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Evaluation of Tools and Models for Assessing Occupational and Consumer Exposure to Manufactured Nanomaterials – Part I: Compilation of tools/models and analysis for further evaluation

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No. 99

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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

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ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
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Objective

1. **Project - "Assessing the global readiness of regulatory and non-regulatory models for assessing occupational exposure to manufactured nanomaterials**": The objective is to compile available regulatory and non-regulatory tools and models for the assessment of occupational exposure to manufactured nanomaterials and to assess their applicability for occupational exposure to manufactured nanomaterials.

2. **Project - "Compilation of available tools and models used for assessing consumer exposure to manufactured nanomaterials and evaluation of their applicability in exposure assessments"**: The objective is to compile available tools and models for the assessment of consumer exposure to manufactured nanomaterials and to evaluate their applicability to manufactured nanomaterials exposure assessment.

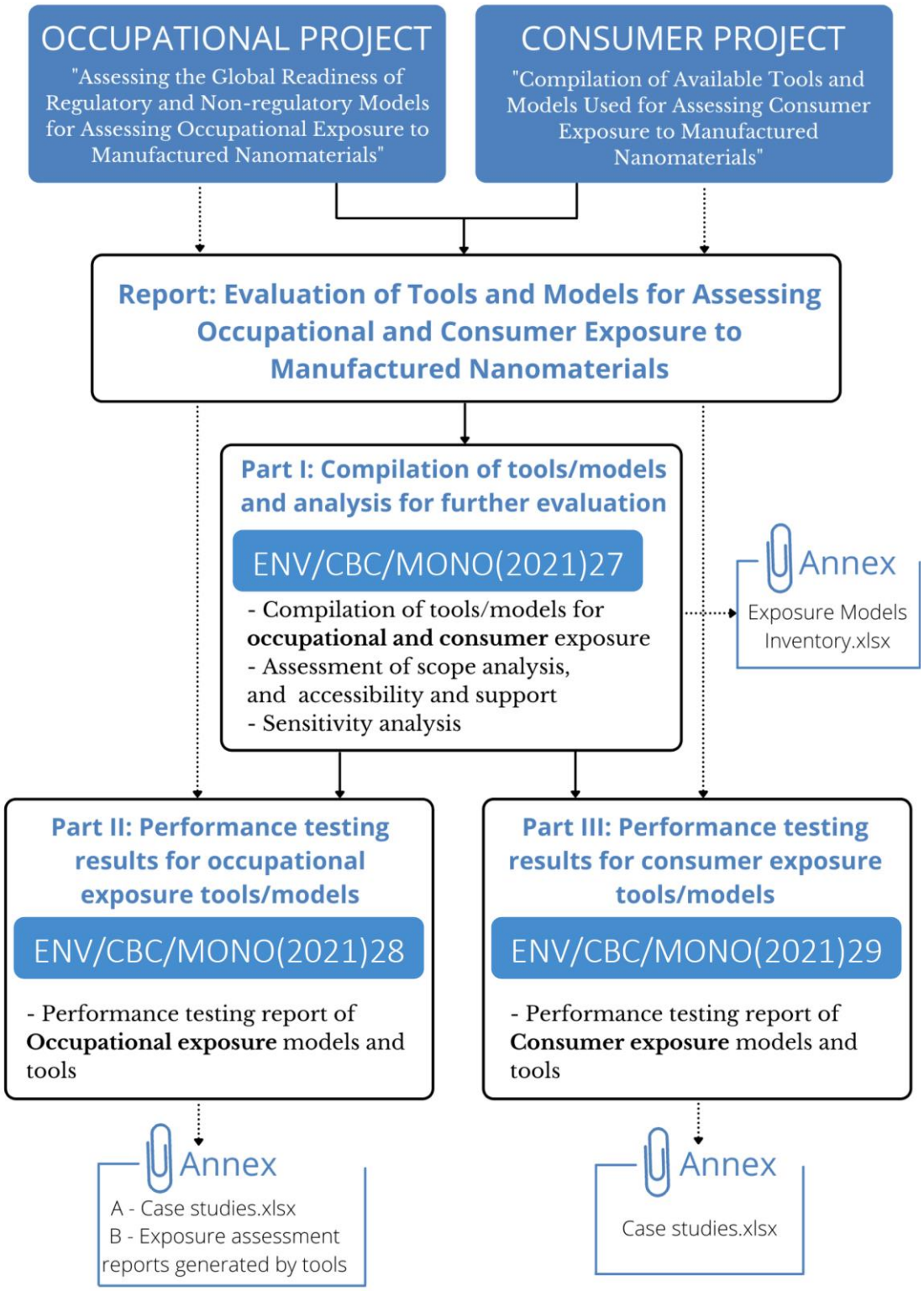
Design

3. These projects assess the compiled models/tools by providing scope analysis, accessibility and support examination, sensitivity analysis, and performance testing. The scope analysis addresses the output of the models/tools, the input parameters required by models/tools, the intended use of the models/tools in terms of scenarios and exposure pathway, and assumptions considered by the models/tools. The accessibility and support examination of the models/tools addresses the user-interface of the models/tools and availability of input parameters. The sensitivity analysis addresses the sensitivity of models/tools against changes in input parameters and identifies the most and least sensitive parameters. The performance testing assesses the predictive capability of models/tools for consumer and occupational exposure separately by comparing output of models/tools with measurement data. Finally, the recommendations for the applicability of the models/tools in exposure assessment of manufactured nanomaterials and for future activity are provided.

Description

4. This joint report provides (1) an inventory of models/tools collected under two projects, (2) outcomes of scope analysis, accessibility and support examination of models/tools, and (3) outcomes of sensitivity analysis of models/tools.

5. Outcomes of performance testing of models/tools are provided in two separate documents: Part II for occupational exposure tools/models and; Part III for consumer exposure tools/models.


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
Part I: Compilation of tools/models and analysis for further evaluation
ENV/CBC/MONO(2021)27
- Compilation of tools/models for occupational and consumer exposure
- Assessment of scope analysis, and accessibility and support
- Sensitivity analysis
Annex
Exposure Models Inventory.xlsx
Part II: Performance testing results for occupational exposure tools/models
ENV/CBC/MONO(2021)28
- Performance testing report of Occupational exposure models and tools
Part III: Performance testing results for consumer exposure tools/models
ENV/CBC/MONO(2021)29
- Performance testing report of Consumer exposure models and tools
Annex
A - Case studies.xlsx
B - Exposure assessment reports generated by tools
Annex
Case studies.xlsx

Executive summary

6. This document provides a compilation of 32 models/tools, 9 of which were assessed under the occupational project, alone 9 under the consumer project alone, and the remaining 14 under both projects. The compilation of the models/tools was created by consultation within the OECD WPMN and by searching in several OECD, EU and US EPA projects, as well as peer-reviewed scientific articles, books, thesis and technical reports. A summary of the 32 compiled tools is provided in the report in table format. From the 32 compiled tools, 27 were assessed by scope analysis, and accessibility and support. The remaining 5 tools, which are part of the consumer project, were not further considered, as they are not nanospecific (the consumer project focuses only on nanospecific models/tools). In the scope analysis, tool description, mapping of input and output parameters, domain and assumptions are detailed. In addition, the tools were assessed according to their accessibility and support, which addresses the user-interface of the models/tools and availability of guidance documents and input parameters. A summary of the assessed tools is provided in the Annex 3 *"Exposure Models Inventory.xlsx*". Following the first assessment, 19 of the tools underwent a sensitivity analysis. These models/tools are ISO/TS CB nanotool, BIORIMA Occupational exposure section, SprayExpo, RISKOFDERM, MEASE, EMKG, ENAE-CPSC, CB nanotool, LiCARA nanoSCAN, NanoSafer, SUNDS, ANSES, Swiss Precautionary Matrix, Stoffenmanager nano, ConsExpo nano, ART, MPPD, Boxall et al. (2007), and Nazarenko et al. (2012 & 2014). The remaining 8 tools were not assessed for sensitivity analysis due to several reasons: (1) the tool was categorized as not-suitable after the scope analysis, (2) the tool has no user interface, (3) the tool has a nano-version which has similar characteristics, or (4) the tool is too complex. The sensitivity analysis (SA) was performed using different methodologies according to the tools characteristics. Main methodologies used are one-at-a-time -methodology with either range scanning or random sampling (Monte Carlo), all-at-once analysis with random sampling, diagnostic method, and regression analysis/design of experiments. The sensitivity analysis addressed the sensitivity of models/tools against changes in input parameters and identified the most and least sensitive parameters. The results of the SA are included in this document, as well as the recommendation for future activities.

7. Based on the SA results, the models/tools are further selected for the performance testing. The performance testing assessed the predictive capability of the models/tools by comparing the outputs with exposure measurement data. The 15 models/tools selected for the performance testing for occupational exposure are ISO, BIORIMA Occupational Exposure section, RISKOFDERM, MEASE, EMKG, Stoffenmanager, ENAE-CPSC, LiCARA nanoSCAN, NanoSafer, GUIDEnano, SUNDS, Swiss Precautionary Matrix, Stoffenmanager Nano, ConsExpo nano and ART. The 7 models/tools selected for the performance testing for consumer exposure include ConsExpo nano, Swiss Precautionary Matrix, GUIDEnano, Stoffenmanager Nano, NanoSafer, Boxal et al. (2007), and ENAE. The results of the performance testing are given in two separate documents: ENV/CBC/MONO(2021)28 and ENV/CBC/MONO(2021)29, also published in the Testing and Assessment **link** for occupational and consumer exposure, respectively.

Table of contents

FIGURES

TABLES

Abbreviation

ACH	Air Changes per Hour
CB	Control Banding
DNEL	Derived No-Effect Level
FF	Far Field
FRC	Functional Residual Capacity
HRA	Human Risk Assessment
LEV	Local Exhaust Ventilation
MF(s)	Modifying Factor(s)
MNM	Manufactured Nanomaterial
MPPD	Multiple-Path Particle Dosimetry
NEPs	Nano-Enabled Products
NF	Near Field
NOAA	Nano-Objects and their Aggregates and Agglomerates
OEL	Occupational Exposure Limits
PPE	Personal Protective Equipment
PROC	Process Category
QEA	Quantitative Exposure Assessment
RA	Risk Assessment
RCR	Risk Categorization Ratio
RL	Risk level
RM	Risk Management
RMM	Risk Management Measures
SA	Sensitivity Analysis
SDS	Safety Data Sheet
TRA	Targeted Risk Assessment
TWA	Time Weighted Average
URT	Upper Respiratory Tract
AAO	All-at-once
OAT	One-at-a-time

MC	Monte Carlo
WPMN	Working Party on Manufactured Nanomaterials

Definitions and vocabulary

8. This document uses the following definitions adopted from the previous EU FP7 SUN project (EC-GA No. 604305):

- **Applicability score** – the term applicability used in the "*applicability score*" refers to how complete and broad a tool is in terms of application domain (consumer / occupational), exposure domain (point source / handling / dispersion / abrasion), exposure routes covered (inhalation / dermal / oral), type of output (qualitative / semi-quantitative / quantitative) and completeness of in the exposure assessment (exposure potential / risk management measures).
- **Application domain** – in this report "*application domain*" refers to the target scenario of exposure of the tool (work, consumer and environmental). Each tool application domain is indicated in Section 2, Table 1. The fact that one tool application domain is defined as for example consumer and worker, does not mean this tool is assessed for both application domains in this work. However, the tools are never assessed outside of their intended application domain except for NanoSafer, Stoffenmanager nano, ART and ANSES (which even though their application domain is work exposure, they were also addressed in the consumer project), and ConsExpo and ConsExpo nano (which even though their application domain is consumer exposure are also considered in the occupational project). This is detailed and summarized in Section 2, Table 1.
- **Control banding (CB) tool** - a system that performs a combined qualitative or semi-quantitative risk assessment with recommended management actions as function of a qualitative, semi-quantitative or quantitative hazard and exposure assessment. It is a process that matches a set of control measures to a range or "*bands*" of hazards and exposures. The CB system determines a set of useful controls that aims to prevent harm depending on known or estimated hazards (bands) and anticipated exposure levels (bands). The function of CB tools is to minimize exposures to hazardous chemicals or other risk factors (see e.g., http://www.ccohs.ca/oshanswers/chemicals/control_banding.html).
- **Difficulty score** – the term difficulty in the "difficulty score" refers to how comprehensive and accessible a tool is by considering its accessibility, interface and support, and guidance provided in order to introduce inputs and running the tool.
- **Exposure assessment framework** - a formalized procedure with elements to address or sets of tools to follow during assessment or ranking the potential exposure to a specific set of chemicals.
- **Exposure management framework** - a formalized procedure with elements to address or sets of tools to use to identify the procedure/best method by which to reduce or prevent exposure to a specific set of chemicals.
- **Exposure assessment tool** - a specific set of parameters applied in equations or decision logics by which the exposure potential can be qualified, scaled or quantified.
- **Exposure categorization tool** - a system that performs a qualitative or semi-quantitative assessment of the exposure likelihood using simple equations or a decision tree. The function of exposure categorization is to identify materials, products and actions with potential exposure.

- **Exposure management tool** - a set of parameters, equations or decision logics that can be used to calculate needs to reduce or prevent exposure in a qualitative, scaled or quantitative way.
- **Important parameters** – are those parameters in a model/tool that due to their own uncertainty or variability contribute substantially to the model uncertainty.
- **Qualitative / Semi-quantitative / Quantitative output** – the tool provides a qualitative output or a scale which is associated to a qualitative parameter (e.g. likelihood of exposure) / the tool provides a semi-quantitative scaled value / the tool provides a quantitative value (e.g. output is given as a potential or estimated concentration). The focus is on the output regardless of the approach used by the tool.
- **Regulatory tools** – the term is used to refer to the tools listed in the Annex 3 which are recommended and included in guidelines by regulatory authorities for assessment of exposure. For this, input was asked to all OECD member countries. However, it is important to note that 1) in this inventory only the input that was received is included (thus some members might not be represented), and 2) the great variability in authorisations between OECD member countries. The tools/models listed and assessed in this work, which are recommended by the European Chemical Agency (ECHA), are clearly identified.
- **Sensitive parameter** – is a parameter for which variation in the value has significant influence on the model output value.
- **Tiered Approach** - a stepwise approach from the original meaning "*A level or grade within the hierarchy of an organization or system*" as defined in Oxford Dictionaries (http://www.oxforddictionaries.com/definition/english/tier). In the REACH guidance R.14 and R.15, exposure assessment tools are defined into two tiers: Tier 1 and higher Tier models (ECHA, 2016a, b). ECHA's Tier 1 models are relatively simple and intended to generally overestimate the exposure while higher Tier models comprise a number of quantitative exposure assessment tools of different levels of complexity and level of documentation and calibration.

9. Due to the nature of risk assessment for manufactured nanomaterials (MNMs) and CB, the tiers and exposure assessment tools were defined in this work by the establishment of three Tiers based on EN 17058 as follows:

- **Tier 1** - Qualitative tools where the exposure estimation and/or risk management is based on assumptions and/or qualitative data to be applied in a binary decision tree or simple equations to complete a simple categorization or ranking of the likelihood for exposure and/or risk management. This class includes risk categorization tools and some simple CB Tools.
- **Tier 2** - Semi-quantitative tools based on assumptions or highly reduced determinants with quantitative input parameters (possibly in combination with precautionary default or expert opinion values) for use in simple calculations and/or decision logics resulting in qualitative or semi-quantitative values of exposure potentials and/or suitable risk management. The result can be either decision trees, scaled or quantitative. This class includes CB tools.
- **Tier 3** - Tools providing a quantitative output, which are based on quantitative data for use in predictive conceptual exposure/risk management modelling. The tools may combine quantitative and precautionary default values, expert opinion values and/or measurements for the assessment.

10. The tier classification adopted here may differ slightly from other adopted classifications.

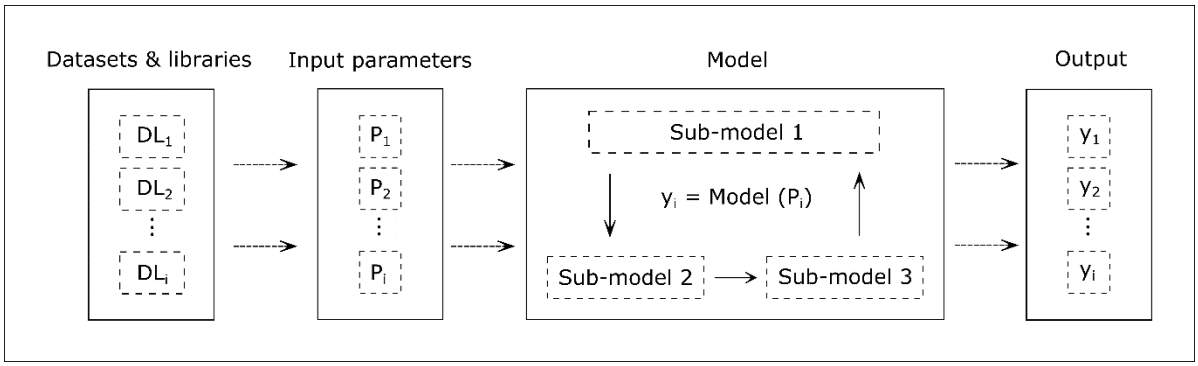


Figure 1. Explains the meaning of 'input parameters', 'model' or 'tool', 'dataset' and 'outputs' in the scope of this project. DL: datasets and libraries; P: input parameters; Y_i: output.

11. Input parameters are defined as data values required by the computational code before it can perform its task. A model or a tool incorporates an algorithm, which is implemented as a computational code that produces an output based on input parameters. Numerical values for quantities that are required by the model are called 'input parameters' within this report. The input parameters can be pre-defined by the tool, which means that they are set by the model developers and they cannot be changed by the user of the model, or need to be filled out by the user.

1 Background and purpose

1.1 Occupational exposure models

12. The OECD WPMN agreed to conduct an informal survey for compiling information on currently existing regulatory and new nano-specific models for occupational exposure assessment of Nano-Objects and their Aggregates and Agglomerates (NOAA). The main challenge encountered in NOAA regulations is the wide range of definitions for Nano-Objects (i.e. nanomaterials). Boverhof *et al*. (2015[1]) identified 14 different nanomaterial definitions from various regulatory authorities and more definitions are coming (e.g. Hansen, 2017[2]). Thus, for some potential NOAA materials, the exposure and risk assessment have to be made using conventional and NOAA exposure and risk assessment methods.

13. There are identified three main differences between the conventional material and NOAA exposure and risk assessment modelling tools (Liguori et al., 2016[2]):

i. The nano-specific Occupational Exposure Limits (OELs) or No Observed (Adverse) Effect Levels (NO(A)ELs) considering the most important biological end-points (Carcinogenicity, Mutagenicity, Allergy and Reproductive Toxicology).

ii. Chemical and physical characteristics of nanoparticles and released fragments.

iii. Exposure scenarios and emission classes for nanomaterials and nano-enabled products (NEPs).

14. To overcome some of these problems, new risk assessment frameworks and CB tools as well as higher-level risk assessment or management tools (Table 1) were developed over the last two decades. Most of the tools were developed for occupational exposure assessment with different scopes and application domains in mind. The majority of these tools focus on exposure via inhalation, even though a full risk assessment should also consider potential effects via oral, dermal, and eye exposure. Only a relatively low number of the models listed in Table 1 are currently mentioned by the European Chemical Agency (ECHA) as accepted options in their regulatory guidance documents for assessment of occupational and consumer exposures (ECHA, 2016[3]; ECHA, 2016[4]). The tools mentioned in ECHA guidance (hereafter denoted ECHA recommended tools) are ECETOC TRA, MEASE, EMKG Expo tool, Stoffenmanager, ART and RISKOFDERM. However, none of these tools were developed nor tested, calibrated and validated for assessment of exposure to MNMs. To meet this apparent lack of proper methodology, a number of new models, ranging from CB to advanced aerosol dynamic models have been developed over the last two decades of which some are intentionally developed for exposure assessment of NOAA taking into consideration the nanospecific requirements and/or a precautionary risk management approach. There is a need to understand to what extent different existing models are applicable and suitable for exposure assessment to MNMs.

15. The OECD WPMN Project “Assessing the global readiness of regulatory and non-regulatory models for assessing occupational exposure to manufactured nanomaterials”, aims to evaluate the suitability of existing regulatory (meaning models that are recommended and included in accepted guidelines by regulatory authorities for assessment of occupational exposure) and new nano-specific models for

assessment of occupational exposure of MNMs in regards to their intended application domains, concepts, input parameters, availability of algorithms and output formats. It is important to note the differences between OECD member countries regarding regulations and guidelines. To evaluate the global readiness of models for assessing occupational exposure, testing and comparison of model output against high-quality observations (real data) is imperative.

16. The models performance testing carried during this Project are the culmination of an extensive effort including:

- **i.** Compilation the available tools and models for assessing occupational exposure to MNMs through an extensive literature review of peer reviewed publications (ECHA, 2016[3]; ECHA, 2016[4]; Liguori et al., 2016[2]; Isigonis et al., 2019[5]; Hristozov et al., 2016[6]; Jantunen, Gottardo and Crutzen, 2017[7]; Jantunen et al., 2018[8]; Oomen et al., 2018[9]; Trump et al., 2018[10]; Brouwer et al., 2012[11]) (Franken et al., 2020[12]), the outcomes from recent international projects and inventories (NanoREG, SUN, caLIBRAte, ENV/JM/MONO(2015)20 (OECD, 2015[13]), ENV/CHEM/NANO(2016)15/REV1 (OECD, 2016[14]), ENV/CHEM/NANO(2016)17 (OECD, 2016[14]), and consultation with the OECD WPMN member countries. The final inventory of tools, finalised in February 2019, is provided in the Annex 3 and is divided into two categories. Category 1 includes a descriptive list of 12 (13 considering ConsExpo nano) nano-specific models/tools relevant to occupational exposure assessments of MNMs. Category 2 includes a descriptive list of 10 chemical exposure tools/ models that in-themselves or adapted could be used in occupational exposure assessments of MNMs.
- **ii.** Identifying regulatory requirements and the criteria for global readiness regarding the potential use and suitability of risk- and exposure assessment tools for occupational exposure assessment to MNMs.
- **iii.** Establishment of an inventory of high quality scenario-specific measurement data of occupational exposure to MNMs.
- **iv.** Evaluation of the global readiness for assessing occupational exposure to MNMs. The evaluation process was carried out based on scope analysis and application domains, accessibility and support examination, function and sensitivity testing of models, and evaluation of the predictive capability of the models by comparing the modelling results with observations (real data) made in actual exposure scenarios. The non-nanospecific models (e.g. SprayExpo 2.3, EGRET2 and Stoffenmanager) will be omitted from the consideration for some parts of the tool assessment in which especially the nano-specific models are considered. By a non-nanospecific model, we mean models that are not designed to take into account nanomaterial specific phenomena (emission and transport characteristics). They could still require nanospecific data as, for instance, product concentration or emission rate.
- **v.** Recommend selection of tools for qualitative (Tier 1), semi-quantitative (Tier 2) and quantitative (Tier 3) nanospecific exposure assessment considering scope, application domain and output format required for purposes ranging from industrial risk management to regulatory exposure assessment.

17. This OECD WMPN project, had direct collaboration with 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.

1.2 Consumer exposure models

18. In 2015, OECD WPMN was tasked with identifying the available data on consumer and environmental exposure and mitigation measures, with the aim of prioritizing future work and research needs. The survey on Consumer and Environmental Exposures to MNMs collected data on the importance and availability of information related to exposure assessment (OECD, 2016[14]). The analysis of the responses to the survey identified exposure models for use in characterizing or estimating consumer and/or environmental exposure to MNMs to be of high importance, requiring further investigation. As such, in the

spring of 2017, Canada submitted a proposal to the OECD WPMN to lead a project entitled "*Compilation of Available Tools and Models Used for Assessing Environmental and Consumer Exposure to Manufactured Nanomaterials and Evaluation of their Applicability in Exposure Assessments*". The project aimed to (1) Compile the available tools and models for assessing environmental and consumer exposure to MNMs, and (2) Evaluate their applicability to MNM exposure assessment. The outcomes of consumer and environmental parts of the project are provided separately. This report includes the consumer part of the project.

19. Under the first objective, an inventory of available models/tools/databases for assessing consumer exposure to MNM was created through an extensive literature review of peer reviewed publications, the outcomes from recent international projects and inventories, and consultation with OECD WPMN. The inventory includes 15 nano-specific models/tools relevant to consumer exposure to MNM and 9 chemical exposure tools/ models that in-themselves or adapted could be used in exposure assessments of MNM. The 15 nano-specific models/tools and the 9 chemical exposure tools are provided in Categories 1 and 2 in the Annex 3 "Exposure Models Inventory.xlsx".

20. Under the second objective, an evaluation of the applicability of the listed models/tools in Category 1 was conducted in consultations with WPMN experts and collaborators. The evaluation process was carried out based on scope analysis, accessibility and support examination, sensitivity analysis (SA), and performance testing. The scope analysis addresses input parameters required by models/tools, their intended domain in terms of scenarios and routes of exposure, output of the models/tools, and assumptions considered by models/tools. The accessibility and support examination of the models/tools provides information on user-interface of models/tools and availability of input parameters required by models/tools. The SA identifies how sensitive models/tools are against changes in input parameters. It also identifies the most and least sensitive parameters for models/tools. The performance testing is aimed at addressing which model(s)/tool(s) would be suitable for consumer exposure assessment of MNMs. It assesses the predictive capability of the models/tools by comparing the outputs with measurement data chosen from case studies. Case studies are taken from a consumer exposure database constructed by compiling measurement data on consumer exposure to MNM during this project.

2 Inventory of models/tools

21. The inventory of models/tools given in Category 1 (nano-specific) and Category 2 (conventional chemical tools and models) of the Excel file was developed by consultation within OECD WPMN, and by searching the following resources:

- Analysis of the survey on available methods and models for assessing exposure to manufactured nanomaterials (OECD, 2015[13]),
- Investigating the different types of risk assessments, tools available for risk management measures, and uncertainties which guide additional nanospecific data needs in member countries (OECD, 2016[15])
- Information and data used for assessing consumer and environmental exposure to manufactured nanomaterials: Light Analysis of the Survey (OECD, 2016[14])
- **European Projects:** NanoREG, SUN, caLIBRAte
- **The NANoREG 2016 report** - Improved and validated occupational exposure models of release, exposure, dispersion and transfer
- **The Danish EPA report** - Exposure assessment of MNM in consumer products
- **Google Scholar** - peer-reviewed online academic journals and books, conference papers, thesis and dissertations, preprints, abstracts, and technical reports

22. Regarding Google scholar, a search strategy covered the following terms, found in the title or abstract:

- Control band/NMs/consumer exposure or Control band/NMs/occupational exposure
- Exposure models/tools/MNMs
- Chemical exposure tools/applicability/MNMs

23. Information collected for Category 1 and Category 2 included models/tools' name, version, contact points and email, references, country of origin, type of model, tier, description, availability, source, intended application domain, product types, product form, MNM properties/characteristics, routes of exposure considered by the models/tools, input parameters, output, validation, and assumptions made, if available. Short descriptions of models/tools included in Category 1 and Category 2 are given in Table 1.

24. High-tier source to receptor inhalation exposure assessment models (also known as a near field/far field (NF/FF) model) has been described considering the transformation of particle sizes and concentrations during transport and the role of contextual conditions (Schneider et al., 2011[5]; Hewett and Ganser, 2017[6]; Jayjock, Armstrong and Taylor, 2011[7]; an advanced multi-box aerosol dynamic dispersion model by Jensen et al., 2018[8]). These physical mass-balance models would be Tier 3 exposure assessment models and could be applicable to both consumer and occupational inhalation exposure assessment, because both the source- and contextual information requirements are generic.

Table 1. Summary of the models/tools.

