologie/sicherer-umgang-mit-nanomaterialien/vorsorgeraster-nanomaterialien-downloadversion.html.

3.9.2. Methods

Selection of measured exposure data

129. The performance testing of SPM developed under caLIBRAte produced two different performance tests, for the occupational and environmental categories. For the occupational tools, from 68 case studies, 48 were categorized as having high quality. For the occupational part, different case studies in terms of nanomaterial and its nano-forms as well as different worker activities were selected. In total 23 scenarios were run in the SPM, named A1-A3, B1-B4, C1-C3, D1, G1, G3, H1-H2, I1-I2, M1, J3-J5. The goal of minimum 25 case studies could not be met due to either limited datasets (e.g. nano-diamonds), the material was out of the tool scope (inorganic fertilizer), or redundant case studies. However, the selection of the case studies represent the variability of the case studies.

[1]https://www.bag.admin.ch/bag/en/home/gesund-leben/umwelt-und-gesundheit/chemikalien/nanotechnologie/sicherer-umgang-mit-nanomaterialien/vorsorgeraster-nanomaterialien-webanwendung.exturl.html/aHR0cDovL3d3dy5iYWctYW53LmFkbWluLmNoLzIwMTZfdGFnbG/FiLzIwMTZfbmFub3Jhc3Rlci9wb3J0YWxfZW4ucGhw.html?SID=ga4o8gqdjo7g47qb9m6gkf1c87

Input parameters (data entered into the model)

130. The SPM requires information on general information of the scenario, specific nanomaterial information, possible uncertainties related to the nanomaterial, effects and stability of the nanomaterial material and regarding the specific exposure situation. Specific input parameters required are described below:

1. General information

General information: Contact person, brief description on nanospecific field, process and step

Choose scenario: employees, consumers or specific disposal step

Coated / functionalized nanomaterials involved? Yes (4.5)/No

Nano-relevance

i) Entry according to EU-proposed definition (2011/696/EU): N-EU, EU recommendation on the definition of nanomaterial. Material containing primary particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the primary particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm or (if the number size distribution is unknown). Material where the specific surface area by volume is greater than 60m^2/cm^3 or Material consists of fullerenes, graphene flakes or single wall nanotubes

ii) Entry according to precautionary approach (external dimensions of primary particle from 1 to 500 nm)

Questions:

N1a: Do the primary particles form agglomerates > 500 nm? No/Yes (N2Av and N2U)

N2Av: In the body does deagglomeration of agglomerates (or aggregates) to primary particles or agglomerates <500 nm occur? Yes/No

N2U: Under the respective environmental conditions does deagglomeration of agglomerates (or aggregates) to primary particles or agglomerates <500 nm occur? Yes/No

N2a: If agglomerates between 500 nm and 10 um are present, can employees or consumers take them in through their lungs? Yes/No

N-EUa: Do you want to include primary particles from 1 to 500 nm in your evaluation? No/Yes (N1)

N1: Order of size of the primary particles in the materials (free, bound, aggregated or agglomerated): Over 500 nm/1-500 nm (N1a)

Uncertainties

Information on the life cycle:

1. Is the origin of the (nanoscale) starting materials known? Yes/No

2. Is sufficient information available to complete the precautionary matrix for nanoscale starting materials? Yes/partly/No

3. Are the subsequent users of the considered nanomaterials known? Yes/partly/No

4. How accurately is the material system known, or can disturbing factors (e.g. impurities) be estimated? Accurately/Not accurately/unknown

Effect

W. Potential effect

W1. Reactivity

W1.1. Cell-free or calculated reactivity

Redox activity: low/medium/high/not known

Photocatalytic activity: low/medium/high/not known

Biological oxidative damage (BOD): low/medium/high/not known

W1.2. Cellular reactivity

Induction of mediators of inflammation (IL-8, IL-1β, TNFα): low/medium/high/not known

ROS induction: low/medium/high/not known

GSH reduction: low/medium/high/not known

Protein carbonylation: low/medium/high/not known

W2. Stability

W2AV. Stability (half-life) of the primary particles present in the nanomaterial in the body: hours/days-weeks/months/not known

W2U. Stability (half-life) of the primary particles present in the nanomaterial under environmental conditions: hours/days-weeks/months/not known

Exposition

E1. Carrier material: air, aerosol (<10 um)/air, aerosol (>10 um)/liquid media/solid matrix, not stable under relevant process conditions or condition of use, nanomaterial mobile/solid matrix, not stable under relevant process conditions or condition of use, nanomaterial not mobile

E2. Maximum possible exposure of humans

E2.1. Amount of nanomaterial which worker handles per day: up to 1.2 mg/1.2-12 mg/ over 12 mg/not known.

E2.2. Amount of nanomaterials with which a worker comes into contact in the "worst case": up to 12 mg/12-120 mg/over 120 mg/not known

E2.3. Frequency with which a worker handles the nanomaterial: monthly/weekly/daily/not known

E3. Maximum possible input into the environment

E3.1. Amount of nanomaterials reaching the environment from wastewater, exhaust gases, solid waste per year: up to 5kg/5-500 kg/over 500kg/not known

Comparison of model estimates with measured exposure

131. The performance testing was organized as a two-tier validation setup by two different partners in caLIBRAte. The answers of both test runs were compared and if necessary, an agreement was arranged following the precautionary principle. Due to the type of questions in the SPM, which were broader than the specific data, assumptions had to be made. Due to the precautionary orientation of this tool, missing parameters were scored as a worst-case. For some missing parameters, it was possible to obtain information from the corresponding authors.

3.9.3. Results

132. In total 23 occupational health scenarios were tested and the performance of the model was assessed. The results for each scenario were additionally separated into a worst-case scenario for employees (worst expectable risk, i.e. most precautionary approach) and for a conventional precautionary need (standard risk associated). Table 13 shows the overview of the scores for each of the scenarios assessed. The scores range from 373 to 4058. The majority of the scenarios scored in the range 3653-4058 points. These scenarios are mainly related to activities that comprised an exposure potential caused by the handling of ENM powders. As the selected ENMs had similar toxicological scores, the main differences were the exposure conditions considered. Despite the scenarios differed in the parametrization (relevant for tools acting in higher stage-gates), the resulting score in the SPM were at a similar level due to the exposure pathway via air. For instance, the SPM was not able to differentiate pouring of 50 kg and 500 kg or spray coating of 5 seconds and 150 seconds, which is why the SPM scored all these scenarios with a high number being in accordance to the tools' purpose to identify the need for precaution and further investigation.

Table 13. SPM results of the performance testing regarding the occupational health scenarios.

Scenario No.	SPM Score [-]	
	Precautionary need for employees	Precautionary need for employees (worst case)
A1	2033	2438
A2	3653	4058
A3	2033	2438
B1	3653	4058
B2	3653	4058
B3	3653	4058
B4	3653	4058
C1	3653	4058
C2	3653	4058
C3	3653	4058
D1	2036	2441
G1	2033	2438
G3	3658	4063
H1	3656	4061
H2	3656	4061
I1	3656	4061
I2	3656	4061
M1	3656	4061
J3	3656	4061
J4	3656	4061
J5	3651	4056
K3	3653	4058
K4	373	413

133. The second scenarios comprise those having a score ranging from approximately 2000 to 2400. The lower scores were caused by shorter exposure duration in the scenarios, which was only once a week instead of a daily basis. This reduction of exposure duration dropped the SPM score by a half compared to the higher score scenarios. This behavior is reasonable, as it assessed scenarios with potential air exposure pathway leading to potential effects. The lowest score was attributed to the K4 scenario. The main difference compared to the other scenarios was the constitution of the exposure that assumed a potential exposure to liquid ENM dispersion during the handling of the precursors in a milling process.

Although this scenario represents the lowest score, it still recommends precautionary needs since the result is above the critical threshold of twenty points. The SPM attributes this scenario a lower risk due to the more favourable exposure medium and related exposure route.

3.9.4. Conclusions

134. The performance of the SPM for occupational environment has been tested by using 23 scenarios. The results have shown that too detailed information does not influence the results in such an extent, as it would do in higher tier models. However, because the purpose of the SPM is risk screening of an activity or product related with ENMs, it gives guidance for a structured assessment and setting priorities in early stage-gates (pre-risk assessment and decision support). The value chain studies focused on nano-products by applying a complete life cycle perspective. These results have shown that by shifting the focus on the nano-product, manufacturing activities became less relevant. This reason is that the SPM is not yet designed to differentiate the transformation of a powder precursor (and its handling) and the end-product that may consist of an annealed ENM composite. Therefore, we recommend assessing the worker activities separately from the nano-product in the case the nano-form changes throughout the life cycle.

3.10. ConExpo nano 2.0

3.10.1. Introduction

135. ConsExpo nano (RIVM, 2016[25]) is a publicly available web tool that can be used to estimate inhalation exposure to nanomaterials in consumer spray products. The model combines predictions of aerosol concentration in indoor air with the predictions of alveolar load in the lungs. In this performance test, the human exposure module of the tool was evaluated against experimental data. The tool can be accessed from https://www.consexponano.nl/.

3.10.2. Methods

Selection of measured exposure data

136. An additional literature search was conducted to find analytical studies that describe measurements of indoor air concentrations of substances in consumer sprays released to the air upon and after spraying. Experimental studies were considered suitable for performance testing of the ConsExpo nano model under the criteria that i) the product evaluated is a consumer spray, ii) the concentration of the measured ingredient (e.g. the nanomaterial) is measured in the product and, iii) the study describes measurements of air concentration (mass or number) of the substance upon or after spraying. The substance ingredient that is evaluated was not required to be a nanomaterial, because the model algorithms to simulate the inhaled dose were not expected to be exclusively applicable to nanomaterials, but to non-volatile substances in general. As a result, measurement studies that consider non-volatile substances that are not a nanomaterial were also considered suitable for the performance testing of the ConsExpo nano model. In total, 5 studies were selected as suitable for model evaluation: (Park et al., 2018[26]; Berger-Preiß et al., 2009[27]; Chen et al., 2010[28]) (Delmaar and Bremmer, 2010[29]; DEPA, 2018[30]).

Input parameters (data entered into the model)

137. To simulate experimental settings in ConsExpo nano, the following input parameters are required:

- exposure duration
- spray duration

- aerosol particle diameter distribution
- mass generation rate spray
- weight fraction nanomateria in product
- density aerosol
- room volume
- room height
- ventilation rate

Comparison of model estimates with measured exposure

138. The performance of the tool was evaluated on the basis of how well the modelled experiment fits the measurements by simulating the experimental set up from the identified studies, and compare these to reported measurement data. The output of the performance test was formatted as a numerical comparison of measured and modelled quantities, with estimated uncertainty bands around the modelled results. Model performance was evaluated against this uncertainty range, loosely interpreting a measured value within the band as an agreement between measurement and model, and a value outside the band as a deviation. It was found that not all identified studies provided adequate descriptions of the experimental set up and results. In cases were model parameters could not be determined unambiguously, representative ranges of parameter values were estimated based on other sources. Based on these ranges, upper and lower bounds of the exposure were simulated, representing an uncertainty range in the model outcomes due to lack of knowledge of the precise experimental conditions.

139. Model simulations were conducted by manually operating the ConsExpo nano tool as a normal user would. For evaluations of the air concentration, simulations were conducted in the ConsExpo Web tool (RIVM, 2016[31]), as ConsExpo nano does not provide air concentrations as an output, but only calculates these as an intermediate (internally used) value. The aerosol release and transport models of ConsExpo Web and ConsExpo nano are identical and share the same implementation in code. Overall, calculations were conducted by two different collaborators independently. Results were discussed and a consensus-based version of the test was finally included in the study.

3.10.3. Results

140. The performance testing for ConsExpo nano was conducted on a case by case basis as the numerical format of the exposure reported vary strongly for each case study (e.g. average air concentration, time series evolution).

Berger-Preiß et al. (2009[27])

141. This case considers five different insect sprays in experiments that reflect worst-case conditions. Each spray contained two active ingredients (no nanomaterials) that were monitored in the air. The weight fractions of two active ingredients, are given for each spray product. In a series reflecting the worst-case conditions, personal aerosol measurements were carried out for 5 minutes in which the product is sprayed for 2 minutes in an unventilated room. Additionally, air concentrations were sampled for 60 minutes after spray use, with a stationary personal monitoring device. The study delivers single values for the “average exposure concentrations”. Measurements represent 5 minute time weighted averages (TWA) and 60 minute TWAs.

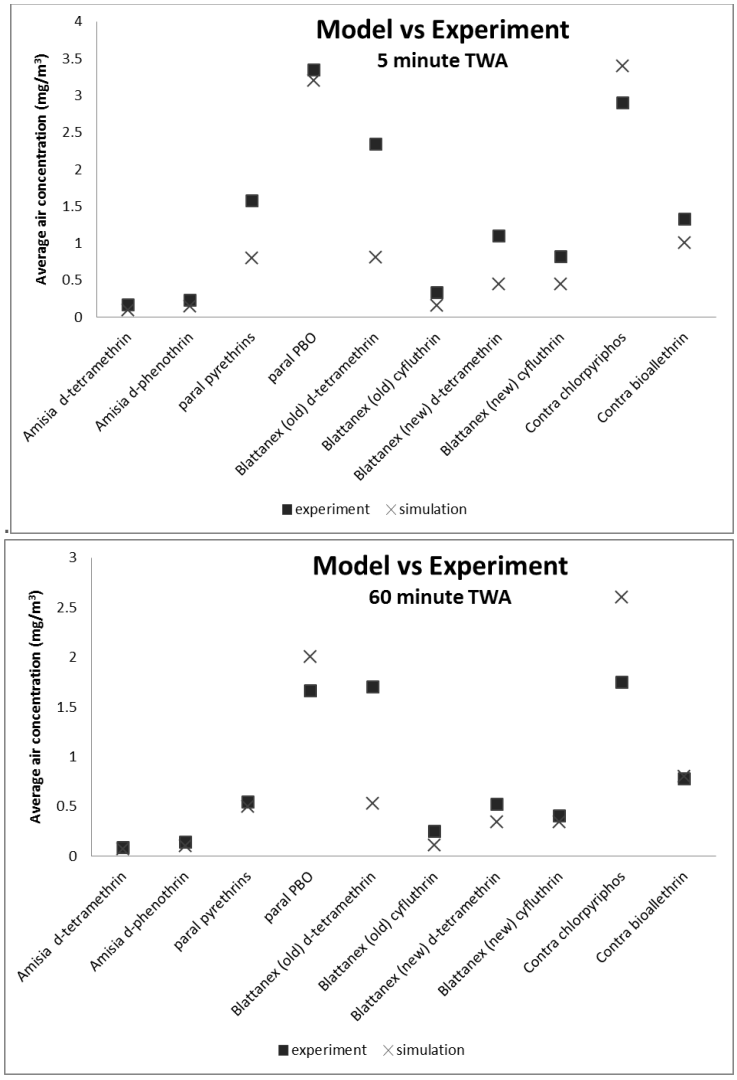


Figure 42. Comparison of ConsExpo nano simulations with data from Berger-Preiss et al., (2009).

Note: Measured and modelled average air concentrations are plotted per simulated product/substance combination in the data set for a) the 5 minute TWA and b) the 60 minute TWA.

142. For the 5 sprays measured, ConsExpo nano simulations are plotted against the data in Figure 42. The 5 minutes and 60 minutes TWAs have been plotted separately. Overall, deviations between measurement and simulation are within a factor of 2. Except for the Blattanex (old) spray and the 5 minute TWA simulation of Blattanex (new), for which modelled air concentrations are slightly less than half the measured values. Overall, the model predictions are below the measured values. For the set of TWA 5 min experiments, the under-prediction is slightly more significant, with model predictions at 65% of the measured values on average. For the 60 minutes TWA simulation, the simulated values are 85% of the measured air concentration on average.

Delmaar and Bremmer (2010[29])

143. The study describes measurements on potential exposure arising from consumer sprays. Briefly, for a range of consumer sprays both the particle size distribution and the air concentration arising after controlled use of the products in a climate chamber of 19.5 m^3 without ventilation were determined. Particle

size distributions were determined and the initial particle size distributions were available as raw data. These were used as input in ConsExpo. The considered products in this study did not contain nano materials.

144. For eight sprays included in the experiments, air concentrations upon use were simulated using ConsExpo. The simulated air concentration profiles are plotted against the data in Figure 43. Generally, simulated air concentrations are close to the measured values for air space sprays (i.e. sprays that were applied directly into the chamber air). For surface sprays, which were applied on a target located on the ground, the model simulations tend to over-predict measured concentrations. For most sprays deviations are within roughly a factor of two, except for 'Flea spray'. Here, the degree of over-estimation is much larger.

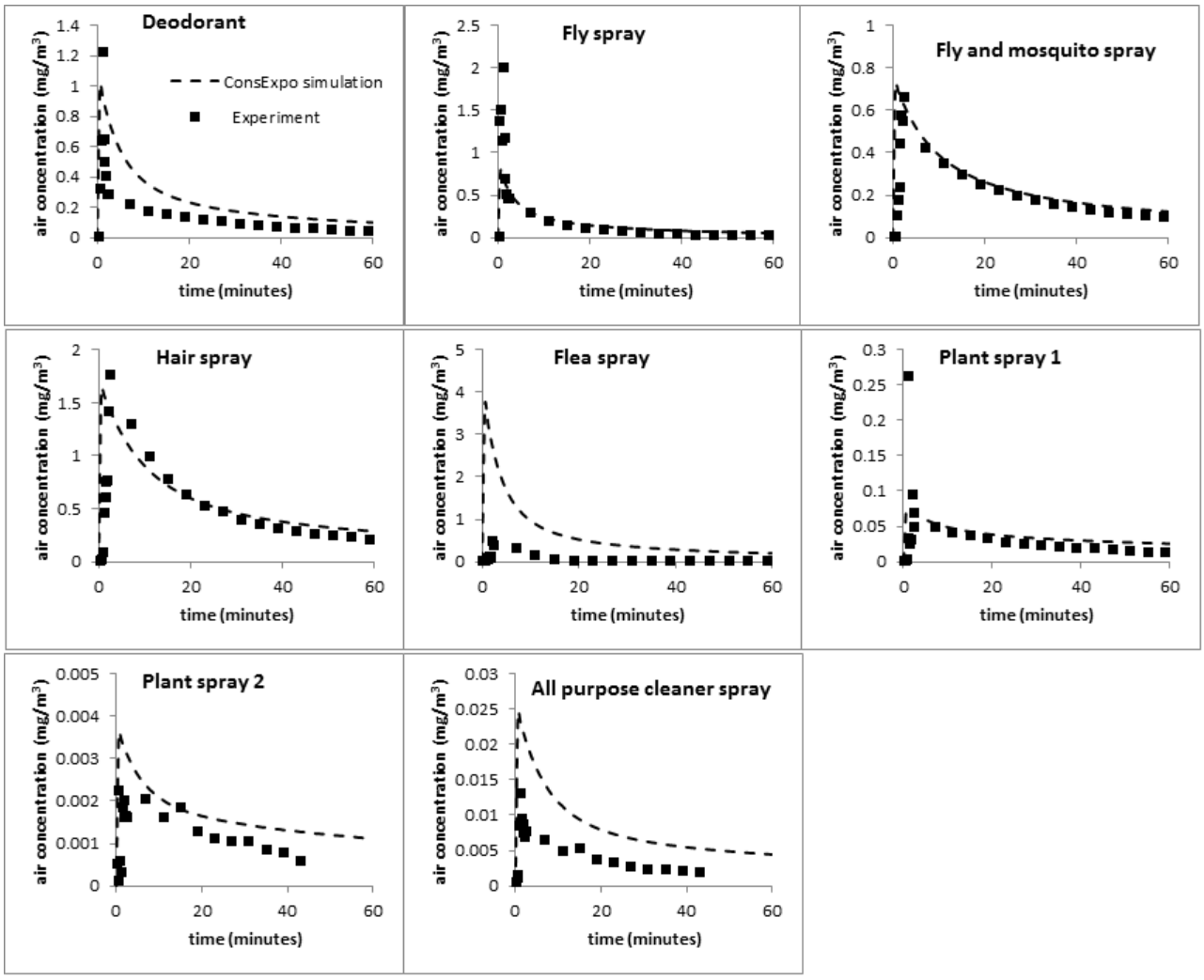


Figure 43. . Comparison of ConsExpo nano simulations with data from Delmaar and Bremmer, 2010.

Note: Time profiles of aerosol concentrations are simulated for fractions of non-volatile components in the spray products that were determined from the ingredient list of each spray.

DEPA (2018[30])

145. This case study describes an experimental study on air concentrations of pesticides arising after simulated use of biocide sprays. The study considered three commercially available spray products: 1) a

propellant spray to control flying insects (Tanaco Fluestop), 2) an indoor insecticide pump spray (Demand CS), and 3) a disinfectant/cleaning pump spray (Ecolab Micro-Quat Extra). Of the three tested spray products, only pesticides from the airspace application 'FlueStop' produced detectable concentrations. The two other products, trigger sprays with very low aerosol emissions, were discarded for the performance test. 'FlueStop' contained 3 different active ingredients (none of which were nano materials), which were all used for model evaluation. From the experiment description the ConsExpo nano model could be adequately parametrized, with one exception: the (initial) particle size distribution of the spray was not specified. For this, ConsExpo defaults for pest control products, 'air space: application' were used (Delmaar and Bremmer, 2010[29]) However, the representativeness of this surrogate value for the experiment is unknown.

146. For the three monitored ingredients in the FlueStop spray, the air concentration was modelled using ConsExpo. Simulated concentrations are plotted against measured values in respirable mass concentration (Figure 44).

147. For the ingredients 'permethrin' and 'pyrethrin' the simulations agree fairly well with experiment, being overall within a factor of 2 for all time points. For piperonyl butoxide, overall the ConsExpo simulation significantly under-estimates the air concentrations measured. The deviation between model and simulation seems largest in the early stages of the experiment.