Model nº	Model and Version	Tier	Owner/publication	Model Type (category)	Application domain	Short description	Project
1	ISO/TS 12901-2:2014 CB nanotool v1.0 (Part 2)	1	ISO	CB (category 1)	Work	It describes the use of a CB approach for controlling the risks associated with occupational exposures to NOAA (<100nm), even if knowledge regarding their toxicity and quantitative exposure estimations is limited or lacking.	Occupational
2	BIORIMA Occupational exposure section	3	ITENE (Aceti, 2017[16])	QEA (category 1)	Work	The online platform contains a web application running a homogenous atmosphere 2-box (NF/FF) model for estimating occupational inhalation exposure to MNM. The outputs are mass and particle number concentrations in air.	Occupational
3	SprayExpo model 2.3	3	Federal Institute for Occupational Safety and Health (BAuA) (Koch et al., 2012[17])	Physical modelling, QEA (category 2)	Cons/Work	SprayExpo is a model that enables the prediction of dermal and inhalation exposure levels to aerosols during spray application of non-evaporating substances. The model calculates airborne concentrations of health-relevant particle size fractions and takes into account the turbulent diffusion, droplet evaporation and sedimentation movements.	Occupational
4	RISKOFDERM (ECHA recommended)	2	TNO (Final Paper Version of Toolkit) (van Hemmen et al., 2003[18])	QEA (category 2)	Work	It is a toolkit for assessment and management of hazard, exposure and risk from dermal exposure to hazardous chemicals at the workplace. It provides broad data categories of hazard and exposure that lead to a rough estimate of health risk from dermal exposure, i.e. the total amount of a substance coming into contact with the protective clothing, work clothing and exposed skin.	Occupational
5	MEASE 2.2.0 (ECHA recommended)	2	EBRC	CB (category 2)	Work	The MEASE exposure model aims to provide a screening tool for the estimation of occupational inhalation and dermal exposure to metals and inorganic substances during manufacturing and use. For inhalation exposure, MEASE is based on the ECETOC targeted risk assessment (TRA) tool and for dermal exposure on the classification system of the estimation and assessment of substance exposure (EASE) system.	Occupational
6	EMKG Expo tool 2.0 (ECHA recommended)	1-2	Federal Institute for Occupational Safety and Health (BAuA)	CB (category 2)	Work	IT-tool that allows the user to estimate and evaluate worker inhalation exposure, and identify risk management measures (RMM) at workplace using a CB approach.	Occupational

Model nº	Model and Version	Tier	Owner/publication	Model Type (category)	Application domain	Short description	Project
7	EGRET 2.0	2-3	ESIG/ESVOC (Zaleski et al., 2014[19])	QEA (category 2)	Cons/Work	EGRET2 - the European Solvents Industry Group Generic exposure scenario Risk and Exposure Tool. The tool has been developed to assess the potential risk to consumers who use products that contain solvents under REACH. Estimates exposure to solvents through dermal, oral and inhalation routes, and provides risk characterisation ratios for each route. EGRET is intended for screening level evaluations	Occupational
8	Dermal Advanced Reach Tool (dART)	2-3	TNO/HSL (Goede et al., 2019[20]; McNally et al., 2019[21])	QEA (category 2)	Work	It is a dermal exposure model especially designed for hand exposures to low volatile liquids including solids-in-liquid products occurring during synthesis and manufacturing use of chemicals.	Occupational
9	Stoffenmanager 8.3 (ECHA recommended)	2-3	Cosanta BV (Marquart et al., 2008[22])	CB/RM (category 2)	Work	It is a risk prioritisation web-based tool which consists of a CB tool for inhalation and dermal exposures and also provides a quantitative inhalation exposure part.	Occupational
10	Engineered Nanoparticle Airborne Exposure (ENAE) Tool (CPSC ENP Model) v1.0	3	National Institute of Standards and Technology (NIST)	QEA (category 1)	Cons/work	The tool estimates air concentration and surface loading of airborne nanoparticles. The estimation is expressed in number of particles per volume for the air concentration and number of particles per area for the surface loading.	Occupational and consumer
11	Control Banding (CB) Nanotool v2.0	1	Lawrence Livermore National Laboratory (LLNL) (Paik, Zalk and Swuste, 2008[23]; Zalk, Paik and Swuste, 2009[24])	CB (category 1)	Cons/Work	The tool estimates an emission probability (without considering exposure controls) and severity band and provides advice on what engineering controls to use. It includes nine domains covering handling of liquids, powders and abrasion of solids. Combines hazard severity and exposure probability scores in a matrix to obtain a level of risk and associated controls out of 4 possible levels of increasing risk and associated controls. It is intended for any laboratory-scale operation involving production and use of MNMs.	Occupational and Consumer
12	LiCARA nanoSCAN v1.0	1	TNO/EMPA (van Harmelen et al., 2016[25])	Risk Benefit (category 1)	Env/Cons/Work	Determines and weighs the benefits and risks over the lifecycle of MNM-based products. This tool is specifically intended for use by SME to support them in communicating with regulators, and potential clients and investors. It uses principles and assessment criteria from the Precautionary Matrix, NanoRiskCat and Stoffenmanager Nano, and integrates them with expert judgement through MCDA.	Occupational and Consumer
13	NanoSafer v1.1	2	NRCWE (Kristensen et al., 2010[26]; Jensen et al., n.d.[27])	CB/RM (category 1)	Work	Occupational inhalation exposure assessment and risk management recommendations during process-specific manufacturing and handling of MNMs. Banding is based on a combination of given or predicted MNM OEL hazard labels, and the estimated exposure potential.	Occupational and Consumer

Model nº	Model and Version	Tier	Owner/publication	Model Type (category)	Application domain	Short description	Project
14	GUIDEnano tool	3	LEITAT (Park et al., 2018[28])	RA/RM (category 1)	Env/Cons/Work	Assessment and mitigation of nano-enabled product risks on human and environmental health considering the whole product life cycle. Using this Tool, industry will be able to evaluate and efficiently mitigate possible health risks for workers, consumers and the environment associated to the use of nanotechnologies.	Occupational and Consumer
15	The SUN Decision Support System (SUNDS)	3	Greendecision Srl. (Subramanian et al., 2016[29]; Hristozov et al., 2018[30])	Combination of multiple approaches, RA / RM (category 1)	Env/Cons/Work	Decision support system for risk management of MNMs and NEPs. SUNDS is a cloud-based nano-product sustainability assessment Decision Support System. SUNDS allows supporting decisions on assessment & management of MNMs and NEPs along their lifecycles. Target users include industry, regulatory bodies and insurance companies. It applies a two-tier approach which, on the basis of the supplied information, is able to generate qualitative or quantitative output results.	Occupational and Consumer
16	ANSES tool	1	French Agency for Food, Environmental and Occupational Health & Safety (ANSES, 2010[31]; Riediker et al., 2012[32])	CB (category 1)	Work	The ANSES CB nanotool was developed to be applied for conducting risk assessment and risk management of work with MNMs or NEPs in industrial settings.	Occupational and Consumer
17	Swiss Precautionary Matrix v3.0	1	Federal Office of Public Health (FOPH) (Höck et al., 2008[33]; Höck et al., 2011[34]; Höck et al., 2013[35])	Risk Cat (category 1)	Env/Cons/Work	The precautionary matrix is a method for assessing the nano-specific health and environmental risks of NEPs. The precautionary matrix for synthetic nanomaterials is geared toward industry and trade.	Occupational and Consumer
18	Stoffenmanager Nano v1.0	2	TNO (van Duuren-Stuurman et al., 2012[36])	CB/RM (category 1)	Work	Occupational inhalation exposure from point source or fugitive emission during synthesis, handling and transfer of powders, dispersion, application of ready-to-use products (e.g. spraying), fracturing and abrasion end-products at work sites (e.g. sanding, milling, cutting, high energy end of life mechanical or thermal processes, etc.).	Occupational and Consumer
19	ConsExpo Nano	3	RIVM (Delmaar, Park and Engelen, 2005[37]; Delmaar and Meesters, 2020[38])	Physical modelling, QEA (category 1)	Cons	Tool for the assessment of consumer exposure to MNMs via inhalation (spray scenario as well as custom scenarios).	Occupational and Consumer

Model nº	Model and Version	Tier	Owner/publication	Model Type (category)	Application domain	Short description	Project
20	ConsExpo	3	RIVM (Delmaar, Park and Engelen, 2005[37]; Delmaar and Bremmer, 2009[39])	Physical modelling, QEA (category 2)	Cons	ConsExpo was developed to estimate exposure to chemicals from various products under various exposure conditions. The tool calculates both external and internal exposure via inhalation, dermal, and oral routes separately.	Occupational and Consumer
21	Advanced REACH Tool v1.5 (ECHA recommended)	2-3	HSL (Fransman et al., 2011[40]; ECHA, 2016[3])	QEA (category 2)	Work	The Advance Reach Tool was developed to estimate inhalation exposure in the workplace. It combines a source-receptor approach with modifying factors (Fransman et al., 2011) and the ability to update the estimates with the users own data. This integration of information is done using an in-built database of class activities with measurement data and Bayesian statistics.	Occupational and Consumer
22	ECETOC TRA v3.1 (ECHA recommended)	1-2	ECETOC (ECETOC, 2017[41]; ECHA, 2016[3]; ECHA, 2016[4])	CB (category 2)	Cons/Work	The tool calculates exposure via inhalation, dermal, and oral routes separately. It is available as an integrated tool that combines worker, environmental, and consumer calculations. Its output is mass-based metrics which can be used to estimate the mass-based exposure to a material from a product	Occupational and Consumer
23	NanoRiskCat	1	DTU (Hansen, Jensen and Baun, 2014[42])	Risk Cat (category 1)	Cons/Work	NanoRiskCat is a categorization tool that communicates knowledge on the potential exposure and hazard of MNM in consumer products. The assessment is based on the location of the MNM in the product, and the potential for exposure to the MNM in the product or article during the intended use.	Occupational and Consumer
24	Multiple-Path Particle Dosimetry Model (MPPD)	3	ARA (Anjilvel and Asgharian, 1995[43]; Asgharian, Hofmann and Bergmann, 2001[44])	QEA – Particle Dosimetry (category 1)	Cons/Work	MPPD estimates human and rat airway particle dosimetry. The tool calculates the deposition and clearance of monodisperse and polydisperse aerosols from nanotechnology-based consumer spray products.	Consumer
25	I-NANO	3	INRS – IOM (Sánchez Jiménez et al., 2016[45])	QEA (category 1)	Cons/Work	I-NANO was developed during the NANoREG project. The tool estimates the time evaluation of air concentration of MNM by taking into account coagulation and losses through gravitational settling (i.e., particles settling to the floor), diffusion (particles settling on walls and surfaces) and dilution (effect of ventilation)	Consumer
26	Boxall *et al*. (2007)	3	(Boxall et al., 2007[46])	QEA (category 1)	Cons	Boxall *et al*. (2007) presents a simple dilution model for estimating exposure from personal hygiene and skin care products. The model estimates air concentration of MNM and does not account for the transmission factors including ventilation and diffusion.	Consumer

Model nº	Model and Version	Tier	Owner/publication	Model Type (category)	Application domain	Short description	Project
27	Nazarenko *et al*. (2012 & 2014)	3	(Nazarenko et al., 2012[47]; Nazarenko, Lioy and Mainelis, 2014[48])	QEA – Particle Dosimetry (category 1)	Cons	The model used by Nazarenko *et al*. (2012 & 2014) estimates inhaled dose from nanotechnology-based consumer sprays and cosmetic powders. The model takes into account the size of MNM for the estimation, and expresses the estimation as mass of particle per body mass per time	Consumer
28	DREAM	2	(van-Wendel-de-Joode et al., 2003[49])	CB (category 2)	Work	DREAM was developed to assess and evaluate occupational dermal exposure to chemical agents. The model estimates potential and actual dermal exposure by taking into account the protection afforded by clothing and gloves	Consumer
29	Consumer Exposure Model (CEM)	3	EPA	QEA (category 2)	Cons	CEM was developed to calculate exposure to chemicals from various consumer products. The tool estimates indoor air concentrations, indoor dust concentrations, dermal exposure, and mouthing exposure for a wide variety of consumer products and materials.	Consumer
30	E-FAST	3	EPA	QEA (category 2)	Cons	E-Fast was developed to estimate general population, consumer, and ecological exposures from environmental releases of chemicals manufactured and used in industrial/commercial settings.	Consumer
31	Exposure Related Dose Estimating Model (ERDEM)	3	EPA	QEA (category 2)	Cons/Work	ERDEM was developed to predict how chemicals move through and concentrate in human tissues and body fluids.	Consumer
32	Wall Paint Exposure Model (WPEM)	3	EPA	QEA (category 2)	Cons/Work	WPEM was developed to estimate indoor air concentrations of chemicals released from wall paint over time.	Consumer

Note: Abbreviations: Env - environmental, Cons - consumer, CB - Control Banding, RA - Risk Assessment, RM - Risk Management, QEA - Quantitative Exposure Assessment, Risk Cat - Risk Categorization). Category 1 means nano-specific and Category 2 means conventional chemical tools and models. Application domain column refers to the intended use and target exposure the tool is designed to be used. Project column indicates in which project (consumer and/or occupational) the tool was assessed.

3 Scope analysis and accessibility and support

25. The scope analysis addressed input parameters required by models/tools, their intended domain in terms of scenarios and routes of exposure, output of the models/tools, and assumptions considered by models/tools. The accessibility and support examination of the models/tools is solely based on user-interface of models/tools and availability of input parameters.

26. In addition, the tools have been graded according to a “difficulty score” and an “applicability score” defined below. The mentioned scores provide summarized information regarding the difficulty and applicability of the tools to be used for fast interpretation and comparison of tools. However, it is important to note that these scores are a very simplified expression of the tools applications and difficulty. Therefore, not useful for an in deep and detailed evaluation of the tools, which would require careful examination of the tools features considering the intended goal.

Difficulty score

27. The difficulty score intends to provide information on the user-interface, accessibility and comprehensiveness of the tools in a summarized number for fast interpretation and comparison. The difficulty score ranges from 1 to 5, 1 being easiest to use and 5 most difficult, and it is defined arbitrarily. The difficulty score is based on five criteria 1) interface, 2) accessibility, 3) inputs difficulty, 4) output format, and 5) user guide. For each criteria, several options are available with different associated weights. The sum of all weights form the final difficulty score. Criteria and associated weight are shown in Table 2. The results of the difficulty score for each tool are provided in each individual section 3. Full details on calculations and results are provided in the Annex 3 “Exposure Models Inventory.xlsx”.

Table 2. Difficulty score criteria and associated weights.

Criteria	*Options*	*Weights*
Interface	Intuitive GUI	0.2
	GUI provided	0.4
	GUI limited or complicated	0.6
	No GUI	1
Accessibility	Web-based	0.2
	Excel	0.4
	Installed	0.6
	Guidance document/Publication	1
Inputs difficulty	Drop-down/multiple choice with guidance	0.2
	Manually entered with guidance	0.4
	Drop-down/multiple choice without guidance	0.6
	Manually with guidance somewhere else	0.8
	Manually without guidance	1
Output format	Downloadable results in usable format	0.2
	Not downloadable results	1
User guide	User guide well written	0.2
	User guide limited or complicated or Helpdesk	0.4
	Publication	0.8
	No guidance available	1

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

3.1.1 Scope analysis

Tool description, domain and assumptions

28. ISO/TS 12901-2:2014 describes the use of an occupational risk management CB approach for controlling the risks associated with inhalation exposure to NOAA and materials containing NOAA (i.e., nanoparticles, nanopowders, nanofibers, nanotubes, nanowires, as well as of aggregates and agglomerates), even if knowledge regarding their toxicity and quantitative exposure estimations is limited or lacking. The fundaments for this approach are the hazard identification process and the assessment of the worker exposure assessment potential. The guideline is intended to help during the manufacturing, processing or handling of NOAA and it is specifically designed for inhalation control although some guidance for skin and eye protection is also given.

29. When there is limited information to guide decisions on the potential for hazard and exposure, reasonable worst-case assumptions should be used along with appropriate management practices.

Input and output parameters

30. Input parameters required are described below:

- NOAA information: name, CAS, formula or molecular structure, composition, morphology, surface chemistry and production method.

- Physicochemical properties: agglomeration/aggregation, solubility in water or other biologically relevant fluids, crystalline phase, dustiness, crystallite size, TEM pictures, particle size distribution and specific surface area, catalytic or photocatalytic activity, pour density, porosity, octanol-water partition coefficient, redox potential, radical formation potential.
- Toxicological data: pharmacokinetics (absorption, distribution, metabolism and elimination), acute, repeated dose, chronic, reproductive, development and genetic, toxicity, human exposure and epidemiological data.
- General exposure characterisation: estimate of exposure for each relevant pathway, evaluation of the quality of the assessment and confidence degree, and critical parameters (physical form of the NOAA, amount of NOAA, dust generation during process and actual exposure data).
- Control measures characterisation: general control measures, reduction of emission, reduction of transmission (e.g., containment, ventilation cabin or natural/mechanical ventilation), and reduction of emission (personal enclosure or separation, segregation, use of personal protective equipment (PPE)).

31. For the hazard and exposure banding, the guideline guides the user through a decision tree with several yes/no questions that lead the user to a final hazard band allocation. The exposure band is determined according to the type of process, which is different depending on the NOAA form, dispersion in liquid, suspension in liquid, solid or powder form. The hazard exposure information is combined to determine and appropriate level of control (e.g., general ventilation, local exhaust ventilation (LEV) or containment of the source). Finally, risk or priority bands are determined according to a matrix merging hazard and exposure band (Table 3).

Table 3. Risk or priority bands matrix. EB – exposure band of ISO CB nanotool.

Hazard band	Exposure band			
	EB 1	EB 2	EB 3	EB 4
A	Low	Low	Low	Medium
B	Low	Low	Medium	High
C	Low	Medium	Medium	High
D	Medium	Medium	High	High
E	Medium	High	High	High

3.1.2 Accessibility and support

32. The ISO/TS 12901-2:2014 has been developed to be an easy-to-understand, pragmatic approach for the control of occupational exposures. It is not implemented as free web-based or excel-sheet but as a guideline with a step-by-step guidance that needs to be purchased. This can be an advantage as it can be accessible without any software limitation. However, relatively good knowledge of the process, materials and CB approach is required. Most input parameters required are available from safety data sheet (SDS) or manufacturers information, and characterisation is made through simple decision-trees. The difficulty score calculated for this tool is 3.6.

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

3.2.1 Scope analysis

Tool description, domain and assumptions

33. BIORIMA is an Integrated Risk Management framework designed to identify and assess the potential exposure, hazard and risk posed by MNM and nanobiomaterials to humans in occupational and consumer 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.

34. The IATA module provides a set of IATAs for human health and environmental endpoints to support the evaluation and generation of data to be used in hazard and risk assessment.

35. The risk assessment and risk control module conduct assessment of occupational and environmental risks during synthesis, product manufacturing, use and end of life. For the human exposure part, the tool estimate exposure for inhalation, dermal, inadvertent oral and ocular. For the environmental part, the model assess exposure to air, soil, sediment and water. The user can select through a selection tree which parts wants to assess.

36. In this project, only the occupational inhalation exposure part of the risk assessment and risk control module was considered.

37. The occupational exposure model is based on the 2-box (NF/FF) as described in Ganser and Hewett (2017[50]). The model is used for estimating occupational inhalation exposure to MNM in the form of solids or liquids. The model assumes homogeneous atmosphere and that the source is located inside the NF boundaries of the model.

Input and output parameters

38. Input parameters required are particle dimeter (nm), density (g/cm^3), percentage of pure MNM, used mass (in g), task duration (min), generation rate (min), number of repetitions, room volume (m^3), air changes per hour, activity generating the release rate. All input parameters are numerical values entered by the user except the activity where the user selects the activity class from a drop down menu which contains >100 options.

The output for the inhalation occupational exposure is currently given in mass concentration (mg/m^3).

3.2.2 Accessibility and support

39. The tool is available to users through an easy-to-use graphical user interface (GUI). The inhalation occupational part only require 10 input parameters and most of them can be easily obtained through SDS and only relatively good knowledge of the environment is required. The tool is publicly available at https://sunds.gd/sections. The difficulty score calculated for this tool is 2.2.

3.3 SprayExpo model 3.2

3.3.1 Scope analysis

Tool description, domain and assumptions

40. SprayExpo is a mechanistic model that serves the purpose of calculating the inhalation and dermal exposures of the worker during application of a non-volatile substance dissolved in a solvent with known volatility, by means of spraying or fogging techniques in enclosed rooms (Koch et al., 2012[17]). The exposure concentration is computed by means of a droplet simulation model. This model takes into account, among other factors, the turbulent mixing of the spray with the indoor air, the gravitational sedimentation of droplets, and droplet evaporation. The corresponding transport balance equations are set up and solved numerically (Koch, 2004). With regard to dermal exposure, the model can only take the sedimentation flow of the airborne droplets into account, but not accidentally occurring splashes.

Input and output parameters

41. The key input parameters are the released droplet spectrum, the release rate, the concentration of the active substance, the spatial and temporal pattern of the release process (surface spraying against floor, ceiling, wall and room spraying), the vapour pressure of the liquid, the size of the room and the Air changes per Hour (ACH). In addition, the path of the sprayer can be explicitly included in the model. The model calculates the airborne concentrations of the respirable, thoracic, inhalable, or any other meaningful size fraction of aerosols generated during working processes. From the calculated concentration the inhalation as well as the dermal exposure is determined. For surface treatment with spraying, a droplet deposition module has been incorporated in the program package. This module calculates the fraction of non-impacting droplets which are of relevance to human exposure.

3.3.2 Accessibility and support

42. SprayExpo can be installed as a program or used as an Excel® worksheet. Recently, to facilitate the use of the SprayExpo model, an MS Excel® worksheet was developed. It is compatible with the operating system MS Windows® XP Service Pack 2 or later and with the program MS Excel® 2007 or later and can be found in https://www.baua.de/EN/Topics/Work-design/Hazardous-substances/Assessment-unit-biocides/Sprayexpo.html. To facilitate its use, program description and installation instructions are available in their webpage. The tool has also been improved by including an internally stored database for droplet distribution of certain spray devices. Therefore, it is only necessary to specify the spraying technique and simple process parameters, such as the spraying pressure. The difficulty score calculated for this model is 1.8.

3.4 RISKOFDERM

3.4.1 Scope analysis

Tool description, domain and assumptions

43. RISKOFDERM consists of a toolkit and a model/tool. The toolkit is defined as data driven deterministic toolkit for assessment and management of hazard, exposure and risk from dermal exposure to hazardous chemicals at the workplace. It applies to health risks from occupational dermal exposure to both, single substances and mixtures.

44. The toolkit can only handle one chemical product and one exposure-scenario at a time and provides broad data categories of hazard and exposure that lead to a rough estimate of health risk from dermal exposure. The toolkit was constructed by analysing the major determinants of dermal hazard and dermal exposure. The results are combined in the form of a decision-tree that leads the user of the toolkit through a number of questions on the hazardous properties of the chemical in use, and on the exposure situation. After going through the decision-tree the user is advised to consider an action to control the risk.

45. The RISKOFDERM tool 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. The 6 DEO units are filling and mixing (DEO1), wiping (DEO2), dispersion with hand held tools (DEO3), spraying (DEO4), immersion (DEO5) and mechanical treatment (DEO6).

46. The tool assumes that the occurrence of local health effects depends mainly on the peak values of actual exposure dose, even if these last only a short time. In addition, because the uptake rate is unknown in many cases, a ”*reasonably worst case*” assumption of complete percutaneous absorption it is used (i.e. the internal exposure equals the actual exposure).

Input and output parameters

47. Main input parameters needed are product and dilution state, ingredients, risk phrases, pH, chemical state of the product, and workplace activity descriptors, selected from predefined options (e.g., task duration, type of process, body parts exposed). According to the selections on the workplace activity descriptions, the tool assigns modifying factors (MFs) depending on e.g., task duration or body parts exposed.

48. Hazard score equals Intrinsic Toxicity score (IT), which is calculated according to risk phrases and pH values. On the other hand, the integrated MF is calculated firstly by multiplication of each single MF with the applicable relative contribution of the respective route of exposure, and then by summing up. This result is later transformed into a banding level that indicates the significance of actual exposure (AE score, which can range from negligible to extreme). Afterwards, the hazard score and the AE score are combined in order to obtain a health risk score (Figure 2).

AE score	Hazard score				
	Low (no risk)	Moderate	High	Very high	Extreme
Negligible	1	1	2	5	6
Low	1	2	5	6	8
Moderate	2	3	6	8	9
High	3	6	8	9	10
Very High	6	8	9	10	10
Extreme	7	9	10	10	10

Figure 2. Basic steps of dermal risk assessment and management in the RISKOFDERM; Toolkit (up), and Health scores (down).

Source: modified from Oppl et al., 2003 (DOI: 10.1093/annhyg/meg069

3.4.2 Accessibility and support

49. RISKOFDERM is intended to be used especially by employers, safety officers, technical staff and consultants in companies of any size, but particularly by small and medium-sized enterprises that should have access to all the input parameters required. The final version of the toolkit executes the decision algorithms behind the scene so that the non-expert user can only see the judgements, the recommendations and the general information. The toolkit and the tool are given as a programmed decision tree in an Excel® file where the user is led through the decision logic without seeing any details of assignment, calculation and ranking of the values in between. This can be easily downloaded from http://www.eurofins.com/Research_occ_hygiene. The difficulty score calculated for this tool is 1.4.

3.5 MEASE 2.2.0

3.5.1 Scope analysis

Tool description, domain and assumptions

50. The MEASE exposure model aims to provide a screening tool for the estimation of occupational inhalation and dermal exposure to metals and inorganic substances in the form of solids, liquid aerosols or gaseous substances during manufacturing and use in workplace environments. The model is not recommended for estimating exposure to organic chemicals.

51. For inhalation exposure, the tool follows the process-category (PROC)-specific approach of the targeted risk assessment (TRA) tool and selects initial exposure estimates from three "*fugacity classes*" i.e.

low, medium, high. This is based on the physical form, the melting point of the metal, the temperature of the process, the vapour pressure and the selected PROC. The initial exposure estimates for PROCs in MEASE are based on measured data from the metals industry. Risk management measures (RMM) are based on a publication of Fransman *et al*. (2008[51]) who analysed >400 publications for data on the efficiency of RMMs. As a result, MEASE gives users the possibility to choose between several RMMs. For dermal exposure, MEASE is based on the classification system of the broadly used EASE system. The exposure estimates are, however, based on real measured data for several metals.

Input and output parameters

52. Input parameters required are PROC selection (type of activity), physical form, level of containment, level of automation, amount of material used, repetition, room size, concentration/purity of the substance, duration of the activity, information on ventilation, worker protective equipment and cleaning practices. Information regarding parallel activities can also be included.

53. Output provided by the tool is the form of 8-h time weighted average (TWA) exposure concentrations.

3.5.2 Accessibility and support

54. MEASE is an Excel®-based tool, which can be downloaded from https://www.ebrc.de/tools/downloads.php when creating a free account. All necessary input parameters information and results are presented in a single worksheet. Background information and user guidance can be found in the glossary within the tool itself and the HERAG Fact Sheet 01 (HERAG, 2007[52]), which contains information about the underlying measured data supporting the dermal model. Additional information can be found in Fransman *et al*. (2008[51]), regarding data about the efficiency of risk mitigation measures which has been incorporated into MEASE. However, a specific user manual is not available and users are referred to sets of underlying publications. The difficulty score calculated for this tool is 2.2.

3.6 EMKG-Expo-Tool 2.0

3.6.1 Scope analysis

Tool description, domain and assumptions

55. The EMKG-Expo-Tool uses a CB approach to quantitatively estimate and evaluate worker inhalation exposure, and identification of RMM from exposure to solids and liquids. The EMKG-Expo-Tool can be used as a generic tool for assessing and comparing the level of exposure with limit values (OEL), Derived No-Effect Level (DNEL), and it is recommended by the ECHA guidance R.14 as a tool that should be used as an approach for filtering the non-risky workplace situations from those that require detailed attention. The exposure estimate of the EMKG-Expo-Tool is defined by the exposure potential of a substance (based on the amount of substance used and its volatility/ dustiness) and the control approach. Exposure to dust by abrasive techniques, spray, gases, pesticides, fumes, wood dust, welding and soldering are beyond the scope of the tool.

Input and output parameters

56. The input parameters for the tool are substance information, dustiness or volatility (for solid or liquids), amount of material handled, task duration, surface application size, and control strategies. Based on the potential exposure band calculated by the tool and the selected control strategy, the corresponding exposure band is determined (Table 4). Considering the expected exposure level and the DNEL or other reference values, the risk categorisation ratio is estimated.

Table 4. Exposure potential bands of EMKG.

Exposure band		Material type	Exposure Potential Band			
			1	2	3	4
Control Strategy	1	Solid (mg/m³)	0.01-0.1	0.1-1	1-10	>10
		Liquid (ppm)	<5	5-50	50-500	>500
	2	Solid (mg/m³)	0.001-0.01	0.01-0.1	0.1-1	1-10
		Liquid (ppm)	<0.5	0.5-5	5-50	5-500
	3	Solid (mg/m³)	<0.001	0.001-0.01	0.01-0.1	0.1-1
		Liquid (ppm)	<0.05	0.05-0.5	0.5-5	0.5-5

Source: modified from DOI 10.21934/baua:praxis20180801.

3.6.2 Accessibility and support

57. The EMKG-Expo-Tool is a generic easy-to-use Java TM Desktop application, originally developed to help small and medium-sized companies derive a tier 1 inhalation exposure value for the workplace. It requires only three input parameters, and its simple structure enables the user to distinguish quickly between critical and non-critical workplace situations. The tool offers a simplified approach to evaluate worker exposure and identify RMMs requiring a small number of input parameters. A new revised and improved software version is now available at https://www.baua.de/EN/Topics/Work-design/Hazardous-substances/REACH-assessment-unit/EMKG-Expo-Tool.html. The new version improves accessibility and support by way of providing a comprehensive user guide, built-in help features and an interactive user interface. User help functions are available during tool usage via help texts. The tool also allows the user to generate a report of the results of the assessment of the exposure scenario which can be exported as a pdf file and saved to an inventory accessible for the user. The user must refer to external control guidance sheets, which can be obtained from the COSHH Essentials homepage (https://www.hse.gov.uk/coshh/essentials/index.htm) and partly the BAuA homepage (German version). The control guidance sheets contain detailed information concerning the use description and implemented RMM that have to be followed in order to ensure an appropriate estimation of exposure. The difficulty score calculated for this model is 1.4.

3.7 EGRET 2.0

3.7.1 Scope analysis

Tool description, domain and assumptions

58. EGRET has been developed to assess the potential risk of exposure to consumers and workers under the REACH legislation. The tool estimates exposure to liquids containing solvents through dermal, oral and inhalation routes, providing risk categorisation ratio (RCR) for each route. EGRET is based on the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (TRA version 2, consumer module) but includes additional refinements.

59. The tool assumes that 100% of the amount of product used on during a spray scenario is released into the air.

Input and output parameters

60. Main input parameters are physical/chemical properties of the substance (molecular weight and vapour pressure), DNEL reference values, and optionally select one of the three RCR. The user can also

select from several Specific Consumer Exposure Determinants (SCEDs), which are sets of refined exposure determinants to be used as input parameters in exposure tools to obtain more realistic exposure estimates. If necessary, the user can modify the default value of one parameter and compensate for this variation by changing the value of another parameter to ensure the safe use of the product (ingredient, surface contact area, dilution factor, dermal factor, amount swallowed, amount used per vent and inhalation factor). Parameters that cannot be modified are frequency, exposure duration, place of use, and oral transfer factor. Exposure output is provided in mg/kg/day for oral and dermal exposure, and 24-h TWA in mg/m^3 for inhalation exposure. Risk assessment is provided in form of RCR.

3.7.2 Accessibility and support

61. EGRET is presented in the form of a nine worksheet Excel®, and its user manual is available for download, free of charge, at http://www.esig.org/en/regulatory-information/reach/ges-library/consumer-gess. The quickness of use reflects the minimum input parameters, DNEL banding approach, and excel macro functions that enable auto-populating of operation conditions (OCs) and RMMs into the exposure narratives. The generic exposure scenario concept implemented within the tool was found to be particularly useful, enabling public assessment of numerous substances and products without disclosure of confidential information. The difficulty score calculated for this tool is 1.6.

3.8 Dermal Advanced Reach Tool (dART)

3.8.1 Scope analysis

Tool description, domain and assumptions

62. The dermal advanced reach tool is a mechanistic dermal exposure model especially designed for hand exposures to low volatile liquids including solids-in-liquid products occurring during synthesis, manufacturing and use of chemicals in workplaces. The model is based on an existing conceptual dermal source-receptor model that has been integrated into the ART framework, and various components of DREAM (Goede, et al., 2019; Figure 3). The model adopts two features from ART, i.e. independent principal MFs and activity classes (ACs) of structured groups of occupational activities. Three key processes involved in mass transport associated with dermal exposure are applied, i.e. deposition, direct emission and contact, and transfer. For deposition, the model adopts all the relevant MFs applied in ART. In terms of direct emission and contact (e.g. splashes) and transfer (e.g. hand-surface contacts), the model defines independent principal MFs, i.e. substance related factors, activity-related factors, localized- and dispersion control and exposed surface area of the hands. To address event-based exposures as much as possible, the model includes crucial events during an activity (e.g. hand immersions) and translates objective information on tools and equipment (manual or automated) to probable events (e.g. splashes) and worker behaviours (e.g. surface contacts). Based on an extensive review of peer-reviewed literature and unpublished field studies, multipliers were assigned to each determinant and provide an approximated (dimensionless) numerical value. In the absence of (sufficient) evidence, multipliers were assigned to determinants based on physical laws complemented by assumptions made during discussions by experts in the consortium.

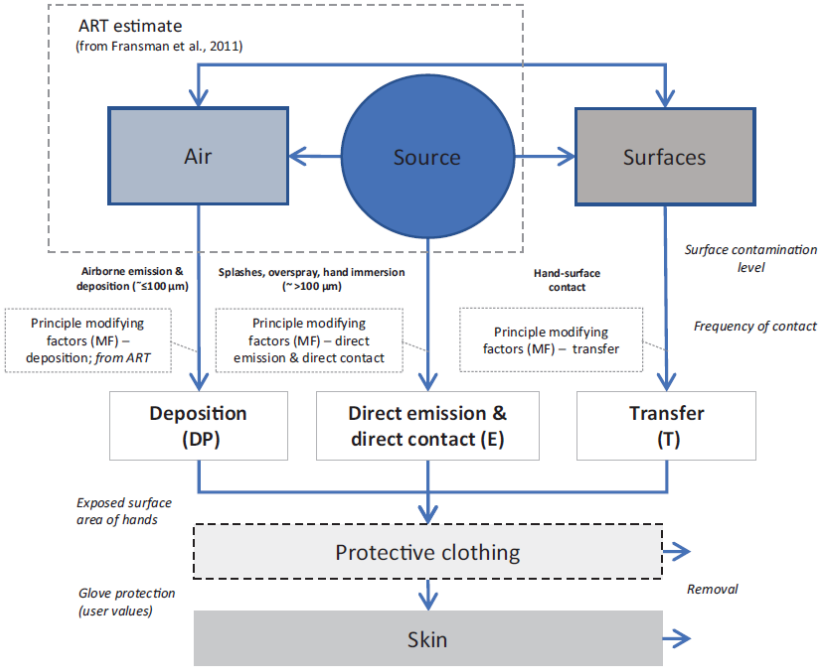


Figure 3. Simplified diagram of dermal exposure with key compartments of the ART model.

Source: Goede et al., 2019 (DOI: 10.1093/annweh/wxy106).

63. The tool assumes that the air concentration is representative of the dermal exposure via deposition, that direct emission and contact is only relevant when a source is located in the NF of the worker, and that low volatile products will always be available due to an almost continuous renewed availability during application of a product.

Input and output parameters

64. The tool considers the ART input parameters, which are extended with a number of additional dermal-specific determinants. Main input parameters are weight fraction of active ingredient, local controls (protection factor, enclosure, exhaust) temperature, vapour pressure, viscosity, type of activity, use rate, direction of application, spray technique, local control, spray room, level of automation, spray pressure, surface shape and exposed surface area.

65. The tool is an activity-specific model that, if taking into account the non-exposure time during a working day, could be used to estimate an overall TWA dermal exposure for a single task within a working day or shift. Exposure results are provided in terms of loading rate on the hands (i.e. mg min^{-1}) per activity which is transformed into mass loading estimate (i.e. mg/cm^2 or mg/hands) by considering the exposure duration. The model does not facilitate combining multiple activities into a single work shift estimate. Removal processes, such as handwashing, are not included in the model.

3.8.2 Accessibility and support

66. From a tool user perspective, the ART user input parameters are merely extended with a limited number of additional dermal-specific determinants. Nevertheless, the translation of the model into everyday

workplace scenarios under REACH could still remain a challenge since the model is prescriptive in character and it will require the implementation of dermal-specific model determinants. A detailed workflow with examples, like that developed for the ART model before software development, will be required (Goede et al., 2019[20]; McNally et al., 2019[21]).

3.9 Stoffenmanager 8.3

3.9.1 Scope analysis

Tool description, domain and assumptions

67. Stoffenmanager is a risk prioritisation web-based tool to assess exposure to chemical substances in occupational environments. The tool provides a quantitative output for the inhalation exposure part and CBs for inhalation and dermal exposures, which helps to prioritise the health risks of working with hazardous products in the workplace and determining effective control measures.

68. The exposure model used for the classification into exposure bands is based on the model presented by Cherrie and Schneider (1999[53]), which was based on earlier work by Cherrie *et al.* (1996[54]). The exposure algorithm follows a source-receptor approach and incorporates MFs related to source emission and dispersion of contaminants (Marquart et al., 2008[22]). Exposure is represented as a multiplicative function of type of handling, intrinsic properties of the product, local controls and general ventilation. For the CB part, Stoffenmanager combines the hazard information of a product with an estimate of exposure by inhalation or skin contact (Table 5). If risks are identified, control measures can be selected. By combining the hazard and exposure bands the tool provides a risk or priority band. Stoffenmanager also enables the user to design a risk reduction scenario or control scenario and a new priority band is assigned based on the modified input parameters.

Table 5. Risk matrix in Stoffenmanager.

Risk band		Hazard band				
		A	B	C	D	E
Exposure band	1	3	3	3	2	1
	2	3	3	2	2	1
	3	3	2	2	1	1
	4	2	1	1	1	1

Note: Hazard: A = lowest hazard and E = highest hazard; exposure 1 = lowest exposure and 4 = highest exposure; overall result: 1 = highest priority and 3 = lowest priority. Source: modified from Marquart et al., 2008 (DOI: 10.1093/annhyg/men032).

69. Stoffenmanager inherently assumes that exposure is linearly dependent on the fraction of a substance in a mixture. To simplify, it is assumed that the same handling and local control measures are conducted in the FF as in the NF. In addition, no distinction is made between one or multiple co-workers in the FF or continuous presence/part time presence of co-workers. The calculated exposure score is based on the assumption that a task is being performed during 8 h a day with a frequency of 5 days per week (totally 40 h per week). If a task is being performed during fewer hours per day and/or in a lower frequency, a linearly proportional reduction is used.

Input and output parameters

70. Information required by the tool is name of the product, publication date of the SDS, whether the substance is a solid or a liquid (for solid, the dustiness is required and for a liquid, the vapour pressure),

supplier of the product, departments in which the product is used, composition of the product (according to the SDS), hazard categories (i.e. symbols according to the SDS), PPE and ventilation needed (according to the SDS), and risk and safety phrases for the product according to the SDS (i.e. not for the individual components).

71. For the exposure output, Stoffenmanager estimates the worst-case task concentration, (90-percentile) as well as other percentiles of the exposure distribution (e.g. 50, 75 or 95-percentile). Subsequently, the daily average concentration can be calculated for one or more tasks. Exposure concentrations are given for substance and chemical components which can be compared with OEL values. For risk assessment, the tool provides risk or priority bands (Table 4).

3.9.2 Accessibility and support

72. The tool is a web application available at https://stoffenmanager.com/ in four different licences, Basic (free), Product+, Risk+ and Premium. Stoffenmanager® Basic is free of charge and is suitable for new users and small and medium-sized companies with a limited number of products (a maximum of 35 products and 35 risk assessments). For these free license users, Cosanta B.V. provides basic support (helpdesk) and complimentary webinars free of charge. The difficulty score calculated for this tool is 1.6.

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

3.10.1 Scope analysis

Tool description, domain and assumptions

73. Engineered Nanoparticle Airborne Exposure Tool, developed under the CONTAM program, is intended to estimate air concentrations and surface loading of airborne nanoparticles in order to provide inhalation and dermal exposure of consumers and workers. The tool is a single-zone model, based on the NIST multizone modelling software CONTAM. The model implements a simple air handling system that provides supply air to and removes return air from the zone. The supply and return airflow rates, and the outdoor air fraction are user input parameters, and the model determines the resulting zone air balance. 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.

Input and output parameters

74. The exposure condition-related input parameters include room geometry (volume, floor area, wall area, ceiling area, penetration factor), ventilation (supply airflow rate, return airflow rate, percent outdoor air, air change rate, outdoor air filter), emission source (source type, release rate, emission time), occupant exposure, initial concentration and surface loadings, resuspension rate (floor, wall, ceiling), and resuspension area (floor, wall, ceiling). The particle-related parameters include particle diameter and density, and particle deposition velocities (floor, walls, and ceiling).

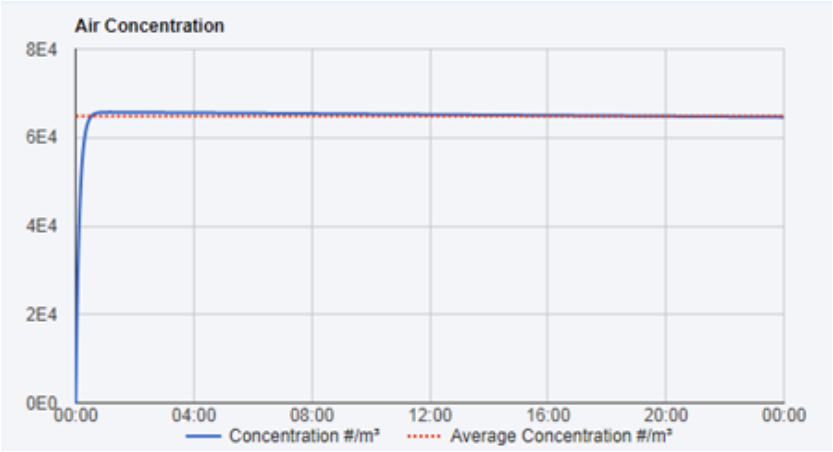


Figure 4. Time evolution of air concentrations (blue) and average air concentrations (red) estimated by Engineered Nanoparticle Airborne Exposure Tool.

75. The outputs of the tool are time average of air concentrations and surface loading, expressed in number of particles per volume and number of particles per area, respectively. As shown in Figure 4, the tool also provides a graphical representation of time evolution of air concentrations.

3.10.2 Accessibility and support

76. Engineered Nanoparticle Airborne Exposure Tool is a free access tool implemented in a web-based user interface and easy-to-use. The tool is available from the following link https://pages.nist.gov/CONTAM-apps/webapps/NanoParticleTool/index.htm, and it can be used as a program or web-based application. With regards to the availability of input parameters, the exposure-condition relevant parameters can be determined from generic exposure factor documents. Values of the resuspension-related parameters can be assumed 0, as they are negligible in the case of MNMs. For the particle-related parameters, values for particle diameter and density can be determined from open sources (e.g., literature, manufacturers, suppliers, and laboratories) while values for the particle deposition velocities may not be easily available. The difficulty score calculated for this tool is 2.4.

3.11 Control banding (CB) Nanotool v2.0

3.11.1 Scope analysis

Tool description, domain and assumptions

77. The CB Nanotool was primarily developed to protect researchers at the Lawrence Livermore National Laboratory by enabling precautionary qualitative risk assessment. It is a simplified approach for experts and non-experts and accounts for factors determining the extent to which occupational workers and consumers may be potentially exposed to MNM through inhalation. The CB Nanotool is primarily intended to address powder handling and synthesis scenarios for evaluating the emission potential, which are not scenarios relevant to consumer exposure. However, owing to its evaluation procedure, there is a possibility that the tool's exposure module could be applied for spraying scenarios and subsequently consumer exposure assessment of MNM.

Table 6. Matrix of control bands/risk level (RL) derived by combinations of severity and probability scores of CB Nanotool.

Control bands		Probability			
		Extremely unlikely (0-25)	Less likely (26-50)	Likely (51-75)	Probable (76-100)
Severity	Very High (76-100)	RL 3	RL 3	RL 4	RL 4
	High (51-75)	RL 2	RL 2	RL 3	RL 4
	Medium (26-50)	RL 1	RL 1	RL 2	RL 3
	Low (0-25)	RL 1	RL 1	RL 1	RL 2

Input and output parameters

78. As shown in Table 6, the output of the tool is 4 control bands in form of risk level (RL) derived by a combination of severity and probability scores in a two-dimensional decision matrix, ranking from lower RL1 to higher RL4. The severity and probability scores represent hazard and exposure scores respectively. The tool estimates an emission probability and a severity (hazard) score, and provides advice on what engineering controls to use. The hazard band is determined by the severity score. The severity score is based on a number of factors; surface reactivity, particle shape, particle diameter, solubility, carcinogenicity, reproductive toxicity, mutagenicity, dermal toxicity, asthmagenicity and toxicity, carcinogenicity, reproductive toxicity, mutagenicity, dermal toxicity and asthmagenicity of the parent material. To estimate the probability score, the CB Nanotool evaluates the emission potential of the product through summation of five exposure factors, where each factor is encoded to a point according to the CB Nanotool Classification Matrix. These factors, which are input parameters required by the tool, include the amount of product used during task, dustiness, number of employees with similar exposure, frequency of operation, and operation duration. Output for exposure assessment is a score between 0-100.

3.11.2 Accessibility and support

79. The CB Nanotool is a free access tool implemented in an Excel-based user interface and easy-to-use. The tool can be downloaded from the following link: http://controlbanding.net/Services.html. With regards to the availability of input parameters, the scores of the amount of product used, frequency of operation and operation duration parameters can be determined from generic exposure factor documents. Score of the dustiness parameter (e.g., high) can be determined based on judgment of relative dustiness/mistiness level. The difficulty score calculated for this tool is 1.4.

3.12 LiCARA nanoSCAN v1.0

3.12.1 Scope analysis

Tool description, domain and assumptions

80. LiCARA nanoSCAN is intended to address both the benefits and risks of new NEPs when compared to non-NEPs along their life cycle. It may also be used to re-evaluate existing NEPs in order to improve them. The tool is addressed to decision makers in the value chain and covers risks and benefits considering seven modules:

- nanoparticle and legislation (type of materials and application, nano-relevance and legislation)
- environment (considers manufacturing, use and end-of-life)
- economy (market potential, profitability, development stage)

- society (technology break through, highly qualified labour, global health or food)
- public health and environmental risks (system knowledge, potential effect, potential input environment)
- occupational health (exposure potential and hazard)
- consumer health (exposure potential, exposed population and hazard)

81. The assessment is based on the location of the nanomaterial in the product, and the potential for exposure to the nanomaterial in the product or article during intended use and expected modification. The tool assumes that exposure potential depends on the location of the nanomaterial in the product. In relation to the consumer risks, LiCARA nanoSCAN uses the NanoRisKCat exposure module for the consumer assessment, and Stoffenmanager Nano hazard module for the hazard assessment. Similar to NanoRiskCat, the tool categorizes products into four exposure classes by assessing the "*location*" of MNM in the product without considering exposure routes and scenarios, and three risk classes. Public health and environment, nanoproduct and legislation modules are assessed by using the Precautionary Matrix. Owing to this, SA and performance testing are not performed on this tool.

Input and output parameters

82. As shown in Figure 5, the output of LiCARA nanoSCAN is a two-dimensional graph derived from the combination of risks and benefits scores. The risk score is obtained by evaluating environmental, occupational, and consumer risks, where each risk is estimated as a function of exposure potential and hazard.

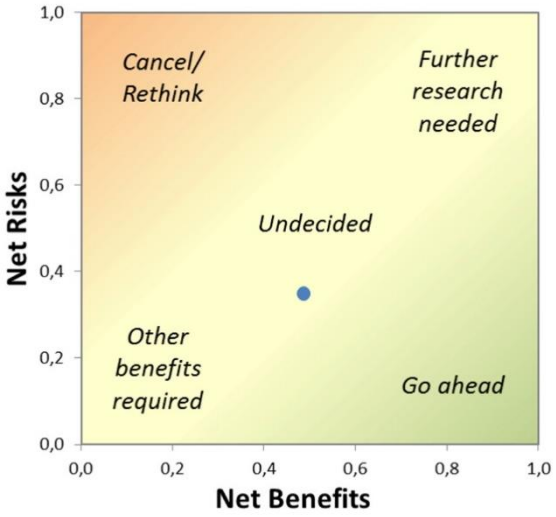


Figure 5. LiCARA nanoSCAN output derived from the combination of risks and benefits scores.

3.12.2 Accessibility and support

83. LiCARA nanoSCAN is a free access tool, implemented in a web-based user interface and easy-to-use. The tool is available from the following link: https://diamonds.tno.nl/licara/. With regards to the availability of input parameters, information on the location of MNM in the product can be easily determined based on understanding of the location of MNM in the chemical substance. The user can also use the following document "*Categories and hazard identification scheme of MNM"* which provides guidance on how to determine the location of the MNM in the product. It is a generic tool and thus it does not require detailed information on specific MNMs and NEPs. Guidelines with a systematic step-by-step procedure can be downloaded from https://www.empa.ch/web/s506/licara. As the tool uses already existing tools, experience

from using is different for each module. However, in general, the tool is easy to use by using the drop down menu. Most complex part is the one assessed by Stoffenmanager nano. The difficulty score calculated for this tool is 1.4.

3.13 NanoSafer v1.1β

3.13.1 Scope analysis

Tool description, domain and assumptions

84. NanoSafer is a CB tool developed to address risks associated with occupational inhalation exposure during production and use of MNM. The tool provides RLs expressed in control bands by combining hazard assessment and case-specific exposure potentials. NanoSafer provides a risk evaluation in the NF and FF, in which the NF is defined as a space (<2 m) around the source and FF as the remainder of the area.

Table 7. Matrix of risk levels (RL) derived by combinations of hazard and exposure bands of NanoSafer.

Control bands		Toxicity			
		0.76-1.00	0.51-0.75	0.25-0.50	0.00-0.25
Exposure	>1.00	RL 5	RL 5	RL 5	RL 5
	0.51-1.00	RL 5	RL 5	RL 4	RL 4
	0.26-0.50	RL 5	RL 4	RL 4	RL 3
	0.11-0.25	RL 4	RL 4	RL 3	RL 2
	<0.11	RL 4	RL 3	RL 2	RL 1

85. For the hazard evaluation, the tool considers MNM properties (water solubility, aspect ratio and presence of coatings), risk sentences and OEL of the nearest bulk analogue compound if no nano-specific limit value can be used. To allocate the exposure band, the tool first estimates the time evolution of air concentrations of MNM by using a two-box model to estimate exposure potentials in the NF and FF assuming instant mixing, and then scales the estimated values using the volume-specific surface area of the nearest analogue bulk material. The beta version is a modified version in development since version 1 described in Kristensen et al. (2010[26]).

Input and output parameters

86. The input parameters required by the tool for allocating the exposure bands include relative density and specific surface area of MNM, constant release rate, volume of the room, ACH, duration of the task, and OEL for analogue bulk material. According to the literature review, the tool generally addresses exposure assessment of powder handling and fugitive/point emissions. Owing to this and the evaluation algorithm, the NanoSafer exposure module could be applied to estimate the air concertation of MNM for powder and spray scenarios, where MNM is released into the air.

87. The output of the tool is 5 risk bands with associated risk management recommendations for acute (15 min) and 8-hour NF and FF exposure. As shown in Table 7, the risk bands are derived from a combination of hazard and exposure bands in a two-dimensional risk matrix, ranking from RL1 (low) to RL5 (high).

3.13.2 Accessibility and support

88. NanoSafer is a free access tool implemented in a web-based user interface and easy-to-use, primarily intended for small and mid-size enterprises (SMEs). The tool is available from the following link: http://www.nanosafer.org/Login . Membership is needed in order to access the tool. The membership is free

and can be obtained directly on the website. A short user guide is available from the member zone. With regards to the availability of input parameters, values for the volume of the room, ACH, and the duration of task parameters can be determined from generic exposure factor documents. Value for the constant release rate parameter may not be easily available and is provided as an estimate or known value. The physical and chemical information can be obtained from technical data sheets, manufacturers or suppliers. Potential missing values on e.g., water solubility and relative density can be obtained from open literature or web-based sources. In absence of size and surface area data the tool will provide more conservative assessments. The difficulty score calculated for this tool is 1.6.

3.14 GUIDEnano tool

3.14.1 Scope analysis

Tool description, domain and assumptions

89. The GUIDEnano tool is intended to assess human (consumers and workers) and environmental health risks of NEPs along their life cycle. The tool includes a database of around 200 exposure activities with default parameters, and addresses dermal, oral and inhalation exposure. The tool is based on computational exposure models. Fate models (e.g., the IOS dispersion model), are implemented in the tool to estimate concentration of MNM in outdoor compartments.

Input and output parameters

90. The input parameters required by the GUIDEnano tool for the estimation can be divided into two groups: (1) exposure condition-related parameters and (2) MNM/product relevant parameters. The exposure condition-related parameters include operational time and frequency, room geometry, ACH, ventilation rate, amount of product used, room temperature and pressure, and PPE used. The MNM/product-related parameters include composition, dustiness, OEL, size distribution, mean diameter, size type (e.g., aerodynamic size, primary size), shape, and density.

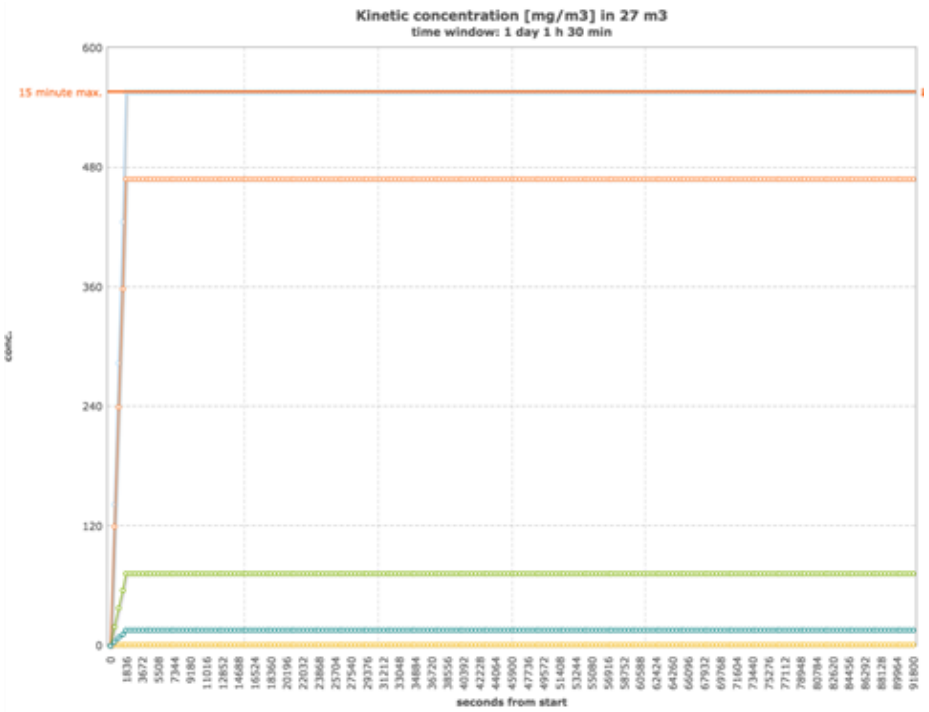


Figure 6. Predicted air concentration of TiO_2 over exposure time for different size ranges with GUIDEnano.

As shown in Figure 6, the tool also provides a graphical representation of air concentrations of MNM over exposure time. In addition, the tool guides the user into appropriate external exposure assessment models based on exposure scenario or route defined by the user. For example, for inhalation exposure, ConsExpo is offered by the tool for the calculation of the air concentration and inhale dose of MNM.

3.14.2 Accessibility and support

91. The GUIDEnano tool is implemented in a web-based user interface and is available from the following link together with a guide tutorial: https://tool.guidenano.eu/. Membership is needed in order to access the tool. With regards to the availability of input parameters, values for the exposure condition-related parameters can be determined from generic exposure factor document or from default values provided by the GUIDEnano tool. For the MNM/product-related parameters, the user can choose values from open sources (e.g., literature, manufacturers, suppliers, and laboratories). It should be noted that if an external exposure model is required, corresponding input parameters are also required. The difficulty score calculated for this tool is 1.8.

3.15 The SUN Decision Support System (SUNDS)

3.15.1 Scope analysis

Tool description, domain and assumptions

92. The SUNDS tool was developed to assess occupational, consumer and environmental risks of MNM along the life cycle of NEPs. The tool offers two levels of assessment. The first assessment level, which is performed by the LiCARA nanoSCAN tool, involves screening risks and benefits associated with MNM. The

second assessment level involves performing quantitative risk assessment of MNM using advanced dose-response, occupational, consumer and environmental exposure models. Six modules are implemented in The SUNDS tool for the second assessment level, which can be used independently. These modules include (1) Ecological Risk Assessment module, (2) Public Health Risk Assessment module, (3) Occupational/Consumer Risk Assessment module, (4) Economic Assessment module, (5) Environmental Impact Assessment module, and (6) Social Impact Assessment module. The Consumer Risk Assessment module incorporates the ConsExpo Nano model, discussed in Section 3.19, for the estimation of inhalation consumer risks of MNM.

Input and output parameters

93. The Input parameters required by the module as well as the output of module and scenarios addressed by the module are the same as those in the ConsExpo Nano model. Owing to this, the SA, performance testing, and validation of ConsExpo Nano will be demonstrated the applicability of the SUNDS tool for assessing consumer exposure to MNMs in a regulatory context.

3.15.2 Accessibility and support

94. The SUNDS tool is implemented in a web-based user interface and is available from the following link https://sunds.dais.unive.it/. Membership is needed in order to access the tool. With regards to availability of the input parameters of the Consumer Risk Assessment module, values for the input parameters can be obtained from the sources used for ConsExpo Nano. Occupational exposure assessment is based on a cloud-link with the basic NanoSafer exposure assessment model and added RMM considering efficacies in provided by the ECEL: Emission Control Efficiency Library for MNMs (Fransman *et al*., 2008). The difficulty score calculated for this tool is 2.4.

3.16 ANSES tool

3.16.1 Scope analysis

Tool description, domain and assumptions

95. The ANSES CB tool was developed to conduct risk assessment and risk management of occupational inhalation exposure to MNM or NEPs in industrial settings during manufacturing or usage. The ANSES CB tool defines the emission potential bands by evaluating the emission potential of the MNM, whether raw or included in a matrix. For the evaluation, it is assumed that the emission potential depends on two factors: (1) the physical state of product, ranging from solid (exposure band 1) to aerosol (exposure band 4), and (2) process operations (i.e., activity emission potential). Basically, the evaluation is performed using the following algorithm: (1) allocating the initial exposure bands based on the physical state of product at the beginning of the process, and (2) modifying the allocated bands if physical state of product is altered due to the process operations. It is noted that the algorithm does not consider the number of workers, frequency and duration of exposure, and the quantity of product. The tool does not account for transmission factors.

Input and output parameters

96. The input parameters required by the tool include the physical state of product and the exposure scenarios arising from process operation activities. The exposure scenarios include handling and transferring of bulk powdered MNM (e.g., bagging or dumping of powder), dispersion of ready-to-use products containing MNM (e.g., spraying), and performing activities resulting in fracturing and abrasion products containing MNM (e.g., sanding of surfaces). Owing to the evaluation algorithm and the exposure activities addressed by the tool, the exposure module of the tool could be applied for qualitative consumer exposure assessment when

exposure occurs through spraying and abrasion scenarios. The tool considers up to five hazard bands, which are defined according to the level of hazard resulting from the analysis of available information. Information may be related to toxicity (suspected or described in literature or technical documentation, ability to cross biological barriers, fibrous nature, biopersistence and chemical properties (surface chemistry, crystalline form, morphology or size).

97. As shown in Table 8, the output of the tool is 5 control bands, derived by combinations of hazard and exposure bands in a two-dimensional decision matrix, ranking from CL1 (control level low) to CL5 (control level high).

Table 8. Matrix of control level (CL) bands derived by combinations of hazard and exposure bands of ANSES.

Control bands		Emission potential bands			
		EP1	EP2	EP3	EP4
Hazard bands	HB1	CL1	CL1	CL2	CL3
	HB2	CL1	CL1	CL2	CL3
	HB3	CL1	CL1	CL3	CL4
	HB4	CL2	CL2	CL4	CL5
	HB5	CL5	CL5	CL5	CL5

3.16.2 Accessibility and support

98. The ANSES CB tool is a free, non-interactive tool and includes decision-making rules available from the following link: https://www.anses.fr/en/system/files/AP2008sa0407RaEN.pdf. Guidance on how to use the tool is available from the link: https://www.anses.fr/en/system/files/-AP2008sa0407RaEN.pdf. With regards to the availability of input parameters, information on the physical state of product can be easily determined from the knowledge of the physical state of the chemical substance. For the exposure scenario, information can be provided from the process operation under which exposure occurs. The difficulty score calculated for this tool is 3.6.

3.17 Swiss Precautionary Matrix v3.0

3.17.1 Scope analysis

Tool description, domain and assumptions

99. The Swiss Precautionary Matrix is a tool that is made to help businesses to assess the need for nanospecific measures (precautionary need) for synthetic MNM and their applications for professional end-users, consumers and the environment. In addition, it helps to identify potential sources of risk in the development, production, use and disposal of synthetic MNM covering the full life cycle. The tool defines a score which is estimated considering nano definition (according to the tool), the potential effect (hazard score), information on life cycle and potential exposure consumer, occupational and environmental. For the consumer exposure, it is assumed that the potential exposure depends on three factors the carrier material of the MNM (air, liquid, solid), where for MNM in the air and liquid media, the type of exposure route considered.

Input and output parameters

100. Based on the previously described factors, the input parameters required by the tool for the estimation of potential exposure include the amount of product used, the type of carrier material, and the frequency of task. The value of each input parameter is a predefined value assigned based on a category chosen by the user from the corresponding categorization matrix detailed in the Precautionary Matrix guidelines document.

101. Based on the output precautionary score, The Swiss Precautionary Matrix classifies the nanomaterials into two risk categories. Nanoparticles with a score below 20 are assigned to class A, and those with a score of 20 or higher are assigned to class B. While class A suggests no concern in relation to the risk management, class B indicates a need for further collection of information or action. Owing to its evaluation procedure and output, the tool could be used in the categorization-based consumer exposure assessment of MNM.

3.17.2 Accessibility and support

102. The Swiss Precautionary Matrix is a free tool implemented in a web-based user interface and easy-to-use. The tool is available from the following link: https://www.bag.admin.ch/bag/en/-home/themen/mensch-gesundheit/chemikalien/nanotechnologie/sicherer-umgang-NMien/-vorsorgeraster-NMien-webanwendung.html. Guidance on how to use the tool is available from the document *"Guidelines on the Precautionary Matrix for Synthetic MNM"*. With regards to availability of input parameters, values for input parameters can be determined from generic exposure factor documents. The difficulty score calculated for this tool is 1.4.

3.18 Stoffenmanager Nano v1.0

3.18.1 Scope analysis

Tool description, domain and assumptions

103. Stoffenmanager Nano is a CB tool developed specifically to manage the potential risk from occupational exposure to MNM. As for the qualitative version of Stoffenmanager, the output of Stoffenmanager Nano is risk bands derived from a combination of hazard and exposure bands in a two-dimensional risk matrix, ranking from 1 (i.e., highest priority) to 3 (i.e., lowest priority). The exposure band is obtained by estimating a relative exposure score described in Stoffenmanager (section 3.9). The score estimated by Stoffenmanager is converted to the exposure bands based on Stoffenmanager Nano categorization matrix. The value of each input parameter is a score assigned based on a category chosen by the user from the corresponding categorization matrix detailed in Stoffenmanager Nano's supporting documentation. For example, if the user selects a category value ranging from 55% to 99% for the weight fraction parameter from the corresponding categorization matrix, the score of the corresponding factor will be 1.

Input and output parameters

104. Input parameters required by the tool include exposure scenarios, dustiness of product, moisture content, weight fraction of MNM in product, room geometry, duration of the task, frequency of the task, ventilation rate, and local control adjustment factor. An assumption made by Stoffenmanager Nano is that the intrinsic emission entirely depends on weight fraction, dustiness, and moisture content. From the evaluation algorithm, it can be found that Stoffenmanager Nano explicitly takes into account exposure scenarios for the estimation. According to Stoffenmanager Nano supporting documentation, the tool

generally addresses four scenarios: (1) MNM synthesis, (2) powder handling, (3) dispersion of ready-to-use products containing MNM, and (4) activities resulting in fracturing and abrasion of products containing MNM. Scenarios 3 and 4 can be related to consumer exposure. Considering μ_{imm} = 1 (i.e., no separation between receptor and source) and $\mu_{\mathrm{ppe}} = 1$ (i.e., no PPE used), Stoffenmanager Nano could be applied for consumer exposure assessment of MNM when exposure to consumer products occurs through the scenarios 3 and 4.

3.18.2 Accessibility and support

105. Stoffenmanager Nano is a free access tool implemented in a web-based user interface. The tool is available from the following link: https://nano.stoffenmanager.nl/. With regards to availability of input parameters, values for ventilation, room geometry, duration of task, and frequency of task parameters can be determined from generic exposure factor documents. For the weight fraction of MNM in product, dustiness, moisture content parameters, the user can choose values from product description label if applicable, otherwise the user can choose values from open sources (e.g., literature, manufacturers, suppliers, and laboratories). To assign a score to the activity parameter, the user needs to have a clear description of the scenario under which exposure occurs. The difficulty score calculated for this tool is 1.6.

3.19 ConsExpo nano

3.19.1 Scope analysis

Tool description, domain and assumptions

106. The ConsExpo nano tool was developed to estimate inhaled dose and alveolar load of aerosol containing MNM from spray products in consumers. It is a physics-based, mechanistic model (Delmaar and Bremmer, 2009[39]). The tool provides the user with two scenarios: (1) spray scenario, where the air concentration of the aerosol is estimated by the tool, and (2) custom scenario, where the air concentration of the aerosol is provided by the user. In order to estimate air concentrations in the spray scenarios, ConsExpo nano uses the model implemented in the ConsExpo tool. For both scenarios, the tool incorporates the ICRP deposition model for estimating deposition of inhaled aerosol in the alveolar region and provides results of a hazard study in rat using Multiple-Path Particle Dosimetry (MPPD) models for comparison if needed.

Input and output parameters

107. The input parameters can be divided into four groups: (1) exposure condition-related parameters, (2) product-related parameters, (3) aerosol-related parameters, and (4) MNM- relevant parameters. The exposure condition-related parameters include exposure duration, mass generation rate, spray duration, room geometry, and inhalation rate. The product-related parameters include weight fraction of MNM in product and airborne fraction. The aerosol-related parameters include density and diameter of aerosol particles, type of diameter distribution. The MNM-related parameters involve the density, diameter and shape of MNM, type of distribution, and dissolution rate for soluble MNM. For the estimation of inhaled dose, the tool assumes that MNM is released as part of aerosol, and the aerosol particles are transported through the respiratory tract. The tool also assumes that the aerosol particles only consist of MNM, and no other components are present. The aerosol particles remain unchanged during inhalation, and they only change when deposited in the alveolar region due to dissolution. Based on the models implemented in the ConsExpo nano tool, the tool could be applied for predicting consumer inhalation exposure to MNMs released from spray products. Thus, the tool will be subjected to SA, performance testing, and validation.

108. For both scenarios, the output dose levels can be expressed as per event in any of the seven metrics: (1) mass, (2) number of aerosol particles, (3) surface area of aerosol particles, (4) volume of aerosol particles,

(5) number of primary MNM, (6) surface area of primary MNM, and (7) volume of primary MNM. As shown in Figure 7, the tool also provides a graphical representation of inhaled dose and alveolar load of MNM over exposure time.