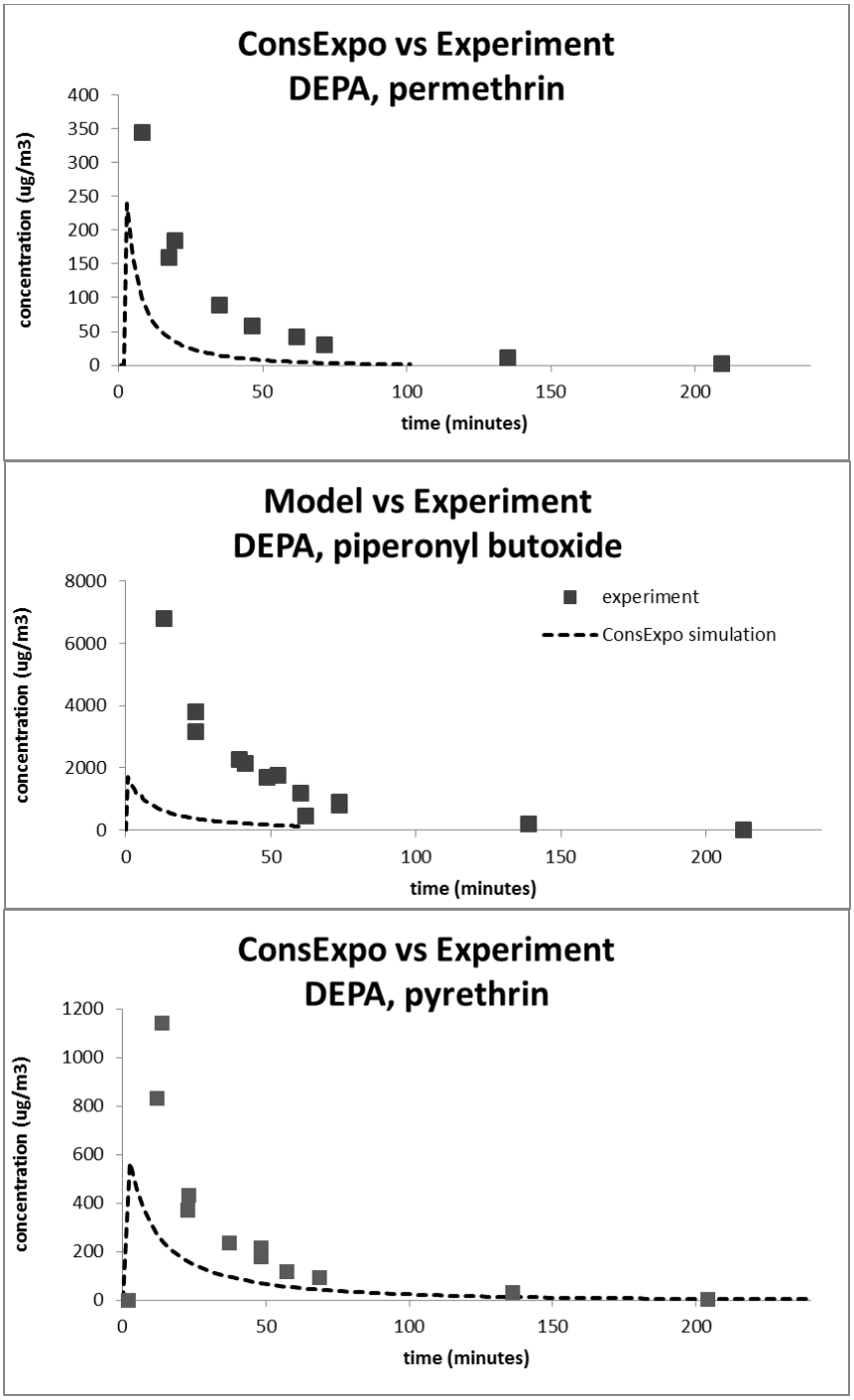


Figure 44. Comparison of ConsExpo nano simulations with data from DEPA, 2018 for the three different marker substances.

Note: a) piperonyl butoxide, b) permethrin c) pyrethrin. Time series of experiment #2 in the DEPA report were used.

Chen et al. (2010)

148. This study characterize nanoparticles released during typical use of a consumer spray (a bathroom cleaner) containing nano-TiO_2. A typical product use was simulated in a well-controlled indoor environment.

The spray's particle size distribution (PSD) was characterized both upon and after spraying. The total air concentration was recorded using gravimetric measurements on personal polytetrafluorethylene (PTFE) filters. The study reports a peak air concentration in the breathing zone of the operator of the spray of 3.4 mg/m^3. This is the only quantity that may be used in model evaluation.

149. To account for uncertainties in the experimental specification, model simulations were performed for the duration of the experiment for two sets of parameter inputs, one set representing the probable maximum air concentration, and the other the probable minimum air concentration that could have been expected. Uncertainty in the specification of the experimental conditions was very large, resulting in a reasonable range of exposure spanning almost two orders of magnitude (see Figure 45). The upper bound of the peak concentrations was estimated to be around 3.1 mg/m^3. Which is comparable with the reported measured value of 3.4 mg/m^3.

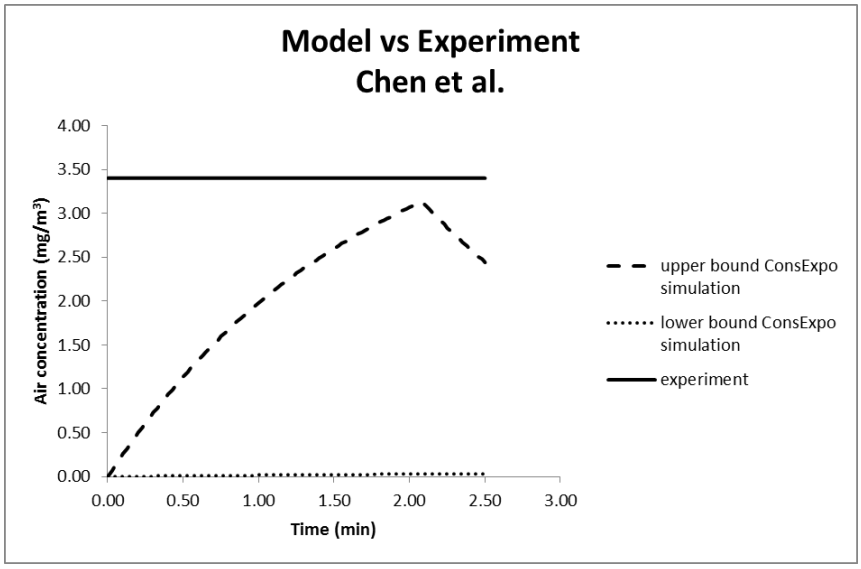


Figure 45. Comparison of ConsExpo nano simulations with data from Chen et al. (2010). The measured air concentration was the average nano TiO_2 air concentration during spraying.

Note: For the ConsExpo model simulations, upper and lower bounds represent uncertainty in the model parametrisation due limitations in the experimental description.

Park et al. (2018)

150. Park et al. (2018) describes testing of a nano-silver (AgNP) contained propellant spray product (an indoor air freshener), simulating the use in climate chamber (40 m^3) under different ventilation conditions. A realistic spray use scenario was performed and air concentrations at 1 m from the spray were recorded. The spray was operated in different scenarios, characterized by different spray durations (5 and 15 seconds, respectively) and different ventilation conditions (0 and 35 ACH). The latter experiment was considered to not be representative for realistic exposure conditions.

151. The reported concentration of Ag was 10% according to the Safety Data Sheet (SDS). This likely represents an upper bound rather than the actual concentration. To account for this ambiguity, an uncertainty range of 1-10% was adopted for this parameter. Two extreme scenarios were considered for the unknown weight fraction of nanoAg in the spray: 10% was taken as a maximum upper bound, as this was given in the SDS. As a reasonable lower bound a value of 1% was taken. This value was reported for a very similar (possibly the same) spray in (Park et al., 2017[32]).

152. For the experiments by Park et al. (2018), model simulations were plotted against the measurements. In Figure 46, the experiments with ventilation of 0 ACH, are displayed. For the two extreme scenario (1 and 10% nanoAg concentration), two extreme time-concentration profiles were obtained, representing roughly the uncertainty in model parametrisation. The measured air concentration is within these bounds. This may be interpreted as the model is not in contradiction with the data given the uncertainty in the experimental setup parametrisation.

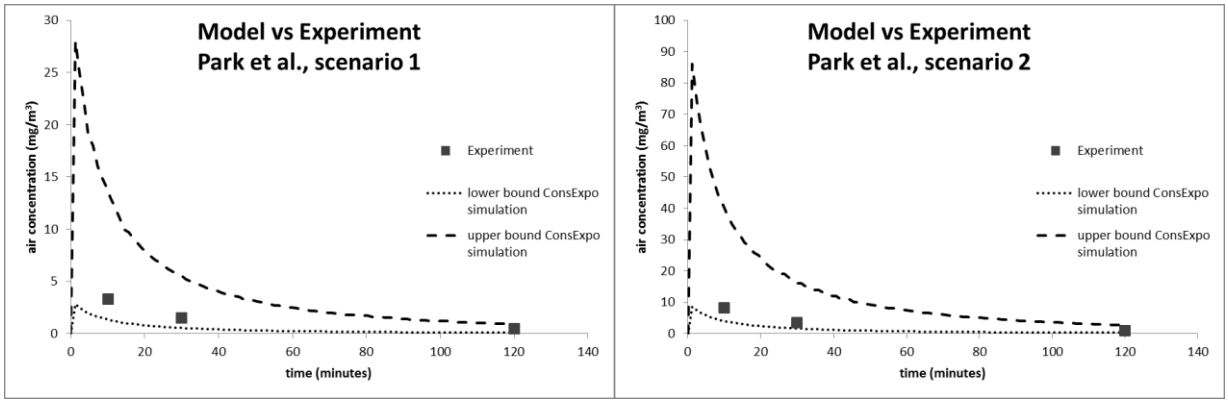


Figure 46. Comparison of ConsExpo nano simulations with data from Park et al., 2018.

Note: Measured nano Ag air concentrations are plotted against upper and lower bounds of the estimate air concentration profile, accounting for uncertainty in the weight fraction of nano Ag in the spray. A) scenario ES(1), with a spray duration of 5 seconds b) scenario ES(2) with a spray duration of 15 seconds.

3.10.4. Conclusions

153. From the performance test conducted for 5 independent studies, the following was concluded:

154. First, the ConsExpo nano spray model appears to describe experimental (chamber) air concentrations reasonably well. The discrepancy is generally within an order of 2. Loosely, we may take this factor of 2 as an indication of the model uncertainty. This uncertainty stems from simplifications in the model formulation, such as assumed complete mixing of indoor air and complete non-volatility of the substance monitored. Other aspects such as losses to vertical surfaces, particle dynamics that result from the hygrosocpic growth of aerosol particles, have also not been included in the model. This may add to the overall error in the model. Overall, the model seems adequate for application in predictive exposure assessment. In this respect, it should be noted that most experiments considered in this model performance were conducted under conditions without ventilation (with exception of the DEPA study). These conditions are less representative of realistic exposure conditions. Also, in real exposure situations the behaviour (e.g. walking through the room) of the exposed person will influence his or her exposure to a large extent. This aspect is not captured in the experimental setups considered. Movement of the exposed person will in fact lead to a better mixing of indoor air, and therefore reduce the error in the ConsExpo nano model due to this simplifying assumption.

155. Finally, of the considered experiments only two were on a product actually containing a nanomaterial. Exposure to substances from sprays is expected to be mainly driven by exposure to the aerosol particles carrying the substance. It is unknown to what extent the presence of a nanomaterial will alter the kinetics of aerosol particles in indoor air, except in cases where the solvent or carrier liquid evaporates and leave the nanomaterial and potentially other condensed matter as airborne particles. However, effect of droplet behaviour due to presence of nanomaterials is expected to be limited. Therefore, the conclusions of this performance test, considering sprays in which solid materials were present from

the start, are expected to be equally valid for sprays with either, nanomaterials and regular non-nano materials.

156. In search of adequate data for model testing, a number of studies was identified. Of this initial set, a large portion was finally rejected as unsuitable for model evaluation purposes. This was mostly because critical information on the experimental settings was lacking, rendering the study useless for model evaluation. The most critical information that needs to be specified in an experiment on spray exposure (be it for model evaluation or to inform a specific exposure assessment) include:

1) Details about the mass being released during a spray experiment. This includes the mass of the product released as well as ingredient concentration in the product.
2) A good characterisation of the spray's particle size distribution (PSD). Ideally, the PSD of the particles should be determined in the overspray shortly after spraying, and specified as raw data. Summarizing statistics such as median and GSD of the particle size distribution lead to very inaccurate model input as a normal or lognormal distribution is often only a very poor approximation of the actual PSD.

157. Where the external exposure module of ConsExpo nano seems, based on these tests, to perform adequately, the other important component of the model, the human deposition and clearance model and the link between the two, was not evaluated. This module is based on the ICRP model (ICRP, 1994[33]; Gregoratto, Bailey and Marsh, 2010[34]; Gregoratto, Bailey and Marsh, 2011[35]). The ICRP model is based on observational data, but it has not been tested separately, in the context of consumer exposure to nanomaterials, given a lack of suitable data. This constitutes a significant uncertainty that should be born in mind when using ConsExpo nano in a regulatory (or any other) context. Further model evaluation on this aspect of the tool should be welcomed, although the possibility of generating relevant experimental data seems remote.

158. In spite of these reservations, the ConsExpo nano represents the current state of the science. The results of this performance test increase confidence in the validity of the methods it implements.

Conventional chemical ECHA recommended tools

3.11. RISKOFDERM

3.11.1. Introduction

159. The RISKOFDERM is a model for estimating potential dermal exposure, i.e. the total amount of a substance coming into contact with the protective clothing, work clothing and/or exposed skin. It includes six dermal exposure operation (DEO) units, where each unit is a cluster of exposure scenarios involving general chemical substances. In the context of nanomaterials, its applicability domain is not yet established. In this section, the performance of the model, while estimating the dermal exposure to nanomaterials, is tested by comparing its output with experimentally measured dermal exposure levels of nanomaterials on hands. The tool can be downloaded from https://webcache.googleusercontent.com/search?q=cache:_vSwomJLicoJ:https://echa.europa.eu/documents/10162/19680902/calculator_riskofderm_enl.xls/9e0c3fa8-4764-4a18-95f9-8fbccf3acf2a+&cd=5&hl=da&ct=clnk&gl=dk.

3.11.2. Methods

Selection of measured exposure data

160. A separate literature search of studies focused on the measurement of dermal exposure to nanomaterials was conducted using the search terms “dermal” or “skin” and “exposure” and “nano” in PubMed and Google scholar. It resulted in a limited number of relevant studies as most of the dermal exposure studies in the literature are generally focused on either chemical substances or micro sized airborne particles (e.g. dust). The available studies were then assessed for their adequacy to be used in the performance test by using three qualifying criteria: i) enough contextual information on process is provided to translate it into input values for the model, ii) experimental parameters used in the study are within the model applicability domain and recommended limit values and, iii) measured exposure is presented as a quantitative value. At the end, 16 measurements were obtained from 4 publications, which corresponded to three DEOs or exposure scenarios of RISKOFDERM: i) filling, mixing or loading (DEO 1), ii) dispersion using hand held too (DEO 3) and, iii) spraying (DEO 4). Relevant measurement data could not be found for the other three DEOs, and therefore the full applicability domain of RISKOFDERM could not be tested.

Input parameters (data entered into the model)

161. The values for the model input parameters were retrieved from the available contextual information and the model output was compared directly with the measured exposure. For parameters with unknown values, a conservative approach was followed and thus it was decided to assume a value that would lead to the highest exposure estimates but within model recommended limits.

162. Input parameters required by the tool are shown in Table 14.

Table 14. Questions and possible answers for the three DEO assessed (DEO 1, 3 and 4).

Question	Options
Filling, mixing (DEO 1)	
What is the quality of the ventilation related to task done?	Poor ventilation Normal or good ventilation
What is the frequency of skin contact with the contaminant?	Rare contact More than rare contact
What kind of skin contact with the contaminant occurs?	Light contact More than light contact
What type of product is handled?	Liquid Low or moderately dusty solid Highly dusty solid
Are significant amounts of aerosols or splashes generated in task	Yes/No
What is the level of automation of the task done by the worker?	Manual Automated or semi-automated*
What is the use rate of the product?	0.008 – 257 L/min 0.56 – 225 kg/min
Percentile for the exposure rate distribution to be assessed	1 – 100 %
What is the cumulative duration of the scenario during a shift?	1 – 20 min (Powders) 1 – 125 min (Liquids)
Dispersion with hand held tools (DEO 3)	
Is application done overhead, level or downward?	Overhead Level Downward
What is the viscosity of the product applied?	Viscosity like water Viscosity like oil Viscosity like syrup or honey
What is the application rate of the product?	0.0001 – 1.1 L/min
What kind of tools are used for application?	Tools with handles > 30 cm in length Tools with handles < 30 cm in length
Percentile for the exposure rate distribution to be assessed	1 – 100 %
What is the cumulative duration of the scenario during shift?	1 – 445 min
Spraying (DEO 4)	
Where is the spray application done?	Outdoors Indoors
Is spraying done overhead, level or downward?	Overhead Level Downward
What is the direction of airflow that comes from the source?	Away from the worker Not clearly away from the worker
Is the worker segregated from the source?	Yes/No
How far is the source from the worker?	More than 1 m Up to 1 m
What is the volatility of the carrier liquid?	Highly volatile Not highly volatile
Is the product sprayed a liquid or a solid?	Liquid Solid
What is the application rate of the product?	0.04 – 50.4 L/min 0.02 – 0.12 kg/min
Percentile for the exposure rate distribution	1 – 100 %
What is the cumulative duration of spraying during shift?	3 – 600 min for liquids 4 – 90 min for solids

Note: *Model based on manual task only for powders.

Comparison of model estimates with measured concentrations

163. RISKOFDERM estimates dermal exposure distribution to powders and liquids in terms of exposure mass (in mg). To consider the entire statistical range of the estimated exposure distribution, bounds of 10th and 99th percentiles were used and compared with the measured exposure on hands. If the measured exposure was in the units other than mg or µl (e.g. µg cm^{-2}), it was converted to mg or µl accordingly, correcting for the hand size of 840 cm^2 used in the RISKOFDERM model. The Spearman correlation coefficient was calculated for each assessed DEO (DEO 1, 3 and 4) to determine the extent to which the model estimated exposure correlated with measured exposure values within each DEO.

3.11.3. Results and discussion

164. The RISKOFDERM tool was used to estimate the dermal exposure of 16 case studies from which 7 corresponded to DEO 1, 3 to DEO 3 and 5 to DEO 4. The results are presented in Figure 47 (a) and (b).

Comparison of dermal exposure estimates with measured exposure on hands and spearman correlation factor

165. In Figure 15 (a), the model estimated median exposure on hands is shown to be overall positively correlated with corresponding measured hand exposure for all three DEOs. A 1:1 line is shown as reference.

166. For filling, mixing or loading (DEO 1), the Spearman correlation coefficient was almost equal to 1 and the model underestimated the hand exposure by an average factor of 87. For dispersion using hand held tool (DEO 3), the model overestimated the three measurements assessed by an average factor of 3. However, the available data was too limited to analyze its correlation. For both DEOs, the reported measured exposure was obtained using interception method i.e. sampling on gloves.

167. For spraying (DEO 4), both interception and wiping of the contaminated hand surfaces were used while reporting the measured exposure and were observed to have a low Spearman correlation coefficient of 0.4. The measured hand exposure obtained using interception method was overestimated by the model by an average factor of 3 while the measured hand exposure obtained via wiping method was severely overestimated by the model by an average factor of 130. Since exposure levels measured using an interception method have been reported in the literature (e.g. Marquart *et al.,* 2017; Franken *et al.,* 2019) to be, on average, higher than measurements using a removal method (e.g. wiping), this severe underestimation of the exposure can be expected.

168. The statistical dispersion of the model estimated exposure is compared with the measured exposure values in Figure 47 (b) for all three DEOs. With the exception of Exp_7, Exp_8 and Exp_9, which correspond to exposure during spraying (measured using wiping method) and have the lowest measured exposure levels, the ranking of measurements (within each DEO) is in the order of increasing exposure consistently for both, estimated median exposure (line segments inside the box plots) and measured exposure (black dots). For example, for DEO 1 (filling, mixing or loading), measured exposure increases in the same order as the estimated median exposure (Exp_1< Exp_2< Exp_3< Exp_4< Exp_5< Exp_6< Exp_7).

169. The measured exposure was within the Interquartile range (IQR) of the estimated exposure for 6 measurements (i.e. Exp_4, 12, 13, 14, 15 and 16) and exceeded the IQR but lied within the bounds of 10th and 99th percentiles (shown as whiskers) for another 4 measurements (i.e. Exp_3, 5, 6, 11). The remaining 6 measurements (i.e. Exp_1, 2, 7, 8, 9 and 10) had their exposure values beyond the statistical dispersion of the estimated exposure (Figure 47 (b)).

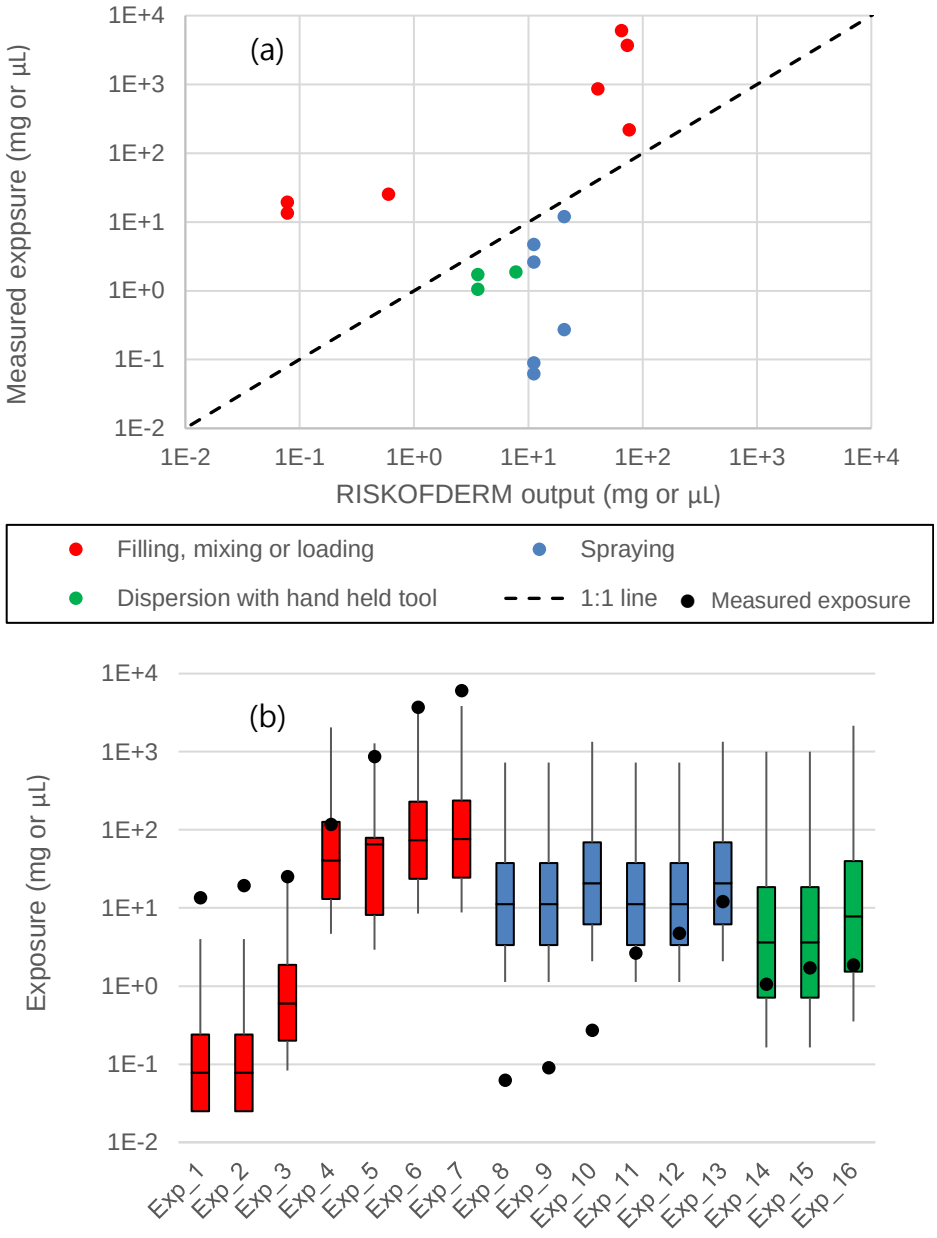


Figure 47. (a) Correlation between model output and measured exposure for three DEOs; (b) Comparison of measured exposure (denoted as black dot) with the statistical range of model estimated exposure.

Note: (b) lower and upper error bars in the box plot represent 10th and 99th percentiles respectively; Exp_1 to 7 denote exposure during filling, mixing or loading (DEO 1; red); Exp_8 to 13 denote exposure during spraying (DEO 4; blue); Exp_14 to 16 denote exposure during dispersion using hand tool (DEO 3; green).

3.11.4. Conclusions

170. The correlation of the measured exposure with the estimated exposure on hands by the RISKOFDERM model was found to be varying with DEO. While it was strongly correlated for filling, mixing or loading (DEO 1) (Spearman correlation coefficient ≈ 1), poor correlation was obtained for spraying (DEO

4) (Spearman correlation coefficient= 0.4). For dispersion using hand held tool, the measured data was too limited for any correlation analysis. For the three tested DEOs, the model underestimated the exposure obtained during filling, mixing or loading (DEO 1) and overestimated it during dispersion by hand held tool and spraying (DEO 3 and 4, respectively). Out of 16 measurements, the measured exposure levels were observed to lie within the estimated IQR for 6 measurements and outside of IQR but within the bounds of 10th and 99th percentiles for another 4 measurements. The model failed to estimate the remaining 6 measurements within its statistical range. The model was also observed to have a bias towards (severe) overestimation of dermal exposure at low measured exposure values. Therefore, the tool appears to provide precautionary assessments.

171. For this performance test, little nanomaterial specific dermal exposure data was available, and not all activities of the model, as well as modifying parameters such as dustiness, concentrations etc. were enough varied to make strong conclusions on the usability of RISKOFDERM for exposure to nanomaterials. Overall, more dermal exposure data concerning working with MNMs is needed to further investigate the applicability of RISKOFDERM for MNMs.

3.12. MEASE2 2.0

3.12.1. Introduction

172. The MEASE exposure model is an Excel®-based tool used to estimate occupational inhalation and dermal exposure to metals and inorganic substances in solid, liquid or gaseous form. MEASE is one of the ECHA recommended tools for exposure assessment. In the present study, the performance of the model is tested by comparing its output with experimentally measured mass concentration exposure levels during handling of MNMs. The tool can be downloaded from https://www.ebrc.de/tools/downloads.php.

3.12.2. Methods

Selection of measured exposure data

173. For the MEASE tool performance testing, a total of 63 exposure scenarios were used. These 63 exposure scenarios were divided in 3 exposure domains i) powder handling with 45 case studies, ii) spraying with 13 cases, and iii) abrasion with 5 cases. Modelled mass concentrations were compared with real measured respirable and inhalable mass concentrations.

174. The case studies that allowed comparison to the measurement data were namely A1-A4, C1-C7, E1-E4, F1, G1, J1-J2, N1-N2, N7, S1-S9, T1-T2, V1-V2, Z1-Z3, FF1-FF7 for powder handling domain, B1-B4, D1, F2-F3, Q2-Q3, GG1-GG4 for spraying domain, and K1-K5 for abrasion domain with an average (min-max) quality score of 0.91 (0.62-1.0), 0.81 (0.59-1.0), and 0.74, respectively. The full list of case studies is available in "*Annex A – Case studies.xlsx*". Input and output parameters entered in the tool for each case scenario are reported in *"Annex B5 – MEASE reports.pdf"* which contains the original tool reports.

175. For higher confidence in the performance testing, a selection of high quality (HQ) cases (quality score ≥0.7) and cases which did not present any limitation (measured concentration under detection limit and interferences of secondary processes) was used for assessment. In the HQ dataset, case studies included were C1-C7, E1-E4, F1, G1, J1-J2, S1-S9, V2, Z1-Z3, FF1-FF7 for powder handling domain, B1-B4, D1, F2-F3, for spraying domain, and K3-K5 for abrasion.

Input parameters (data entered into the tool)

176. A total of 24 input parameters are required for the exposure assessment with the MEASE tool. From these 24 entries 4 are related to the personal protective equipment, 4 to the substance and 16 to the process itself. Input data required is fully described in Table 15.

Table 15. Input data required by MAESE.

Input	Options	Units
Substance information		
Name	Free alphabetical characters	[-]
Molecular weight (not mandatory)	Free numerical characters	[g/mol]
Vapour pressure	Free numerical characters	[Pa]
Melting point	Free numerical characters	[ºC]
Type of operation		
Process category (PROC)	PROC according to REACH	[-]
Physical form of the substance	- Liquid - Suspension - Paste - Solid, high dusty - Solid, medium dusty - Solid, low dusty - Massive object	[-]
Level of containment	- Completely closed - Essentially closed - Partly closed - Open	[-]
Level of automation	- Fully automated - Highly automated - Semi-automated - Manual	[-]
Scale of operation		
Container capacity	- 1 L - 200 L - 1000 L - 25 kg - >500 kg - Piping system - Conveyer belt - Open truck, waggons	[L; kg; -]
Room size	- Outdoors - Large size workroom only - Any size workroom	[-]
Specific process parameters		
Concentration of the substance	- >25 - 5-25 - 1-5 - <1	[%]
Specific exposure settings		
Adjacent workplace	- Yes - No	[-]
Distance to adjacent emission source*	- =4 - =8 - >8	[m]
Exposure estimates at adjacent workplace*	Free numerical characters	[mg/m^3]

Duration of exposure	- <15 - 15-60 - 60-240 - >240	[min]
Air change rate	- Open ventilation - Basic mechanical ventilation (>1) - Mechanical ventilation (>3) - Enhanced mechanical ventilation (>10)	[h^{-1}]
Cleaning activities	- Occasional general cleaning - Regular cleaning - Immediate cleaning of overspill/splash	[-]
Technical measures		
Extraction devices	- No LEV - Fixed LEV - Mobile LEV - Integrated LEV	[-]
Efficacy of extraction device	- General purpose LEV - Specifically designed LEV - Specifically designed and regular testing	[-]
Dust suppression	- No dust suppression	[-]
Personal protective equipment		
Respiratory protective equipment	- No RPE - APF = 4 - APF = 5 - APF =10 - APF = 20 - APF = 40	[-]
Gloves	- No gloves - Appropriately selected gloves - Appropriately selected gloves with trained worker	[-]
Face/eye protection	- No - Goggles - Face protection/visor	[-]
Chemical protective clothing	- Standard safety clothing - Safety clothing with neck covered	[-]

Note: * Only if "Yes" selected for "Adjacent workplace".

177. A single person entered the data from all the case studies to the tool manually and afterwards randomly selected cases were assessed for model parametrisation agreement with a second expert. User variability was not tested.

Comparison of model estimates with measured exposure

178. The performance of the tool was assessed by comparing the tool inhalable mass concentration outputs to the real measured 8h TWA respirable and inhalable concentrations. For higher confidence on the performance testing comparisons, the preferences described in section 2.1 were followed.

179. To determine the extent to which modelled and measured mass concentrations correlated, the Spearman correlation factor for all the data set and for the individual application domains was calculated. In addition, Pearson correlation and the percentage of underestimation were also determined.

3.12.3. Results

180. Relevant information corresponding to 63 case studies used for performance testing (for powder handling, spraying and abrasion domains separately) were retrieved and complied in Table 16.

181. Measured respirable BG subtracted mass concentrations ranged from 0.02-137.4, 0.06-66.2, and 0.00001-0.00010 (not BG subtracted) µg/m^3 for powder handling, spraying and abrasion domains, respectively. Inhalable BG subtracted mass concentrations ranged from 1.0-1209.6 and 9.9-670.0 µg/m^3 for powder handling and spraying domains, respectively. On the other hand, modelled inhalable mass concentrations ranged between 1.0-32340.0, 363.0-7762.0, and 63.0-1764.0 µg/m^3 for powder handling, spraying and abrasion domains, respectively. The statistical parameters of the measured and modelled exposure mass concentrations in all the cases considered in each application domain are shown in Figure 48 and Figure 49.

Table 16. Relevant information on data graduation, measurement data used for performance testing and MEASE tool estimated values.

	Application domain	Powder Handling	Spraying	Abrasion
Report data from actual measurements	Number of studies considered	45	13	5
	Personal exposure data used	28	5	5
	Stationary exposure data NF used	17	8	0
	Stationary exposure data FF used	0	0	0
	Substance specific data	30	5	0
	Non-substance specific data	15	8	5
	Measured Respirable mass (BG sub) (µg/m^3)	0.02-137.4	0.06-66.2	N/A
	Measured Respirable mass (not BG sub) (µg/m^3)	0.04-160.0	0.13-92.0	0.00001-0.00010
	Measured Inhalable mass (BG sub) (µg/m^3)	1.0-1209.6	9.92-670.0	N/A
	Measured Inhalable mass (not BG sub) (µg/m^3)	26.8-2128.4	11.67-670.0	N/A
Report data from modelling	Range of Inhalable exposure concentration (µg/m^3)	1.0-32340.0	363.0-7762.0	63.0-1764.0
	Range of ratio modelled/measured Respirable	0.02-26151.7	28.8-10883.9	N/A
	Range of ratio modelled/measured Respirable (not BG sub)	0.02-251.3	3.95-10883.9	2417266.2-17603326.4
	Range of ratio modelled/measured Inhalable	0.79-32340.0	0.54-106.8	N/A
	Range of ratio modelled/measured Inhalable (not BG sub)	0.03-673.7	0.54-106.8	N/A

Note: 8h TWA (daily) concentration provided, N/A: not available.

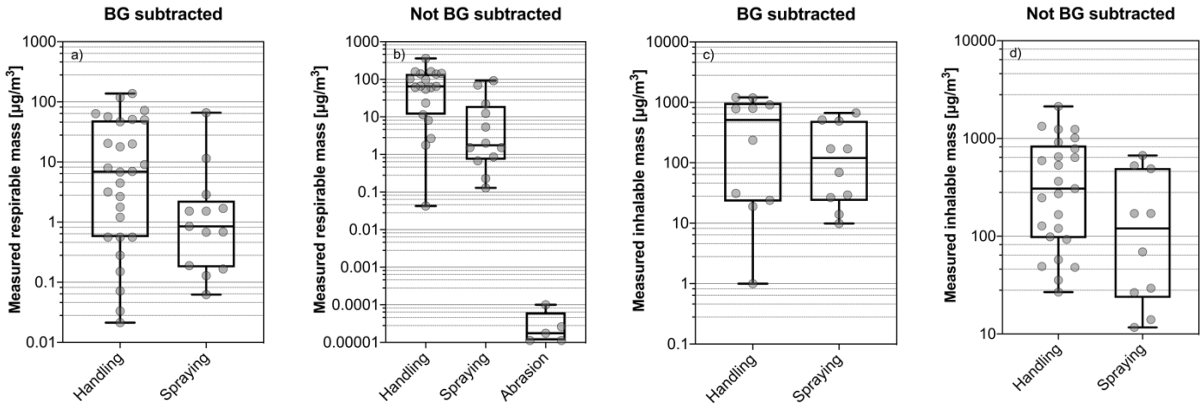


Figure 48. Vertical box plots for the measured daily respirable (a and b) and inhalable (c and d) mass concentrations for each application domain.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

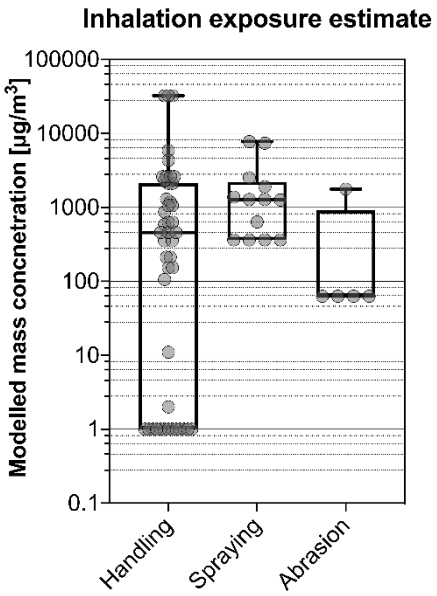


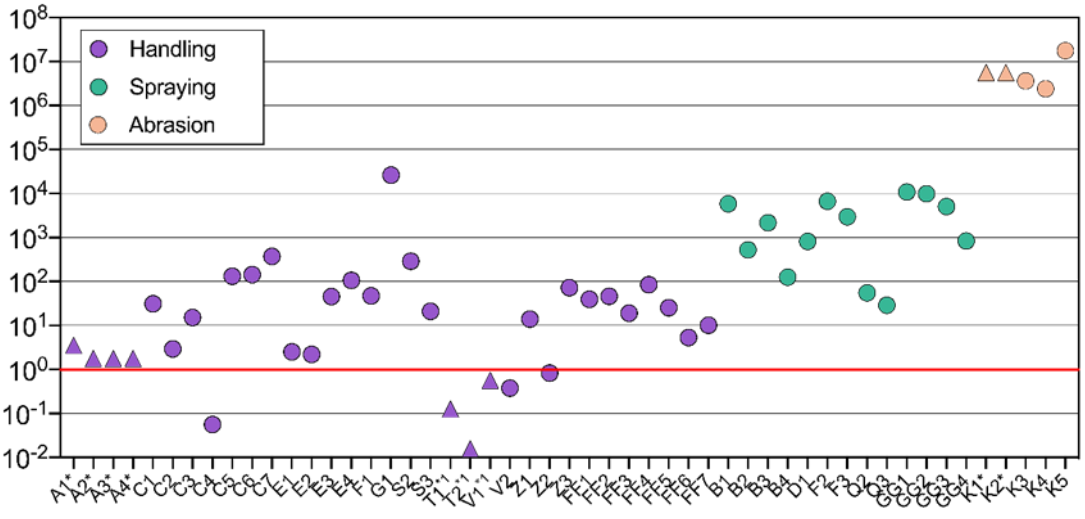
Figure 49. Vertical box plots for the modelled mass concentration for each application domain.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

Comparison of exposure score with measured mass concentrations

182. A total of 63 exposure scenarios, from which 43 were classified as HQ case studies, are used for comparison as detailed in section 3.4.2. The ratios of modelled inhalable mass concentration/measured respirable and inhalable mass concentrations are shown in Figure 50 and Figure 51, respectively together with the percentages of underestimation for each activity domain.

183. Measured respirable mass concentrations were underestimated (ratio <1) in 6 cases (representing a 12% of underestimations in total). All the 6 cases correspond to the powder handling domain, which represents a 18% underestimation in the specific domain. However, 3 of these 6 underestimations can be explained by the fact that the measured values were affected by secondary emissions. When considering only HQ cases (removing cases were influence of secondary emissions and mass concentrations were under the detection limit), the percentages of underestimation dropped to 8% considering all domains and 11% for the powder handling domain, which is in the limit of the 10% underestimation acceptance defined for this performance testing. Generally, respirable mass concentration were overestimated with ratios ranging between 1-10000 for powder handling and spraying domains, and 1,000,000-100,000,000 for abrasion processes. High overestimation were expected since modelled inhalable concentrations are compared to measured respirable concentrations. Measured inhalable concentrations were generally overestimated but with lower ratios ranging between 1 and 100 for most of the cases. Ratios of modelled inhalable mass concentration/inhalable measured mass concentrations, show consistent underestimation percentages for powder handling and spraying domains between 20-24%. For the powder handling domain, the underestimations can be explained by the use of measured not BG subtracted values. Thus, when not considering those values the percentage of underestimation is 0.

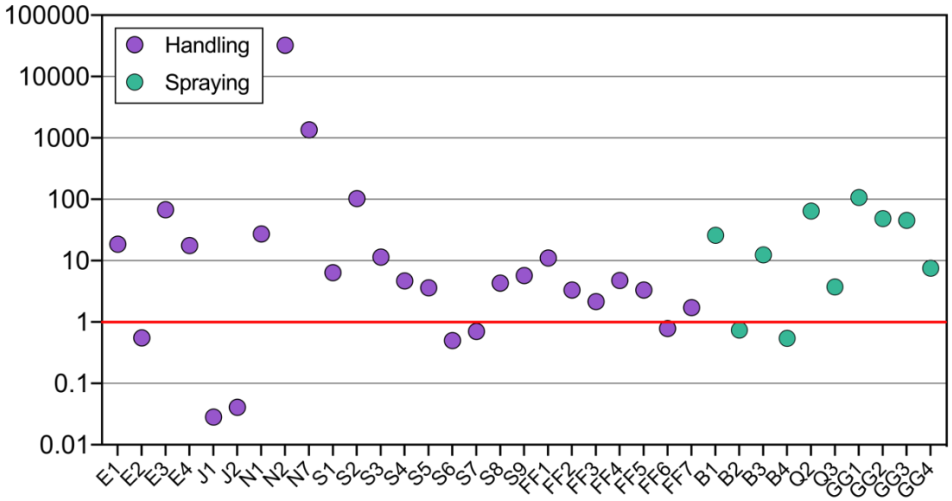


184.

All domains	All_HQ	Handling	H_HQ	Spraying	S_HQ	Abrasion	A_HQ
6/51 (12%)	3/39 (8%)	6/33 (18%)	3/26 (11%)	0/13 (0%)	0/13 (0%)	0/5 (0%)	0/3 (0%)

Figure 50. Ratio of inhalable modelled mass concentrations/measured respirable BG subtracted mass concentrations.

Note: E1-E2, K1-K5, FF1, FF5, FF7 not BG subtracted values shown. Values represented with a triangle represent *measured concentration under detection limit and *1 considering other processes. The Table below the graph shows the percentage of underestimation for each activity domain.



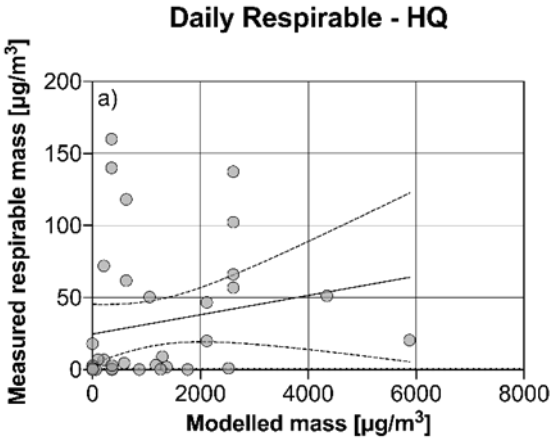
All domains	Handling	Spraying
8/35 (23%)	6/25 (24%)	2/10 (20%)

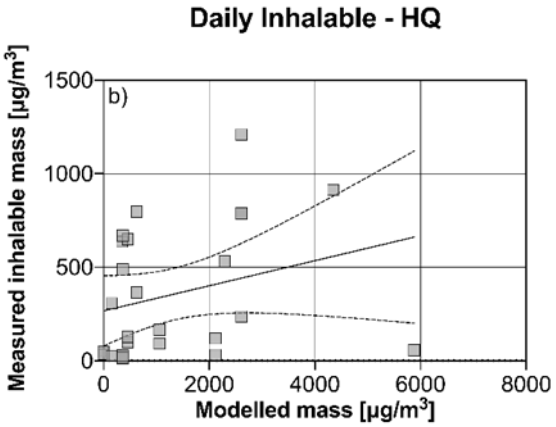
Figure 51. Ratio of inhalable modelled mass concentrations/measured inhalable BG subtracted mass concentrations.

Note: E2, E4, J1-J2, S1-S9, FF5, FF7 not BG subtracted values shown. The Table below the graph shows the percentage of underestimation for each activity domain.

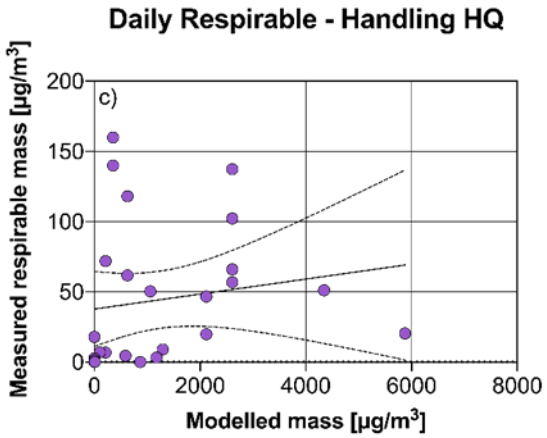
Spearman correlation factor

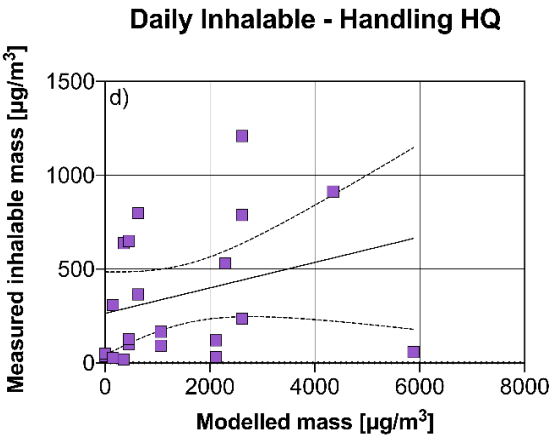
185. Modelled inhalable fraction correlation with measured respirable and inhalable fractions for all domains, handling, spraying and abrasion are shown in Figure 52. Under each figure, number of cases used (n) for correlation, Pearson and Spearman correlation coefficients for all case studies as well as only HQ studies are provided.



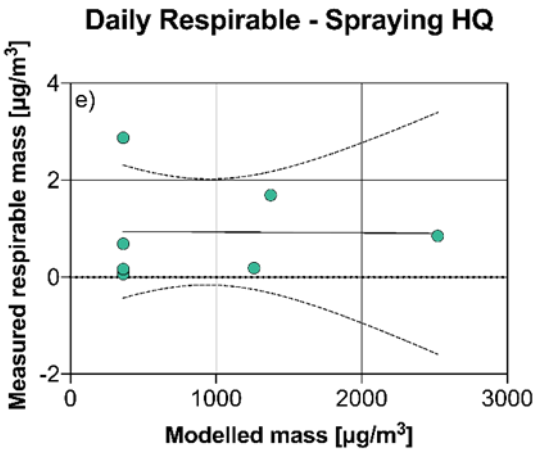


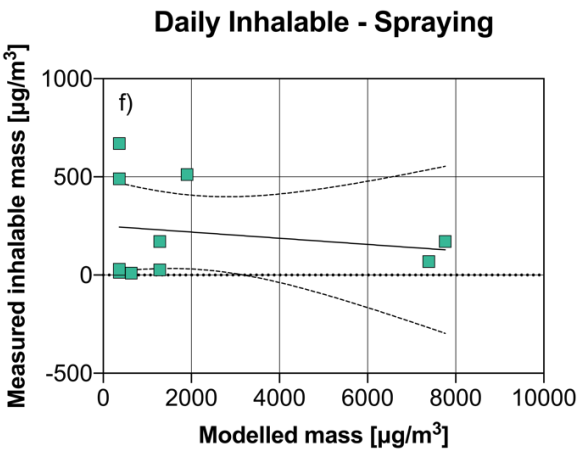
All domains	Respirable	Resp. HQ	Inhalable	Inh. HQ
n	51	36	35	26
Pearson	0.083	0.193	0.080	0.282
Spearman	0.343*	0.401*	0.177	0.463*



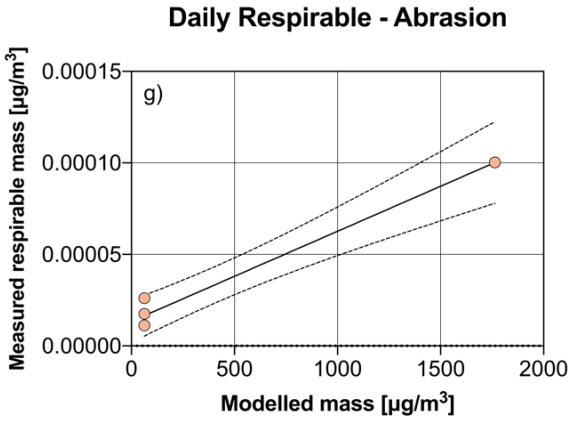


Handling	Respirable	Resp. HQ	Inhalable	Inh. HQ
n	33	26	25	22
Pearson	0.246	0.159	0.068	0.290
Spearman	0.570***	0.494*	0.223	0.469*





Spraying	Respirable	Resp. HQ	Inhalable	Inh. HQ
n	13	7	10	4
Pearson	-0.043	-0.014	-0.184	Vertical line
Spearman	0.256	0.355	0.079	Vertical line



Abrasion	Respirable	Resp. HQ
n	5	3
Pearson	0.987**	0.996
Spearman	**0.725**	**0.866**

Figure 52. Correlation of inhalable modelled mass concentrations with measured respirable and inhalable mass concentrations for a and b) all domains, c and d) powder handling, e and f) spraying and g) abrasion.