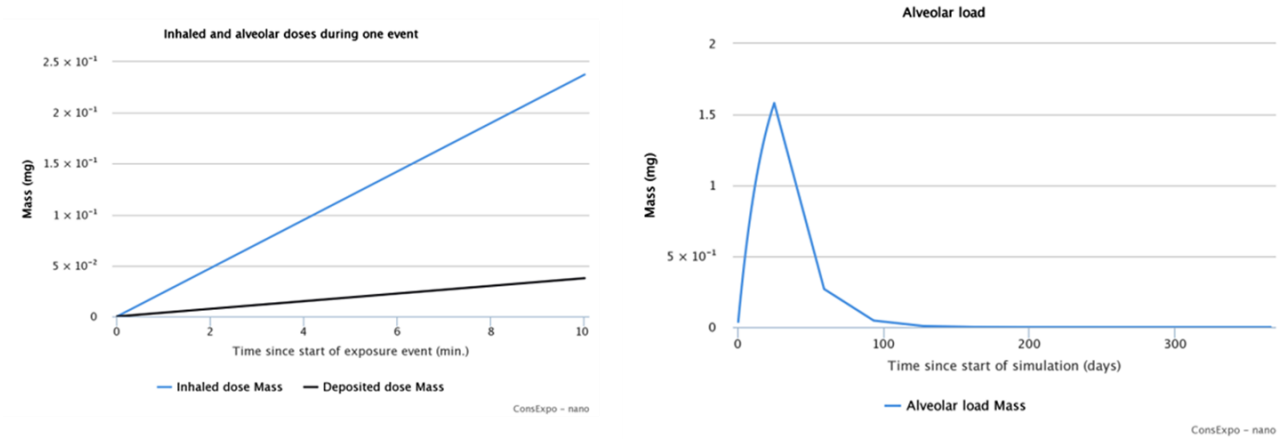


Figure 7. Graphical representation of inhaled dose and alveolar load over exposure time in ConsExpo nano.

3.19.2 Accessibility and support

109. ConsExpo nano is a free access tool implemented in a web-based user interface and easy-to-use. The tool is available from the following link: https://www.consexponano.nl/. With regards to the availability of input parameters, values for the exposure condition and product relevant parameters, except for the mass generation rate parameter, can be determined from the generic exposure factor documents and product description label respectively. Value of the mass generation rate parameter may not be easily available. For the aerosol-related parameters, the user can choose values from laboratory testing. For the MNM-related parameters, the user can choose values from open sources (e.g., literature, manufacturers, suppliers, and laboratories). The difficulty score calculated for this tool is 1.6.

3.20 ConsExpo

3.20.1 Scope analysis

Tool description, domain and assumptions

110. ConsExpo is a web-based tool that enables the estimation and exposure assessment via inhalation, the skin or oral intake to chemical substances (i.e. paint, cleaning agents and personal care products). The ConsExpo program implements a set of process models (of both screening models and higher tier models) that facilitate the estimation of chemical exposure arising from the indoor, non-professional use of consumer products. The program contains algorithms which have also been included in the EU revised Technical Guidance Document on Risk Assessments (ECB, 2003[55]). For all routes of exposure, ConsExpo Web offers models of increasing complexity, from simple, rough estimate models to more detailed mechanistic models. The simple, first order models require only limited, general information, whereas the more advanced models often require very specific data that may be hard to obtain.

111. The tool assumes that the product is applied to skin instantaneously for dermal exposure, and direct uptake of the compound from a product that is swallowed for oral exposure.

Input and output parameters

112. General information required by the tool is frequency of use, body weight, amount or concentration of product (and fraction of the compound), exposure duration, room volume and ventilation rate. For vapour and spray inhalation exposure, application duration, release area, mass transfer rate, molecular weight, cloud volume, mass release rate, airborne fraction, density, particle distribution and inhalation cut-off diameter are also required. More details on equations and requirements of the models can be found in Delmaar, Park and Engelen (2005)[24] and in "*ConsExpo Web. Consumer exposure models - model documentation: Update for ConsExpo Web 1.0.2 (doi: 10.21945/RIVM-2017-0197)*". The output is provided as internal and external exposure dose per body weight.

3.20.2 Accessibility and support

113. ConsExpo tool, general information, manual, publications or frequently asked questions are available at https://www.rivm.nl/en/consexpo. In newer version, the tool was also made available as web-based and exposure estimations can be imported into Chesar (CHEmical Safety Assessment and Reporting tool developed by ECHA) through a ConsExpo Web export file. Information about circumstances under which consumers are exposed to chemical substances from consumer products is available in fact sheets. For several product categories, default parameter values are provided which can be used as a basis for the calculations in ConsExpo Web. The difficulty score calculated for this tool is 1.

3.21 Advanced REACH Tool v1.5

3.21.1 Scope analysis

Tool description, domain and assumptions

114. The Advanced Reach Tool (ART) was developed to estimate inhalation exposure to vapours, mists, dust and metal fumes in the workplace. As represented in Figure 8, the ART tool is based on a source-receptor approach (Fransman et al., 2011[40]), which describes the transport of a contaminant from the source to the receptor. The calculation is conducted using an in-built database of class activities with measurement data and Bayesian statistics. The model also has the ability to update the estimates with the user's own data The tool defines independent principal MFs (i.e. substance emission potential, activity emission potential, localized controls, segregation, personal enclosure, surface contamination, and dispersion), which are estimated from input parameters (i.e. for substance emission potential of powders dustiness, moisture and weight fraction are considered). The workspace is divided into two compartments, the NF (within 1 m from the worker's head) and the FF (comprising the remainder of the workspace). Personal exposure from a NF source is a multiplicative function of substance emission potential, activity emission potential, (primary) localized controls e.g. wet suppression and LEV, and dispersion. The algorithm for a FF source also includes segregation and personal enclosure/separation. The level of surface contamination for each activity depends on the location of the source, i.e. NF, FF, or both. Details of equations are described in Fransman *et al*. (2011[40]). The tool assumes that exposure determinants for the analogous scenario relevant to the ART mechanistic model are similar to those pertaining to the user's scenario. The overall exposure is estimated by an algorithm that considers multiple activities and exposure time to calculate an 8-h work shift or long-term exposure periods with assumingly zero exposure.

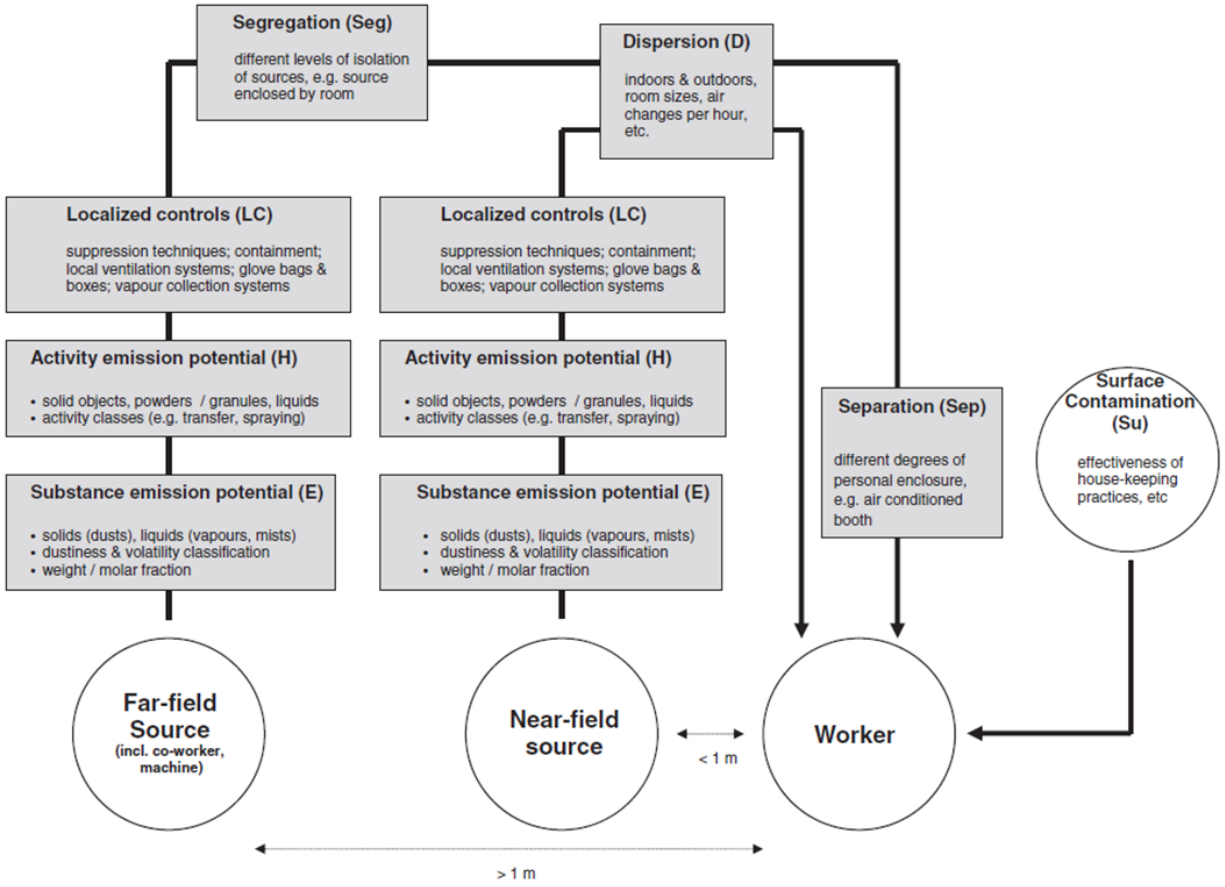


Figure 8. Flow diagram of the ART model.

Source: Fransman et al., 2011 (DOI : 10.1093/annhyg/mer083)

Input and output parameters

115. The tool requires numerous inputs and they vary with the different selections. A full and detailed description of the tool inputs is described in the performance testing report. In summary, main inputs required are chemical name, CAS n, duration of the activity, product type (powder, liquid, powder in liquid…), dustiness, moisture content, process temperature, vapour pressure, boiling temperature, activity coefficient, viscosity, powder/liquid weight fraction, whether or not the activity is located in the worker breathing zone, activity class, description of activity situation and type pf handling (e.g. amount of material handled, spray application rate…), selection of localized controls, type of site, size of the room and air changes per hour.

116. The tool provides mass concentrations for full shift or long term exposure in the form of 50, 75, 90, 95 and 99th percentiles. The confidence interval is also provided and user can select between inter-quartile, 80, 90 or 95%.

3.21.2 Accessibility and support

117. The advanced REACH tool is a web-based tool publicly available at www.advancedreachtool.com. Regarding input parameters, most can be easily obtained from manufacturers or suppliers. For those which are more complex to obtain, the tool provides drop-down definitions (i.e. dustiness index, protective

measures). A good knowledge of the workplace scenario under study is necessary. The difficulty score calculated for this tool is 1.6.

3.22 ECOTOC TRA v3.1

3.22.1 Scope analysis

Tool description, domain and assumptions

118. The tool calculates exposure to cleaning agents, coating products, textiles and sprays via inhalation, dermal, and oral routes separately. It is available as an integrated tool that combines worker, environmental, and consumer calculations and as a standalone exposure estimation tool. In ECETOC TRA worker exposure is estimated using, as basis, a scenario-based source-receptor type model (ECETOC, 2012; Figure 9). Data entry occur via the interface or via the datasheets. The initial 8-hour exposure prediction is a function of the fugacity of the substance and its circumstances entered using the PROCs. Afterwards, according to OCs and/or RMM selected, the initial prediction is modified using simple multipliers.

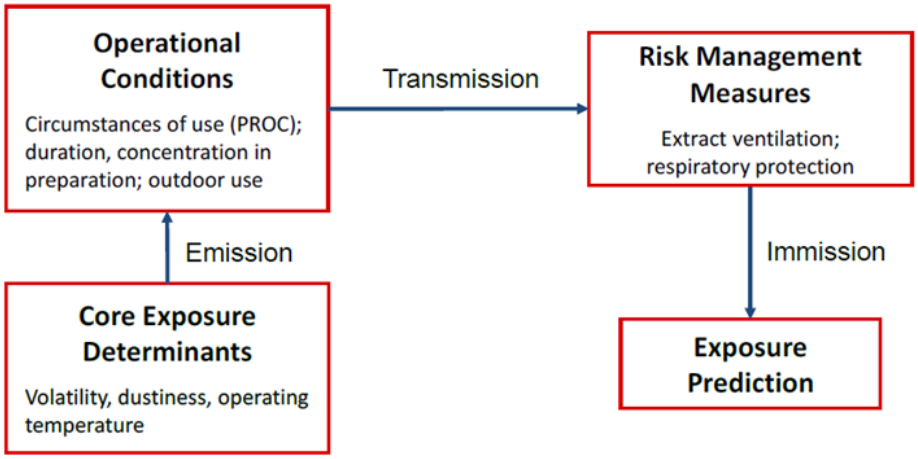


Figure 9. Principle elements of TRAv2 worker inhalation exposure prediction.

Source: ISSN-2079-1526-114

119. It is assumed that the substance transfer to air happens instantaneously and the released substance is homogeneously distributed in the room volume.

Input and output parameters

120. Main input parameters are identification of substance and its general physicochemical characteristic (i.e. molecular weight, vapour pressure, water solubility and the relevant partition coefficients and biodegradability test result), and data entry for worker, consumer and environment assessment. For worker assessment, fifteen different uses can be entered, each with its own combination of PROC, operating conditions and exposure MFs. The tool output is mass-based metrics of inhalation exposure (mg/m^3) and dermal exposure (mg/kg/day). TRA version 3.0 adds short-term inhalation and long-term dermal local exposure.

3.22.2 Accessibility and support

121. ECETOC TRA is meant to be used by a wider user community to make rapid and conservative assessments, which can be used as a first tier to demonstrate low risk for a specific scenario of use. The tool, user manuals and supporting documents are available for download at http://www.ecetoc.org/tools/targeted-risk-assessment-tra/. In December 2010, additional modifications were made in order to improve its accuracy, flexibility and functionalities. The difficulty score calculated for this tool is 2.4.

3.23 NanoRiskCat

3.23.1 Scope analysis

Tool description, domain and assumptions

122. NanoRiskCat is a categorization tool that is applied for communication of knowledge on potential exposure and hazard of nanomaterials in consumers and professional end-users. NanoRiskCat uses a simple framework for assessing the exposure potential, where the exposure is categorized into four different levels: (1) high exposure potential, (2) medium exposure potential, (3) low exposure potential, and (4) unknown due to lack of information. For the categorization, it is assumed that the exposure entirely depends on the location of the MNM in the products (i.e., is the MNM located in the product, on the surface, liquid or airborne), and judgment of the potential for MNM exposure based on the product use description. High exposure potential is assigned to products containing "*nanoparticles suspended in liquids*" or result in "*airborne nanoparticles*" during use, while low exposure potential is given to products containing "*nanoparticles suspended in a solid*". Medium exposure potential is given to products containing *"surface-bound nanoparticles*" or the use description involves mechanical modification by cutting, sanding or grinding.

Input and output parameters

123. The input parameter required by model is the information on the location of the MNM in the products. NanoRiskCat does not include the amount of product used and an evaluation of exposure routes and scenarios for the categorization.

Figure 10. Example of a NanoRiskCat's output of exposure and hazard potential for a given nanoproduct.

124. As shown in Figure 10, the output of NanoRiskCat is five coloured dots. The first three dots refer to the qualitative exposure potential during intended use for workers, consumers and the environment, and the last two dots refer to hazard potential for humans and the environment. Each dot can be assigned one of the four different colours, i.e. red, yellow, green, and grey indicating high, medium, low, and unknown, respectively.

3.23.2 Accessibility and support

125. NanoRiskCat is a non-interactive tool and includes descriptive rules available from the following link https://link.springer.com/content/pdf/10.1007%2Fs11051-013-2195-z.pdf. With regards to the availability of

input parameters, information on the location of the MNM in the products can be obtained based on understanding of the location of MNM in the chemical substance. The user can also use the following document "*Categories and hazard identification scheme of MNM"* which provides guidance on how to determine the location of the MNM in the product. The difficulty score calculated for this tool is 3.4.

3.24 Multiple-Path Particle Dosimetry (MPPD) Model

3.24.1 Scope analysis

Tool description, domain and assumptions

126. The MPPD model was developed to calculate the deposition and clearance of monodisperse and polydisperse airborne particles, ranging from ultrafine (10nm) to coarse (20,000 nm) sizes, in the respiratory tract of rats, and human adults and children. The MPPD model is based on complex, multi-path lung models for particle exposure, in which various lung models for humans of different age groups, such as Yeh-Schum 5-Lobe, are implemented. The underlying algorithm of the model consists of four components: (1) upper respiratory tract (URT) modelling, where impaction and diffusion mechanisms are considered for the deposition, (2) lower respiratory tract geometry, (3) lung ventilation models, and (4) particle transport modelling, where mass balance is used.

Input and output parameters

127. The information required by the model for estimating the deposition can be divided into three groups: (A) airway-morphometry-related information, (B) exposure condition-related information, and (c) particle-related information. The airway morphometry-related information includes functional residual capacity (FRC), URT volume, flow, species (e.g., human), and lung model. The exposure condition-related information consists of gravity, body orientation, air concentration of particles, breathing frequency, tidal volume, inspiratory fraction, and breathing scenario (e.g., nasal, oral). The particle-related information includes density, diameter, type of diameter (e.g., mass median dimeter and count median dimeter), and geometric standard deviation. Considering the intended application of the model, the model could be applied for estimating the deposition of MNM in the respiratory tract of human when exposure occurs through inhalation.

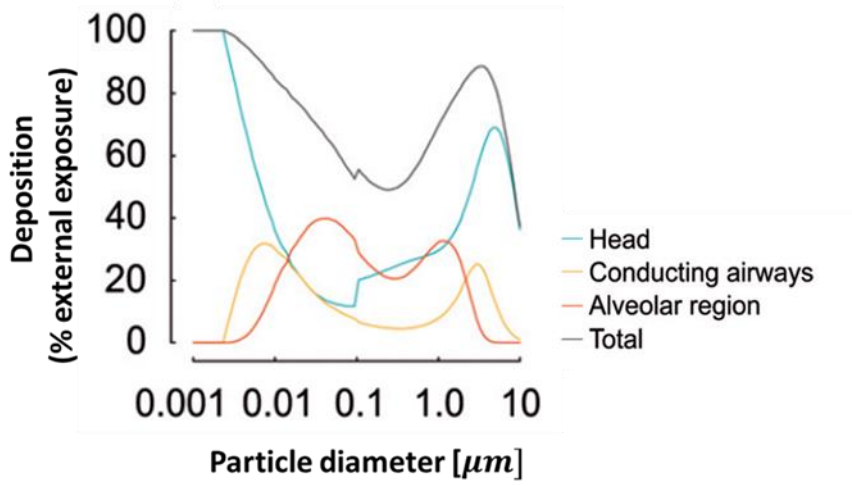


Figure 11. Relative deposition of particles (% external exposure) against their particle diameter [µm] of MPPD.

Note: Relative deposition in head (blue), conduction airways (yellow), and alveolar region (red).

128. The output of the model is the deposition of the particle. The model does not calculate the air concertation of MNM. As shown in Figure 11, the model also provides a graphical representation of size-dependent depositions in three compartments of the respiratory tract: (1) head, (2) conducting airways, and (3) alveolar region.

3.24.2 Accessibility and support

129. The MPPD model is a free access model that needs to be installed on the user's computer. The model (v 3.04) can be downloaded from the following link: https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-304. With regards to the availability of input parameters, values of the airway morphometry-related parameters can be determined from default values that are provided by the MPPD model. For the exposure condition-related parameters, except for the air concentration of particle parameters, the user can choose the values from the generic exposure factor documents or defaults values provided by the model. For the air concentration of particle parameter, the user can use measurement data or output of external models/tools (e.g., ConsExpo Nano) that predict air concentration of MNM. For the particle-related parameters, the user can choose values from open sources (e.g., literature, manufacturers, suppliers, and laboratories). Compared to other models/tools, the MPPD model requires more input parameters, which makes the model less user friendly. The difficulty score calculated for this model is 1.8.

3.25 I-NANO

3.25.1 Scope analysis

Tool description, domain and assumptions

130. The I-NANO tool was developed during the NANoREG project to estimate the time evaluation of air concentration of MNM released from emission sources in work and consumer scenarios. The underlying algorithm of the I-NANO tool is based on a two-box source-receptor model and considering the singularities of MNMs, where the space around the source is defined as a local control Influencing zone (LCIZ), and the remainder of the area is defined as a FF (Sánchez Jiménez et al., 2016[45]). In order to estimate the air concentration over time, the I-NANO tool first defines a number of bins for particle sizes, and then estimates the air concentration of particles in each bin separately for both LCIZ and FF. The I-NANO tool takes into account coagulation and losses through gravitational settling (i.e., particles settling to the floor), diffusion (particles settling on walls and surfaces) and dilution (effect of ventilation) for the estimation.

Input and output parameters

131. The input parameters can be divided into exposure-condition-related and particle-related parameters. The exposure-condition-related parameters include the geometry of a room (i.e., height, width, and length), ACH, emission rate and task duration, whereas the particle-related parameters include the density, geometric mean diameter, and geometric standard deviation. Local controls adjustment was decided to be based on those used in the development of the ART model. Output is provided as air concentration of NPs for a range of size.

3.25.2 Accessibility and support

132. I-NANO is a tool that has been implemented in a web-based user interface http://www.inanotool.com/. However, the webpage is currently inactivated. Owing to this, SA and performance testing are not performed on this tool. With regards to the availability of input parameters, values of the exposure-condition-related parameters can be determined from generic exposure factor documents.

For the particle-related parameters, the user can choose values from open sources (e.g., literature, manufacturers, suppliers, and laboratories).

3.26 Boxall *et al*. 2007

3.26.1 Scope analysis

Tool description, domain and assumptions

133. Boxall *et al*. (2007[46]) presents a dilution model for estimating cumulative exposure from personal hygiene and skin care products for spraying application. The model assumes that the air concentration of MNM diminishes exponentially with the time and air change rate.

Input and output parameters

134. The input parameters include the amount of the product used, proportion of MNM in the product, air change rate, the fraction of product escaping as aerosol, room volume, and time. As reported by Boxall *et al*. (2007[46]), if time is short (e.g., 10 minutes), dilution with air change can be ignored. Considering the equations used for the estimation and the intended application of the model, the model could be applied for consumer exposure assessment of MNM when exposure occurs through spraying scenarios.

3.26.2 Accessibility and support

135. The model presented by Boxall *et al*., is a non-interactive and non-descriptive tool, which makes the model difficult to use, as the tool needs to be coded. With regards to the availability of input parameters, values of the input parameters, except for the proportion of MNM in product, can be determined from generic exposure factor documents. The value of the proportion of MNM in product can be generally obtained from product description label. The difficulty score calculated for this model is 3.8.

3.27 Nazarenko *et al*. 2012 & 2014

3.27.1 Scope analysis

Tool description, domain and assumptions

136. The model used by Nazarenko *et al.* (2012[47]; 2014[48]) estimates inhaled dose of MNMs from consumer sprays and cosmetic powders. The inhalation dose model is based on the work by Hansen et al. (Hansen et al., 2008[56]) but using the size-resolved concentrations of airborne particles released during the realistic application accounting for inhalation.

Input and output parameters

137. The model considers inhalation flow rate (for a giving gender), duration of contact per application, body weight, air concentration particulate matter, mass fraction of MNM in the product, inhalation fraction and particle diameter. It should be noted that the model can be applied to particles up to 100 μm diameter. The tool assumes all substance is released as a gas, vapor or airborne particulate, and does not account for ventilation.

3.27.2 Accessibility and support

138. The model used by Nazarenko *et al*. (2012[47]; 2014[48]) is not implemented in a web/excel –based user interface. Concerning the availability of input parameters, values for inhalation flow rate, duration of contact, and body weight can be determined from generic exposure factor documents. Value of the mass fraction of MNM in the product parameter can be obtained from product description label if applicable. For the size parameter, the user can choose values from open sources (e.g., literature, manufacturers, suppliers, and laboratories). Value for the mass concentration of particulate matter needs to be obtained from measurement data or from the models/tool that predict the air concentration of MNM and additional input parameters may be required. The difficulty score calculated for this model is 4.2.

4 Sensitivity analysis

139. Following the scope analysis and the accessibility and support examination, tools/models were subjected to SA. SA is defined here as a study of model output value variation, when values of model input parameters are changed over a predetermined range. Such testing depends on parameter ranges representing variability in the parameter values. In the SA, the model itself is seen as a black box and the interest is solely on the input and output values and on how changes to an input parameter value affect the output values. Hence, this method can be used even if the model equation or algorithm itself is not known. Furthermore, in case the model algorithm is available, sensitivity could be analysed by evaluating the model equations and inferring the sensitivity from the model structure. SA can provide answers to multiple questions (Hamby, 1994[57]):

1. Which parameters require additional research for strengthening the knowledge and databases, thereby reducing output uncertainty?
2. Which parameters are least sensitive?
3. Which input parameters contribute most to output variability?
4. How does changing of a given input parameter affect the modelling result?

140. In this report, the parameters sensitivities to the tool output are characterized and used to identify the most- and least sensitive parameters on model prediction and possible unexpected behaviour (Riedmann, Gasic and Vernez, 2015[58]).

4.1 Methods used in sensitivity analysis

141. The statistical approaches used for the sensitivity analysis are mathematical tests used to examine the influence that the change of an input parameter has on the output values over a predetermined range. The final purpose is to determine which input parameters exert most influence on output values, which in turn allows elimination of insignificant parameters and provides further knowledge to reduce parameter uncertainties and increase model accuracy. There are many different methods to conduct a sensitivity analysis and they may not produce identical results. In this project, some of the considered most practical methods (Hamby, 1994[57]) for sensitivity analysis were used as described in the following sections. The methods were used to assess the most "*sensitive parameters*", understood as those for which variation has a high influence on output values. It is important to point out the difference with "*important parameters*" which are those whose own uncertainty contributes substantially to the uncertainty of the model as defined in Crick et al. (Crick and Hill, 1987[59]).

142. Overall, models can be sensitive to input parameters in two different ways:

1) the variability, or uncertainty, associated with an input parameter is propagated through the model - **important parameters**

2) model results are highly correlated with an input parameter, small changes in the input value result in high changes in the output - **sensitive parameters**

143. It is important to mention that an "*important parameter*" will always be "*sensitive*" or otherwise variability does not appear in the output, but a "*sensitive parameter*" does not necessarily have to be "*important*" as it may be known precisely. In order to determine "*important parameters*", an uncertainty analysis needs to be conducted, which was not carried out in this work. With the SA methodology used in this project, only "*sensitive parameters*" can be identified independently of whether they are also "*important parameters*" or not.

144. Sensitivity analyses are conducted by generating an input matrix through an appropriate random sampling method and calculating an output vector, and assessing the influences and relative importance of each input/output relationship. The influence of each input/output relationship can be represented by using a sensitivity coefficient, which is the ratio of the change in output to the change in input while all other parameters remain constant (Hamby, 1994[57]). The model result while all parameters are held constant is defined as the "*base case*".

145. One of the major drawback of the type of models used for sensitivity analysis is that the behaviour detected may be localized and not applicable for values far from the base case and the ranges defined in cases where for example, not all range of possible values could be considered and the response of the output is non-linear. Therefore, it is important to have that in mind when analysing and considering the results obtained in the SA. The results from the tests are used exclusively to assess the most and least sensitive parameters for each tool/model as well as to identify possible unexpected behaviours. However, no conclusions are extracted regarding goodness of performance of the tools or predictive capability. This is assessed in the performance testing section, where tools outputs are compared to measured exposures (Part II for occupational exposure and Part III for consumer exposure).

146. The methods used for SA are described in detail below.

4.1.1 One-at-a-time (OAT) with range scanning

147. OAT with range scanning means that the range of each input parameter is scanned by varying one input at a time, with the input range divided in N subranges. Thus, an input parameter with a value range from 0 to 100 would get N values spaced evenly at $X_i = i \cdot 100/N$ (on linear or logarithmic scale). The model is then run N times for each of the X_i, and all other input parameters are kept constant at their mean (most likely) values. The results (output variables, Y) of the model runs are saved together with the input parameters in Excel tables. A measure of sensitivity, called sensitivity index (SI), can be calculated by minimum and maximum output values, $SI = (Y_{max} – Y_{min})/ Y_{max}$, where Y is the output value (Hamby, 1994[57]).

148. This is conceptually the simplest method, where sensitivity measures are determined by varying each parameter while all others are held constant. The factorial design is easy to conceptualize, but its procedure can become quite intensive with larger models. A more powerful test (not conducted here) examines the change in output as each parameter is individually increased by a factor of its standard deviation, taking into account parameter´s variability and associated influence on model output.

4.1.2 One-at-a-time – Monte Carlo (OAT-MC)

149. It is implemented as a module that can perform MC SA on the outputs of the model/tool to assess how they are affected by variations in the input parameters. The proposed methodology uses the notions of OAT as SA practice and MC as sampling practice. OAT consists of the analysis of the effect of varying one model input parameter X at a time while keeping all other fixed. MC analysis is based on performing multiple evaluations with randomly selected model input, where results of these evaluations determine both uncertainty in model predictions and sensitivity of the model output to input parameter.

150. Random sampling of input parameters generates input and output distributions useful in assessing model and parameter uncertainties in a 'global' sense. Distribution effects are meaningful because parameter sensitivity depends on the range and distribution of an individual input parameter, but also on those of other

sensitive parameters (Hamby, 1994[57]) as parameter sensitivity is dependent on the interactions and influences of all parameters.

4.1.3 All-at-once (AAO)

151. In some cases, it may be desirable to explore the model phase space more comprehensively, e.g. to find possible outliers when several input parameters cause simultaneous extreme behaviour. For this, the model outputs can be explored using AAO methodology, in which the model inputs are all varied simultaneously, and sampled using either fully randomly, or using Latin Hypercube Sampling (LHS). The methodology is mostly the same as for the abovementioned OAT-MC method.

4.1.4 Diagnostic method

152. The set of risk assessment models includes models that are based on selecting answers to different question instead of filling in numerical values. These models are identified to be, e.g., binary question-based CB models or decision tree type of models based on solely multiple-choice questions. For these diagnostic models, exploring the input parameters sensitivity should be performed with a system that can deal with binary (yes/no) answers and detect how well such a model performs. This diagnostic method will be applied for ANSES and ISO/TS 12901-2:2014 models.

153. In the diagnostic SA, the tool is used repeatedly to create data for the SA. The process is automatic, and the answer to any model question is picked at random from the Bernoulli distribution. The terms "*success*" and "*failure*" are frequently used to distinguish between the two outcomes of the Bernoulli distribution, and here "*success*" is taken to be an answer that does not lead to increasing the band value. This outcome is given the probability of 80 % at every question. For SA purposes the tool is used twice. The first run creates reference band values to which the values obtained from the second run are compared. On the second run, the model is given a certain probability that the answer to any encountered question is erroneous. This means that the answer to any question is shifted from a yes-answer to a no-answer or conversely at a pre-determined probability. The first run can also be understood as the "*real*" result as if representing the true nanomaterial properties, whereas the second run represents a "*model*" result, where the properties are simulated. The probability of answering erroneously is analogous to errors and uncertainties present in any simulation.

154. The results gained are analysed by comparing the two produced values and by classifying the pairs of results as True Positive (TP), True Negative (TN), False Positive (FP) and False Negatives (FN). These are defined with respect to a control band as

- TP: number of results correctly identified in a band
- TN: number of results correctly identified outside a band
- FP: number of results incorrectly identified in a band
- FN: number of results incorrectly identified outside a band.

155. Then the True Positive rate (TPR), True Negative rate (TNR) and accuracy measures are calculated for each control band. TPR = TP/(TP+FN), TNR =TN/(TN+FP), accuracy = TP+TN/(TP+TN+FP+TN)

156. Finally, this procedure is repeated for several different values of the probability of error. In addition to the investigation method described above ('real' vs 'model'), the path through the questions is traced for each run. This information can be used to illustrate how the tool proceeds through different questions.

4.1.5 Modified OAT analysis employing diagnostic method

157. The second method used to analyse the diagnostic CB tools was an OAT variant, where each question is picked individually and its error rate and answer distribution are varied, while every other question is given default values for these 'parameters'.

158. The ranges of the error rate and answer distribution both cover all possible values, and the default values were chosen to be either 0 or 5 % error rate and 80 % probability of 'success' in the answer distribution. This analysis was done twice to see the effects of the changing default value for the error rate. The outcome of this procedure is an error estimate for the tool calculated as the percentage of misclassified results. Additionally, the effect of the error rate at each question can be calculated theoretically from the error rate and distribution information. These values reflect the responsiveness of a single question to the answer distribution and probability of making an error.

4.1.6 Regression analysis/design of experiments

159. For HRA models which can have both dependent questions as independent questions (like the Stoffenmanager Nano tool for which this method was applied). Dependent questions may or may not be asked depending on the answer to previous questions. Independent questions are asked in all cases. The questions of Stoffenmanager Nano that are required for the inhaled exposure estimate are considered separately from the questions that are required for the hazard characterization. For the estimation of the inhaled exposure and the hazard characterization, the total number of possible outcomes is calculated and an optimal dataset is generated that allows identifying the influence of each question on the tool's output.