Note: f) and g) graphs show all cases due to low data point for the HQ cases. For E1-E2, K1-K5, FF1, FF5, FF7 cases respirable not BG subtracted values shown. For E2, E4, J1-J2, S1-S9, FF5, FF7 cases inhalable not BG subtracted values shown.

186. Significant Spearman correlation between modelled inhalable mass fraction and respirable and inhalable measured mass concentrations were obtained when considering the HQ cases, with coefficients of 0.401 and 0.463, respectively. However, even though correlation was considered significant, it did not reach the 0.6 standard value considered acceptable in this performance testing. Analyzing the correlation for each domain individually showed higher correlation coefficients for powder handling with significant values of 0.494 (0.570 for non-HQ cases) and 0.469 for the respirable and inhalable fractions, respectively, which are closer to the 0.6 threshold value. Conversely, no significant Spearman correlations were obtained for the spraying domain, with coefficients lower than 0.4 in all cases. For the abrasion domain, non significant Spearman correlation coefficients obtained where higher than the threshold value (0.725 and 0.866 for all cases and only HQ cases, respectively).

3.12.4. Conclusion

187. The performance testing of the MEASE tool was based on 63 exposure scenarios, from which 43 were classified as HQ case studies. The total cases were divided in 45 cases of powder handling scenarios, 13 of spraying, and 5 of abrasion. Overall, the correlation of modelled concentrations with measured respirable and inhalable concentration was found to be 0.401-0.463, respectively for the HQ cases. However, coefficients did not reach the 0.6 threshold value. In addition, inhalable fraction was underestimated in 23% of the cases. When considering only powder handling activities, significant Spearman correlation coefficient were obtained with values up to 0.57 and 0.49 for respirable mass concentrations and HQ cases, respectively. However, mass concentrations were underpredicted in more than 10% of the total comparisons.

188. No significant correlations were found for spraying domain (spearman correlation <0.4), plus measured inhalable mass fractions were underestimated in 20% of the total cases. In the case of the

abrasion domain, even though good correlations were obtained (spearman correlation 0.866) and respirable mass fractions were not underestimated in any case, the low data points of the dataset are not sufficient to reach any solid conclusions.

3.13. EMKG Expo tool 2.0

3.13.1. Introduction

189. The EMKG expo tool is presented as a Java TM Desktop application and uses a CB approach to estimate and evaluate worker inhalation exposure to solids and liquids. Similarly as MEASE, EMKG expo tool is an ECHA recommended tool for chemical exposure assessment. Here we evaluate whether or not EMKG tool has potential to be used to estimate inhalation exposure during handling of MNM by comparing the tool output with experimentally measured mass concentration exposure levels. The software is available at https://www.baua.de/EN/Topics/Work-design/Hazardous-substances/REACH-assessment-unit/EMKG-Expo-Tool.html.

3.13.2. Methods

Selection of measured exposure data

190. A total of 40 exposure scenarios, divided in 2 exposure domains (35 cases for powder handling and 5 for spraying) were used for the performance testing of the tool. Modelled mass concentrations were compared with real measured respirable and inhalable mass concentrations.

191. The case studies that allowed comparison to the measurement data were namely A1-A4, C1-C7, E1-E4, G1, I1-I3, J1-J2, L1, S1-S3, S7-S8, T1-T4, V1-V2, Z1-Z2 (0.91; 0.70-1.0) for powder handling domain, and B1-B4, D1 (1.0; 0.99-1.0) for spraying domain, with an average (min-max) quality score of 0.91 (0.70-1.0) and 1.0 (0.99-1.0), respectively. The full list of case studies is available in "*Annex A – Case studies.xlsx*". Input and output parameters entered in the tool for each case scenario are reported in *"Annex B6 – EMKG reports.pdf"* which contains the original tool reports.

192. For higher confidence in the performance testing, cases which presented measured concentrations under the detection limit (A1-A4) and were influenced by secondary processes (T1-T3 and V1) were leave out of the HQ analysis.

Input parameters (data entered into the tool)

193. The tool requires only a total of 13 input parameters for liquids and 12 for solids as shown in Table 17.

Table 17. Input data required by EMKG expo tool.

Input	Options	Units
Substance information		
Name	Free alphabetical characters	[-]
CAS n	[xxxxxxx-xx-x]	[-]
Physical state	- liquid - solid	[-]
DNEL	Free numerical characters	[ppm-mg/m^3]
DNEL type	- Not specified - Systemic - Local	[-]
Molecular weight	Free numerical characters	[g/mol]
Boiling point	Free numerical characters	[C-F-K]
% of substance	Free numerical characters	[%]
Process conditions		
Dustiness band (release group-solids)	- Low (pellet-like) - Medium (coarse powders) - High (fine, light powders)	[-]
Volatility band (release group-liquids)	- Low - Medium - High	[-]
Quantity group	- Low (g-1kg; ml-1L) - Medium (1-1000kg; 1L-1000L) - High (> 1 ton; > 1m^3)	[-]
Duration of exposure < 15min for 8h?	- Yes - No	[-]
Application on surfaces > 1m^2$_{(only\ liquids)}$	- Yes - No	[-]
Control strategy		
Applied control strategy	- Minimum requirements: good standard of general ventilation and good working practice - Engineering control: local exhaust ventilation, e.g. single point extraction close to source, ventilated partial enclosure and good work practice. - Containment: enclosure or containment and good work practice.	[-]

194. A single person entered the data from all the case studies to the tool manually and afterwards randomly selected cases were assessed for model parametrisation agreement with a second expert. User variability was not tested.

Comparison of model estimates with measured exposure

195. The performance of the tool was assessed by comparing the tool inhalable mass concentration outputs to the real measured 8h TWA respirable and inhalable concentrations. For higher confidence on the performance testing comparisons, the preferences described in section 2.1 were followed.

196. To determine to what extent modelled and measured mass concentrations correlated, the Spearman correlation factor for all the data set and for the individual application domains were calculated. In addition, Pearson correlation and the percentage of underestimation were also determined.

3.13.3. Results

197. Relevant information corresponding to the 40 case studies (35 for powder handling and 5 for spraying) used for performance testing is summarized in Table 18.

198. Ranges of measured respirable mass fraction (BG subtracted) were between 0.03-193.13 and 0.06-2.88 µg/m^3 for powder handling and spraying, respectively. Inhalable BG subtracted mass concentrations ranged from 19.0-511.9 µg/m^3 for powder handling and 0.44-20.9 µg/m^3 for spraying. Tool output inhalable mass fractions were consistently higher than measured concentrations with a range of 1.0-100000 µg/m^3 for all domains. The statistical parameters of the measured and modelled exposure mass concentrations in all the cases considered and for each application domain are shown in Figure 53 and Figure 54.

Table 18. Relevant information on data graduation, measurement data used for performance testing and EMKG expo tool estimated values.

	Application domain	Powder handling	Spraying
Report data from actual measurements	Number of case studies considered	35	5
	Number of personal exposure data used	25	5
	Number of stationary exposure data NF used	7	0
	Number of stationary exposure data FF used	0	0
	Number of substance-specific data	24	5
	Number of non-substance-specific	8	0
	Range of measured respirable mass (BG subtracted) (µg/m^3)	0.03-193.13	0.06-2.88
	Range of measured respirable mass (not BG subtracted) (µg/m^3)	2.66-320.0	0.13-3.83
	Range of measured inhalable mass (BG subtracted) (µg/m^3)	19.0-511.88	0.44-20.94
	Range of measured inhalable mass (not BG subtracted) (µg/m$_3$)	35.52-1012.5	0.88-27.92
Report data from modelling	Range of max mass concentration (µg/m^3) (max)	1.0-100000.0	16339.6
	Range of ratio modelled/respirable measured (BG subtracted)	1.25-30094.04	5683.3-261433.6
	Range of ratio modelled/respirable measured (not BG subtracted)	0.04-788.18	4262.5-130716.8
	Range of ratio modelled/inhalable measured (BG subtracted)	5.25-32.04	780.4-37347.7
	Range of ratio modelled/inhalable measured (not BG subtracted)	0.10-16.82	585.3-18673.8

Note: 8h TWA (daily) concentration provided, N/A: not available.

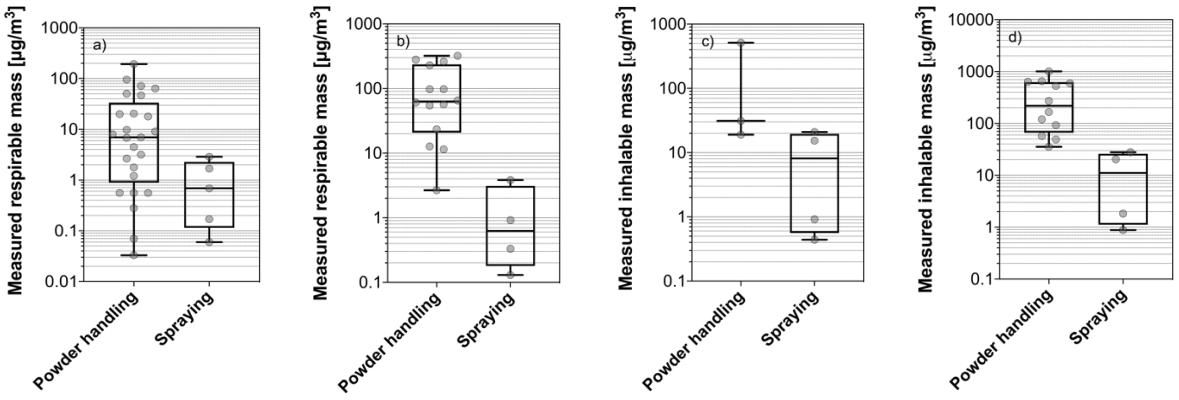


Figure 53. Vertical box plots for the measured daily exposure mass concentration in each application domain.

Note: a) respirable mass fraction BG subtracted, b) respirable mass fraction not BG subtracted, c) inhalable mass fraction BG subtracted, and d) inhalable mass fraction not BG subtracted. The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

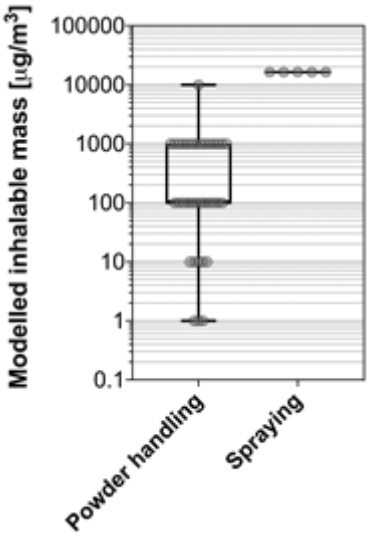
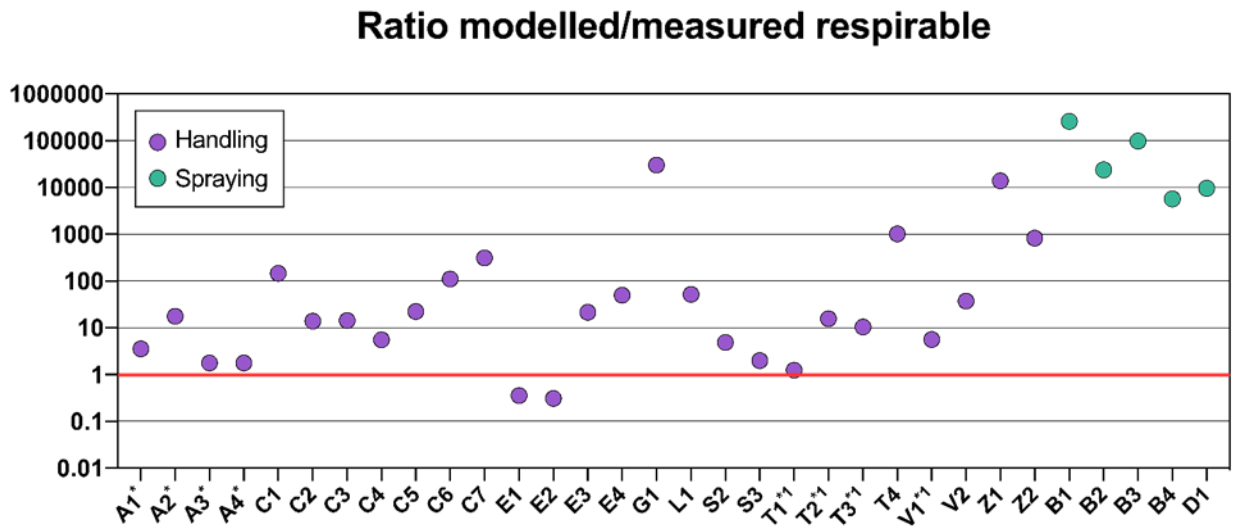


Figure 54. Vertical box plots for the modelled mass concentration for each application domain.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

199. A total of 40 exposure scenarios are used for comparison. The ratios of modelled inhalable mass concentration/measured respirable and inhalable mass concentrations are shown in Figure 55 and Figure 56, respectively together with the percentages of underestimation for each activity domain.

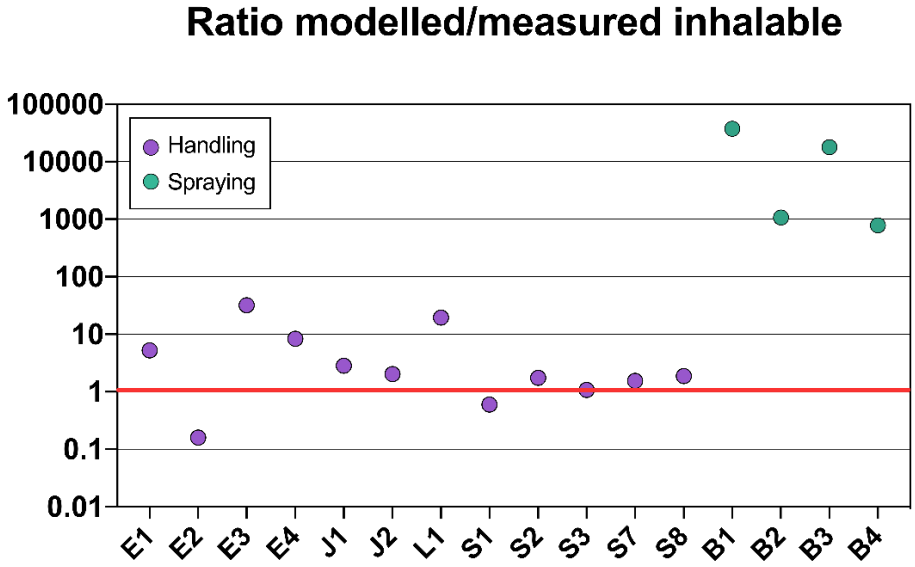
200. Measured respirable mass concentrations were underestimated (ratio <1) in 2 cases, which represent a 6.3% of the total cases and a 7.4% of the powder handling domain cases. Spraying domain scenarios were not underestimated in any case, thus meeting the 10% underestimation criteria used. This was expected since respirable concentrations are being compared to inhalable modelled concentrations. Inhalable measured mass concentrations were underestimated in higher percentages than respirable concentrations. The EMKG expo tool underestimated 12.5% of the total cases and 16.7% of the powder handling cases. However, this underestimation can be explained by the fact that not BG subtracted were used for the 2 underestimated cases (E2-S1). When not considering those values, the EMKG expo tool did not underestimate any case study. Overall, the EMKG expo tool was able to predict inhalable mass concentrations due to powder handling activities in a ratio range of 0.1-100, and spraying in a ratio range of 1000-100000 thus, the tool consistently overestimated cases in the spraying domain.



All domains	Handling	Spraying
2/32 (6.3%)	2/27 (7.4%)	0/5 (0%)

Figure 55. Ratio of inhalable modelled mass concentrations/measured respirable BG subtracted mass concentrations.

Note: E1-E2 not BG subtracted values shown. *measured concentration under detection limit and *1 considering other processes. The Table below the graph shows the percentage of underestimation for each activity domain.



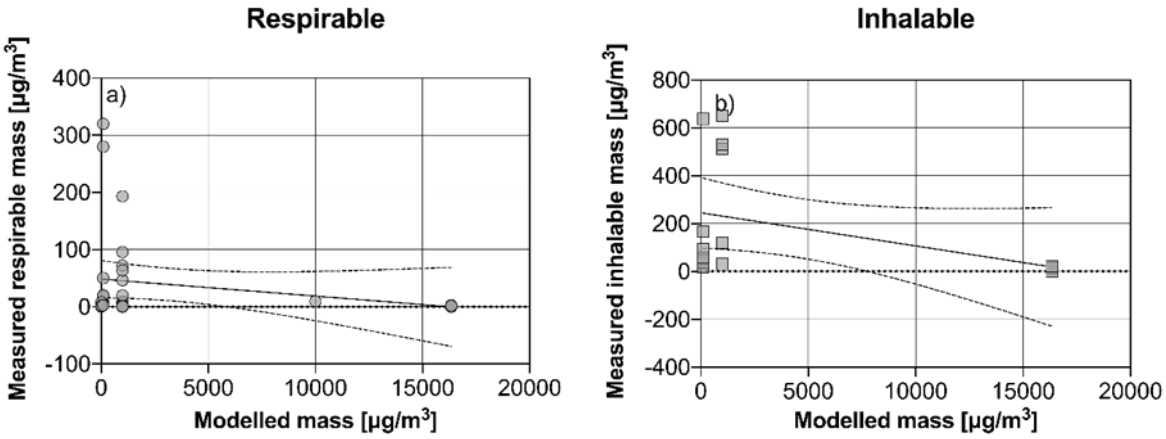
All domains	Handling	Spraying
2/16 (12.5%)	2/12 (16.7%)	0/5 (0%)

Figure 56. Ratio of inhalable modelled mass concentrations/measured respirable BG subtracted mass concentrations.

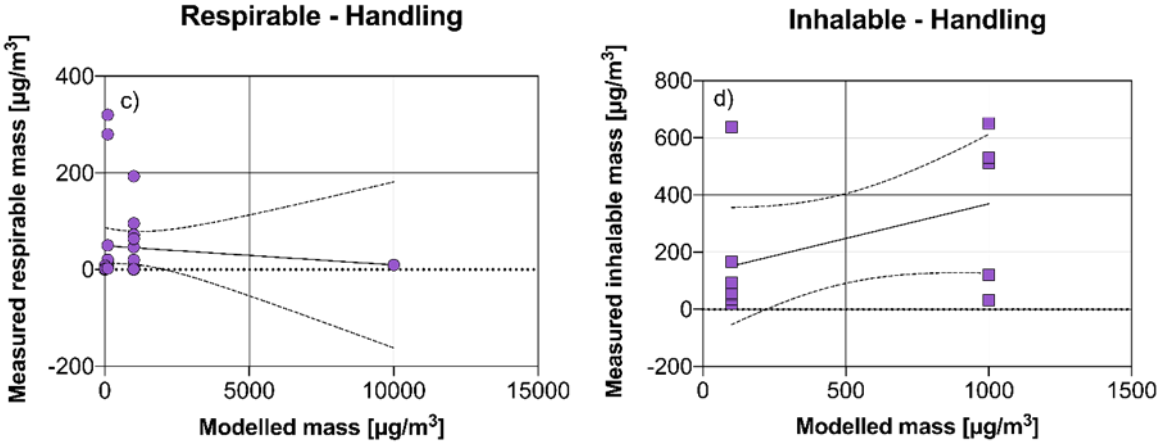
Note: E2, E4, J1-J2 and S1-S8 not BG subtracted values shown. The Table below the graph shows the percentage of underestimation for each activity domain.

Spearman correlation factor

201. Modelled inhalable fraction correlation with measured respirable and inhalable fractions for all domains, and handling are shown in Figure 57. Under each figure, number of cases used (n) for correlation, Pearson and Spearman correlation coefficients for all case studies as well as only HQ studies are provided (when available).



All domains	Respirable	Respirable HQ	Inhalable
n	32	24	16
Pearson	-0.224	-0.293	-0.403
Spearman	-0.050	-0.541**	-0.430



Handling	Respirable	Respirable HQ	Inhalable
n	27	19	12
Pearson	-0.088	-0.168	0.435
Spearman	0.307	-0.250	0.367

Figure 57. Correlation of inhalable modelled mass concentrations with measured respirable and inhalable mass concentrations.

Note: for a) and b) all domains, c) and d) powder handling. For E1-E2 cases respirable not BG subtracted values shown. For inhalable concentrations all data points except E1, E3, L1, and B1-B4 are not BG subtracted values.

202. Overall, no positive correlations were found when considering all case studies for modelled inhalable mass concentrations with measured mass concentrations (Spearman correlation coefficient of -0.541 and -0.430 for respirable and inhalable mass fractions, respectively).

203. Similarly, for powder handling domain cases, no significant spearman correlations were found between inhalable modelled concentrations and respirable measured mass concentrations, with spearman correlation coefficients of 0.307 and -0.250 for all cases and HQ cases, respectively. For inhalable measured mass concentrations slightly improved Spearman coefficient was obtained (0.367) with a Pearson coefficient correlation of 0.435. However, this is still far from the 0.6 benchmark used in this performance testing. In the case of spraying domain, only 4 to 5 data points were available and correlation coefficients could not be calculated.