160. To reduce the complexity of the SA for the inhaled exposure estimate, the dependent questions are separated from the independent questions by dividing the optimal dataset into two subsets. The first subset takes into account all the independent questions and makes use of an average outcome of the dependent questions, whereas the second subset takes into account all the dependent questions while making use of an average outcome of the independent questions. A regression model is then fitted to each subset to allow the estimation of the contribution of each question to the variety in the exposure scores. Finally, the contributions of the questions in each subset are rescaled to allow for comparisons across the subsets.

4.2 Methods and results of the sensitivity analysis on individual models

161. In this section, SA for each tool is presented individually. The method used to perform the SA, model inputs and outputs, and SA results are described. SA was not performed for EGRET, dART, I-NANO, NanoRiskCat, GUIDEnano, ConsExpo and Stoffenmanager nano because the user interfaces of dART and I-NANO were not available, NanoRiskCat incorporates only one input parameter, EGRET and ECETOC TRA are not appropriate for exposure assessment of MNMs (will not be further considered), and GUIDEnano is too complex, segmented and number of parameters to take into account differ for each specific case. Moreover, SA was not performed for ConsExpo and Stoffenmanager as it was conducted for their corresponding nano versions (ConsExpo nano and Stoffenmanager nano) although they present some differences.

4.2.1 ISO/TS 12901-2:2014 CB nanotool v1.0

Method

162. The ISO/TS CB model (ISO, 2014[60]) is a decision tree type model with yes/no and multiple choice questions. The answers to each question were chosen from a Bernoulli probability distribution, 80/20% for yes/no answers and even distribution for multiple choice answers. The model was first run with given

probabilities for each answer and resulting band values saved. In a second run, the probabilities were changed by introducing a possibility of an error to each question the model user is answering. The resulting control, hazard and exposure bands from the second *erroneous* run was subtracted from the first "*true*" run yielding a value that describes the difference of the bands. The model was run N = 100 000 times to yield a distribution of the band differences. This was repeated five times with the probabilities of error of 5, 10, 30, 50 and 70 % used at the second run, yielding into total number of runs of N = 500 000 for ISO/TS CB model.

Model output and inputs

163. The ISO/TS CB model gives the output in three bands (control band, hazard band and emission band). The SA method applied on ISO/TS CB model did not allow the identification of sensitivity to individual input parameters. Therefore, tables showing input parameters and most and least sensitive input parameters are not presented for this tool.

Results

164. The results show that an increasing error rate leads generally to over-estimated values of the hazard and emission potential band. Furthermore, there is a clear trend of the control band differences concentrating more on the non-negative values. This indicates that in the majority of cases the *true* result is at least as high as the *erroneous* result. Additionally, as the probability of error increases, it becomes more likely for the two values ("*true*" and "*erroneous*") to differ from each other.

165. Table 9 summarizes the percentage of erroneous occurrences for different error rates. The percentages increase for CB, HB and EB with increasing error rate. The percentage for CB increases rapidly from 0 to 50 percent, when the error rate is increased to 30 %.

Table 9. Percentage (%) of erroneous occurrences as a function of the error rate of ISO CB nanotool.

Error rate (%)	CB	HB	EB
5	13	8	11
10	24	16	22
30	49	38	52
50	58	50	68
70	60	56	74

Note: control (CB), hazard (HB) and emission band (EB) difference distributions.

166. Further increase in the error rate has only slight effect on the percentage of erroneous occurrences. In other words, the amount of erroneous occurrences increases more rapidly at lower error rates than at the higher error rates.

167. Unexpected result is that in the occurrence of hazard band differences of -2 and 2 were higher than the ones for -1 and 1. This means that there is higher probability to increase or decrease the hazard band by two bands than by only one band, when an error is introduced to the model. Furthermore, the results for control and exposure bands show opposing results. Since for the control band, there is always lowest probability for the highest increase in the band and highest probability for lowest increase. The SA method applied on ISO/TS CB model did not allow the identification of sensitivity to individual input parameters.

168. In conclusion, the presented results reflect the precautionary principle behind the design of the ISO/TS CB tool. In a majority of cases, the tool should result in a high enough band when compared to the real situation. The effect of the increasing probability of error on the distribution of the control band differences

suggests that the resulting control band is at least as high as it should be. Therefore, the use of this tool to aids risk analyses relating to nanomaterial processing.

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

Method

169. The BIORIMA occupational exposure section is designed to assess exposure in occupational environments to nanobiomaterials. The occupational exposure part is based on the 2-box (NF/FF) as described in Ganser and Hewett (2017[50]) and it requires 10 input parameters. The SA was performed by OAT methodology as described in section 4.1. Base values were selected, according to probable values in occupational scenarios, and variations of ±10, 25, 50, 75, 90 and 99% were considered for diameter, density, used mass, task and generation duration, volume and ACH in order to cover the maximum range of probable values in an occupational exposure scenario. For the input parameters % of MNM and nº of repetitions variations of ±50, 80 and 98% were considered. For the activity class selection, the model has more than 100 options. From those options, only 13 were selected and used for the SA. The 13 selected activities are representative of different typical occupational exposure scenarios. However, this 13 activities represent only a ~10% of the total activity options which may not be sufficiently representative. In total 118 runs were considered for SA.

Model output and inputs

170. The BIORIMA occupational exposure module gives the output in mass in the NF and the FF and in number concentration. The particle number concentration (particles/cm^3) is provided as an approximate number with a limit value of 100000 particles/cm^3, whereas particle mass is provided as an exact mass concentration (mg/m^3) with no concertation limit. All three outputs where considered for the SA. Values used for SA are provided in Table 10 and Table 11.

Table 10. Input parameters for SA of BIORIMA occupational exposure section.

Input	-99%	-90%	-75%	-50%	-25%	-10%	Base	10%	25%	50%	75%	90%	99%
Diameter (nm)	1	10	25	50	75	90	100	110	125	150	175	190	199
Density (g/cm^3)	-	0.2	0.5	1	1.5	1.8	2	2.2	2.5	3	3.5	3.8	4.0
Used mass (g)	10	100	250	500	750	900	1000	1100	1250	1500	1750	1900	1990
Task duration (min)	0.3	3	7.5	15	23	27	30	33	38	45	53	57	60
Generation rate (min)	0.3	3	7.5	15	23	27	30	33	38	45	53	57	60
Volume (m^3)	100	1000	2500	5000	7500	9000	10000	11000	12500	15000	17500	19000	19900
ACH	0.1	1	2.5	5	7.5	9	10	11	12.5	15	17.5	19	20

Note: Base = default value for OAT.

Table 11. Percentage (%) of MNM and nº of repetitions used for BIORIMA SA.

Input	-98	-80	-50	Base	50	80	98
% of MNM	1	10	25	50	75	90	100
nº repetitions	1	3	5	10	15	18	20

Note: Input parameters for SA of BIORIMA occupational exposure section. Base = default value for OAT.

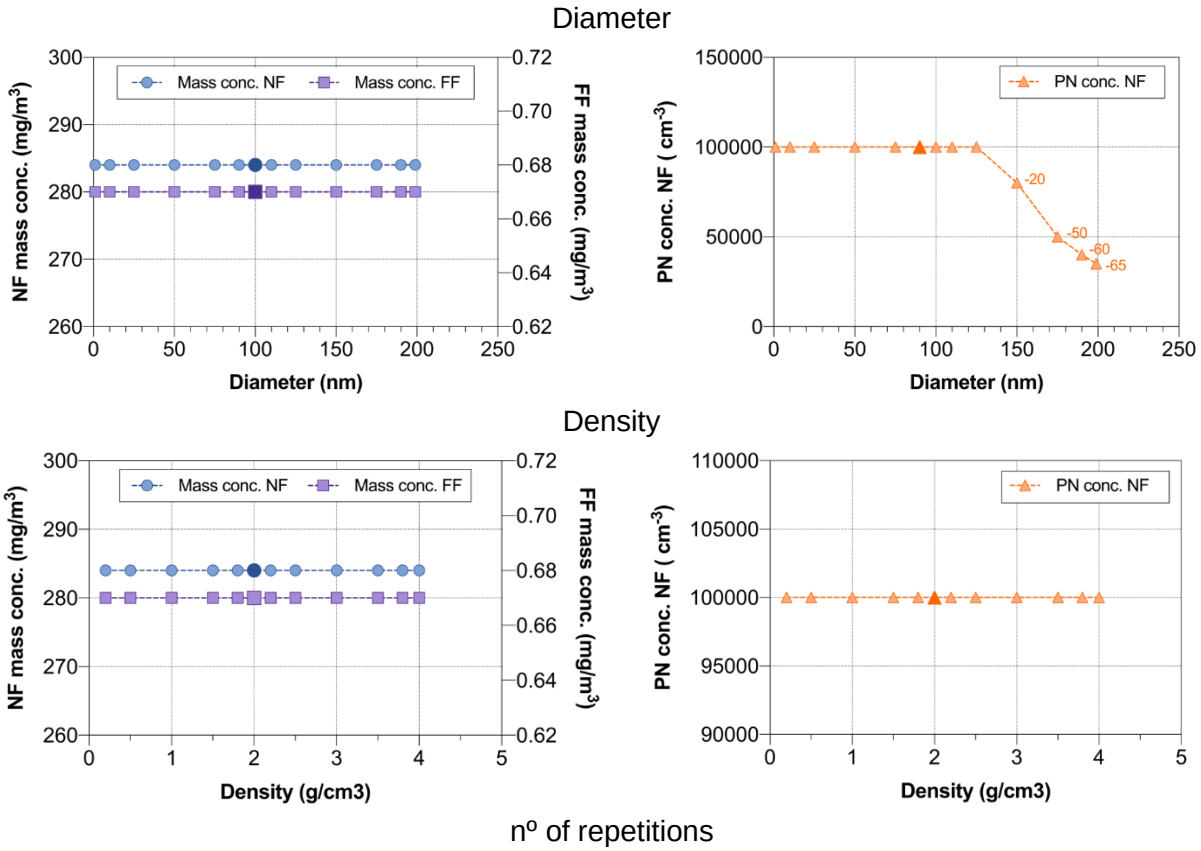
171. For the activity class option, the following activities were used for SA testing: pouring (base), bagging solids, dumping solids in mixers, filling of bottles, grinding minerals, laser ablation, powder coating, spray

application of paints on e.g. ships, spraying of dispersions containing MNMs onto surfaces (indoor), wiping, cleaning of liquid spills, sanding, welding.

Results

172. Diameter, density and nº of repetitions, showed as non-sensitive input parameters and had no effect on NF and FF mass concentrations on the ranges tested (Figure 12). Similarly, no effects were observed for particle number concentrations for density and nº of repetitions. Density sensitivity was also tested for an activity other than pouring in order to confirm this behavior. Density variations showed no sensitivity as well for the activity "*spraying of dispersions containing MNMs onto surfaces*". However, due to the large amount of activity class options (>100), density variations for each activity class could not be assessed.

173. Effects on particle number concentrations were observed with diameter changes. A 50% increase (50 nm) of the base diameter value (100 nm) resulted in a decrease on particle number concentration of 20% with respect to the base case (Figure 12 a). A 75, 90 and 99% increases on the particle diameter resulted in 50, 60 and 65% increases on particle mass. A 97.5% decrease of the particle number concentration was observed with a 500% increase of the base diameter (500 nm diameter; results not shown). For all the other values, particle number concertation remained constant at > 100000 particles/cm^3. It is important to note that maximum concentration provided by the tool is > 100000 particles/cm^3, thus changes over that are not considered.



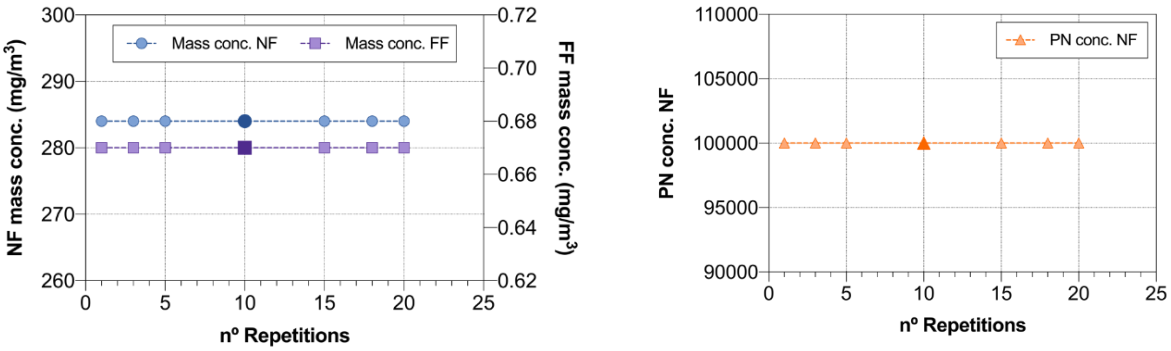


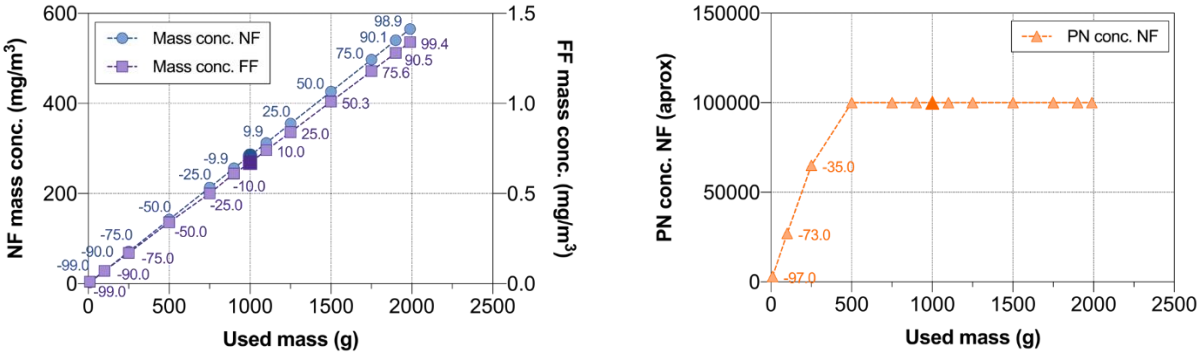
Figure 12. NF and FF mass, and particle number concentrations variations with diameter, density and nº of repetitions variations for BIORIMA SA.

174. NF and FF mass concentrations varied accordingly with the % of increase and decrease of the used mass and % of MNM input parameters, with an increase of used mass and % of MNM translating into an increase of the NF and FF mass concertation. On the other hand, particle number concentrations were 97, 73 and 35% lower than the base case when a decrease of 99, 90 and 75% was applied to the used mass, and 45% and 95% lower when decreasing the % of MNM 80 and 98%, respectively (Figure 13a and 13b). For all the other cases particle number remained constant at >100000 particles/cm^3.

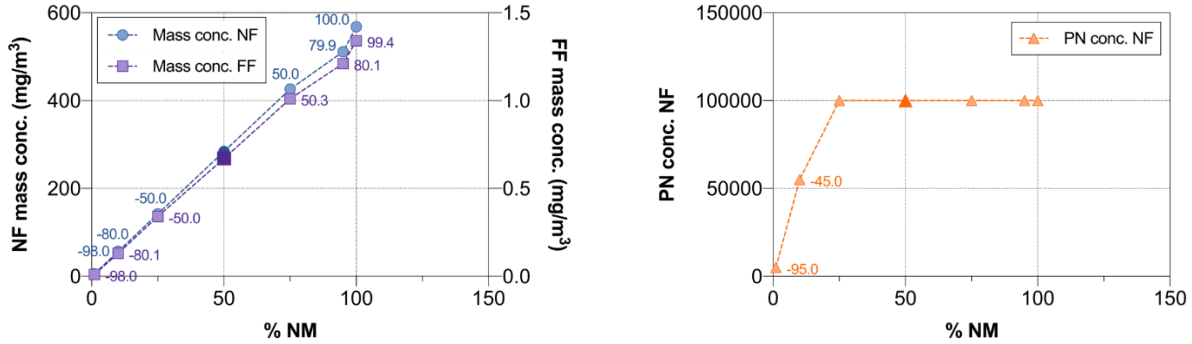
175. An increase on task and generation time input parameters (when varied together) had a decreasing exponential effect on NF mass concentration. The longer time to conduct the task, the lower the concentration. On the contrary, the FF mass concentration suffered an increase for between times 0.3-7.5 min and a decrease from 7.5-60 min (Figure 13 c). Particle number concentrations remained constant at 100000 particles/cm^3. When changing only task input parameter and keeping generation time constant at 30 min (base), mass and particle number concentrations suffered a decrease with task time increase (data shown only for particle number). A similar but opposite response is observed when fixing generation time to 30 min (data shown only for particle number) with maximum concentrations remaining constant at values reached for the 30 min task as even though task time increase, generation time is still 30 so concentrations suffer no variations.

Room volume and ACH variations had slight effects on NF mass concentrations whereas stronger effects where observed for FF mass concentrations. Effects on mass concentrations were stronger for smaller volumes < 5000 m^3 and remained nearly constant for volumes > 5000 m^3. ACH variations had nearly no effect on NF mass concentrations whereas a slight decrease exponential effect was observed for the FF mass concentrations. No effects were observed on particle number concentrations due to variation in volume or ACH input parameters.

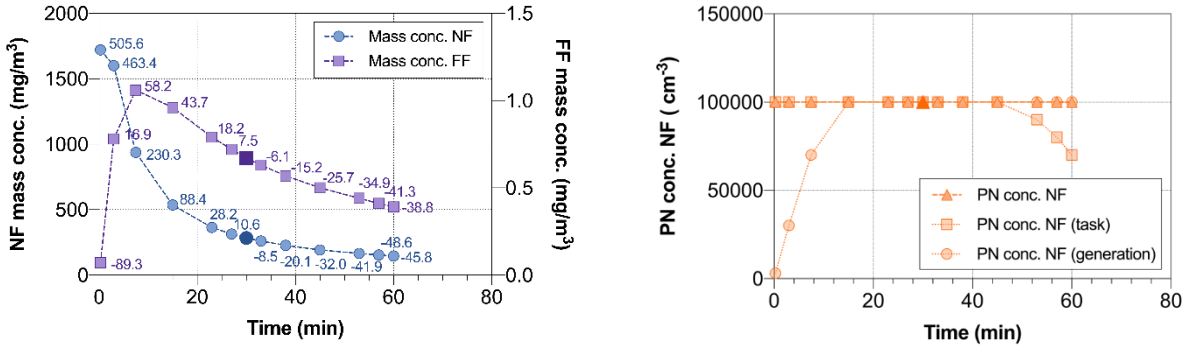
Used mass



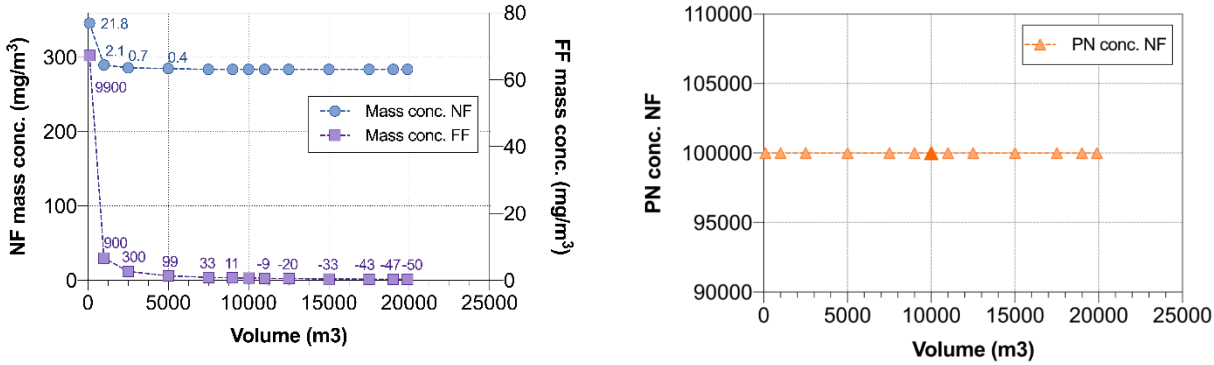
% of MNM



Task & Generation time



Room volume



ACH

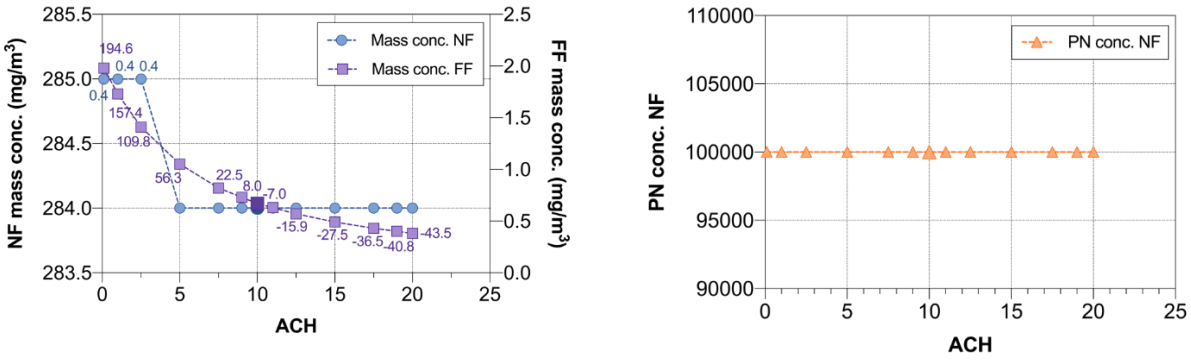


Figure 13. NF and FF mass, and particle number concentrations variations with used mass, % of MNM, task and generation time, room volume and ACH variations for BIORIMA SA.

176. The activity class selection had strong effects on particle mass concentrations (NF and FF) with increase percentage > 3000% when compared to the base activity (pouring) (Figure 14). Therefore, special care should be taken when selecting the activity class.

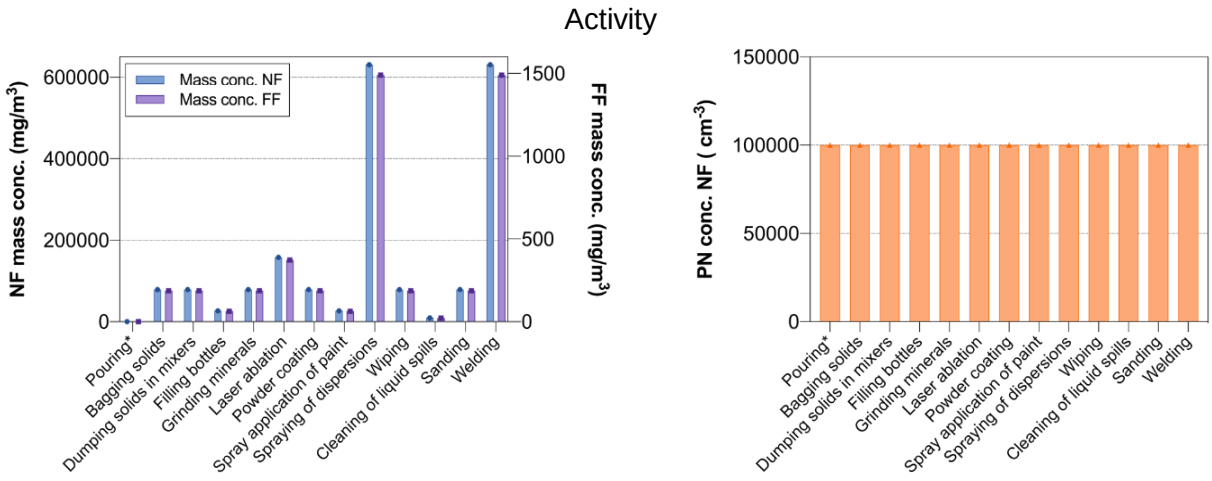


Figure 14. NF and FF mass, and particle number concentrations variations with different activity class for BIORIMA SA.

177. The analysis performed to the BIORIMA occupational exposure section revealed that the model is especially sensitive to activity selection, used mass, % of MNM, task and generation time. The model is also sensitive, for mass concentrations, to volume and ACH input parameters. On the other hand, the model showed no sensitivity to density and nº of repetitions. Diameter changes affected only particle number concentrations. The most and least sensitive input parameters are summarized in Table 12.

Table 12. Most and least sensitive parameters of BIORIMA occupational exposure section.

Most sensitive inputs	Least sensitive inputs
Activity	Density
Used mass	nº of repetitions
Percentage of MNM	
Task & Generation time	

4.2.3 SprayExpo model 2.3

Method

178. The SA on the SprayExpo tool was performed by range scanning OAT (number of model runs = 75) and AAO-MC methods (number of model runs = 1000) within the caLIBRAte project. The spraying of antifouling paints standard scenario (prefilled scenario) in the SprayExpo tool was implemented and used as a starting point. For the OAT and the AAO-MC methods, the type of distribution the input values for each parameter where chosen from was normal with the exception of the "*vapour pressure of the solvent*" which was log-normal. The standard deviations were chosen appropriately to make all values within $\mu \pm 2\sigma$ (normal distribution) possible input parameters. The results from the two methods are used in conjunction to discuss the sensitivity of the Spray Expo model to its input parameters. The OAT results enable identification of parameters that are likely to cause larger variability in the output values, and the Monte Carlo results can be used to identify regions of input parameter values where this may occur.

Model outputs and inputs

179. Two model outputs were used as the model performance metric, namely the average concentration and the inhaled dose. Model input parameters that were subjected to the SA in the OAT and the AAO-MC methods are given in the Table 13 and Table 14, respectively. A list of inputs that were not tested in the simple OAT method is given in Table 15, with justification for the exclusion. The chosen input parameter ranges differ between the two methods (OAT and AAO-MC), because the observations in the OAT analysis were considered when designing the MC simulations. This may restrict the comparability of the results from the two methods.

Table 13. Input parameters for SA of SprayExpo. Most Likely Value = default value for OAT.

Input Name	Most likely value	Minimum value	Maximum value	Unit
Ventilation rate	1	0.01	2	1/h
Coefficient of turbulent diffusion	0.1	0.001	2	m^2/s
Spray angle	40	0.1	180	Deg(^{0})
Nozzle diameter	0.53	0.000001	1	mm
Non-evaporating fraction of solvent	1	10^{-6}	10	%
Vapor pressure of solvent	1	10^{-2}	10^3	hPa
Release rate of paint	30	1	100	ml/s
Time resolution	1	1	5	–

Table 14. Input parameters for SA of SprayExpo. Most Likely Value = mean of distribution for AAO-MC.

Input Name	Most likely value	Minimum value	Maximum value	Unit
Ventilation rate	6	4	8	1/h
Coefficient of turbulent diffusion	0.06	0.02	0.10	m^2/s
Spray angle	40	0	80	Deg (°)
Nozzle diameter	0.53	0.18	0.88	mm
Non-evaporating fraction of solvent	1.0	0.6	1.4	%
Vapor pressure of solvent	6.000	0	–	hPa

Note: the AAO-MC analysis was performed at all of the "*time resolutions*".

Table 15. Input parameters excluded from SA for SprayExpo.

Input name	Justification for exclusion
Room dimensions	The standard scenario was used
Application pattern	
Droplet spectrum	
Spray time	
Sprayer distance to target	
Nozzle distance to target	
Paint release rate	Not varied in MC because this was added later
Nozzle area	Nozzle diameter is varied instead

Results

180. Figures 15 and 16 show the variation in the outputs of model across the changes in the input parameters, obtained from the OAT method. The input parameters causing relatively large changes in the output variables are the nozzle diameter, release rate of paint, spray angle and the non-evaporating fraction of solvent. Variation in the other input parameters do also affect the output values, but their effect is lower. The ventilation rate showed the lowest sensitivity of the studied parameters. Computed using AAO-MC methods, distribution of the output variables for each of the five time resolution values of the model are plotted in Figure 17. The distributions shown by the box plots are almost identical for both output variables, from which it is concluded that their distributions are the same.

181. Judging by the lengths of the whiskers in Figures 17, it is clear that the distribution of the output values is very narrow. Because of this, the interval between the lower and the upper quartiles is chosen to represent the most probable output values. For these points of the output data, the corresponding input parameter values can be traced to find the approximate regions of each parameter that is likely to result in output values between the quartiles. This procedure is repeated for all time resolutions, and the shortest possible interval is chosen to represent the common region of each input parameter. The bounds of these intervals are collected to Table 15. The bounds for each input parameter are identical between both output variables in this case.

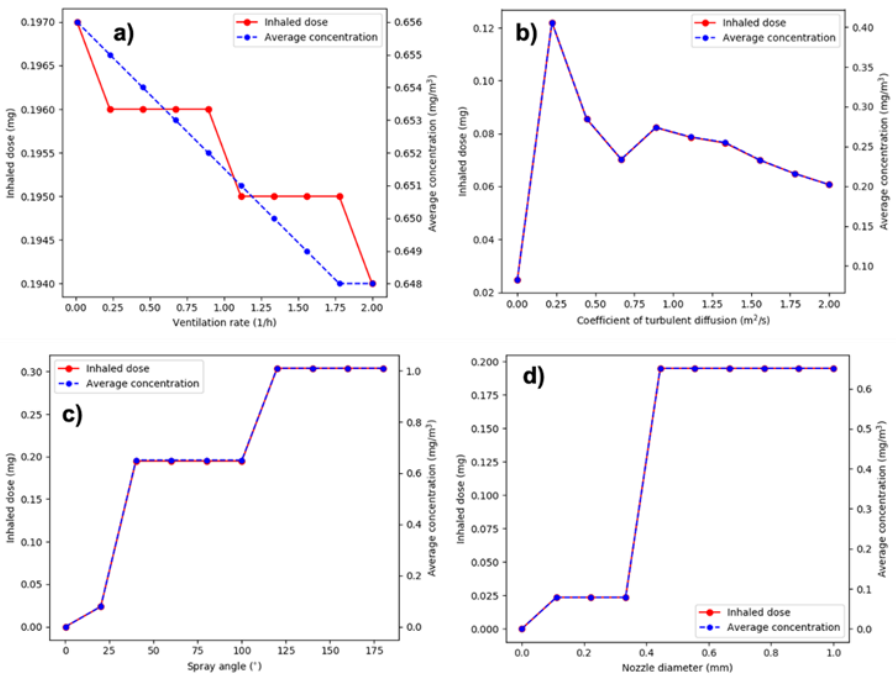


Figure 15. Variation in the outputs of the SprayExpo model.

Note: Variation as function of changes in a) ventilation rate, b) coefficient of turbulent diffusion, c) spray angle, and d) Nozzle diameter.

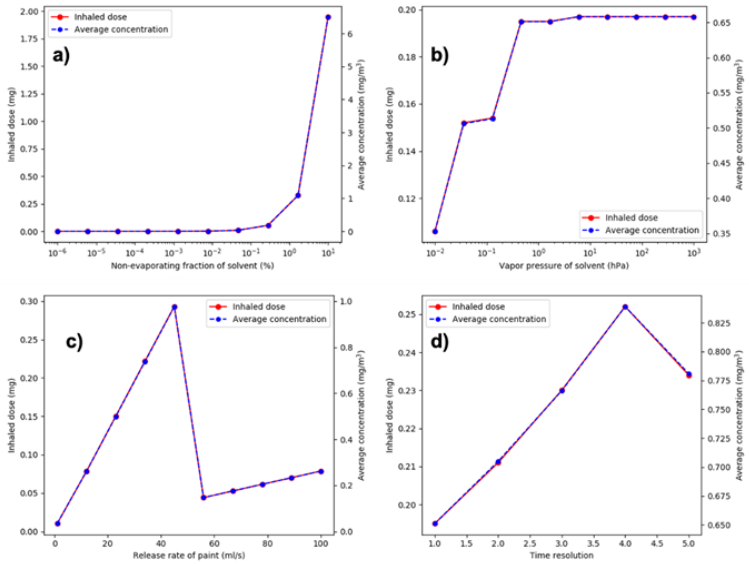


Figure 16. Variation in the outputs of the SprayExpo model.

Note: Variation as function of changes in a) non-evaporating fraction of solvent, b) vapour pressure of solvent, c) release rate of paint, and d) time resolution.

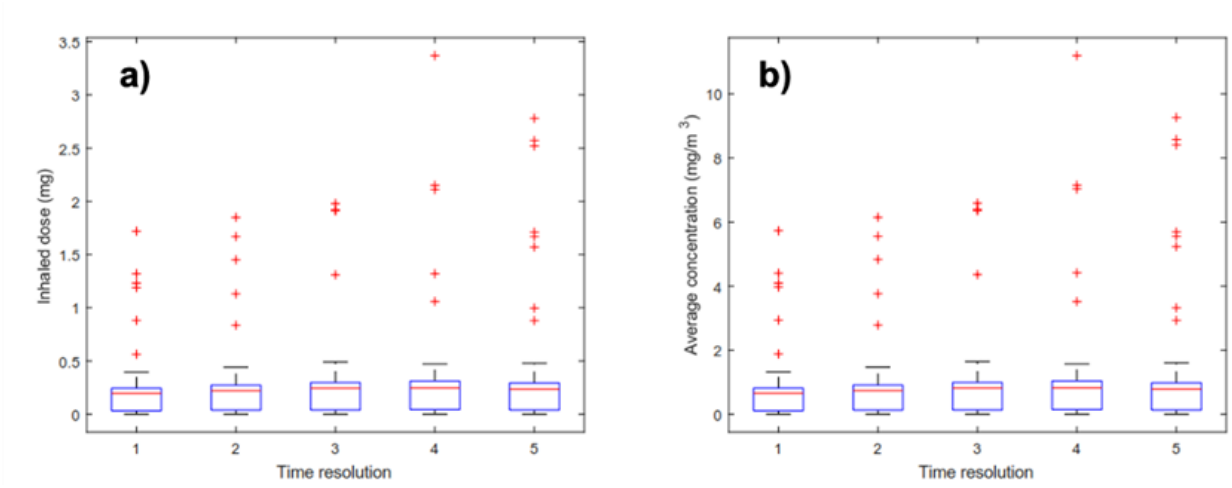


Figure 17. SprayExpo a) Inhaled dose by time resolution and b) Average concentration by time resolution.

Note: Red line is the median, the box limits represent the lower and upper quartiles, the red + signs show outliers and the whiskers are at most 1.5 interquartile ranges in length.

Table 16. Regions of input parameters likely to restrict output values within the lower and upper quartiles for SprayExpo.

Parameter	Lower bound	Upper bound
Inhaled dose (mg)	0.0414	0.2739
Average concentration (mg/m^3)	0.1380	0.9090
Ventilation rate (1/h)	4.09	7.85
Coefficient of turbulent diffusion (m^2/s)	0.023	0.099
Spray angle (°)	12.3	78.7
Nozzle diameter (mm)	0.22	0.87
Non-evaporating fraction of solvent (%)	0.61	1.40
Vapor pressure of solvent (hPa)	0.196	241.846

182. The intervals of input parameter values leading to output values between the lower and upper quartiles with high probability can also be used when analysing the sensitivity. Comparing these intervals from Table 16 with the boundaries in the original distributions of the parameters' values can reveal a certain kind of sensitivity for the spray angle and the nozzle diameter, especially in the upper part of the distribution. The less the tabulated region covers the whole range of possible input parameters values, the higher the chances are for a parameter to cause deviations from the common trend. The spray angle and the nozzle diameter have relatively high lower bounds of the intervals in Table 15 compared to those of their distributions. This indicates that the SprayExpo model is likely to produce values below the lower quartile when run with these low values of the spray angle and the nozzle diameter. In other words, the model seems to be sensitive to the parameters in a sense that below certain input parameters values the output values drop to zero.

183. The two analyses performed to the SprayExpo 2.3 reveal at least two input parameters that the model seems to be sensitive to, namely the spray angle and the nozzle diameter. Other input parameters identified as possibly critical in this sense are the non-evaporating fraction of solvent and the release rate of paint. However, because of the short range of values selected in the OAT and the fact that the scale of the

parameter was chosen to be logarithmic whereas Figure 16 suggest possible linear relationship, no conclusions can be made.

184. The most and least sensitive input parameters are summarised in Table 17.

185. For the release rate, an unexpected drop in the output variables when release rate is over 50 ml/s was detected, before and after the trend is approximately linear. No intuitive physical explanation to the phenomenon could be found. Additionally, this parameter was not included in the MC analysis, so results could not be compared. Therefore, more analysis is required to make conclusions about the model's sensitivity to the release rate of paint.

186. In addition, some sensitive parameters showed no sensitivity in some subranges as well as sudden jumps between ranges (as shown in Figures 15 and 16). Examples of this are "*spray angle*" from 30-100 and 120-180 degrees, "*nozzle diameter*" in 0.1-0.3 and 0.5-1 mm, "*non-evaporating fraction of solvent*" in range from 10^{-6} to 10^{-2}, and "*vapour pressure of solvent*" from 10-1000hPa).The methodologies used AAO and MC seem to have provided complementary results, with the OAT serving to identify sensitive parameters, whereas the MC methods provided a more detailed view. However, some unexpected behaviours were detected. These unexpected behaviours, for which no clear explanation was found with the results of the conducted assessments, may be explained by the fact that in SprayExpo some parameters are dependent on each other and should not be varied independently as the methodology of the used SA methods required. Thus, more research and further analysis are needed (e.g. variance based methods) in order to make decisive conclusions on the sensitivity of the tool.

Table 17. Most and least sensitive parameters of SprayExpo.

Most sensitive inputs	Least sensitive inputs
Nozzle diameter	Ventilation rate
Release rate of paint	Time resolution of the model
Spray angle	
The non-evaporating fraction of solvent*	

4.2.4 RISKOFDERM

Method

187. The SA of RISKOFDERM was conducted following the OAT approach as described in Section 4.1.1. The RISKOFDERM tool either demands an order of magnitude estimation (i.e. qualitative classes) for some of its input parameters or quantitative numerical values (within permissible ranges) for the rest of the input variables. In the case of qualitative classes, the variation in the input variable was made by merely changing one qualitative class to another, whereas for quantitative numerical values, a 50% increase or decrease is made in the numerical baseline value. The base values were selected as a most likely value from the possible range of values or qualitative classes.

Model output and inputs

188. The tool provides output values of either median body or median hand dermal exposure loading per shift for the six dermal exposure operation (DEO) units (DEO units described in Table 18, which are, respectively, the clusters of various exposure scenarios. Model input parameters subjected to the SA are given in the Table 18.

Table 18. Input parameters for SA of RISKOFDERM.

Input parameter	Options	Most likely value	Units
DEO 1: Filling, mixing or loading			
Quality of the ventilation	Normal or good ventilation	X	[-]
	Poor ventilation		
Frequency of (skin) contact with the contaminated surface	Rare contact	X	[-]
	More than rare contact		
Intensity of (skin) contact with the contaminated surface	Light contact	X	[-]
	More than light contact		
Type of product	Liquid		[-]
	Low or moderately dusty solid	X	
	Highly dusty solid		
Aerosol generation	Yes		[-]
	No	X	
Level of automation of the task	Manual task		[-]
	Automated or semi-automated task *(applicable only when type of product is liquid)*	X	
Use rate of the product	0.56 to 225 for powders	100	kg/min
	0.008 to 257 for liquids	100	L/min
Cumulative duration of the scenario during a shift	1 to 20 for powders	10	min
	0.33 to 125 for liquids	50	min
DEO 2: Wiping			
Contact with freshly wiped surfaces	Yes		
	No	X	
Use rate of the product	0.0017 to 1.18	0.005	L/min
Cumulative duration of the scenario during a shift	5 to 35	12.5	min
DEO 3: Dispersion with a hand tool			
Direction of application	Level or overhead		[-]
	Downward	X	
Viscosity of the applied product	Viscosity like water		[-]
	Viscosity like oil	X	
	Viscosity like syrup or honey		
Kind of tools used for application	Tools with handles < 30 cm in length		[-]
	Tools with handles > 30 cm in length	X	
Use rate of the product	0.0001 to 1.1	0.4	L/min
Cumulative duration of the scenario during a shift	1 to 445	160	min
DEO 4: Spraying			
Indoors or outdoors	Indoors		[-]
	Outdoors	X	
Direction of application	Overhead		[-]
	Level	X	
	Downward		
Direction of airflow that comes from the source	Away from the worker	X	[-]
	Not clearly away from the worker		
Worker segregated from the source	Yes	X	[-]
	No		
Distance source-worker	Up to 1 meter		[-]
	More than 1 meter	X	
Volatility of the carrier liquid	Not highly volatile	X	[-]
	Highly volatile		
Type of product	Liquid		
	Solid		
Use rate	0.04 to 50.4 for liquids	25	L/min

Input parameter	Options	Most likely value	Units
	0.02 to 0.12 for powders	0.04	Kg/min
Cumulative duration of the scenario during a shift	3 to 600 for liquids	200	min
	4 to 90 for powders	40	min
DEO 5: Immersion			
Adequate local exhaust ventilation (LEV) used	Yes	X	[-]
	No		
Distance source-worker	Up to 30 cm		[-]
	30 cm to 1 m	X	
	More than 1 m		
Cumulative duration of the scenario during a shift	4 to 483	200	min
DEO 6: Mechanical treatment of solid objects			
Physical state of the product or substance assessed	Liquid		[-]
	Solid		
Distance source-worker	Less than or about arm's length		[-]
	More than arm's length	X	
Frequency of (skin) contact with the contaminated surface	Rare or irregular contact	X	[-]
	Frequent or constant contact		
Cumulative duration of the scenario during a shift	18 to 154 for solids	50	min
	47 to 214 for liquids	100	min

Note: Most Likely Value (reference) = default value for OAT.

Results

189. In Figure 18a and 18b, the SA for the median exposure loadings on hands for both powders and liquids, respectively is shown for DEO1 (filling, missing and loading). Body exposure loadings are not shown as the tool does not calculate them for DEO1. The input parameters are shown on the y-axis while the resulting median exposure loading values per shift are shown on x-axis. As previously mentioned, the tool requires certain qualitative values for all its input parameters, except for "*cumulative duration of material use*" and its "*use rate*". The resulting median exposure loading of powders per shift on hands changes from 25 to 192 mg (i.e. OTV = 192-25 = 167 mg) when dustiness changes from "*Low or moderate*" to "*High*" (Figure 18a). Thus, dustiness is the most influencing input parameter for the estimation of exposure loading of a powder in the case of DEO1. For liquids, however, it is the level of Automation which shows the highest OTV of 3510 mg when it is changed from "*Automated*" to "*Manual*" (Figure 18b). The least influential variable for both powders and liquids is the material use rate, which produces the least variation of 34.5 mg and 32 mg in the median exposure loading per shift of powders and liquids on hands respectively.

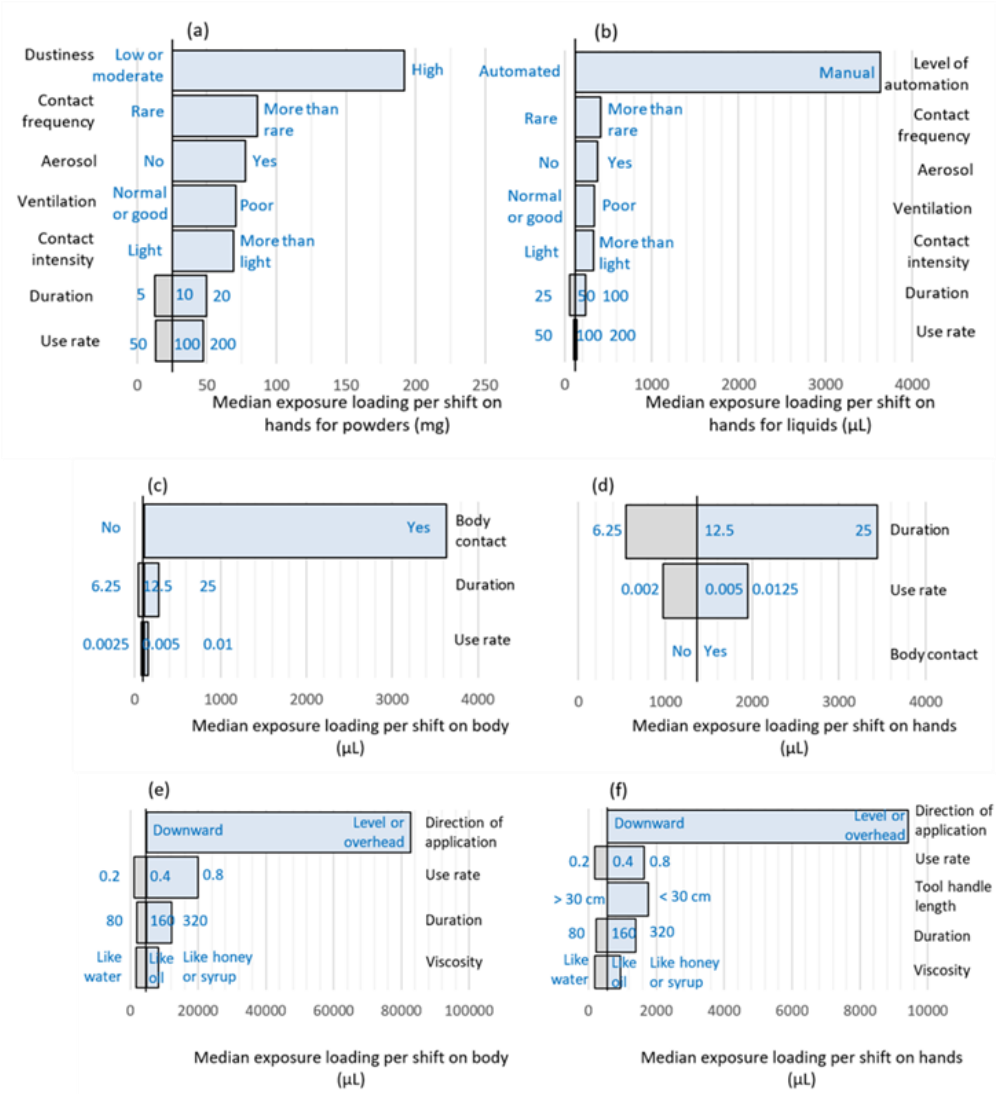


Figure 18. OAT SA results for RISKOFDERM DEO1 (a and b), DEO2 (c and d) and DEO3 (e and f).

190. The influence of the input parameters on the median exposure loading per shift on body and hands during DEO2 are shown in Figure 18c and 18d, respectively in decreasing order. The input variable "*Body contact*" produces the highest change (3517 µL) in the median exposure loading value when changed from "*No*" to "*Yes*" being the most influential variable for estimating the median exposure loading per shift on body. On the contrary, it is least influential for exposure loading on hands. The most influential input parameter for estimating the median exposure loading per shift on hands is "*Duration*".

191. For DEO3, the input variable "*Direction of application*" produces the highest change on body (Figure 18e) and hands (Figure 18f) in the median exposure loading per shift when changed from its most likely. Thus, it is the most influential input variable in the case of DEO 3 followed by "*Use rate*" on body and "*Tool handle length*" on hands, "*Duration*" and least influential "*Viscosity*".

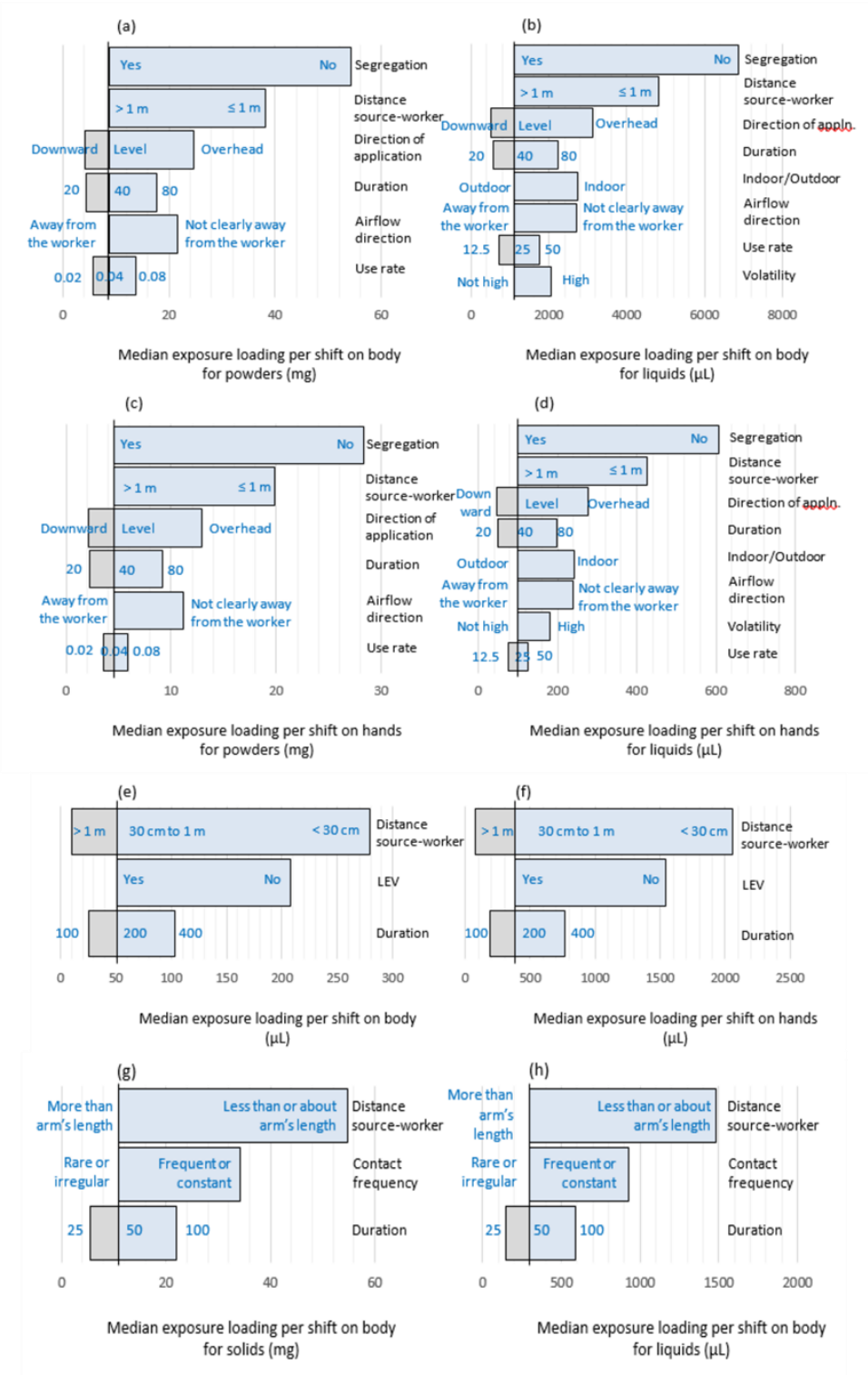


Figure 19. OAT SA results for RISKOFDERM DEO4 (a, b, c and d), DEO5 (e and f) and DEO6 (g and h).

192. Out of the eight input variables for the DEO 4, the "*segregation*" of the worker from the process is the most influential variable, whether being assessed for the exposure loading per shift on body or hands and, for both powders and liquids (Figure 19a, 19b, 19c and 19d). The least influential variable in all cases,

except for the exposure of liquids on body where "*volatility*" appeared as the least influential parameter, is the material "use rate. Most and least input parameters are listed in Table 19.

193. For the DEO5, whether it is an exposure on body or hands, the "*distance source-worker*" always has the highest influence (Figure 19e and 19f). The factor of "*LEV*" is 1.7 times less influential in both cases (body and hands) but twice influential as compared to ± 50% change in "*duration*".

194. Irrespective of the solids or liquids, the "*distance source-worker*" is the most influential input variable in the case of DEO6. The influence decreases by a factor of two (approx.) in the case of "*contact frequency*" and further by 1.4 times for the least influential variable "*duration*".

195. Unexpected behaviour of RISKOFDERM is reported in Table 20. Unexpected behaviour, non-linear variation of exposure loading with material use rate, was detected for DEO1, 2, 3 and 4. These unexpected behaviours observed are probably due to the fact that body exposures are proportional to the application rate to the power of a number different to 1, as detailed in Warren et al. (2006[61]), which result in ratio of body and hand exposures increasing with higher application rates.

Table 19. Most and least sensitive input parameters of RISKOFDERM.

Subcategories			Most sensitive input(s)	Least sensitive input(s)
DEO 1. Filling, mixing and loading	Powder		Powder dustiness	Use rate
	Liquid		Level of automation	
DEO 2. Wiping	Body		Body contact intensity	Use rate
	Hands		Duration	
DEO 3. Dispersion hand-held tools	Body		Direction of application	Viscosity
	Hands			
DEO 4. Spraying	Powder	Body	Segregation	Use rate
		Hands		
	Liquid	Body		Volatility
		Hands		Use rate
DEO 5. Immersion	Body		Distance source-worker	Duration
	Hands			
DEO 6. Mechanical treatment	Solids		Distance source-worker	Duration
	Liquids			

Table 20. Unexpected behaviour of RISKOFDERM.

Conditions	Description/Explanation	
Non-linearity of output when linear behavior is expected	DEO 1. Filling, mixing and loading	The exposure loading per shift on hands varies non-linearly against material use rate for an automated or semi-automated task.
	DEO 2. Wiping	The exposure loadings per shift on body and hands vary non-linearly against material use rate.
	DEO 3. Dispersion hand-held tools	The exposure loadings per shift on body and hands vary non-linearly against material use rate.
	DEO 4. Spraying	

4.2.5 MEASE 2.2.0

Method

196. The MEASE tool follows the process-category (PROC)-specific approach of the targeted risk assessment (TRA) tool to estimate and evaluate worker inhalation and dermal exposure. The tool requires a total of 19 input parameters to calculate dermal and inhalation exposure. As only the inhalation exposure

part was assessed, input parameters related to the use of gloves, clothing and face/eye protection were not considered. Input parameters related to adjacent workplaces and dust suppression technique were also not considered for SA. Moreover, PROC selection could not be tested for SA as each PROC has different associated options thus it was not possible to only assess the effect on mass concentration due to PROC selection. The SA was performed by OAT methodology as described in section 4.1.

Model output and inputs

197. The tool inhalation exposure output is in mass concentration (mg/m^3). All the input parameters have a drop down menu from which the user selects the most appropriate value or option. Options given for each input parameter considered in the SA vary between 3 and 8 options. The most likely value or qualitative class was selected as a base and all the range of possible options was considered for variations. Detailed range of values tested for each input parameter considered in the SA are provided in Table 21.

198. For some parameters, the tool has predefined options when selecting certain options for other inputs. For example, when selecting level of containment "*completely closed*", the level of automation can only be "*fully automated*", for this reason, there are certain variations in the base values used to assess sensitivity for different input parameters. However, base values were kept the same as much as possible. Detailed description of base values used to test SA to different inputs is provided in Table 22.

Table 21. Range of values tested for MEASE SA.

Input parameter	Range of values							
Phys. form	Liquid	Suspension	Paste	Solid, high dusty	Solid, medium dusty	Solid, low dusty	Massive object	-
Containment	Completely closed	Essentially closed	Partly closed	Open	-	-	-	-
Automation	Fully automated	Highly automated	Semi-automated	Manual	-	-	-	-
Container	1L	25kg bags	<200L	<1000L	>500Kg bags	Piping system	Conveyer belt	Open truck, waggons…
Nº containers	= 2	= 10	= 100	>100	-	-	-	-
Room size	Any size	Large	Outdoor	-	-	-	-	-
Conc.	>25	5-25	1-5	<1	-	-	-	-
Duration	<15 min	15-60 min	60-240 min	>240 min	-	-	-	-
ACH	Open	=1	=3	=10	-	-	-	-
Cleaning	Occasional	Regular	Immediate	-	-	-	-	-
LEV	No LEV	Fixed	Mobile	Integrated	Rim vent.	-	-	-
Efficacy LEV	General	Specific	Specific & maintained	-	-	-	-	-
Resp. PPE	No PPE	APF 4	APF 5	APF 10	APF 20	APF 40	-	-

Table 22. Base values used for MEASE SA testing. *changed base values due to predefined options.

Inputs	Base values for SA												
	Physical form	**Containment**	**Automation**	**Container**	**nº containers**	**Room size**	**Conc.**	**Duration**	**ACH**	**Cleaning**	**LEV**	**Efficacy**	**Resp. PPE**
PROC	9*	26	26	19* & 26	26	26	26	26	26	26	26	26	26
Physical form	-	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty	Solid, medium dusty
Containment	Partly closed	-	Partly closed	Partly closed	Partly closed	Partly closed	Partly closed	Partly closed	Partly closed	Partly closed	Partly closed	Partly closed	Partly closed
Automation	Semi-automated	Fully automated*	-	Manual*	Semi-automated	Semi-automated	Semi-automated	Semi-automated	Semi-automated	Semi-automated	Semi-automated	Semi-automated	Semi-automated
Container	1L*	25kg	25kg	-	25kg	25kg	25kg	25kg	25kg	25kg	25kg	25kg	25kg
nº containers	≤ 10	≤ 10	≤ 10	≤ 10	-	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Room size	Any size	Any size	Any size	Any size	Any size	-	Any size	Any size	Any size	Any size	Any size	Any size	Any size
Conc.	≥25%	≥25%	≥25%	≥25%	≥25%	≥25%	-	≥25%	≥25%	≥25%	≥25%	≥25%	≥25%
Duration	15-60 min	15-60 min	15-60 min	15-60 min	15-60 min	15-60 min	15-60 min	-	15-60 min	15-60 min	15-60 min	15-60 min	15-60 min
ACH	≥ 3	≥ 3	≥ 3	≥ 3	≥ 3	≥ 3	≥ 3	≥ 3	-	≥ 3	≥ 3	≥ 3	≥ 3
Cleaning	Regular	Regular	Regular	Regular	Regular	Regular	Regular	Regular	Regular	-	Regular	Regular	Regular
LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	-	Fixed	No LEV
Efficacy LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	No LEV	General	-	No LEV
Resp. PPE	No	No	No	No	No	No	No	No	No	No	No	No	-

* No gloves and face/eye protection, and standard safety clothing were selected for SA.

Results

199. Variations on type of operation-related input parameters are represented in Figure 20. No variation in mass concentration due to changes in material's physical form was observed with the exception of high dusty materials that was 5.5 times higher than the rest. This low level of variation and sensitivity was unexpected. However, this behaviour could be different for other PROC selections, which was not addressed here.

200. No difference in mass concentration was observed when selecting completely or essentially closed. However, selecting partly closed or open implied tenfold increases in mass concentration.

201. Selecting highly or semi-automated level of automation implied no difference in inhaled mass concentration. Conversely, the selection of fully automated and manual options implied a decrease of 90% and increase of 80% of mass concentrations, respectively.

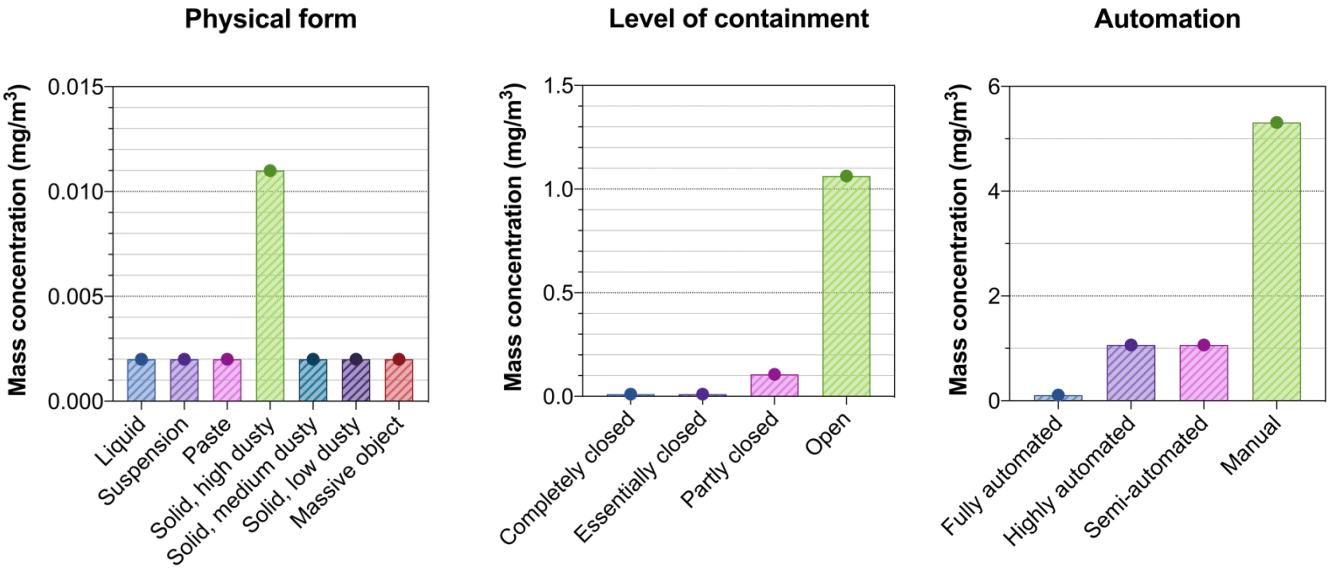


Figure 20. OAT SA results for MEASE type of operation input parameters.

202. Scale of operation input parameters influence in mass concentrations are shown in Figure 21. In order to test the sensitivity to all range of container capacity options two PROCs were used (19 and 26, Table 21 and Figure 21). For PROC 19, no changes in mass concentration were observed when changing the container capacity (1L, 200L and 25kg). On the other hand, for PROC 26, variations of container capacity implied changes in output mass concentration. Selecting 200 or 1000L made no difference in output concentration, but when compared to selecting 25kg, mass concentration was 5 times lower. Between 25 and 500Kg, piping system, and open truck options, output mass concentration suffered no variations. Finally, conveyer belt implied an increase of 5 times the 25kg option.

203. Changes in number of containers implied a gradual increase from 2 to 10 and 10 to >=100 of 10 and 5 times, respectively.

204. Relatively small decreases (9.1 and 13.6%) on output mass concentration were observed from changing the room size for large and outdoor when compared to any size workroom option.

205. Specific process input parameters include only the material concentration (Figure 22). For material concentration, gradual decreases were observed with decreasing material concentration with a maximum decrease of 90% when concentration was under 1% compared to >25% option. Specific exposure settings

input parameters include task duration, ACH and cleaning routine (Figure 23). Output mass concentrations suffered increases between 40 and 67% with the increase on task duration. Similarly, but with a lower level of impact in output concentrations, increases in ACH implied steady decreases between 8 and 11% of the output mass concentration. Finally, an increase on the cleaning routine implied decreases of exposure mass concentrations of 9 and 13% when compared to only occasional cleaning option.

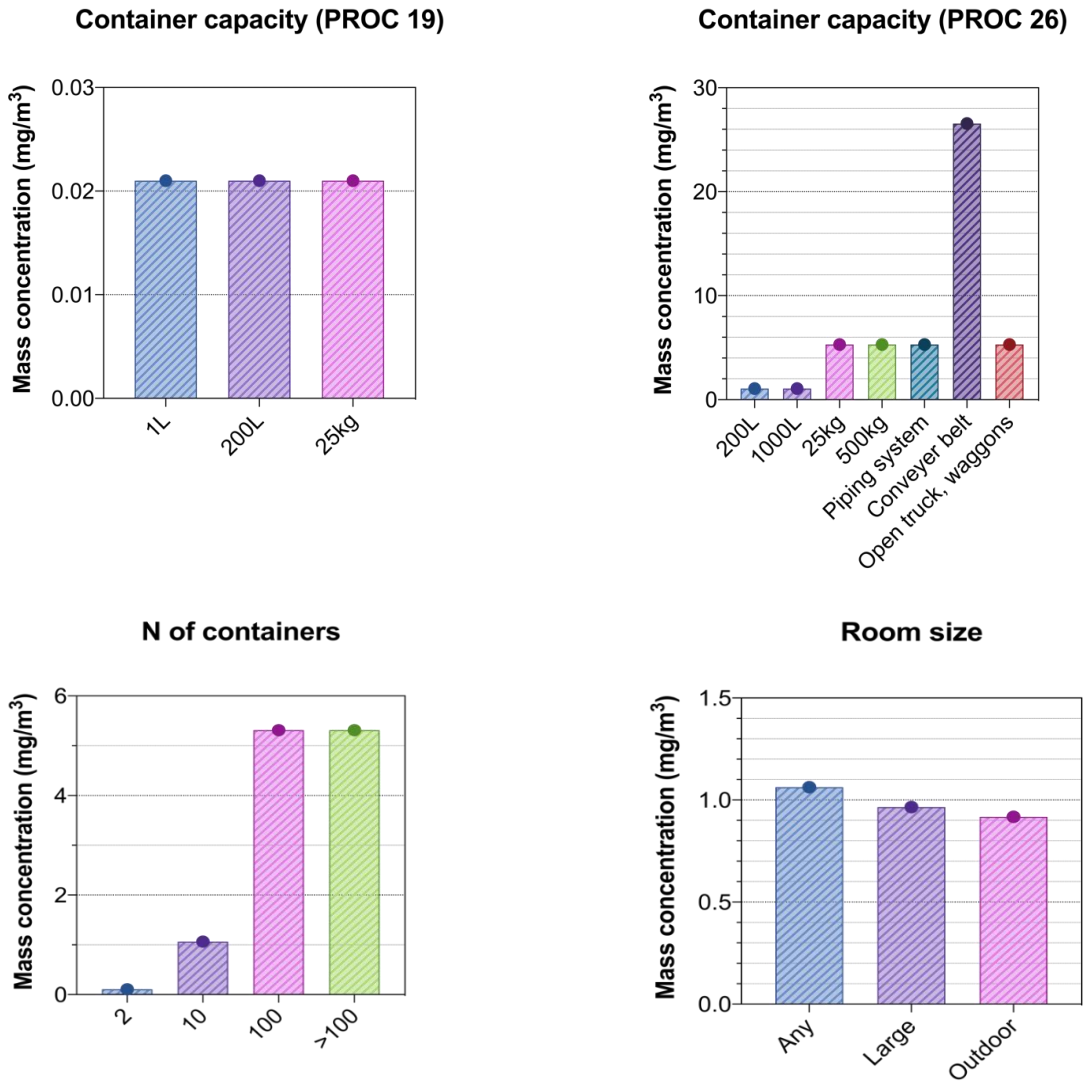


Figure 21. OAT SA results for MEASE scale of operation input parameters.