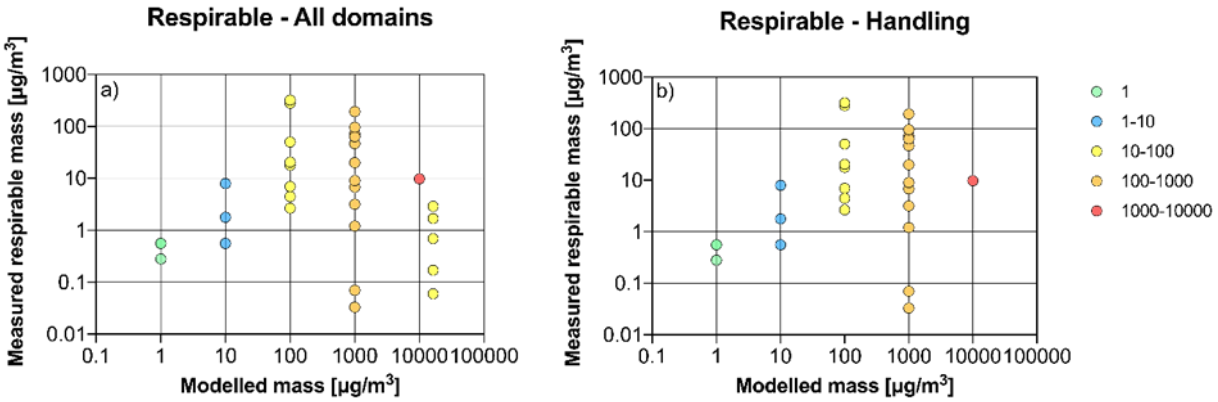


Figure 58. Correlation between model mass estimate and measured respirable mass for the different exposure bands considering a) all case studies, and b) powder handling case studies.

Note: graphs are in log-scale.

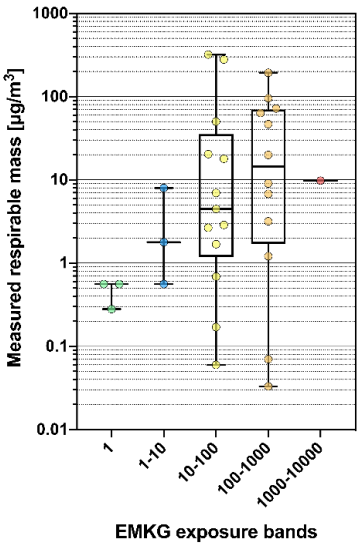


Figure 59. Classification of measured exposure in the model estimated exposure bands.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

204. In Figure 58 the correlation of the measured respirable mass with the modelled mass is presented for the different exposure bands considered by the tool. The majority of the data points lie below a perfectly linear fit indicating the tendency of the tool to overestimate exposure levels for the different exposure level bands. This is concordance with the goal of the tool, which is to provide guidance on the level of exposure and to filter non-risky workplace situations. The measured exposure concentrations classified in the model estimated exposure bands are represented in Figure 59. The mean and median of the exposure concentrations are equal to 0.47 and 0.56 µg/m^3, 3.44 and 1.78 µg/m^3, 54.48 and 4.47 µg/m^3, 42.63 and 14.50 µg/m^3, and 9.79 and 9.79 µg/m^3 for the exposure bands <1, 1-10, 10-100, 100-1000 and 1000-10000 µg/m^3, respectively. This shows the tendency of the tool to associate higher exposure bands to higher exposure concentration with the exception of the highest bands. Moreover, there is overlapping between ranges in the higher exposure bands (10-10000).

3.13.4. Conclusion

205. The performance testing of the EMKG expo tool was based on 40 exposure scenarios, from which 32 were classified as HQ case studies. The total cases were divided in 35 cases of powder handling scenarios and 5 of spraying. Even though the tool did not underestimate the measured exposure concentration in any of the case studies, the correlation of modelled concentrations with measured respirable and inhalable concentration for all studies and for powder handling domain, was not found to be significant with spearman coefficients ranging between -0.541 and 0.367. In the case of spraying domain, only 4 to 5 data points were available with a vertical line correlation, thus no major conclusions could be extracted for this specific domain. In addition, the tool was found to overestimate measured exposure concentrations, which would be expected from the tool, and to associate higher bands to higher exposures but with band overlapping.

3.14. Stoffenmanager 8.3

3.14.1. Introduction

206. Stoffenmanager is an ECHA recommended risk priorization web-based tool designed to estimate inhalation exposure to chemical substances at workplaces. The performance of the model is tested for handling of MNM by comparing its quantitative output with experimentally measured mass concentration exposure levels. The tool can be accessed from https://stoffenmanager.com/.

3.14.2. Methods

Selection of measured exposure data

207. For the Stoffenmanager performance testing, a total of 51 exposure scenarios were used. The total case studies were divided in 3 activity domains, powder handling with 37 cases, spraying with 9 cases, and abrasion with only 5 cases. Modelled mass concentrations were compared with real measured respirable and inhalable mass concentrations.

208. The case studies that allowed comparison to the measurement data were namely A1-A4, C1-C7, E1-E4, F1, G1, J1-J2, L1-L2, N1-N2, N5, N7, S1-S9, and Z1-Z3, for powder handling domain, B1-B4, D1, F2-F3, Q2-Q3 for spraying domain, and K1-K5 for abrasion domain with an average (min-max) quality score of 0.89 (0.62-1.0), 0.92 (0.71-1.0), and 0.74, respectively. The full list of case studies is available in "*Annex A – Case studies.xlsx*". Input and output parameters entered in the tool for each case scenario are reported in "*Annex B7 – Stoffenmanager reports.pdf"* which contains the original tool reports.

209. For higher confidence in the performance testing, a selection of high quality (HQ) cases (quality score ≥0.7) and cases which did not present any limitation (measured concentration under detection limit and interferences of secondary processes) was used for the performance testing assessment. In the HQ dataset, case studies included were C1-C7, E1-E4, F1, G1, J1-J2, L1-L2, S1-S9 and Z1-Z3 for powder handling domain, B1-B4, D1, F2-F3, Q2-Q3 for spraying domain, and K3-K5 for abrasion.

Input parameters (data entered into the tool)

210. The tool total number of inputs required for a case scenario are dependent on the case scenario and previous selections. Overall, the tool requires information on the product and components, and process and workplace. Input data required is fully described in Table 19.

Table 19. Input data required by Stoffenmanager.

Input	Options	Units
Component		
Name	Free alphabetical characters	[-]
CAS number	[xxxxxxx-xx-x]	[-]
EC number	[xxx-xxx-x]	[-]
REACH number	[xx-xxxxxxxxx-xx-oooo]	[-]
Physical properties	- Solid - Liquid - Solid and liquid	[-]
Molecular weight	Free numerical characters	[g/mol]
Limit value	- Acute (15min TWA) - Daily (8h TWA) - Ceiling - Others	[mg/m^3]
Vapour pressure	Free numerical characters	[Pa]
Product		
Name	Free alphabetical characters	[-]
Supplier	Free alphabetical characters	[-]
Unique formula identifier	[xxxx-xxxx-xxxx-xxxx]	[-]
Health and safety information	H-/P-statements or R-/S-phrases	[-]
Composition	Components	[%]
Workplace instruction card	First aid and safety instructions	[-]
Explosion safety (ATEX)	Relevant information for ATEX required	[-]
Storage and transport	Relevant information for storage and transport	[-]
Vapour pressure	Free numerical characters	[Pa]
Dustiness	- Objects - Solids/granules/grains/flakes - Coarse dust - Fine dust - Extremely fine dust	[-]
Supplier		
Name and legal information	Free alphabetical characters	[-]
Job title		
Name, code, number of employees and explanation	Free alphabetical characters	[-]
Process		
Name and description	Free alphabetical characters	[-]

Input	Options	Units
Type of substance	- Liquid - Solid - Solid: cutting stone - Solid: cutting wood	[-]
Type of task	Several options available dependent on previous selections	[-]
REACH PROC category	REACH PROC categories available 0-28	[-]
Duration	Free numerical chcracters	[min]
Frequency task	- 1 time year - 1 time month - 1 time 2 weeks - 1 time week - 2-3 times a week - 4-5 times a week	[-]
Task carried out at worker breathing zone?	Yes/No	[-]
More than one employee carrying out the same task simultaneously?	Yes/No	[-]
Task followed by evaporation, drying or curing?	Yes/No	[-]
Respiratory protective equipment	- No protection - Disposable half mask - Reusable half mask respirator – gas/vapour filter - Full face mask respirator – gas/vapour - Powered respirators with mask - Reusable half mask respirators – particle filter - Full face mask respirator – particle filter - Powered respirators with hoods/helmets - Fresh air hose (FAH) breathing apparatus - Constant flow airline breathing apparatus with a mask – light duty - Constant flow airline breathing apparatus with mask - Constant flow airline breathing apparatus with hoods/helmets – light duty - Constant flow airline breathing apparatus with hoods/helmets - Constant flow airline breathing apparatus with full suit - Demand valve breathing apparatus	[-]
Workplace		
Name and description	Free alphabetical characters	[-]
Volume of the working room	- Under 100 m^3 - 100-100 m^3 - Over 1000 m^3 - Outdoors	[m^3]
Ventilation	- Spraying booth - General ventilation (open windows) - General ventilation (mechanical) - No general ventilation	[-]
Working room cleaned daily?	Yes/No	[-]
Inspections and maintenance at least monthly?	Yes/No	[-]
Control measures	- Containment of the source with LEV - Containment of the source - Local exhaust ventilation - Use of product that reduces the emission - No control measures at source	[-]

Input	Options	Units
Protection of the employee	- Worker in a separated (control) room with independent clean air supply - Employee in an open or closed cabin without specific ventilation system - Employee does not work in a cabin	[-]

211. A single person entered the data from all the case studies to the tool manually and afterwards randomly selected cases were assessed for model parametrisation agreement with a second expert. User variability was not tested.

212. The following assumptions were considered when information was not available 1) frequency of task selected in all cases was 4-5 times a week, 2) multiple employees working at the same time – no, 3) room temperature was assumed, 4) working room cleaned daily, and 5) monthly inspections. In addition, it is important to note that for abrasion activities, Stoffenamanger only considers wood or stone materials. Here, the material under study in the case used (case K) to test the abrasion domain is a nanocomposite. Therefore, results obtained regarding the abrasion domain should be treated with caution.

213. Stoffenmanager output concentration is inhalable mass fraction. Therefore, for powder handling activities, the tool requires inhalable dustiness fraction. However, in many of the case studies from the data set, only respirable dustiness was available. Thus, respirable dustiness values were converted to inhalable dustiness index by using the conversion shown in Table 20, and tool output values were assumed to be inhalable mass concentrations. In addition, only for powder handling, the respirable dustiness value was entered to the tool and output concentration was assumed to be respirable mass concentration.

Table 20. Table used to convert respirable dustiness index values to inhalable dustiness values inputs for Stoffenmanager tool.

Respirable dustiness	ART conversion for Inhalable dustiness
Low < 70	Granules/grains/flakes
Medium < 150	Coarse dust
Medium > 150	Fine dust
High > 300	Extremely dusty products

Comparison of model estimates with measured exposure

214. The performance of the tool was assessed by comparing the tool 90th percentile inhalable mass concentration outputs to the real measured 8h TWA respirable and inhalable concentrations. For higher confidence on the performance testing comparisons, the preferences described in section 2.1 were followed.

215. To determine to what extent modelled and measured mass concentrations correlated, the Spearman correlation factor for all the data set and for the individual application domains were calculated. In addition, Pearson correlation and the percentage of underestimation were also determined.

3.14.3. Results

216. Relevant information corresponding to the 51 case studies, divided in 37 for powder handling and 9 for spraying and 5 for abrasion activity domains used for performance testing is summarized in Table 21.

217. Ranges of measured respirable mass fraction (BG subtracted) were between 0.021-193.13 µg/m^3 and 0.063-66.15 µg/m^3 for powder handling and spraying, respectively. Not BG subtracted respirable mass concentrations ranged between 0.000011-0.00010 µg/m^3 for abrasion domain. Inhalable BG subtracted mass concentrations ranged from 1.0-1189.0 µg/m^3 for powder handling and 9.9-670.9

µg/m^3 for spraying. Tool output inhalable mass fractions ranged between 0.098-44950.0 µg/m^3, 0.48-4852.9 µg/m^3, and 170.0-1060.0 µg/m^3 for powder handling, spraying and abrasion. The statistical parameters of the measured and modelled exposure mass concentrations in all the cases considered and for each application domain are shown in Figure 60 and Figure 61.

Table 21. Relevant information on data graduation, measurement data used for performance testing and Stoffenmanager estimated values.

	Application domain	Powder handling	Leak/point source/Spraying	Abrasion
Report data from actual measurements	Number of case studies considered	37	9	5
	Number of personal exposure data used	25	5	5
	Number of stationary exposure data NF used	12	4	0
	Number of stationary exposure data FF used	0	0	0
	Number of substance-specific data	31	5	0
	Number of non-substance-specific	6	4	5
	Range of measured respirable mass (BG subtracted) (µg/m^3)	0.021-193.13	0.063-66.15	n/a
	Range of measured respirable mass (not BG subtracted) (µg/m^3)	0.043-228.75	0.23-92.0	0.000011-0.00010
	Range of measured inhalable mass (BG subtracted) (µg/m^3)	1.0-1189.0	9.9-670.9	n/a
	Range of measured inhalable mass (not BG subtracted) (µg/m$_3$)	26.8-1331.0	11.67-670.0	n/a
Report data from models	Range of Inhalable concentration (µg/m^3)	0.098-44950.0	0.48-4852.9	170.0-1060.0
	Range of ratio inhalable modelled/respirable measured	0.25-377.6	0.49-2868.7	6522781-15111111*
	Range of ratio inhalable modelled/inhalable measured	0.88-21170.0	0.0021-0.57	n/a
	Range of hazard class (-)	A-E	A-E	E
	Range of exposure class (-)	1.0-3.0	1.0-2.0	1.0
	Range of risk score (-)	III-I	III-I	I

Note: 8h TWA (daily) concentration provided. *Not BG subtracted, N/A: not available.

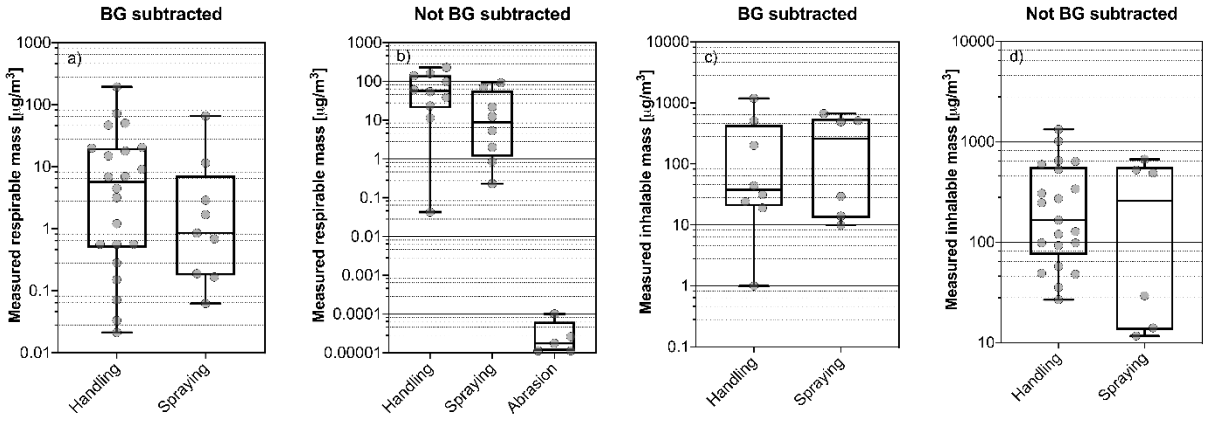


Figure 60. Vertical box plots for the measured daily exposure mass concentration in each application domain.

Note: a) respirable mass fraction BG subtracted, b) respirable mass fraction not BG subtracted, c) inhalable mass fraction BG subtracted, and d) inhalable mass fraction not BG subtracted. The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

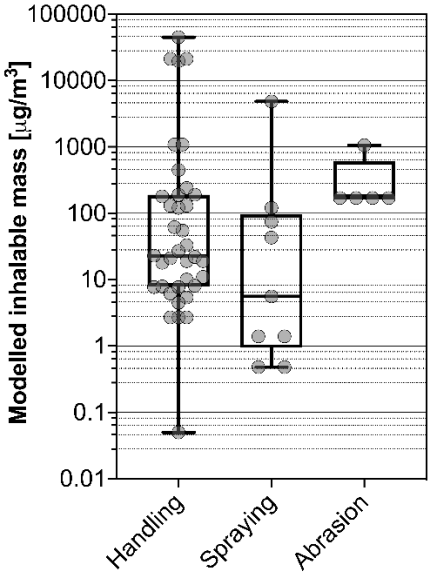


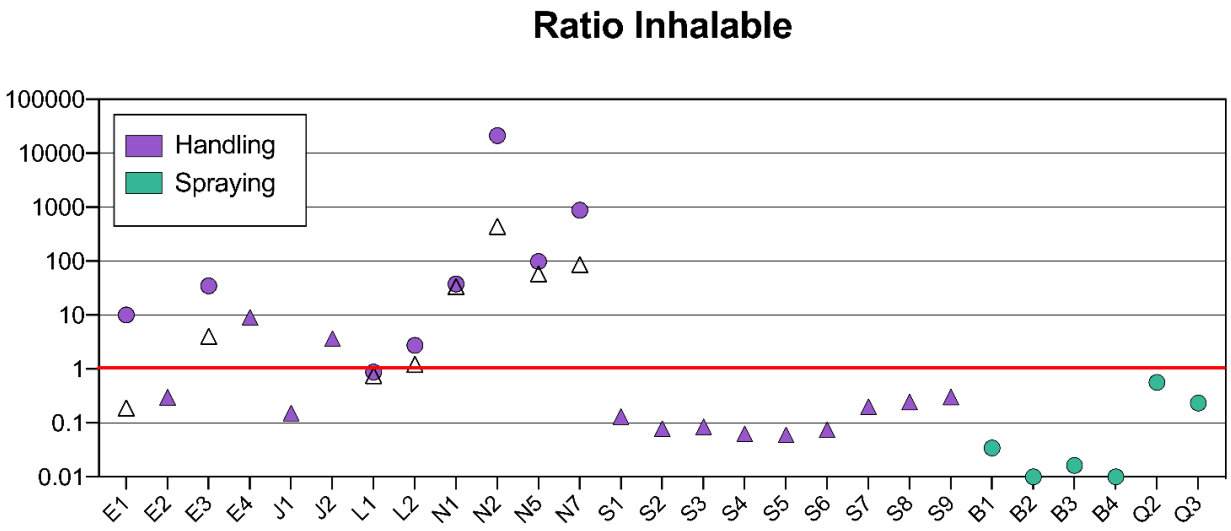
Figure 61. Vertical box plots for the 90th percentile modelled mass concentration for each application domain.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

Comparison of exposure score with measured mass concentrations

218. A total of 51 exposure scenarios are used for comparison. The ratios of modelled inhalable mass concentration/measured respirable and inhalable mass concentrations are shown in Figure 62 and Figure 63, respectively together with the percentages of underestimation for each activity domain.

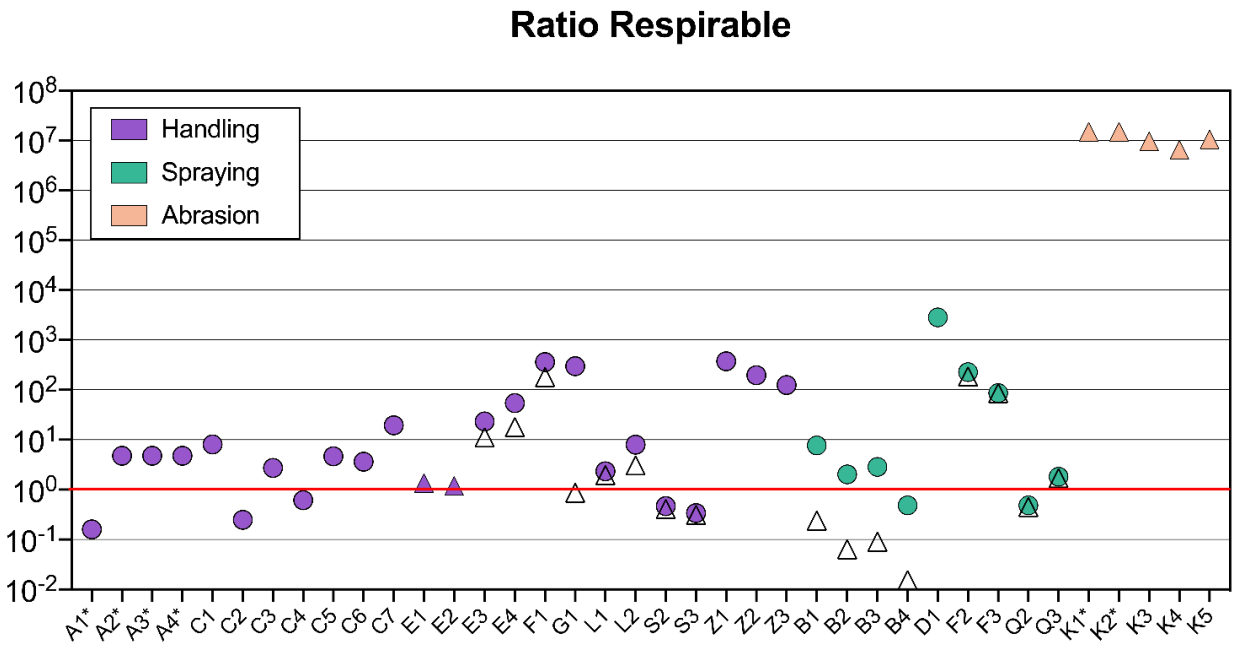
219. Measured inhalable mass concentrations were underestimated (ratio <1) in 12.5% and 100% of the cases for powder handling domain and spraying, respectively, with an overall underestimation of 50%. When no background subtracted values are used for powder handling domain, increasing the total number of comparisons up to 21, the tool output underestimates 62% of the cases. Due to low data points for inhalable mass fraction comparison, modelled inhalable mass fraction was additionally compared to respirable measured mass concentration. Handling and spraying domains were underestimated in 22.7 and 22.2% of the cases whereas for abrasion Stoffenmanager highly overestimated respirable mass concentrations (ratio 10^7). Overall the real respirable concentrations exceeded the model estimates for 19.4% of the total comparisons which is above the 10% limit considered in this work. The use of HQ case studies or not background corrected values did not result in notable improvements.



All domains	Handling	Handling_Not BG subtracted	Spraying
7/14 (50%)	1/8 (12.5%)	13/21 (62%)	6/6 (100%)

Figure 62. Ratio of inhalable modelled mass concentrations/measured inhalable BG subtracted mass concentrations.

Note: E2, E4, J1-J2, S1-S9 not BG subtracted shown (identified with a triangle). Not coloured triangles are used when data for BG subtracted values is also shown for the same case scenario. The table below the graph shows the percentage of underestimation for each activity domain.



All domains	Handling	Handling_Not BG subtracted	Spraying	Spraying_Not BG subtracetd	Abrasion
7/36 (19.4%)	5/22 (22.7%)	3/10 (30%)	2/9 (22.2%)	5/8 (62.5%)	0/5 (0%)

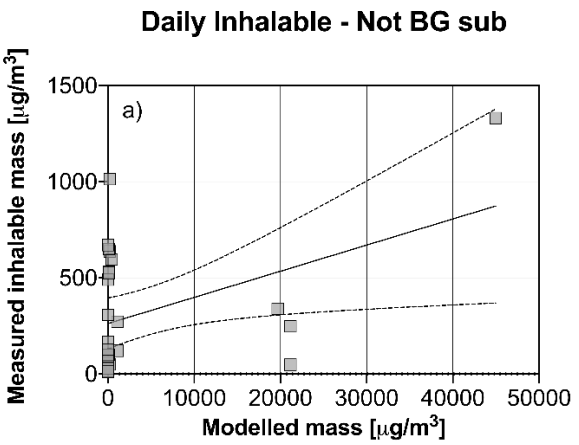
Figure 63. Ratio of inhalable modelled mass concentrations/measured respirable BG subtracted mass concentrations.