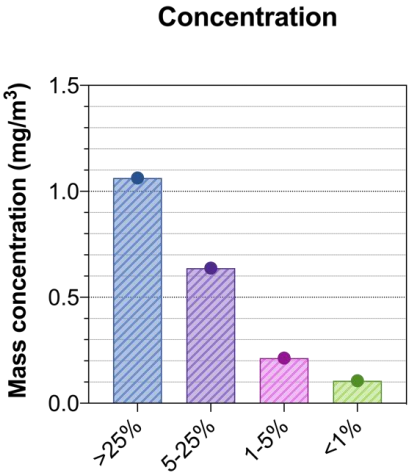


Figure 22. OAT SA results for MEASE specific process input parameters, concentration in product.

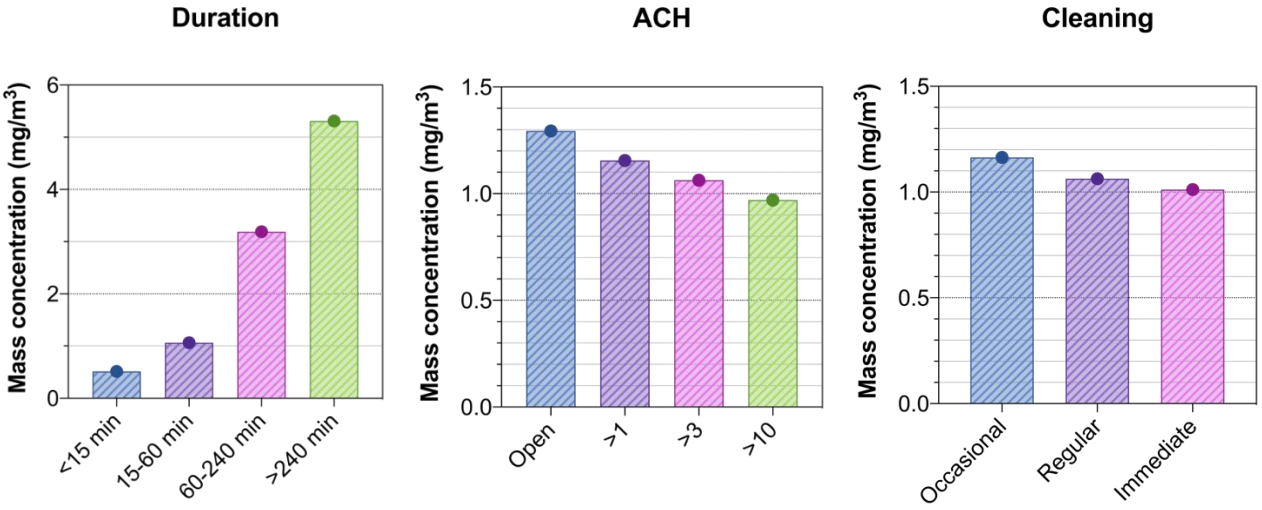


Figure 23. OAT SA results for MEASE specific exposure settings input parameters.

206. Technical measures and PPE input parameters variations in mass concentration are represented in Figure 24. The selection of any type of LEV (fixed, mobile, integrated or rim ventilation) implied a decrease in mass concentrations when compared to no LEV option between 75 and 84%. Thus, no big difference in mass concentration was observed between LEV types. In the same way, small differences (11-18%) were detected between LEV efficacies (general, specific, and specific and maintained).

207. On the other hand, the use of respiratory PPE and it´s increase on filtration efficiency implied a strong decrease in mass concentrations between 75 and 98% when compared to mass concentrations obtained without using respiratory PPE.

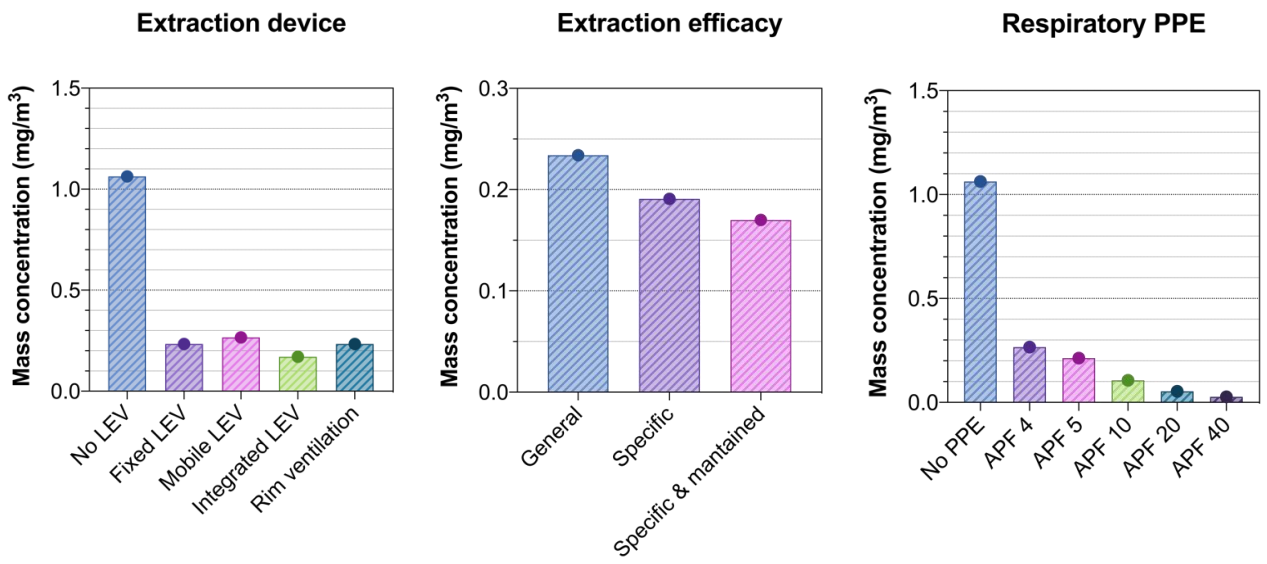


Figure 24. OAT SA results for MEASE technical measures and PPE input parameters.

Note: APF: "*assigned protection factor*" given in BS EN 529:2005 (as a guide: APF4 = FFP1; APF10 = FFP2; APF20 = FFP3).

208. Overall, high differences in output mass concentrations were observed due to changes in level of containment, automation, material concentration, task duration and respiratory PPE. Conversely, low impacts in mass concentrations were seen for changes in room size, cleaning routine, extraction efficacy and ACH. Most and least input parameters are listed in Table 23.

Table 23. Most and least sensitive input parameters of MEASE tool.

Most sensitive inputs	Least sensitive inputs
Level of containment	Room size
Automation	Cleaning
Concentration	Extraction efficacy
Duration	ACH
Respiratory PPE	

crc4.2.6 EMKG Expo tool 2.0

Method

209. The EMKG-Expo-Tool uses a CB approach to estimate and evaluate worker inhalation exposure, and identification of RMM from exposure to solids and liquids. The tool requires only 10 input parameters: substance information (name, CAS, molecular weight, boiling point (only for liquids) and DNEL), dustiness or volatility (for solid or liquids, respectively), amount of material handled, task duration, surface application size, and control strategies. The SA was performed by OAT methodology as described in section 4.1.

Model output and inputs

210. The tool output is a range (min-max) of concentration in mg/m^3 for solids and ppm for liquids. The concentration range corresponds to an exposure band, which is calculated based on the potential band

(calculated by the tool considering quantity group and dustiness/volatility) and the selected control strategy. The RCR is estimated considering the expected exposure level and the DNEL (or other reference value introduced). The most likely options for the exposure situation input parameters were selected and all the range of options was assessed in the SA. For the substance specific inputs a most likely value was introduced as a base and minimum-maximum values with physical sense were analysed for variation. Base and range values/qualitative classes used for SA are provided in Table 24.

Table 24. EMKG input parameters used for SA.

Substance	Base	Range
Name & CAS	TiO2 (13463-67-7)	SiO2 (60676-86-0)
Mol. Weight (g/mol)	100 (*79.87*)	20-500
Boiling point* (ºC, ºF and K)	2990	100-2990
DNEL (ppm or mg/m^3)	20 (*17**1*)*	1-20

* Stone et al. (2010); *1 only for liquids.

Exposure situation	Base	Range tested	
Dustiness/Volatility band	Medium	Low	High
Quantity group	Medium	Low	High
Duration of exposure < 15 min	Yes	n/a	No
Application on surfaces > 1m^2	No	n/a	Yes
Control strategy	Engineering controls	Minimum requirements	Containment

Results

211. Variations on substance (name and CAS), molecular weight, boiling point and DNEL had no effect on estimated exposure band and concentration range, which kept stable at output base concentrations of 0.01-0.1 mg/m^3 and 0.5-5 ppm for solids and liquids, respectively (data not shown).

212. As shown in Figure 25 and 26, dustiness, volatility and liquid quantity group changes between medium and high bands implied no difference in estimated concentration (Figure 25 a, and 26 a and b). Conversely, a factor of 10 was observed between low and medium bands. Tenfold increases were detected for low to medium, and from medium to high solid quantity group (Figure 25b). Similarly, tenfold decreases were observed for minimum requirements to engineering controls, and engineering controls to containment (Figure 25 c and 26 c). This, behaviour concur with the exposure band table provided in the tool (Figure 27). Thus, no unexpected behaviours were observed. For exposure duration (solids and liquids) and application surface size, tenfold concentration increase were detected between <15 min and >15 min, and <1m^2 and >1m^2 options, respectively (Figure 25d, and 26d and 26e).

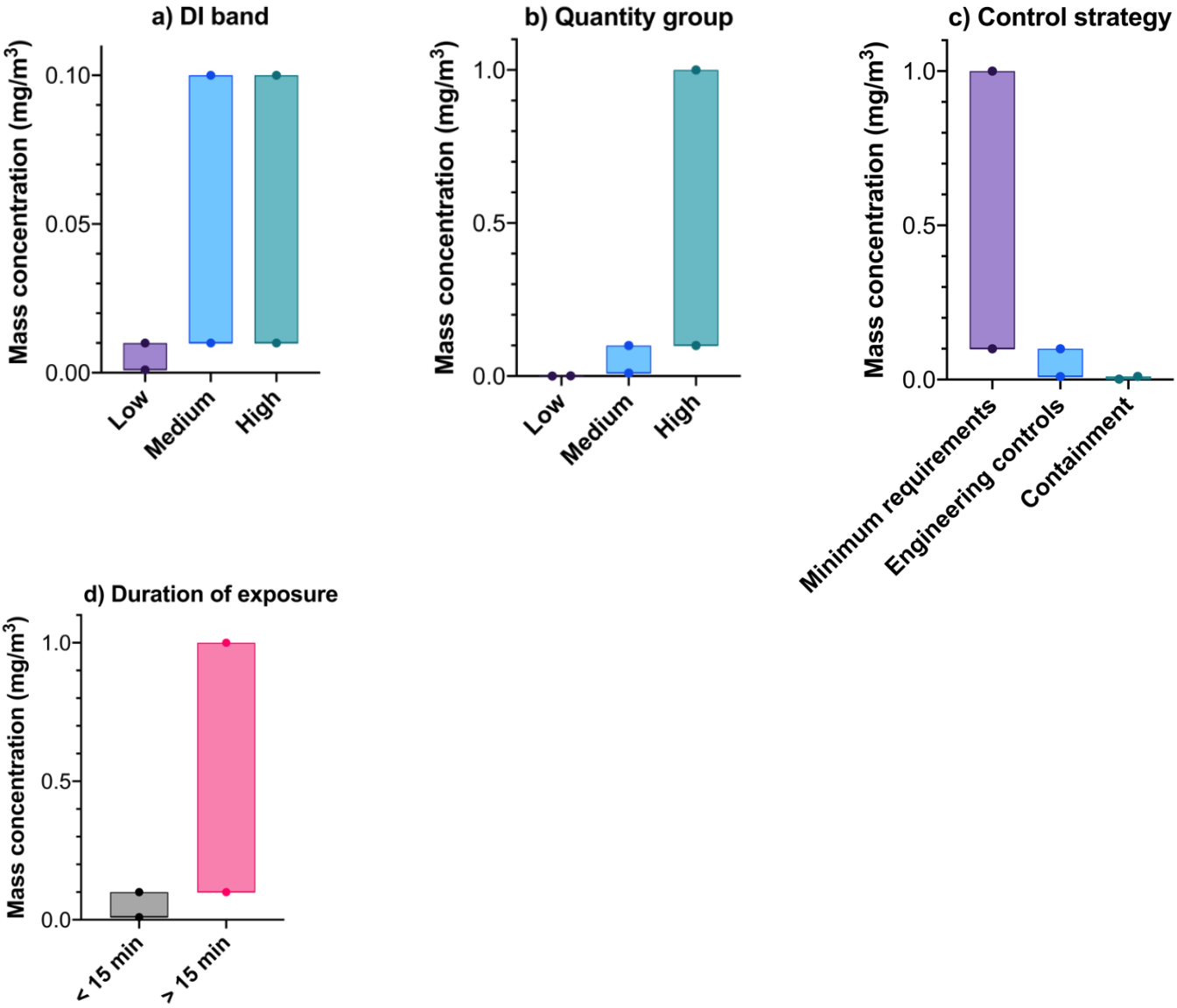


Figure 25. EMKG OAT SA results for solid materials.

Note: Minimum and maximum concentration range provided.

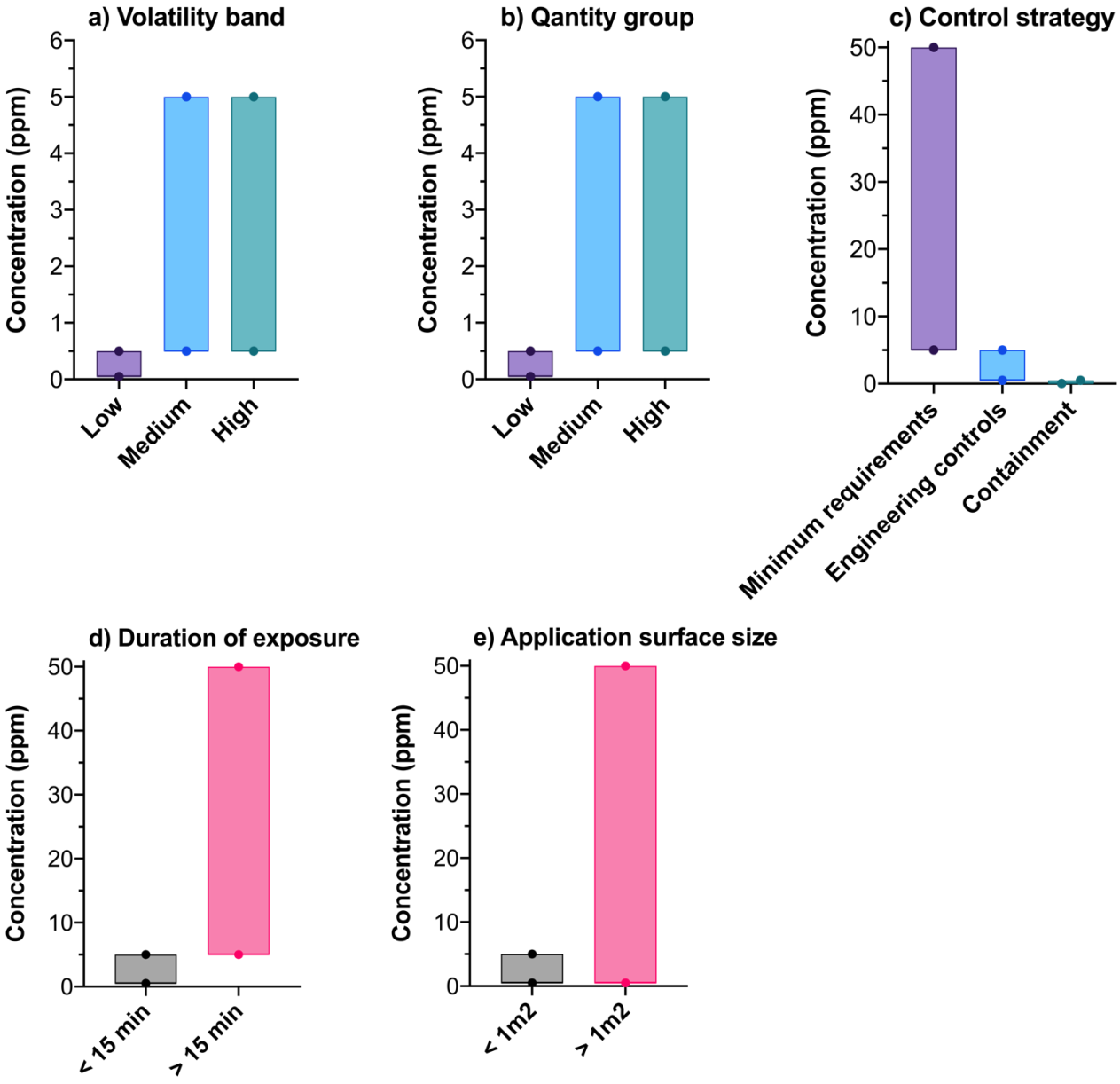


Figure 26. EMKG OAT SA results for liquids.

Note: Minimum and maximum concentration range provided.

Exposure potential band

Exposure potential band	Quantity group	Dustiness band (release gro...	Description
1	Low	Low or medium	Grams of low / medium dusty solid
2	Low	High	Grams of high dusty solid, Kg / Tonnes of low dusty solid
	Medium or large	Low	
3	Medium	Medium or high	Kg of medium / high dusty solid
4	High	Medium or high	Tonnes of medium / high dusty sold

Exposure band

Predicted exposure level for dust, mg/m³

Control strategy	Solids EP Band 1	Solids EP Band 2	Solids EP Band 3	Solids EP Band 4
1	0.001 - 0.01	0.01 - 0.1	0.1 - 1	1 - 10
2	< 0.001	0.001 - 0.01	0.01 - 0.1	0.1 - 1
3	< 0.001	< 0.001	0.001 - 0.01	0.01 - 0.1

Exposure potential band

Exposure potential band	Quantity group	Vapour pressure	Description
1	Low	Low	Mililitres of low volatility liquid
2	Low	Medium or high	Mililitres of medium / high volatility liquid, litres / cubic metres of low volatility liquid
	Medium or large	Low	
3	High	Medium	Cubic metres of medium volatility liquid, litres of medium / high volatility liquid
	Medium	Medium or high	
4	High	High	Cubic metres of high volatility liquid

Exposure band

Predicted exposure level for vapour, ppm

Control strategy	Liquids EP Band 1	Liquids EP Band 2	Liquids EP Band 3	Liquids EP Band 4
1	< 0.5	0.5 - 5	5 - 50	5 - 500
2	< 0.05	0.05 - 0.5	0.5 - 5	0.5 - 50
3	< 0.05	< 0.05	0.05 - 0.5	0.05 - 0.5

Figure 27. EMKG exposure band allocation table for solids and liquids.

Source: EMKG tool.

213. The analysis performed revealed that the tool is not sensitive to the substance, molecular weight, boiling point and DNEL, whereas similar sensitivity (tenfold) was detected for control strategy, duration, surface size, quantity group, dustiness, and volatility. Most and least sensitive input parameters are detailed in Table 25.

Table 25. Most and least sensitive input parameters of EMKG tool.

Most sensitive inputs	Least sensitive inputs
Control strategy	Name & CAS
Duration	Mol. weight
Application surface size	Boiling point
Quantity group	DNEL
Dustiness and volatility	

4.2.7 Engineered Nanoparticle Airborne Exposure (ENAE) tool (CPSC ENP model) v1.0

Method

214. The SA on this web tool was performed using the OAT method discussed in Section 4.1.1. A specific scenario, the use of a MNM in a deodorant spray, was used for the analysis, which ensures that the parameters refer to the same scenario. The OAT range scanning was performed by varying reference values of 12 input parameters from -50% to +50% with an increment of 10%, resulting in 120 model runs. The reference values of input parameters, except for the particle deposition velocity, particle resuspension area and particle resuspension rate, were adapted from the work of Park et al. who studied airborne manufactured

nano-objects released from a deodorant spray product. The reference values for particle deposition velocity, particle resuspension area and particle resuspension rate were chosen from the default value provided by the tool. For the ventilation rate, the reference value was taken from the ConsExpo fact sheet on Cosmetics.

Model outputs and inputs

215. The average air concentration predicted by the tool was used as an output metric. Model input parameters that were subjected to the SA are given Table 26. A list of inputs that were not tested in the OAT method is given in Table 27, with justification for the exclusion.

Table 26. Input parameters for SA of ENAE – Most Likely Value = default value for OAT.

Input Name	Most likely value	Minimum value	Maximum value	Unit
Release amount	400	200	600	mg
Air change rate	3	1.5	4.5	1/h
Volume	40	20	60	m^3
Floor area	16	8	24	m^2
Particle diameter	250	175	425	nm
Particle density	1.2	0.6	1.8	g/cm^3
Floor particle deposition velocities	0.005	0.0025	0.0075	m/s
Floor resuspension area	0.028	0.014	0.044	m^2
Floor resuspension rate	0.0025	0.00175	0.00425	1/s
Initial zone concentration	2E8	1E8	3E8	$\#/m^3$
Initial floor loading	5E8	2.5E8	7.5E8	$\#/m^2$
Exposure time	10	5	15	min

Table 27. Input parameters excluded from ENAE SA.

Input name	Justification for exclusion
Ceiling and wall area	Not affecting the average air concentration
Wall and ceiling particle deposition velocities	Not affecting the average air concentration
Wall and ceiling resuspension rate and area	Not affecting the average air concentration
Initial wall and ceiling loading	Not affecting the average air concentration
Outdoor concentration	Not related to the scenario used.

Results

216. Figures 28 and 29 show the variations in output of the model across the changes in the input parameters for mass-based and particle-based estimations respectively. For the mass-based estimation, the particle size and density parameters have no influence on the output of the tool while they have an influence on the output for the particle-based estimation. The initial zone concentration and initial floor loading parameters have no effect on the output, as they are too low comported to the released amount. The other parameters have an influence on the output for both mass-based and particle-based estimations in the investigated scenarios. The most and least sensitive input parameters are given in Table 28 and Table 29 for mass-based and particle-based estimations respectively.

Table 28. Most and least sensitive input parameters of ENAE - mass-based estimation.

Most sensitive inputs	Least sensitive inputs
Released amount	Floor resuspension rate
Exposure time	Floor resuspension area
Room volume	Air flow rate

Table 29. Most and least sensitive input parameters of ENAE - particle-based estimation.

Most sensitive inputs	Least sensitive inputs
Released amount	Floor resuspension rate
Exposure time	Floor resuspension area
Room volume	Air flow rate
Particle density	
Particle diameter	

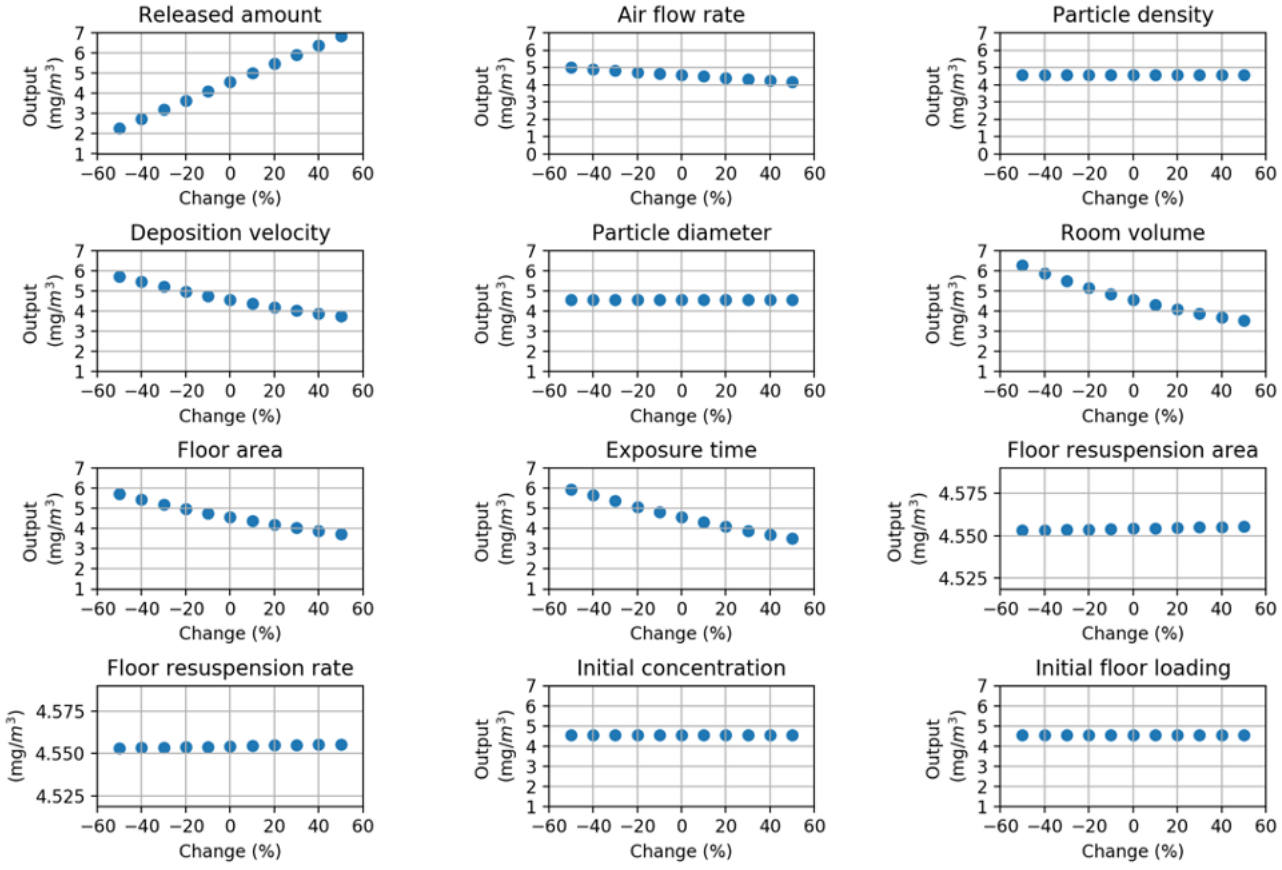


Figure 28. Variation in the output of ENAE as function of changes in input parameters for mass-based estimation.

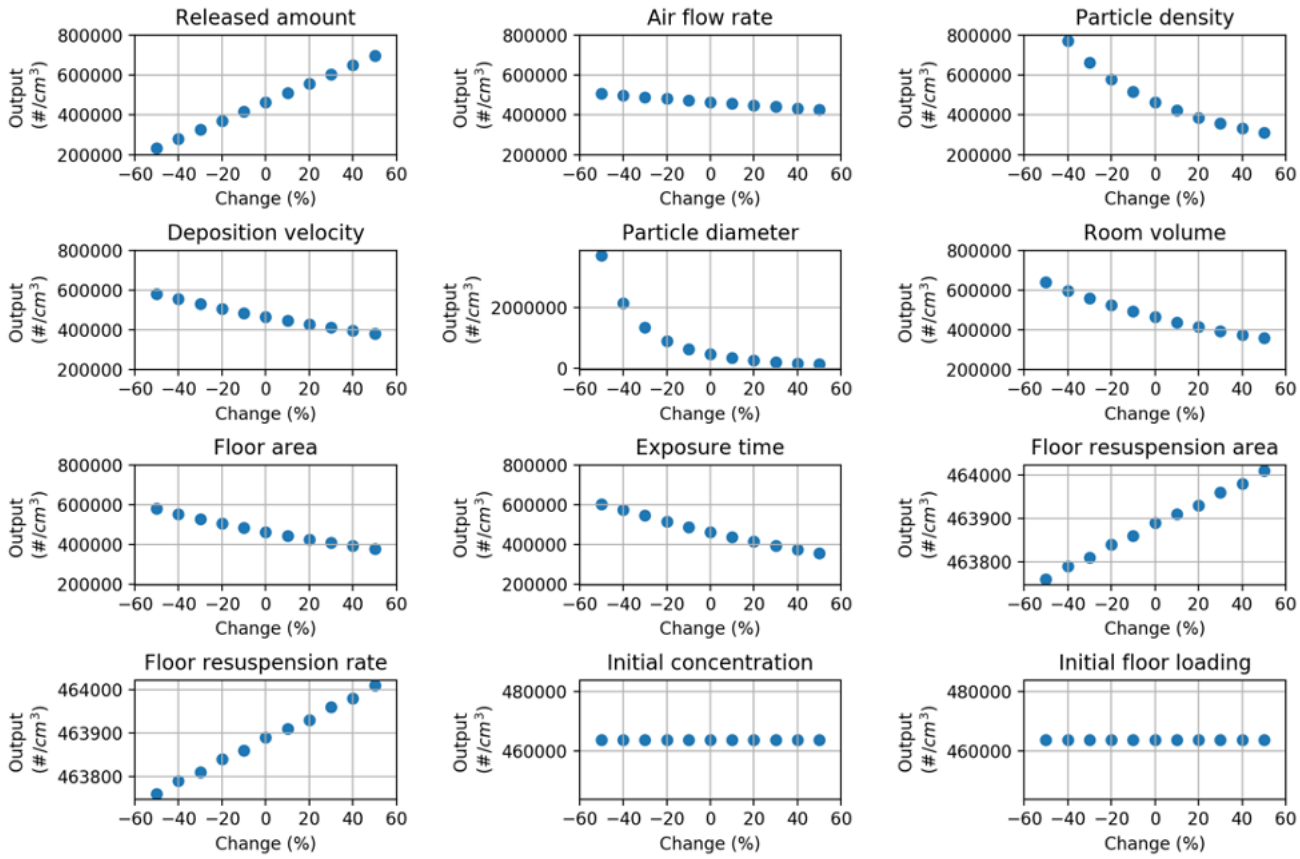


Figure 29. Variation in the output of ENAE as function of changes in input parameters for particle-based estimation.

4.2.8 Control Banding (CB) Nanotool v2.0

Method

217. The SA on this tool was performed by the OAT method within the caLIBRAte project. Considering that the vast majority of input parameters in the CB Nanotool are fixed and can only be chosen from a drop list menu, the SA of the CB Nanotool is done by evaluating a combination of all input parameters from drop list menus, with no possibility to vary along a range of values, by changing one value at time and obtaining different defined set of input parameters. To generate a reference scenario, a set of input parameters values was defined based on the experts' judgements on the most likely options.

Model outputs and inputs

218. The RL (control band) derived by a combination of hazard and exposure scores (see Section 3.11) was used as an output metric. Model input parameters that were subjected to the SA are given in Table 30. A list of inputs that were not tested in the OAT method is given in Table 31, with justification for the exclusion.