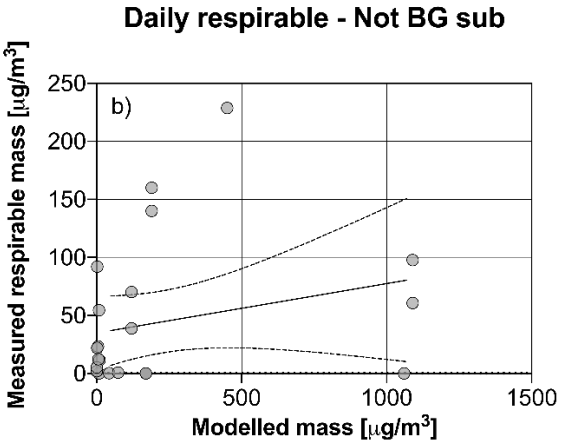
Note: E1-E2, and K1-K5 not BG subtracted values shown (identified with a triangle). Not coloured triangles are used when data for BG subtracted values is also shown for the same case scenario. *measured concentration under detection limit. The Table below the graph shows the percentage of underestimation for each activity domain.

Spearman correlation factor

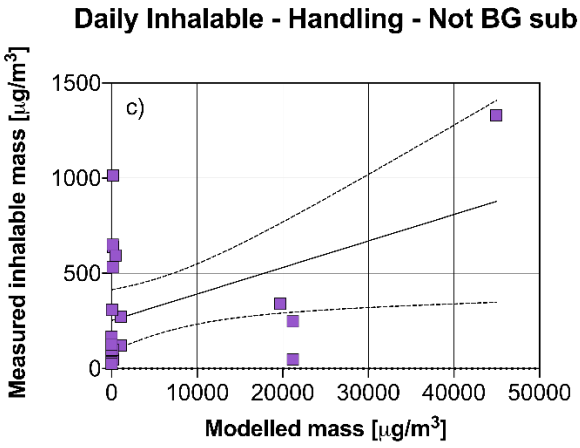
220. Modelled inhalable fraction correlation with measured respirable and inhalable fractions for all domains, powder handling, spraying and abrasion are shown in Figure 64. Under each figure, number of cases used (n) for correlation, R^2, Pearson and Spearman correlation coefficients are provided.

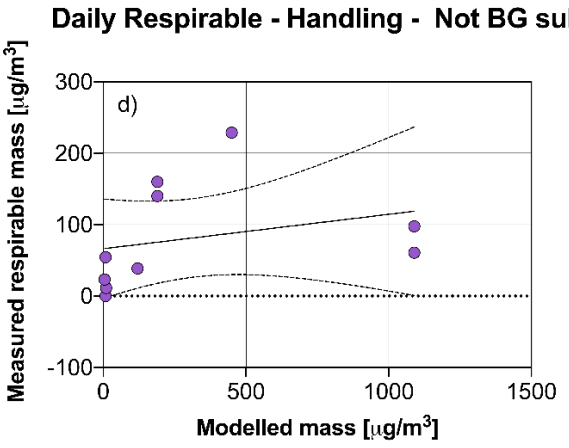
221. When considering all case studies, Spearman coefficient correlation obtained for measured respirable and inhalable mass concentrations were under 0.6 in all cases. However, significant Spearman correlation coefficient for measured not background subtracted inhalable mass fraction of 0.4394 was obtained, suggesting a slight correlation between measured and modelled inhalable fractions. When analysing the results for the different activity domains, a Spearman correlation coefficient of 0.4889 and 0.7256 for measured not background corrected inhalable and respirable mass concentrations, indicating a moderate to strong correlation between measured and modelled concentrations. The fact that correlations improve when using not background corrected concentrations, even though underestimations increase, maybe due to the fact that Stoffenmanager calibration dataset does not use background corrected data. On the contrary, for spraying only a Spearman correlation > 0.6 is obtained for respirable background corrected data. In the case of the abrasion domain, although a Spearman correlation coefficient of 0.726 was obtained for not background corrected respirable fraction, due to the clustered data and low data points (5) no clear conclusions can be extracted. It is important to note the fact that Stoffenmanager considers only wood and stone materials for the abrasion domain and the material under study in the case used was a nanocomposite.



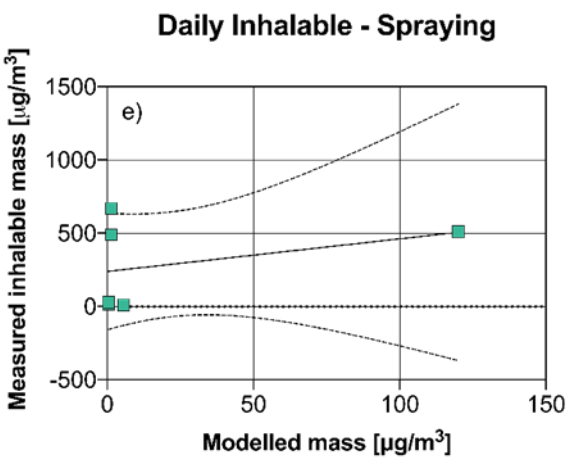


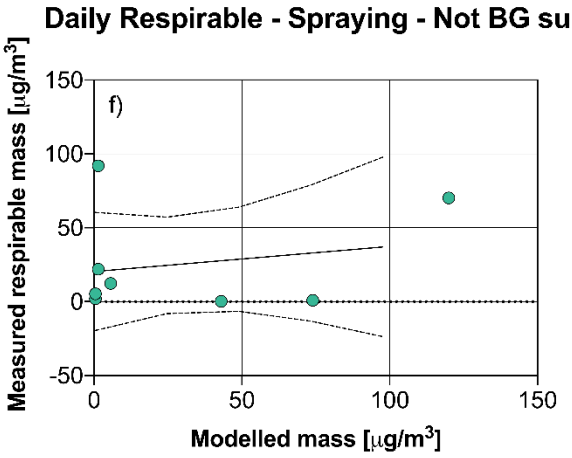
All domains	Inhalable		Respirable	
	BG subtracted	Not BG subtracted	BG subtracted	Not BG subtracted
n	27	27	38	23
Pearson	0.3858*	0.4236*	0.0013	0.2441
Spearman	0.1166	0.4394*	0.1782	0.1567



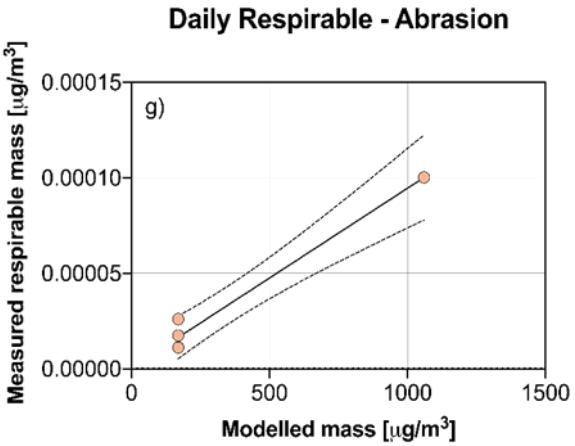


Handling	Inhalable		Respirable	
	BG subtracted	Not BG subtracted	BG subtracted	Not BG subtracted
n	21	21	24	10
Pearson	0.4598*	0.4617*	0.2680	0.2797
Spearman	0.0403	0.4889*	0.5117*	**0.7256***





Spraying	Inhalable	Respirable	
	BG subtracted	BG subtracted	Not BG subtracted
n	6	9	8
Pearson	0.3558	-0.1131	0.2164
Spearman	0.2354	**0.6219**	-0.0362



Abrasion	Respirable
n	5
Pearson	0.987**
Spearman	**0.726**

Figure 64. Correlation of inhalable modelled mass concentrations with measured respirable and inhalable mass concentrations.

Note: a and b) all domains, c and d) powder handling, e and f) spraying, and g) abrasion. For E1-E2 and K1-K5 cases, respirable not BG subtracted values shown. For inhalable concentrations all E2, E4, J1-J2 and S1-S9 not BG subtracted values.

3.14.4. Conclusion

222. The performance testing of the Stoffenmanager tool was based on a total of 51 case studies, 37 for powder handling, 9 for spraying and 5 for abrasion domains. Overall, Stoffenmanager underestimated measured concentrations for more than 10% of the total comparisons, which was the limit considered acceptable. Only for the abrasion domain, measured mass concentrations were not underestimated in any case. Regarding correlation of modelled with respirable measured concentrations, spearman coefficient correlations >0.6 were obtained for handling (when not background corrected data was used), and spraying and abrasion domains, although only 9 and 5 data points, respectively were available. In sum, and

according to the performance testing criteria defined in section 2.1, the tool does not meet all the criteria established in order to be currently used for MNM exposure assessment of powder handling and spraying at this stage and for the conditions assessed as even though Spearman correlation was >0.6, underprediction of exposure concentrations occurred in more than 10% of the total comparisons. For the abrasion domain, the tool met both criteria (>0.6 Spearman correlation and underestimation <10% of the total cases). However, due to low data points, data clustering and the difference between material under study in the case used (nanocomposite) and materials which Stoffenmanager can handle (wood and stone) a final conclusion cannot be reached.

3.15. Advanced REACH Tool v1.5

3.15.1. Introduction

223. The Advanced REACH tool is a web-based tool designed to estimate occupational inhalation to vapours, mists, dust and metal fumes. It combines a source-receptor approach with MFs, and a Bayesian model were estimates can be updated with the user´s own data (Fransman et al., 2011[36]). ART is tool recommended by ECHA for workplace chemical exposure assessment. Here, the performance of the model is tested for handling of MNM by comparing its output with experimentally measured mass concentration exposure levels. The ART is available at https://www.advancedreachtool.com/.

3.15.2. Methods

Selection of measured exposure data

224. For the ART tool performance testing, a total of 61 exposure scenarios were used. The total case studies were divided in 3 activity domains, powder handling with 47 cases, spraying with 9 cases and abrasion with only 5 cases. Modelled mass concentrations were compared with real measured respirable and inhalable mass concentrations.

225. The case studies that allowed comparison to the measurement data were namely A1-A4, C1-C7, E1-E4, G1, J1-J2, L1-L2, N1-N2, N5, N7, S1-S9, T1-T3, V1-V2, Z1-Z2, FF1-FF7 for powder handling domain, B1-B4, D1, F2-F3, Q2-Q3 for spraying domain, and K1-K5 for abrasion domain with an average (min-max) quality score of 0.90 (0.62-1.0), 0.90 (0.71-1.0), and 0.74, respectively. The full list of case studies is available in "*Annex A – Case studies.xlsx*". Input and output parameters entered in the tool for each case scenario are reported in *"Annex B8 – ART Inhalable fraction reports.pdf"* and *"Annex B9 – ART Respirable fraction reports.pdf"* which contain the original tool reports.

226. For higher confidence in the performance testing, a selection of high quality (HQ) cases (quality score ≥0.7) and cases which did not present any limitation (measured concentration under detection limit and interferences of secondary processes) was used for the performance testing assessment. In the HQ dataset, case studies included were C1-C7, E1-E4, G1, J1-J2, L1-L2, S1-S9, V2, Z1-Z3, FF1-FF7 for powder handling domain, B1-B4, D1, F2-F3, Q1-Q3 for spraying domain, and K3-K5 for abrasion.

Input parameters (data entered into the tool)

227. The tool total number of inputs required for a case scenario are dependent on the case scenario and previous selections. Overall, the tool requires information on the scenario overview, primary emission source and proximity, description of the activity situation and type of handling, localized controls, dispersion, and secondary emission source if any. Input data required is fully described in Table 22.

Table 22. Input data required by ART REACH tool.

Parameter	Options	Units
Scenario Overview		
Name and description	Free alphabetical characters	[-]
Chemical	Free alpha-numerical characters	[-]
CAS No	Free numerical characters	[-]
Configure activities (Time duration; non-exposure time optional)	Free numerical characters	min
Primary emission source		
Product type	- Powder, granules or pelletized material - Solid objects - Liquids - Powders dissolved in a liquid or incorporated in a liquid matrix - Paste, slurry or clearly (soaked) wet powder (not containing volatile liquid components)	[-]
Dustiness (only if "powders, granules or pelletized materials" or "contaminated paste/slurry" selected)	Free numerical characters or drop down selection: - Extremely fine and light powder - Fine dust - Coarse dust - Granules, flakes or pellets - Firm granules, flakes or pellets	[mg/kg] inhalable fraction
Moisture content (only if "powders, granules or pelletized materials" or "solid object" selected)	Select from: - Dry product (<5% moisture content) - 5-10% moisture content - >10% moisture content	[%]
Solid material (only if "solid object" selected)	Select from: - Wood - Stone	[-]
Process temperature (only if "liquids" selected)	Free numerical characters: Temperature of the liquid in the process or drop down selection: - Hot process (50-150) - Above room temperature (25-50) - Room temperature (15-25) - Bellow room temperature (<15)	[°C]
Vapour pressure (only if "liquids" selected)	Free numerical characters (if not know, leave in blank)	[Pa]
Boiling temperature (only if Vapour pressure not known)	Free numerical characters	[°C]
Activity coefficient	Number from 0.001-1000.0	[-]
Viscosity (if "liquid" selected or "powders dissolved in liquids")	- Liquids with low viscosity (like water) - Liquids with medium viscosity (like oil)	[-]
Contamination of paste/slurry (only if "paste/slurry or clearly (soaked) wet powder" selected)	Yes/No	[-]
Powder/Liquid weight fraction	Introduce number 0.0-1.0 or drop down selection: - Pure material (100%) - Main component (50-90%) - Substantial (10-50%) - Minor (5-10%) - Small (1-5%) - Very small (0.5-1%) - Extremely small (0.1-0.5%) - Minute (0.01-0.1%) - Extremely minute (<0.01%)	[%]
Primary emission source proximity		

Parameter	Options	Units
Is the primary emission source located in the breathing zone of the worker (i.e. the volume of air within 1 m in any direction of the worker's head)?	Yes/No	[-]
Activity class	*For "powders, granules or pelletized material"*: - Impaction on contaminated solid objects - Handling of contaminated solid objects - Spray applications of powders - Movement and agitation of powders, granules or pelletized material - Transfer of powders, granules or pelletized material (falling or vacuum transfer) - Fracturing of powders, granules or pelletized material *For "solid objects"*: - Fracturing and abrasion of solid objects - Abrasive blasting *For "liquids" and "Powders dissolved in a liquid or incorporated in a liquid matrix"*: - Spray application of liquids (surface spray or space spraying) - Activities with open liquid surfaces or open reservoirs (undisturbed surfaces or agitated surfaces) - Handling of contaminated objects - Spreading of liquid products - Application of liquids in high speed processes (e.g. rotating tools) - Transfer of liquid products (bottom loading or falling) *For "paste, slurry or clearly (soaked) wet powder (not containing volatile components"*: - Handling of contaminated solid objects or paste	[-]
Activity situation and type of handling		
Impaction on contaminated solids	Impaction on substantially and visibly contaminated objects (layers of more than 0.5 kg) Impaction on objects with visible residual dust Impaction on objects with limited visible residual dust Impaction on slightly contaminated (layers of less than few grams) objects Impaction on apparently clean objects Heavy mechanical impaction Normal impaction (manual or light mechanical)	[-]
Handling of contaminated solid objects or paste	Handling of substantially and visibly contaminated objects (layers of more than 0.5 kg) Handling of objects with visible contamination (object covered with fugitive dust from surrounding dusty activities) Handling of objects with limited residual dust (thin layer visible) Handling of slightly contaminated (layers of less than few grams) objects Handling of apparently clean objects Handling that departs from regular work procedures and involves large amounts of energy (e.g., rough handling or throwing of bags) Normal handling, involves regular work procedures Careful handling, involves workers showing attention to potential danger, error or harm and carrying out the activity in a very exact and thorough (or cautious) manner	[-]
Spray application of powders	Powder coating Dusting using blower Spraying in any direction (including upwards) Only horizontal or downward spraying Only downward spraying	[-]

Parameter	Options	Units
Movement and agitation of powders, granules or pelletized material	Movement and agitation of: 1000 kg or more 100 - 1000 kg 10 - 100 kg 1 - 10 kg 0.1 - 1 kg 10 - 100 gram < 10 gram Application of compressed air Other handling with high level of agitation Handling with low level of agitation Open process Handling that reduces contact between product and adjacent air	[-]
Transfer of powders, granules or pelletized material	Transferring more than 1000 kg/minute Transferring 100 – 1000 kg/minute Transferring 10 – 100 kg/minute Transferring 1 – 10 kg/minute Transferring 0.1 – 1 kg/minute Transferring 10 – 100 gram/minute Transferring less than 10 gram/minute Routine transfer Careful transfer involves workers showing attention to potential danger, error or harm and carrying out the activity in a very exact and thorough (or cautious) manner e.g., careful weighing in laboratory Drop height > 0.5 m Drop height < 0.5 m Open process Handling that reduces contact between product and adjacent air	[-]
Compressing of powders, granules or pelletized material	Compressing more than 1000 kg/minute Compressing 100 – 1000 kg/minute Compressing 10 – 100 kg/minute Compressing 1 – 10 kg/minute Compressing 0.1 – 1 kg/minute Compressing 10 – 100 gram/minute Compressing less than 10 gram/minute Open process Handling that reduces contact between product and adjacent air	[-]
Fracturing of powders, granules or pelletized material	Fracturing more than 1000 kg/minute Fracturing 100 – 1000 kg/minute Fracturing 10 – 100 kg/minute Fracturing 1 – 10 kg/minute Fracturing 0.1 – 1 kg/minute Fracturing 10 – 100 gram/minute Fracturing less than 10 gram/minute Open process Handling that reduces contact between product and adjacent air	[-]

Parameter	Options	Units
Fracturing and abrasion of solid objects	Mechanical sanding of wood resulting in large amounts of dust Mechanical handling of wood resulting in large amounts of dust (e.g., large speed of moving work pieces or rotating cutting blades) Mechanical handling of wood resulting in limited amount of dust Manual handling of wood resulting in limited amount of dust Manual handling of wood resulting in very limited amount of dust Open process Handling that reduces contact between product and adjacent air	[-]
Abrasive blasting	Abrasive blasting of very large surfaces Abrasive blasting of large surfaces Abrasive blasting of small parts Micro-abrasive blasting Dry abrasive blasting Wet abrasive blasting Abrasive blasting in any direction (including upwards) Only horizontal or downward blasting Only downward blasting	[-]
Spray application of liquids	High application rate (> 3 l/minute) Moderate application rate (0.3 - 3 l/minute) Low application rate (0.03 - 0.3 l/minute) Very low application rate (< 0.03 l/minute) Spraying in any direction (including upwards) Only horizontal or downward spraying Downward only Spraying with high compressed air use Spraying with no or low compressed air use	[-]
Activities with open liquid surfaces or open reservoirs	Open surface > 3 m² Open surface 1 - 3 m² Open surface 0.3 - 1 m² Open surface 0.1 - 0.3 m² Open surface < 0.1 m²	[-]
Handling of contaminated objects	Activities with treated/contaminated objects (surface > 3 m²) Activities with treated/contaminated objects (surface 1 - 3 m²) Activities with treated/contaminated objects (surface 0.3 - 1 m²) Activities with treated/contaminated objects (surface 0.1 - 0.3 m²) Activities with treated/contaminated objects (surface < 0.1 m²) Contamination > 90 % of surface Contamination 10-90 % of surface Contamination < 10 % of surface	[-]
Spreading of liquid products	Spreading of liquids at surfaces or work pieces > 3 m² / hour Spreading of liquids at surfaces or work pieces 1 - 3 m² / hour Spreading of liquids at surfaces or work pieces 0.3 - 1 m² / hour Spreading of liquids at surfaces or work pieces 0.1 - 0.3 m² / hour Spreading of liquids at surfaces or work pieces < 0.1 m² / hour	[-]
Application of liquids in high-speed processes (e.g. rotating tools)	Large-scale activities involving high speed movements Small-scale activities involving high speed movements Open process: no separation between process and worker Handling that reduces contact between product and adjacent air	[-]

Parameter	Options	Units
Transfer of liquid products	> 1000 l/minute 100 - 1000 l/minute 10 - 100 l/minute 1 - 10 l/minute - 1 l/minute < 0.1 l/minute Open process Handling that reduces contact between product and adjacent air Splash loading, where the liquid dispenser remains at the top of the reservoir and the liquid splashes freely Submerged loading, where the liquid dispenser remains below the fluid level reducing the amount of aerosol formation	[-]
Localised controls (primary and secondary)		
No localized controls	[-]	[-]
Containment – no extraction	Low level of containment Medium level of containment High level of containment	[-]
Local exhaust ventilation (LEV)	Receiving hoods (canopy hood, other receiving hoods) Capturing hoods (movable capturing hood, fixed capturing hood, on-tool extraction) Enclosing hoods (fume cupboard, horizontal/downward laminar flow, other enclosing hoods) Other LEV systems	[-]
Glove boxes and glove bags	Glove bags (non-ventilated, ventilated) Glove boxes (low, medium and high specification)	[-]
Vapour recovery systems	[-]	[-]
Is the process fully enclosed and is the integrity of that enclosure regularly monitored?	Yes/No	[-]
Are demonstrable and effective housekeeping practices in place (e.g. daily cleaning using appropriate methods (e.g. vacuum), preventive maintenance of machinery and control measures, and use of protective clothing that will repel spills and reduce personal cloud)?	Yes/No	[-]
Dispersion		
Indoors	Size: - Any size workroom - Large workrooms only - Small workrooms only - 30 m^3 - 100 m^3 - 300 m^3 - 1000 m^3 - 3000 m^3 ACH: - No restriction on general ventilation characteristics - Only good natural ventilation - Mechanical ventilation giving at least 1 ACH - Specialised room ventilation with more than 10 ACH - 0.3 ACH - 1 ACH - 3 ACH - 10 ACH - 30 ACH	[-]
Outdoors	Yes/No	[-]

Parameter	Options	Units
Spray room	Cross-flow spray room Down-flow spray room	[-]
Downward laminar flow booth	No barriers or screens Partial screen Partial screen fitted with glove ports Full screen fitted with glove ports	[-]
Secondary emission source		
Are secondary sources present in the workroom in addition to the source in the breathing zone of the worker?	Yes/No Carry over near field inputs? Yes/No If Yes, activity can be defined	[-]

228. A single person entered the data from all the case studies to the tool manually and afterwards randomly selected cases were assessed for model parametrisation agreement with a second expert. User variability was not tested.

229. When moisture content was not available, “dry product (<5% moisture content)” was selected. The ART tool output concentration is inhalable mass fraction. Therefore, for powder handling activities, the tool requires inhalable dustiness fraction. However, in many of the case studies from the data set, only respirable dustiness was available. Thus, respirable dustiness values were converted to inhalable dustiness index by using the conversion shown in Table 23, and tool output values were assumed to be inhalable mass concentrations. In addition, only for powder handling, the respirable dustiness value was entered to the tool and output concentration was assumed to be respirable mass concentration.

Table 23. Table used to convert respirable dustiness index values to inhalable dustiness values inputs for ART tool.

Respirable dustiness	ART conversion for Inhalable dustiness
Low < 70	Granules, flakes or pellets
Medium < 150	Coarse dust
Medium > 150	Fine dust
High > 300	Extremely fine and light powder

Comparison of model estimates with measured exposure

230. The performance of the tool was assessed by comparing the tool full shift 90th percentile modelled inhalable and assumed respirable mass concentration to the real measured 8h TWA inhalable and respirable concentrations. For higher confidence on the performance testing comparisons, the preferences described in section 2.1 were followed.

231. To determine the extent to which modelled and measured mass concentrations correlated, the Spearman correlation factor for all the data set and for the individual application domains was calculated. In addition, Pearson correlation and the percentage of underestimation were also determined.

3.15.3. Results

232. Relevant information corresponding to the total 61 case studies used for performance testing is in Table 24. From the total 61 case studies, 47 correspond to powder handling domain, 9 to spraying and 5 to abrasion.

233. Measured respirable BG subtracted mass concentrations ranged from 0.03-193.13, 0.19-66.15, and 0.00001-0.00010 (not BG subtracted) µg/m^3 for powder handling, spraying and abrasion domains, respectively. Inhalable BG subtracted mass concentrations ranged from 1.0-1209.6 and 9.92-511.88 µg/m^3 for powder handling and spraying domains, respectively. Modelled inhalable mass concentrations ranged

between 0.15-230000.0, 18.0-560.0, and 360.0-2600.0 µg/m^3 for powder handling, spraying and abrasion domains, respectively. Modelled respirable mass concentration could only be estimated for powder handling domain, with a concentration range of 0.051-23000.0 µg/m^3. The statistical parameters of the measured and modelled exposure mass concentrations in all the cases considered in each application domain are shown in Figure 65 and Figure 66.

Table 24. Relevant information on data graduation, measurement data used for performance testing and ART tool estimated values.

	Application domain	Powder handling	Spraying	Abrasion
Report data from actual measurements	Number of case studies considered	47	9	5
	Number of personal exposure data used	30	5	5
	Number of stationary exposure data NF used	17	4	0
	Number of stationary exposure data FF used	0	0	0
	Number of substance-specific data	29	5	0
	Number of non-substance-specific	16	4	5
	Range of measured respirable mass (BG subtracted) (µg/m^3)	0.03-193.13	0.19-66.15	n/a
	Range of measured respirable mass (not BG subtracted) (µg/m^3)	2.66-539.2	0.23-3350.0	0.000011-0.00010
	Range of measured inhalable mass (BG subtracted) (µg/m^3)	1.0-1209.6	9.92-511.88	n/a
	Range of measured inhalable mass (not BG subtracted) (µg/m$_3$)	26.79-2128.4	11.67-525.0	n/a
Report data from modelling*	Range of Inhalable concentration (µg/m^3)	0.15-230000.0	18.0-560.0	360.0-2600.0
	Range of ratio inhalable modelled/inhalable measured	0.00789-95000.0	0.0352-1.8	n/a
	Range of ratio inhalable modelled/inhalable measured (not BG subtracted)	0.00015-1979.2	0.034-1.5	n/a
	Range of Respirable concentration (µg/m^3)	0.051-23000.0	n/a	n/a
	Range of ratio respirable modelled/respirable measured	0.01-300.9	n/a	n/a
	Range of ratio respirable modelled/respirable measured (not BG subtracted)	0.00016-7.4	n/a	n/a

Note: 8h TWA (daily) concentration provided, N/A: not available.

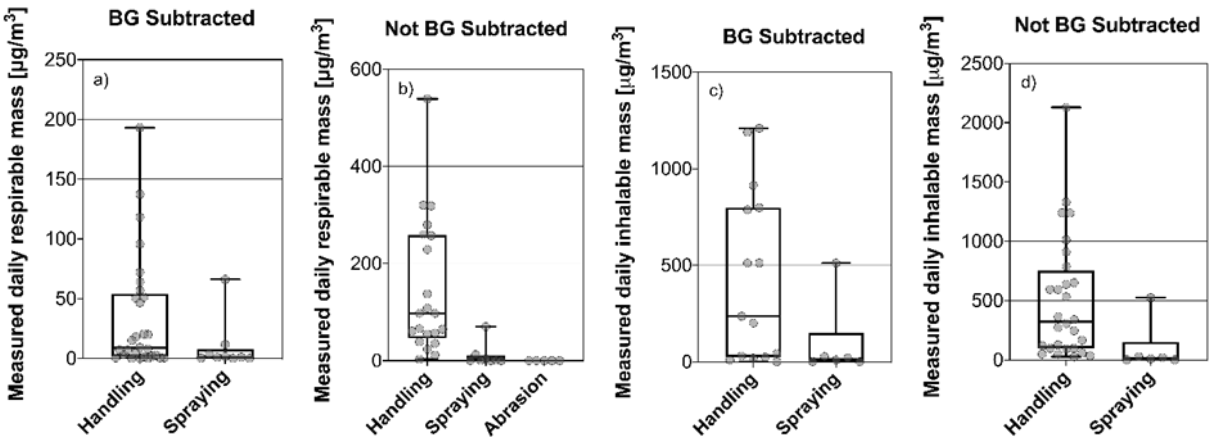


Figure 65. Vertical box plots for the measured daily respirable (a and b) and inhalable (c and d) mass concentrations for each application domain.

Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

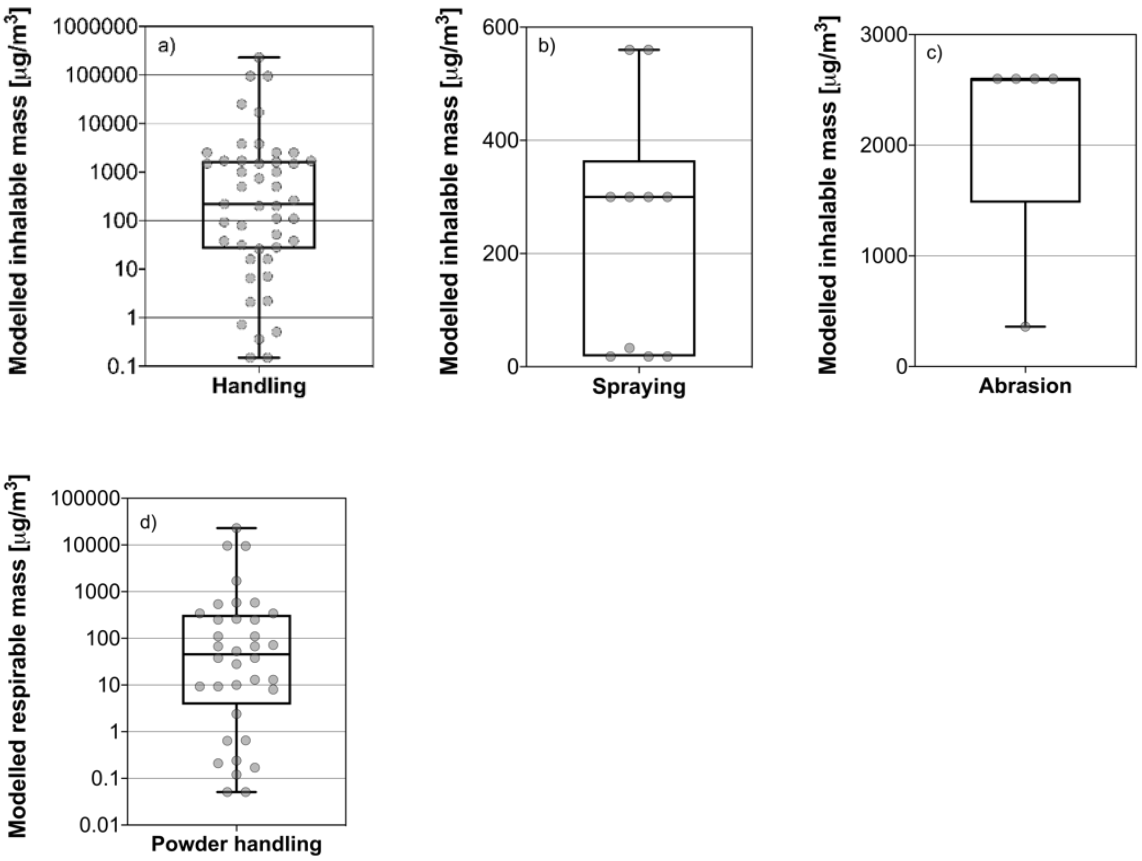


Figure 66. Vertical box plots for the full shift 90th percentile modelled mass concentration for each application domain.

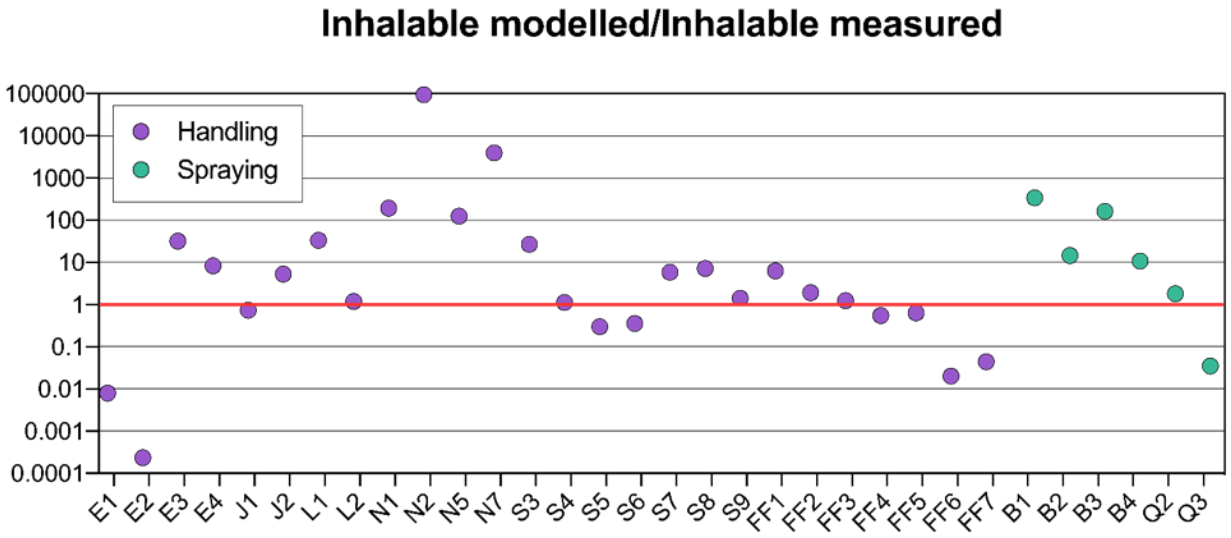
Note: The lower and upper limits of the box plots represent the 25th and 75th percentiles, and the line within the box marks the median. Whiskers (error bars) above and below the box indicate the maximum and the minimum mass concentration, respectively. Individual values are represented as grey dots.

Comparison of exposure score with measured mass concentrations

234. A total of 61 exposure scenarios, from which 49 were classified as HQ case studies (37 for powder handling, 9 for spraying and 3 for abrasion), were used for ART performance testing as detailed in section 3.4.2. The ratios of modelled inhalable/measured inhalable and respirable mass concentrations are shown in Figure 67 and Figure 68, respectively together with the percentages of underestimation for each activity domain. In addition, for powder handling domain, ratios of modelled respirable/measured respirable are depicted in Figure 69.

235. Measured inhalable mass concentrations were underestimated (ratio <1) in a total of 10 cases, representing a 32.2% of the total cases assessed which is well above the 10% value considered for acceptance in this performance testing. For the powder handling domain, 34.6% of the cases were underestimated, and for spraying 16.7%. It is important to mention that for the powder handling domain, in 6 of the underestimated case studies modelled concentrations were compared to not BG subtracted measured concentrations. Thus, when do not consider those values, underestimation percentage drop to 16.7%.

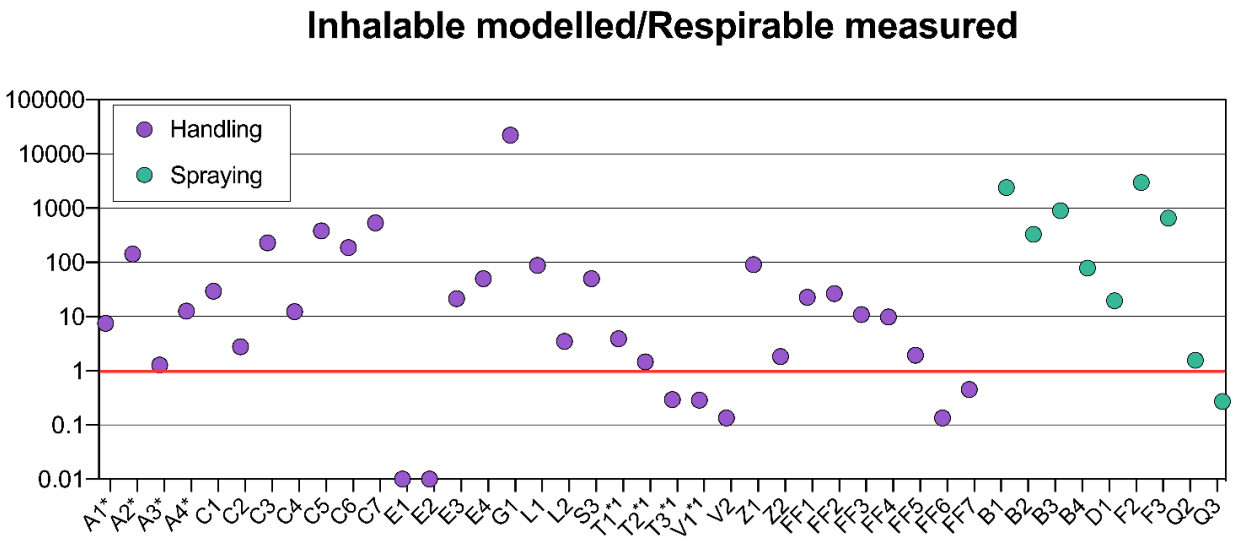
236. When modelled inhalable concentrations were compared to measured respirable concentrations, lower percentages of underestimation were obtained, as it would be assumed, although still over the 10% limit value of the total comparisons. The total underestimation percentage was 19% (22.2% for powder handling domain and 11.1% for spraying). However, again, some of the underestimated were cases that presented limitations (not BG subtracted values used, measured concentration under detection limit and considering other processes). Thus, when considering only HQ cases and BG subtracted values, measured concentration were underestimated in 8.6% of the total cases, and 7% of the powder handling cases, which is under the 10% threshold value considered acceptable. For the abrasion domain (ratio values not shown) measured respirable concentrations were highly overestimated by modelled inhalable concentrations, with ratios >100000.



All domains	Handling	Spraying
10/32 (32.2%)	9/26 (34.6%)	1/6 (16.7%)

Figure 67. Ratio of inhalable modelled mass concentrations/measured inhalable BG subtracted mass concentrations.

Note: E1, E3, J1-J2, S1-S9, FF5, and FF7 not BG subtracted values shown. The Table below the graph shows the percentage of underestimation for each activity domain.



All domains	Handling	Spraying
8/42 (19%)	7/33 (22.2%)	1/9 (11.1%)

Figure 68. Ratio of inhalable modelled mass concentrations/measured respirable BG subtracted mass concentrations.

Note: E1-E2, FF1, FF5, FF7 not BG subtracted values shown. *measured concentration under detection limit and *1 considering other processes. The table below the graph shows the percentage of underestimation for each activity domain.

237. Even though, the ART tool is designed and optimized in order to estimate *inhalable* mass concentrations, for the powder handling domain, respirable mass concentration were calculated by introducing the *respirable* dustiness index. Overall, respirable measured concentrations were underestimated in a 33.3%. However, when only HQ case studies and BG subtracted values were considered, underestimation decreased to 3 out of 21 representing a 14.3% of the cases (Figure 69).

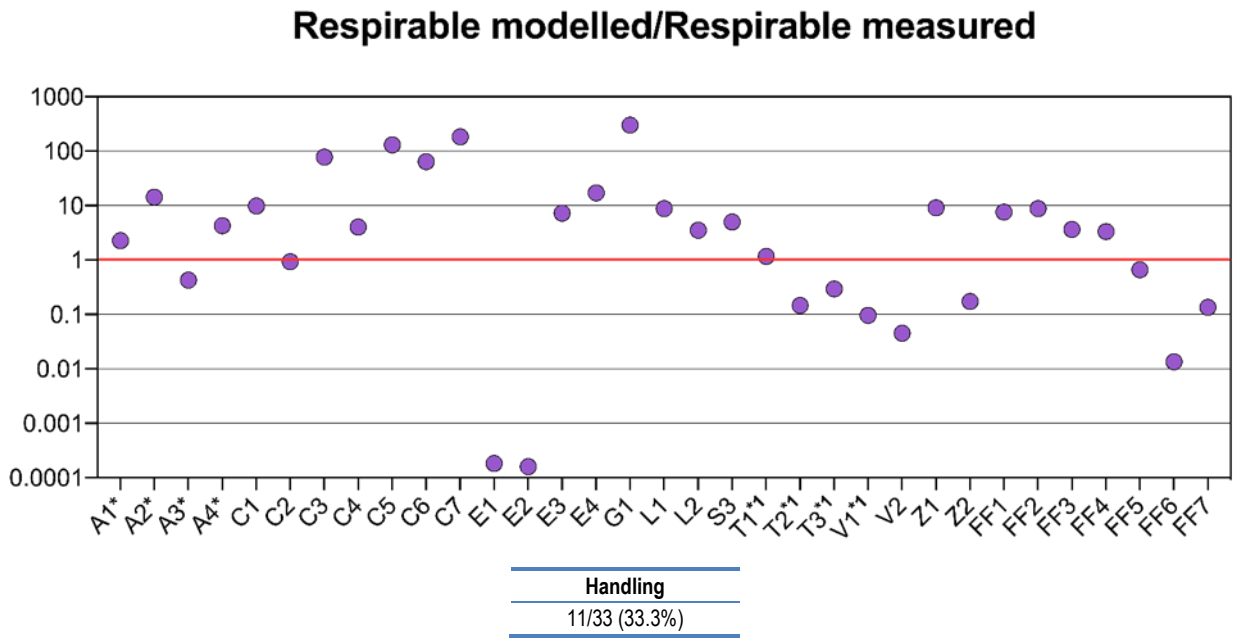


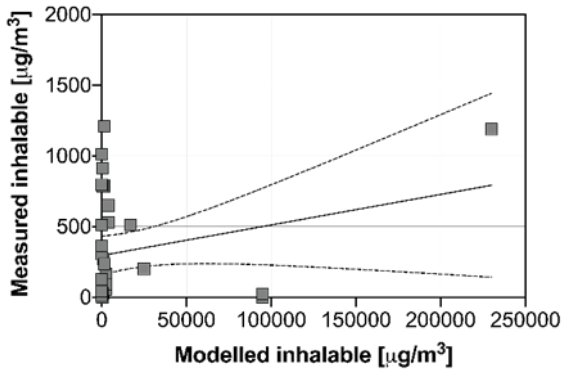
Figure 69. Ratio of respirable modelled mass concentrations/measured respirable BG subtracted mass concentrations.

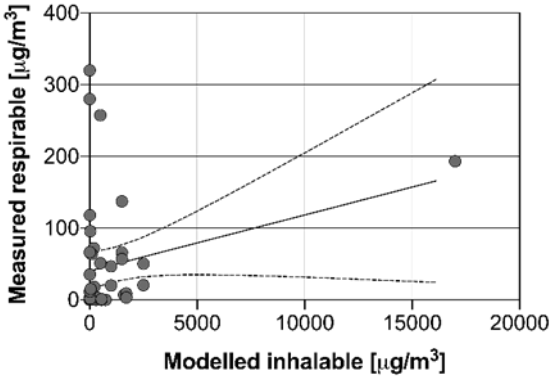
Note: E1-E2, FF1, FF5, FF7 not BG subtracted values shown. *measured concentration under detection limit and *1 considering other processes. The Table below the graph shows the percentage of underestimation for each activity domain.

Spearman correlation factor

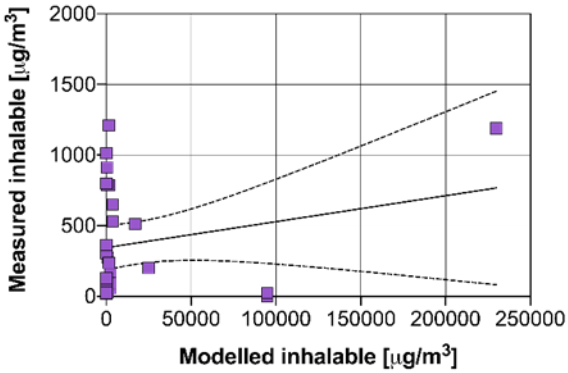
238. Modelled inhalable fraction correlation with measured inhalable and respirable mass fractions for all domains, handling, and spraying are shown in Figure 70. Under each figure, number of cases used (n) for correlation, Pearson and Spearman correlation coefficients for all case studies as well as only HQ studies (when available) are provided.

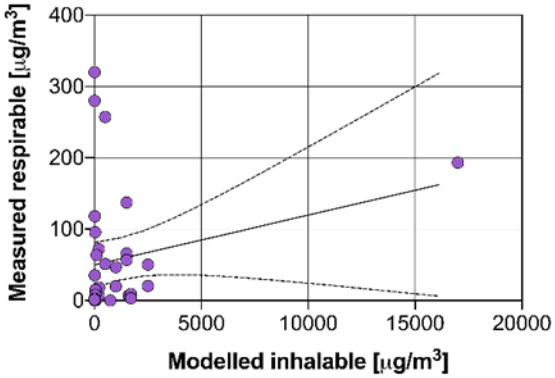
239. Overall, no positive significant or (>0.6) spearman correlations were obtained in any case when comparing modelled inhalable mass concentrations to measured respirable and inhalable mass concentrations. Spearman coefficient correlation for all domains and for powder handling showed positive correlations that ranged between 0.047 and 0.188. Conversely, negative correlations of -0.414 to -0.747 for spraying and -0.726 (not shown) for abrasion were obtained.



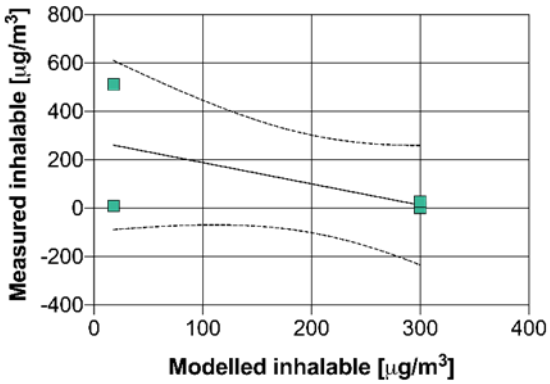


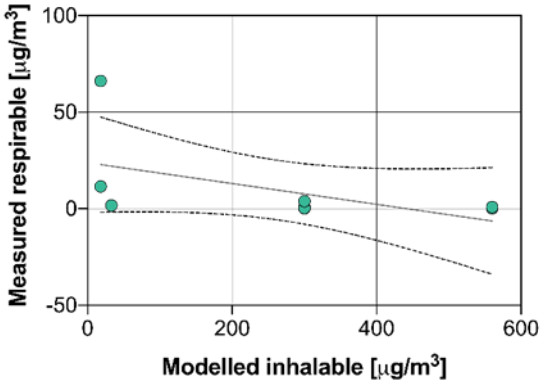
All domains	Inhalable	Inh. HQ	Respirable	Resp. HQ
n	34	30	43	35
Pearson	0.255	0.158	0.258	0.242
Spearman	0.122	0.213	0.117	0.024





Handling	Inhalable	Inh. HQ	Respirable	Resp. HQ
n	28	24	34	26
Pearson	0.229	0.110	0.238	0.202
Spearman	0.047	0.190	0.188	-0.019



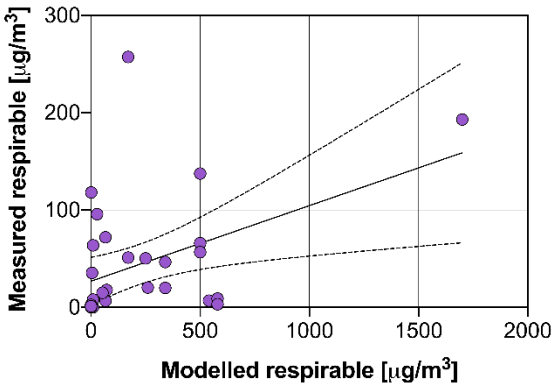


Spraying	Inhalable	Respirable
n	6	9
Pearson	-0.627	-0.527
Spearman	-0.414	-0.747*

Figure 70. Correlation of inhalable modelled mass concentrations with measured respirable and inhalable mass concentrations for a and b) all domains, c and d) powder handling, and e and f) spraying.

Note: For E1-E2, K1-K5, FF1, FF5, FF7 cases respirable not BG subtracted values shown. For inhalable E1, E3, J1-J2, S1-S9, FF5, and FF7 not BG subtracted values shown. For respirable E1-E2, FF1, FF5, FF7 not BG subtracted values shown.

240. On the other hand, significant spearman correlation was obtained for modelled respirable mass concentration correlation with measured respirable mass concentrations (Figure 71), with a coefficient of 0.513, which, however, did not meet the 0.6 threshold defined for this performance testing.



Handling	Respirable	Resp. HQ
n	31	25
Pearson	0.436*	0.109
Spearman	0.513**	0.058

Figure 71. Correlation of respirable modelled mass concentrations with measured respirable mass concentrations for powder handling domain.

Note: For E1-E2, K1-K5, FF1, FF5, FF7 cases respirable not BG subtracted values shown. For E1-E2, FF1, FF5, FF7 not BG subtracted values shown.

3.15.4. Conclusion

241. The performance testing of the ART tool was based on 62 exposure scenarios, from which 49 were classified as HQ case studies. The total cases were divided in 3 domains, powder handling, with 47 (37 HQ) cases, spraying, with 10 cases, and abrasion with 5 (3 HQ) cases.

242. Inhalable measured mass concentrations were highly underestimated for all domains in 32.2% of the total cases, 34.6% for handling and 16.7% for spraying domains. Underestimation decreased up to 16.7% when only HQ cases were used, although still higher than the 10% threshold value. On the other hand, respirable measured mass concentration were underestimated by inhalable modelled mass fraction in only 8.6% of the total cases (7% powder handling and 11.1% for spraying) when HQ studies were considered. However, when comparing respirable modelled to respirable measured, underestimations for powder handling domain were 33.3% and 14.3% for HQ cases. In addition, no significant positive spearman coefficient correlations were obtained in any case with the exception of modelled respirable with measured respirable, with a value of 0.513 for powder handling scenarios. It is important to note that ART is designed to use inhalable dustiness index and provides inhalable mass concentrations. However, in the cases under study, only respirable dustiness values were available and were converted to inhalable dustiness as described to the table 23. Therefore, the results presented here should be interpreted with care as dustiness levels introduced in the tool may be different from the reality.

4. Conclusions

243. In this section, a summarized overview of the results of the individual performance tests performed for the individual models is presented. In total 14 models were tested. For the SUNDS performance testing was not conducted as the sensitivity testing was considered sufficient and it includes tools which are assessed under this project. The below Table 25 summarizes the number of comparisons against data, and compares against key performance testing criteria listed in Section 2.1. Finally, the potential usability of the tools for the assessment of MNM is pointed out in order to simplify and provide guidance. However, the final decision on whether the tools can or cannot be used for regulatory MNM assessment is to be made by relevant authorities at regional and national level.

244. The obtained Spearman correlations for measured respirable mass concentration (all domains, powder handling, spraying or leak/point source and abrasion) is provided, whether more than 10% of the total measured values exceeded the modelled values, and the final recommendation on whether or not has potential to be used to estimate exposure to MNM are indicated in Table 25.

245. For most of the performance testing, the number of comparisons against available data or reference values was above or equal to 25, with only ConsExpo Nano, LiCARA nanoSCAN, and RISKOFDERM below this number. For ConsExpo Nano and LiCARA nanoSCAN this was due to the application area and purpose of the model, which makes finding literature values for comparison unlikely. For RISKOFDERM the number of studies found in the literature was lower than the limit of 25, and the performance test should be considered somewhat limited due to the low availability of comparison data. A relatively large and complete data set of cases was created under this project, and the requirement of using at least 25 cases for performance testing could be achieved for most of the tools. However, there is still the need for additional high-quality measured exposure data to MNM in occupational environments, which would be of high value for development and refinement of tools/models and for further validation. Powder handling scenarios are the most studied while no or very limited data exist for several application domains (e.g., spraying, abrasion and several production and handling process). The limitation of number of exposure scenarios may be of importance in regards to the reliability of the modelled outcome.

246. The requirement of computing the Spearman correlation with comparison values was fulfilled by some of the models specifically designed for MNM (GUIDEnano, ISO CB, NanoSafer, RISKOFDERM, Stoffenmanager Nano, BIORIMA and ENAE-CPSC). For all these, the obtained Spearman correlations were above 0.6 with the exception of the ISO CB tool for which the correlation for the particle mass concentration was 0.38.

Table 25. Overview of performance testing results.

Model	Tested in	Nano-specific	Number of comparisons	Spearman correlation (All / H / S / A)	< 10% of total cases underpredicted	Potential to be used for exposure assessment to MNM
ISO/TS 12901-2:2014 CB nanotool v1.0 (Part 2)	caLIBRAte	yes	28	(0.63 / - / - / -)*	yes	Suitable with comments
BIORIMA Risk assessment and risk control module (Occupational exposure section)	OECD	yes	53	(0.84 / 0.80 / 0.31 / -)	yes	Suitable with comments
Stoffenmanager nano v1.0	caLIBRAte	yes	82	(0.78 / - / - / -)	N/A	Suitable
Engineered Nanoparticle Airborne Exposure (CPSC ENP Model) v1.0	OECD	yes	39	(0.63 / 0.61 / 1.0 / -)	no (10.7% and 18% when LC applied)	Suitable with comments
LiCARA nanoSCAN v1.0	caLIBRAte	yes	2	N/A	N/A	Suitable
NanoSafer v1.1β (original and simplified version)	caLIBRAte + OECD update	yes	50	Original: (0.72 / 0.80 / 0.40 / -) Simplified: (0.72 / 0.80 / 0.40 / -)	Original: yes Simplified: no	Suitable with comments
GUIDEnano	caLIBRAte	yes	25	(- / 0.96 / 1.0-0.98 / -)*[1]	no	Suitable with comments
Swiss Precautionary Matrix v3.0	caLIBRAte	yes	25	N/A	N/A	Suitable with comments
ConsExpo nano 2.0	caLIBRAte	yes	5	N/A	yes	Suitable with comments
RISKOFDERM	caLIBRAte	no	16	1.0 (filling mixing or loading) and 0.4 (spraying)	no	Suitable for indicative use
MEASE2 2.0	OECD	no	63	(0.40 / 0.49 / 0.35 / 0.87)	yes	no
EMKG Expo tool 2.0	OECD	no	40	(-0.54 / -0.25 / - / -)	yes	no
Stoffenmanager 8.3	OECD	no	52	(0.18 / 0.51 / 0.62 / 0.73)	no	no
Advanced REACH Tool v1.5	OECD	no	60	(0.51 / 0.51 / - / -)	no	no

*Note: for ISO CB nanotool correlation is given for particle number concentration. *[1]Note: For GUIDEnano Spearman correlation was calculated individually for spraying and leak/point source domains. For each model it is indicated under which project it has been tested, whether or not the model is nanospecific, total number of comparisons used for the performance testing, Spearman correlations obtained, and whether the tool underpredicted in more than 10% the cases tested. In the final column, it is indicated whether the tool has potential to be used for exposure assessment to MNM based on the results obtained and the criteria established in this report. N/A: Not applicable. Spearman correlation is provided for all domains / powder Handling / Spraying or leak-point source / Abrasion (All / H / S / A).

247. The criterion concerning the under/overestimation by the models is fulfilled in 6 of the tested tools (ConsExpoNano, ISO, NanoSafer CB v1.1beta, BIORIMA, MEASE and EMKG) for which such a comparison is feasible. In several cases (e.g. Stoffenmanager Nano, Swiss Precautionary Matrix) such a comparison cannot be made due to the model output not corresponding to measurable quantities. In three of the tools (GUIDEnano, RISKOFDERM, and ENAE-CPSC), several cases exist for which the model underestimates the measured values. However, the correlation between the observed values and predicted values is good for all three models, and the underprediction in the case of GUIDEnano can be argued to be related to the source definition assumptions, and in RISKOFDERM the number of test data and underprediction is influencing the recommendation that it should be used only for indicative use. In the 3rd case of ENAE-CPSC, the underprediction of exposure occurred in almost 10% of the total cases tested. Regarding overestimations, in general, most of the models tended to overestimate the exposures when

compared to observed concentrations, which can be interpreted as tending to favour 'worst-case' scenarios.

248. In sum, all the tools, which were originally designed to assess exposure to MNM, were found to meet the criteria established in this performance testing (spearman correlation >0.6 and underestimations in < 10% of the total comparisons), whereas conventional chemical tools generally failed to meet the selected criteria. However, for some of the tools, even though the criteria was fulfilled, the performance testing procedure revealed aspects that need to be considered. These considerations are summarized below for each specific tool. In addition, some caution should be taken due to the sensitivity of the models regarding potential assumptions on sensitive parameters. The information regarding the sensitivity analysis of the tools is reported in ENV/CBC/MONO(2021)27

4.1. ISO/TS 12901-2:2014 CB nanotool v1.0 (Part 2)

- The ISO tool seems to yield favourable precautionary results by assigning higher exposure band for situations that could result in lower exposure. However, Spearman correlation between measured and modelled data was only >0.6 for particle number concentration (0.63) whereas the respirable mass had lower correlation factors.

4.2. BIORIMA Risk assessment and risk control module (Occupational exposure section)

- Even though the model had a Spearman correlation coefficient with respirable measured mass of 0.84 for the total cases and less than 10% of total cases underestimated exposure concentrations, the model was observed to have a bias towards (severe) overestimation of inhalation exposure for powder handling domain. Therefore, care must be taken when using this model in that range of exposure;
- The tool is in its early stage of development (lunch date October 2020). Therefore, slight modification are expected. The results obtained will be shared with the tool owners in order to inform them of the behaviour observed.

4.3. Stoffenmanager nano v1.0

- The correlation between modelled and observed values improved from poor to strong with higher exposure concentrations (> 10^3 cm^{-3}) or higher exposure bands;
- Stoffenmanager nano in its current form, is suitable to be recommended for exposure assessment (prioritization) of MNM.

4.4. Engineered Nanoparticle Airborne Exposure (ENAE) Tool (CPSC ENP Model) v1.0

- The model showed spearman correlations for respirable mass concentration >0.6 for all domains. However, real measurements exceeded the model estimates for more than 10% of the total comparisons.
- Overall, the tool seems to be acceptable for MNM use, but caution should be taken due to the potential underprediction of exposure concentrations in occupational scenarios.

4.5. LiCARA nanoSCAN v1.0

- The process itself and the questions/topics to be explored during the product development might be more important than the absolute results of the tool. As indicated in the model guidelines "*the LiCARA nanoSCAN gives a first, inherently uncertain, indication of the pros and cons of a new nanoproduct*".

4.6. NanoSafer v1.1β (Simplified and Original version)

- It is essential that the user adheres to the specific information provided in the technical and safety data sheets. In case these parameters are unknown, precautionary default values may be used or data should be generated or provided by experts;
- The two available versions of NanoSafer were tested and although good performances of both, slight differences were registered. While for the original 1.1beta model underestimations were <10% of the total comparisons, the full mass-balance (simplified) model version underestimated up to 20% of the total cases.

4.7. GUIDEnano

- Assumptions regarding the activity mass balance are strongly influencing the model outcome and therefore we recommend to limit the use of assumptions or ask for an "expert" advice. It should also be noted that all performance tests were made using stationary measurements, which is expected to result in higher similarity between measured and predicted values in contrast to personal exposure measurements.

4.8. Swiss Precautionary Matrix v3.0

- The results have shown that by shifting the focus on the nano-product, manufacturing activities became less relevant;
- Thus, assessing the worker activities is recommended to be done separately from the nano-product in the case the nano-form changes throughout the life cycle. Nevertheless, the tool seems to be acceptable for MNM use, when this fact is adequately mentioned for the potential user.

4.9. ConsExpo nano 2.0

- The model uncertainty stems from simplifications in the model formulation, such as assumed complete mixing of indoor air and complete non-volatility of the substance monitored. Other aspects such as losses to vertical surfaces, particle dynamics that result from the hygrosocpic growth of aerosol particles, have also not been included in the model. This may add to the overall error in the model;
- The other important component of the model, the human deposition and clearance model and the link between the two, was not evaluated. The ICRP model is based on observational data, but it has not been tested separately, in the context of consumer exposure to nanomaterials, given a lack of suitable data. This constitutes a significant uncertainty that should be born in mind when using ConsExpo nano in a regulatory (or any other) context. Further model evaluation on this

aspect of the tool should be welcomed, although the possibility of generating relevant experimental data seems remote.

4.10. RISKOFDERM

- The model was observed to have a bias towards (severe) overestimation of dermal exposure at low measured exposure values. Therefore, the tool appears to provide precautionary assessments. Overestimations should be expected for low exposure concentrations;
- For three tested DEOs, the model underestimated the exposure obtained during filling, mixing or loading;
- The RISKOFDERM, in its current form, seems suitable to be used for indicative purposes. However, more dermal exposure data concerning working with nanomaterials is needed to further investigate whether RISKOFDERM is suitable to use for nanomaterials.

4.11. MEASE2 2.0

- The model was concluded not to meet the acceptance criteria defined in this work for MNM exposure assessment in its current state. However, relatively good correlations for powder handling domain and respirable mass fractions, with spearman correlation coefficient close to 0.6, and underprediction of exposures for more than 10% of the total comparisons were obtained.

4.12. EMKG Expo tool 2.0

- Even though the model did not underpredict respirable concentrations in more than 10% of the total comparisons, correlations found were to be weak and therefore the model does not seem suitable for MNM exposure assessment in its current state.
- The tool was found to associate higher exposure bands to higher exposure concentrations, as it would be expected according the purpose of the tool, with the exception of the highest bands were overlapping between band ranges occurred.

4.13. Stoffenmanager 8.3

- The model was observed to underestimate respirable mass concentration in more than 10% of the cases considered within powder handling and spraying domains. However, decent spearman correlation coefficients were obtained for powder handling, spraying and abrasion domains 0.5, 0.6 and 0.7, respectively. Considering this, the tool did not meet bot threshold criteria defined in this work. Hence, in its current state it does not seem to be suitable for MNM exposure assessment. The tool site also refers to Stoffenmanager Nano for assessment of MNM.

4.14. Advanced REACH Tool v1.5

- Even though the tool underestimated respirable mass concentration in more than 10% of the total case scenarios, and spearman correlation was less than 0.6, a significant correlation of 0.5 was obtained. Considering this, the tool did not meet bot threshold criteria defined in this work. Hence, in its current state and based on the comparisons conducted in this work, the tool does not seem to be suitable for MNM exposure assessment.

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Annex A: Case studies.xlsx

The Annex A contains the inventory of case studies used for performance testing, quality score and a summary of the performance testing results are given in the Excel file – *Case studies.xlsx*.

Annex B: Exposure assessment reports generated by tools

The Annex B contains the original exposure assessment reports generated by the tools as follows:

B1 – BIORIMA
B2 – ENAE-CPSC
B3 – NanoSafer Original
B4 – NanoSafer Simplified
B5 – MEASE
B6 – EMKG
B7 – Stoffenmanager
B8 – ART Inhalable fraction
B9 – ART Respirable fraction

Appendix I: Example of common descriptors for inhalation, dermal and oral exposure assessment

Table I.1. Example of common descriptors for inhalation, dermal and oral exposure assessment

	Example of data/information needed for models performance testing
Demands on study design. We would like to compare the modelling results with the observations (real data) and therefore, we would like to have data on aerosol measurements:	
Pre- and/or post-activity measurements (mass concentrations preferably)	mass concentrations available
Breathing zone measurements (mass concentrations preferably)	mass concentrations available
NF and FF measurements (mass concentrations preferably)	mass concentrations available
Material identifiers	
Material name	CuO nanoparticles
Manufacturer	PlasmaChem GmbH
CAS number	317-38-0
EINICS number	N/A
Material information	
Is the nanomaterial labelled with a nano-specific word or term? Yes/No	Yes
Is the nanomaterial coated or surface modified (Yes/No)	No
Weight fraction (NM in the product; relevant for NM-enabled products and dispersions)	100%
Physical state (solid or liquid)	Solid
Moisture (for powders; %)	N/A
Morphology (Spherical; granular; flake or clay; rod; fibre etc…)	Spherical
Dimensions of the primary nano-object ($a \leq b \leq c$)	40 nm; Normal distribution has been considered with mean size 40 nm and standard deviation 10 nm (obtained from TEM images)
Relative density (specific gravity)density of the nanomaterial	6.5 g/cm^3
Solubility of the material [is the material water-soluble?]	Insoluble (< 1 g/L)
The specific surface area of the nanomaterial	15 m^2/g
Respirable dustiness of powder (please specify the method)	104 mg/kg (continuous drop method)
Safety data /Hazard	
Is there a nanospecific occupational exposure limit (OEL_{nano}) or target value?	No
Respirable OEL for the nearest analogue material	1 mg/m^3
Known hazards of analogue bulk material	No risk sentences or GHS/CLP hazard statements
Contextual information (activity information and occupational exposure situation)	
Description of the work processes and activities	Powder handling; Pouring process under fume hood 700 g CuO/min
Number of workers	1
Activity/Exposure frequency	4 to 5 days a week
Production volume/ use rate	0.7 kg/min
Particle emission rate if constant source emission or leak (mass/time)	In this case, the emission rate calculated by continuous drop dustiness test method (104 mg/kg x0,7 kg/min CuO='72.8' mg/min)
Activity handling energy factor[£]	H2 (0.25)

	Example of data/information needed for models performance testing
Total mass of material handled in each work cycle	0.7 kg
Duration of the work cycle	1 min
Pause between work cycles	0 min
Number of work cycles per day	1 time
Amount of material handled in each transfer	0.7 kg
Time required per task in cycle (spoon, bag, big-bag etc.)	1 min
Volume of the work room (width x length x height)	5.24 m x 7.25 m x 3.52 m
General ventilation system (mechanical, natural, etc...)	Mechanical
Air exchange rate	9 times/h
Ventilation rate in the room	139.55 L/s
Type of risk management measures/local controls	Type: Fume hood (standard, 1.35 m height, 1.8 m width and 0.7 m depth); exhaust flow of 300 m^3/h)
Personal protective equipment (PPE)	Respirator, lab coat and gloves
Temperature of room	22 ºC
Relative humidity in the room (%)	N/A
Room pressure	1 atm
Description of secondary sources/other indoor activities (diesel engines, cigarette smoke, welding, busy road, etc.)	N/A
Cleaning and maintenance of the room	Yes (daily)
Contextual information (dermal exposure)	
Surface loading (µg/cm^2)	N/A
Dermal contact area (cm^2)	N/A
Number of contacts	N/A
Dermal loading (µg/cm^2)	N/A
Contextual information (oral exposure)	
Transfer efficiency from hand to perioral region	N/A
Hand/finger loading (µg/cm^2)	N/A
Contact area (cm^2)	N/A
Number of contacts	N/A

Note: H0 "Zero energy" (e.g. Removal and handling of clean barrels and plastic containers)
H1 (e.g. Pouring of powders with up to 1 cm drop in free air; careful balancing)
H2 (e.g. Pouring of powders with 1-2 cm drop in free air; careful wet mixing)
H3 (e.g. Pouring of powders with 2-5 cm drop in free air; wet mixing)
H4 (e.g. Pouring of powders with 5-10 cm drop in free air; open conveying of powder)
H5 (e.g. Pouring of powders with 10-20 cm drop in free air; handling contaminated or leaking bags)
H6 (e.g. Pouring of powders with 20-40 cm drop in free air; filling of bags and big bags)
H7 (e.g. Pouring of powders with 40-60 cm drop in free air; careful dry mixing)
H8 (e.g. Pouring of powders with 60-80 cm drop in free air; dry mixing)
H9 (e.g. Pouring of powders with 80-100 cm drop in free air; vigorous handling, folding open bags)
H10 (e.g. drop heights > 1 m, dry mixing, cleaning with brusher or compressed air, accidents)

Appendix II: Criteria used to qualitatively evaluate the strength of the exposure study

Table II.1. Criteria for the assessment of the quality of the exposure study.

Overall quality criteria	Weighing factor
Relevance parameters	
Is any of the pre-defined MNM (TiO_2, SiO_2, Ag, CuO, MWCNT) investigated in the study?	0
Is the activity belonging to any of these source domains (Release of primary particles during actual synthesis; Handling of bulk aggregated/agglomerated nanopowders; Spraying or dispersion of ready-to-use nanoproduct)?	0
Reliability (=Quality) parameters	
Study design	
Background measurements (mass preferably; If mass concentrations are not available a factor of 0.5 should be used)	4
Offline measurements	3
Personal sampling (mass preferably; If mass concentrations are not available a factor of 0.5 should be used)	5
NF and FF measurements in study? (mass preferably; If mass concentrations are not available a factor of 0.5 should be used)	4
Substance information	
NM identity (safety data sheet of the specific material available)	5
Primary particle size/particle size distribution	3
Weight fraction (of NM in the product)	3
Morphology/Shape of the NM	3
Activity information	
Description of the activity	5
Indoor/outdoor information	3
Production volume / use rate	3
Duration of the activity (h)	3
Used RMM/ local controls	5
Used PPEs - Note that for model testing WP6 will consider that no PPEs have been used	-
Completeness parameters	
Dustiness of NM	5
Emission rate	3
Daily cleaning and monthly inspection	1
Room Size (m3)	3
Ventilation system (natural, mechanical, …)	3
Air exchange per hour (times / h)	1