Table 30. Input parameters for SA of the CB Nanotool. Most Likely Value = default value for OAT.

Input name	Most likely value	Minimum value	Maximum value	Unit
Lowest OEL (PM*)	5	100	0.0005	µg/m³
Carcinogen (PM*, MNM**)	Unknown	No	Yes	[-]
Reproductive hazard (PM*, MNM**)	Unknown	No	Yes	[-]
Mutagen (PM*, MNM**)	Unknown	No	Yes	[-]
Dermal hazard (PM*, MNM**)	Unknown	No	Yes	[-]
Asthmagen (PM*, MNM**)	Unknown	No	Yes	[-]
Surface reactivity	Unknown	Low	High	[-]
Particle shape	Unknown	Compact or spherical	Tubular or fibrous	[-]
Particle diameter	11-40 nm	>40 nm	1-10 nm	nm
Solubility	Unknown	Soluble	Insoluble	[-]
Estimated maximum amount of chemical used in one day	1	0.001	500	
Dustiness	Unknown	None	High	[-]
Number of employees with similar exposure	1-5	1-5	> 15	n
Frequency of operation (annual)	Unknown	Yearly	Daily	[-]
Operation duration (per shift)	30-60	< 30	> 4	min

* PM: Parent Material; **NM: Nano Material.

Table 31. Input parameters excluded from CB nanotool SA.

Input name	Justification for exclusion
Activity number	Not affecting the RL
Scenario description	Not affecting the RL
(Free text)	Not affecting the RL
Name or description of nanomaterial	Not affecting the RL
CAS#	Not affecting the RL
Activity classification	Not affecting the RL

Results

219. Table 32 provides the sensitivity of the model output across the tested parameters. As can be observed, both the exposure-related and hazard-related parameters contribute almost all the same with the exception of the Frequency of Operation (annual) and Lowest OEL that demonstrate non-sensitivity to the change. The most and least sensitive exposure-related input parameters are summarized in Table 33.

Table 32. Results of SA to CB Nanotool.

Input name		Minimum value	Most likely value	Maximum value
Hazard	Lowest OEL (PM*)	RL2	RL2	RL2
	Carcinogen (PM*, MNM**)	RL2	RL2	RL3
	Reproductive hazard (PM*, MNM**)	RL2	RL2	RL3
	Mutagen (PM*, MNM**)	RL2	RL2	RL3
	Dermal hazard (PM*, MNM**)	RL2	RL2	RL3
	Asthmagen (PM*, MNM**)	RL2	RL2	RL3
	Surface reactivity	RL2	RL2	RL3
	Particle shape	RL2	RL2	RL3
	Particle diameter	RL2	RL2	RL3
	Solubility	RL2	RL2	RL3
Exposure	Estimated maximum amount of chemical used in one day	RL2	RL2	RL3
	Dustiness	RL2	RL2	RL3
	Number of employees with similar exposure	RL2	RL2	RL3
	Frequency of operation (annual)	RL2	RL2	RL2
	Operation duration (per shift)	RL2	RL2	RL3

* PM: Parent Material; **NM: Nano Material.

Table 33. Most and least sensitive exposure-related input parameters of the CB Nanotool.

Most sensitive inputs	Least sensitive inputs
Estimated maximum amount of chemical used in one day	Frequency of operation (annual)
Dustiness	
Number of employees with similar exposure	
Operation duration (per shift)	

4.2.9 LiCARA nanoSCAN v1.0

Method

220. The SA on this tool was performed by the OAT method within the caLIBRAte project. For each change in input parameters, the corresponding output value is manually estimated in terms of output transition value. The output transition value can be mathematically expressed as the numerical difference between the possible maximum and minimum values of a particular output. This allows quantifying the sensitivity associated with an input parameter. The ranges in which an input parameter is varied cover all possible arguments an input parameter can take.

Model output and inputs

221. The tool provides seven outputs, among which occupational health risks and consumer health risks were used as output metrics for the SA of the tool for occupational and consumer risks. Occupational and consumer risk-related inputs that were subjected to the SA are given in Table 34.

Table 34. List of input parameters and their possible responses for each output of LiCARA nanoSCAN.

Input name	For which output?	Possible responses
Hazard & exposure during manufacture of the nanomaterial	Occupational Health Risks	Hazard and exposure score (from 0 to 1) from Stoffenmanager
Hazard & exposure during processing the nanomaterial		Hazard and exposure score (from 0 to 1) from Stoffenmanager
Hazard & exposure during application of the nanoproduct		Hazard and exposure score (from 0 to 1) from Stoffenmanager
At what location is the nanoelement situated in the article or the product?	Consumer Health Risks	In bulk / In liquid / On surface
What is the size of the consumer population using the nanoproduct and hence which may be exposed?		Low fraction / High fraction / Unknown
Hazard score		From 0 to 1 (Occupational Health Risks)

Results

222. As mentioned in Section 3.12, the LiCARA nanoSCAN tool assesses the occupational health risks through the hazard and exposure scores from Stoffenmanager Nano 1.0 during the manufacturing, processing, and application stages of the product containing nanomaterial. As shown in Figure 30, all these three scores also have an equal influence over the output with the output transition value equal to 1. The baseline value of the three input parameters is 0.57.

223. Regarding the consumer health risk, Figure 31 shows that the occupational health risks is the most influential input parameter with the output transition value equal to 0.57 when its value changes from 0 to 0.57 to 1. It also shows the nanoelement location in the article has approx. 50% lower influence than the first input parameter as its output transition value is equal to 0.28 when the responses are changed from "*In bulk*" to "*On surface*" to "*In liquid*". The influence over the output further decreases by 24% in the case of the size of the consumer population which has the output transition value equal to 0.14. As done before, the baseline values of the input parameters are mentioned along the bold orange coloured line at Consumer health risks = 0.43. The most and least sensitive input parameters relevant to the occupational and consumer health risks are summarized in Table 35.

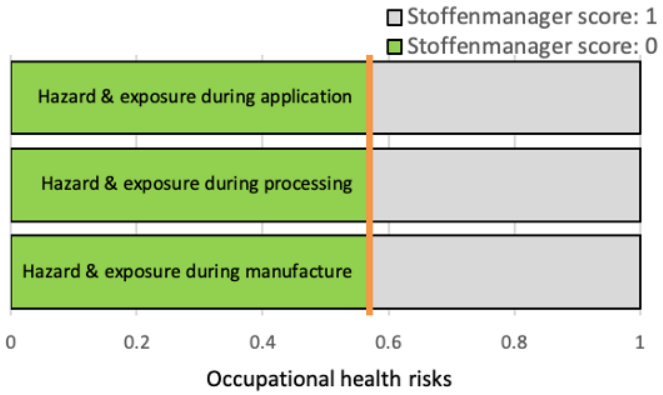


Figure 30. Influence of the input parameters on the occupational health risks of LiCARA nanoSCAN.

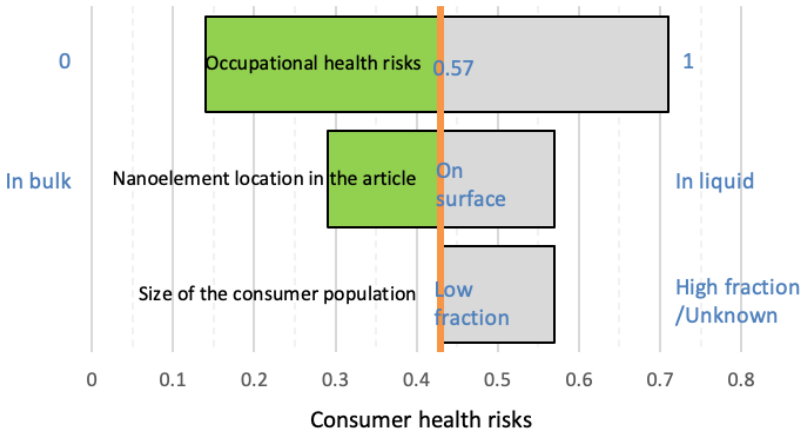


Figure 31. Influence of the input parameters on the consumer health risks of LiCARA nanoSCAN.

Table 35. Most and least sensitive parameters of the LiCARA nanoSCAN for occupational and consumer health risks. N/A: not applicable.

Most sensitive inputs	Least sensitive inputs
Stoffenmanager's hazard & exposure score during product manufacturing	N/A
Stoffenmanager's hazard & exposure score during product processing	
Stoffenmanager's hazard & exposure score during product application	
Occupational health risks	

4.2.10 NanoSafer v1.1β

Method

224. The SA of the NanoSafer CB v. 1.1β was conducted following the OAT approach as described in Section 4.1.1. Due to the model characteristics, a deterministic SA approach was taken in which reference ("*most likely*") values of the input parameters and relative ranges of changes were predefined considering the NanoSafer algorithms and restrictions, and the authors' judgments. The SA testing of the tool was conducted only for powder handling scenarios and not for the point source release. This was because the aerosol dispersion algorithm for point source release is the same as the one used for powder handling scenarios, and the emission rate is used directly with no modification in the aerosol dispersion model.

Model output and inputs

225. The RL (resulting from combination of the hazard and exposure bands) provided by the NanoSafer was used as output parameter for the SA. Model input parameters subjected to the SA are given in the Table 36. Input parameters not included in the SA and the justification for exclusion are provided in Table 37.

Table 36. Input parameters for SA of NanoSafer.

Input name	Most likely value	Minimum value	Maximum value	Unit
Material Options				
Is the material named with any of the following words? [mandatory] (Y/N) Nano Dot Cluster Fullerene Fulleroid Fullerol Quantum Organoflake Organoclay Tube Dendrimer Ultrafine	Yes	no	yes	(Y/N)
Is the material chemically surface-modified (coated / functionalized)? [mandatory] (Y/N)	Yes	no	yes	(Y/N)
Is the shape of the primary particles known? [mandatory](Y/N)	Yes	no	yes	(Y/N)
Size of particles [mandatory] is there any information on the size of the primary particles? (Y/N)	N/A	no	yes	(Y/N)
Average size [mandatory] Are the primary particles reported to have an average size? (Y/N)	N/A	no	yes	(Y/N)
Specific size-range [mandatory] Are the primary particles reported to have a size range? (Y/N)	N/A	no	yes	(Y/N)
Specific surface area [mandatory] Is the specific surface area known? (Y/N)	Yes	no	yes	(Y/N)
Morphologies (select option):				
Granular	Not selected			
Shortest dimension	100	1	6000	nm
Spherical / Isometric	Selected			
Shortest dimension	100	1	6000	nm
Flake / Plate / Tabular / Clay	Not selected			
Shortest dimension	100	1	6000	nm
Intermediate dimension	100	1	6000	nm
Longest dimension	100	1	6000	nm
Needle	Not selected			
Shortest dimension	100	1	6000	nm
Longest dimension	100	1	6000	nm
Rod	Not selected			
Shortest dimension	100	1	6000	nm
Longest dimension	100	1	6000	nm
Whiskers	Not selected			
Shortest dimension	100	1	6000	nm
Longest dimension	100	1	6000	nm
Wire	Not selected			
Shortest dimension	100	1	6000	nm
Longest dimension	100	1	6000	nm
Fibre	Not selected			
Shortest dimension	100	1	6000	nm
Longest dimension	100	1	6000	nm
Tube	Not selected			
Shortest dimension	100	1	6000	nm
Longest dimension	100	1	6000	nm
Fullerene	Not selected			
Shortest dimension	100	1	6000	nm
Dendrimer	Not selected			
Shortest dimension	100	1	6000	nm
Average size [mandatory] Enter average size (nm)	100	1	6000	nm
Size range lower [mandatory] Specific lower size range (nm)	100	1	6000	nm
Size range upper [mandatory] Specific upper size range (nm)	100	1	6000	nm

Input name	Most likely value	Minimum value	Maximum value	Unit
What is the specific surface area of the powder material? [mandatory] (m^2/g)	30	10	2260	nm
What is the relative density (specific gravity) of the material [mandatory] As an example the density of rutile TiO2 is typically given as 4.23 g/cm^3. If the value is not given, data on most materials is available at http://webmineral.com/ [g/cm3]	3	1	17	g/cm^3
What is the solubility of the material in water? [mandatory] For precautionary reasons, a material is not considered water-soluble unless the solubility limit exceeds 1 g/L or is listed as soluble or highly water-soluble. If a value is not given, information is typically available in handbooks or through internet searches. [please choose from the list]	Non-soluble	Non-soluble	Soluble	g/L
What is the respirable dustiness index (choose dustiness level if you do not have the test result) [mandatory] For precautionary reasons, we suggest to use "high" dustiness level as a default value for new materials with no information. [mg/kg] [or select from list]	187.5	5	950	mg/kg
Process Options				
Energy level	0.50	0.01	1.00	N/A
Enter the total amount of nanomaterial used per cycle at the workstation?	50	0.1	900	kg
How long does it take to perform one cycle at the work-station?	30	5	45	min
How many minutes pass between each work cycle?	5	1	19	min
How many times is the work cycle repeated daily?	4	1	7	N/A
Enter the mass handled per scoop, bag, big-bag etc. in the work cycle	5	0.1	160.1	kg
Enter the time required to pour one scoop, bag, big-bag etc. in the work cycle	3	1	26	min
Length of workroom	15	5	45	meters
Width of workroom	15	5	45	meters
Height of workroom	15	5	45	meters
ACH in the work room	3	0	25	1/h
Activity level in the work room	Moderate	Low / Not Known	High	N/A
Hazard Options				
Is there a nanospecific occupational exposure limit (OELnano) or target value? (Y/N)	No	N/A	N/A	(Y/N)
Nanospecific OEL (OELnano) [if Yes to the previous question]	10	0.01	9.76	mg / m^3
Exposure limit for respirable dust (OEL) [if No to the first question]	10	0.01	9.76	mg / m^3
Toxicological information – choose Risk Sentences or Hazard Statements	No	N/A	N/A	N/A

Note: Most Likely Value (reference) = default value for OAT, mean of distribution for OAT-MC and AAO-MC.

Table 37. Input parameters excluded from SA of NanoSafer and justification for exclusion.

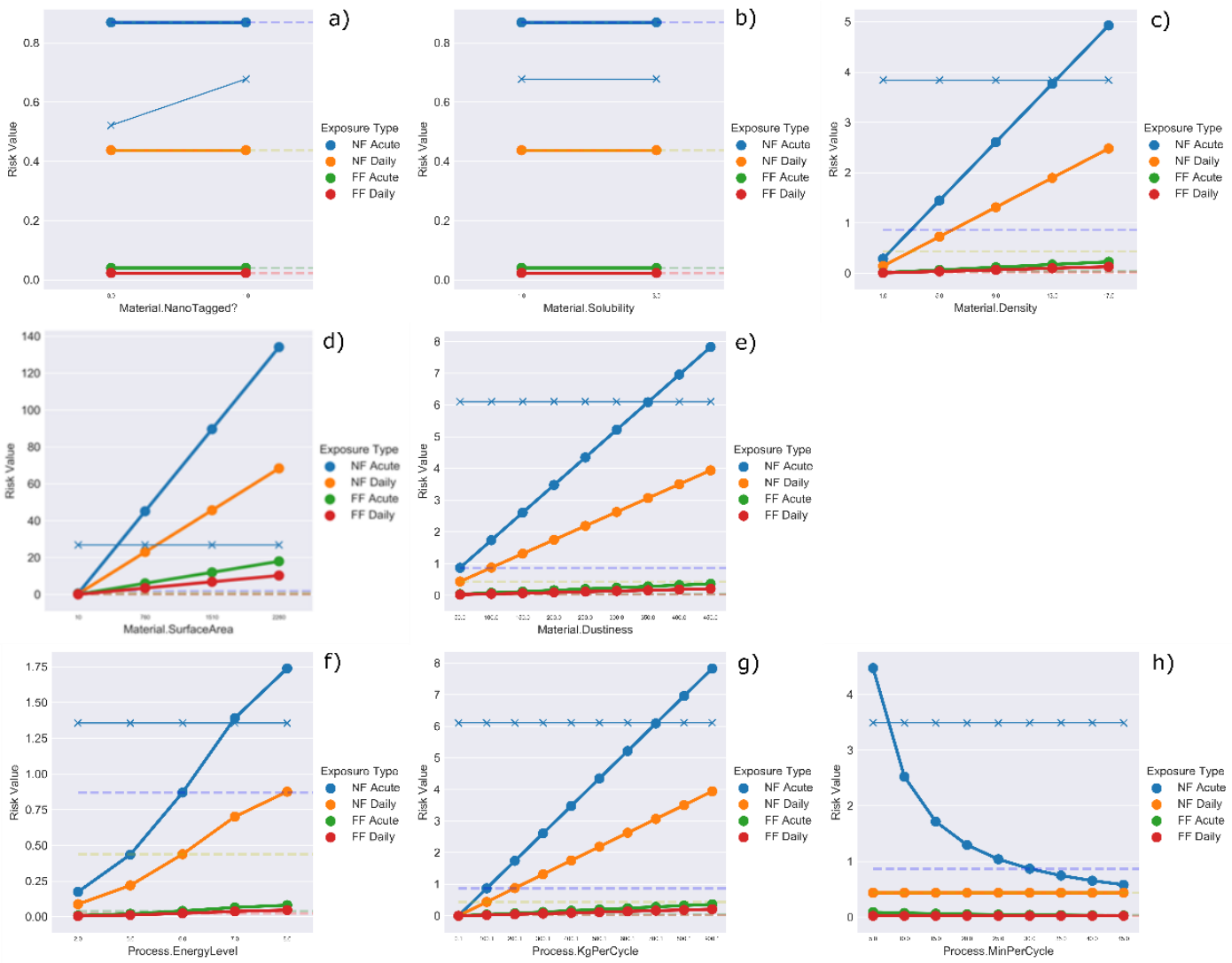
Input name	Justification for exclusion
MATERIAL inputs: Material name, Main substance, Manufacturer, CAS number and EINECS	These inputs are for keeping track of contextual information for the user and will not affect the model calculations. In the future, they may be used as an entry point for a database search.
PROCESS inputs: Name the work situation or process to be modelled	This input merely attaches an ID to the process for saving purposes.
HAZARD inputs: None	N/A

Results

226. Results of the RL variation for the different input parameters considered in the SA are shown in Figure 32. Variation for the different outputs provided by NanoSafer (NF Acute/Daily, FF Acute/Daily and Tox Score) were considered in the SA. Results show high sensitivities in the NF (acute and daily) for density, specific surface area, dustiness, process energy level, duration of work cycle, number of cycles, amount

used per cycle, pause between cycles, room size, air-exchange rate, process activity level and OEL. In general, input parameters sensitivity was similar regardless of the output considered (NF Acute/Daily, FF Acute/Daily). However, RL sensitivity was in general more marked for the NF than FF, and for acute than daily outputs. For example, dustiness and amount of material used input parameters showed a stronger liner behaviour in the NF acute (15 min) exposure than for daily (480 min) exposure, whereas nearly no effect was observed in the FF for both, acute and daily exposure. However, number of cycles and pause between cycles showed higher sensitivity for daily than acute output. For most parameters, positive linear correlations were obtained; however, some parameters showed exponential decay curves (e.g. duration of work cycle, room size or air-exchange rate). A summary of general most and least sensitive inputs detected on the SA is given in Table 38.

227. Lack of sensitivity was observed in the amount used per activity and duration of the activity (data not shown). This lack of sensitivity is correct as these two values are intended to trigger a warning if averaging the release rate over the work cycle is at risk of estimating misleading low acute exposure risks due to spaced high peak exposures in the work cycle.


a)
Risk Value
Material.NanoTagged?
Exposure Type
NF Acute
NF Daily
FF Acute
FF Daily
b)
Material.Solubility
c)
Material.Density
d)
Material.SurfaceArea
e)
Material.Dustiness
f)
Process.EnergyLevel
g)
Process.KgPerCycle
h)
Process.MinPerCycle

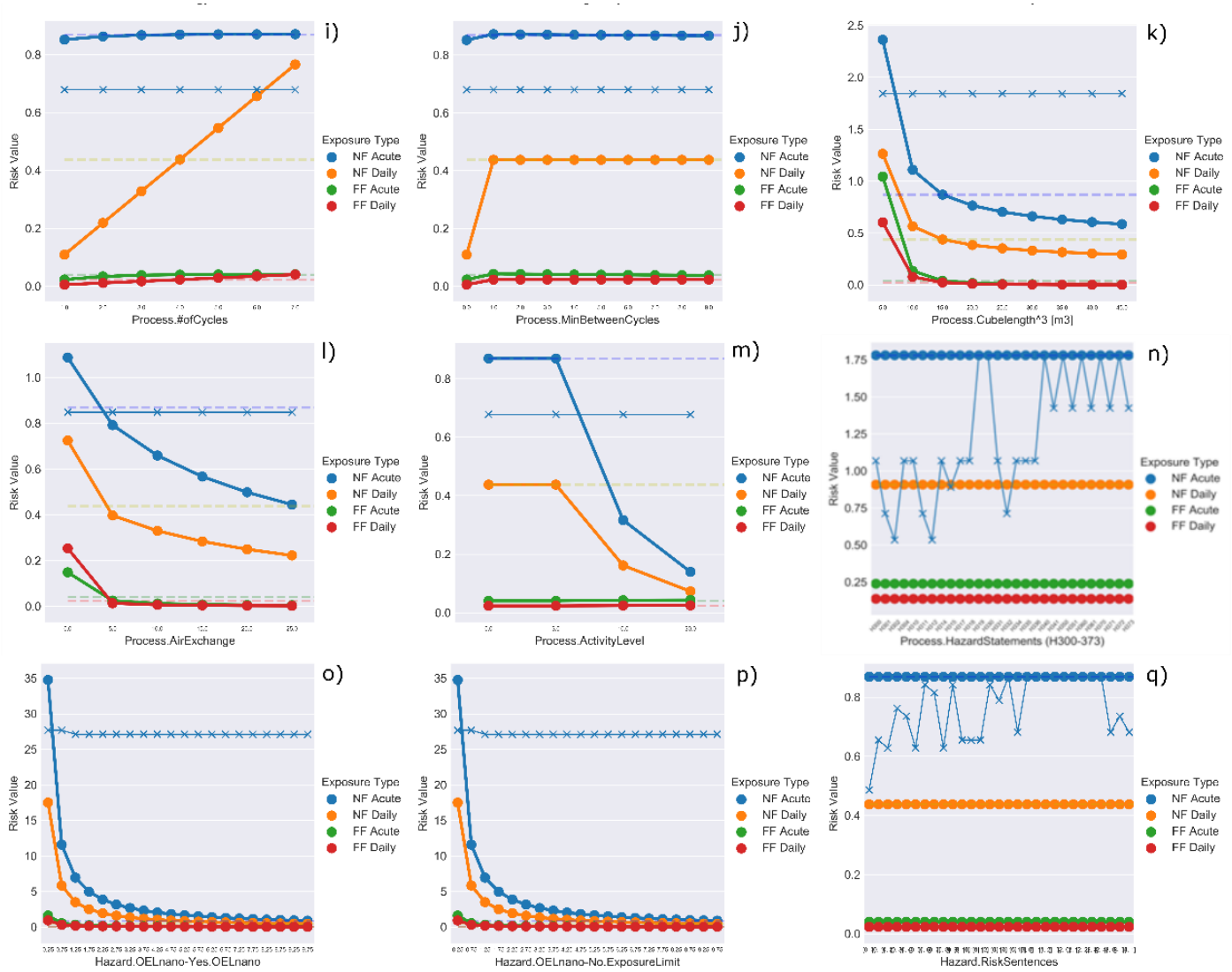


Figure 32. OAT SA results for NanoSafer output values (NF Acute/Daily, FF Acute/Daily and Tox Score) as functions of single input parameters.

Note: Note that the Tox Score (blue 'x') is defined as a score limited between 0.2 and 1, hence the result is normalized to the graph height, i.e. half height of y-axis corresponds to score = 0.5. The influence on the hazard and exposure RL due to: a) to whether the material is identified as a MNM or not; b) being insoluble or soluble in water; c) change in material skeletal density (i.e. relative gravity); d) change in specific surface area when material is defined as a MNM and the OEL for the nearest analogue bulk material is used; e) change in dustiness; f) change in process energy level (handling energy factor); g) kg used in a work cycle; h) changes in the duration of the work cycle; i); changes in number of work cycles; j) changes in the duration of pause between work cycles; k) changes in room size (volume); l) changes in ventilation rate; m) changes in activity level in the work area (unknown, low, moderate, high); n) changes due to presence of specific risk sentences (not used simultaneously with H-phrase); o) changes in nano-specific occupational exposure limit (OELnano); p) changes in occupational exposure limit of the nearest analogue bulk material; q) changes due to presence of specific hazard phrases (not used simultaneously with R-sentences).

Table 38. Most and least sensitive input parameters of NanoSafer.

Most sensitive inputs	Least sensitive inputs
OEL nano and bulk	Activity level
Material density	Process energy level
Specific surface area	ACH
Amount of material used in cycle	Number of work cycles per day
Dustiness	Pause between work cycles
Duration of work cycle	Coating
Room size	Amount of material used per activity in work cycle
GHS/CLP statements or R-phrases*	Duration of activity in work cycle
	Solubility in water

*Only for the Tox score.

4.2.11 The SUN Decision Support System (SUNDS)

Method

228. The SA used to examine influence of input parameters on SUNDS tool outputs was conducted by applying the OAT method with range scanning (Section 4.1.1). One hundred model runs were performed under the caLIBRAte project for each of the 52 analysed input parameters, therefore a total of 5200 model runs were performed.

Model output and inputs

229. The model provides seven outputs based on five modules of the Decision Support System: Social Impact Assessment (SIA), Economic Assessment (EA), Life Cycle Impact Assessment (LCIA), Ecological Risk Assessment (ERA) and Human Health Risk Assessment (HH). The different methodologies included in the five modules of SUNDS provide heterogeneous results, therefore the tool uses a sustainability portfolio to visualize the single outputs for global and lifecycle stage scores for all methodologies. Outputs of the methodologies are classified as high-medium-low benefit or high-medium-low impact by using a scale from 0-7.

230. For the HH class and RCR distribution, objectives of the present report, the model provides probabilistic distributions of risk along the four lifecycle stages and routes of exposure, for each analysed scenario, which are then assigned to the respective classification of the sustainability portfolio. In addition, the RCR is described through probabilistic distribution.

231. Input parameters for the HH assessment subjected to the SA for the SUNDS are given in Table 39. No input parameters were excluded in this SA.

Table 39. Input parameters for SA of SUNDS.

Input name	Most likely value	Minimum value	Maximum value	Unit
HH - Synthesis - Inhalation - Mean	0.13	1.00E-11	5	[-]
HH - Synthesis - Inhalation - SD	5.89	1	8	[-]
HH - Formulation - Inhalation - Mean	1.97	1.00E-11	5	[-]
HH - Formulation - Inhalation - SD	5.92	1	8	[-]
HH - Use - Inhalation - Mean	14.40	1.00E-11	5	[-]
HH - Use - Inhalation - SD	5.71	1	8	[-]
HH - End of life - Inhalation - Mean	1.4E-05	1.00E-11	5	[-]
HH - End of life - Inhalation - SD	5.88	1	8	[-]
HH - RCR - Exposure - Mean	0.08	3E-10	0.32	[-]
HH - RCR - Exposure - SD	0.13	5E-10	0.53	[-]
HH - RCR - Effect - Mean	-2.37	-5.416	0.64	[-]
HH - RCR - Effect - SD	1.76	1.68	1.9	[-]

Note: Most Likely Value = default value for OAT, mean of distribution for OAT-MC and AAO-MC.

Results

232. It was observed that changes in the output of HH module were mainly caused by life cycle stage distribution parameters. Figure 33 shows variations in the HH inhalation output across the changes in life cycle stage distribution mean and standard deviation (SD) for the synthesis, formulation, use and end-life cycle stages. The changes in the mean have the same influence on the outputs for the life cycle stages. Variations in other input parameters affect the output values, but their effect is significantly lower. Most and least sensitive input parameters are shown in Table 40.

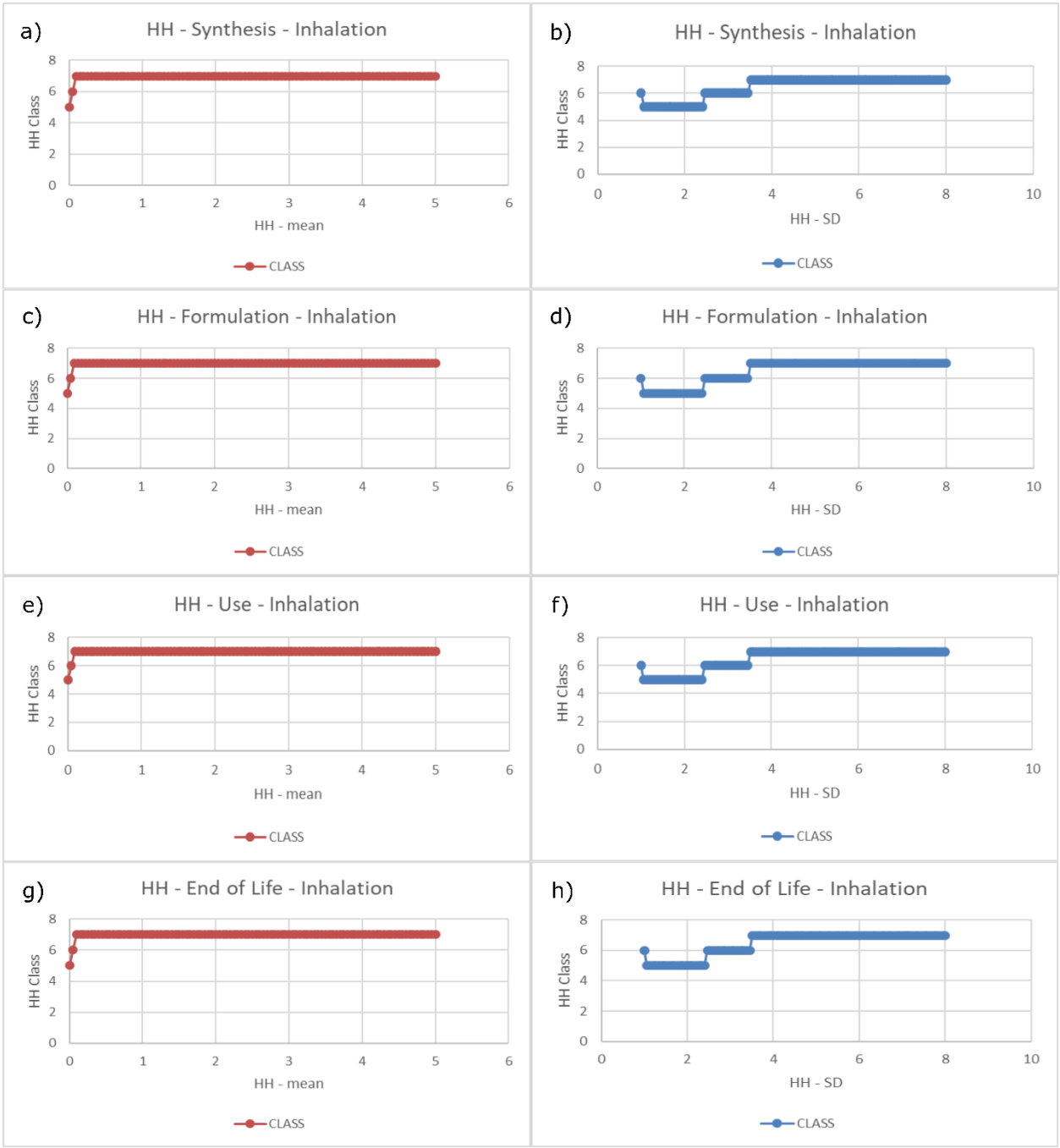


Figure 33. Output dependence on HH life cycle stage distribution Synthesis – Inhalation of SUNDS.

Note: a) mean and b) SD; Formulation – Inhalation – c) mean and d) SD; Use – Inhalation – e) mean and f) SD; and End of life – Inhalation – g) mean and h) SD.

233. The mean risk categorization ratio (RCR mu) and corresponding standard deviations (sigma) are illustrated in Figure 34. Figure 34a and 34b show variations in the HH exposure risk probability distribution mu for mu and sigma, respectively. The RCR mu has a linear trend to RCR exposure mu (Figure 34a) whereas the sensitivity of RCR sigma to the change of RCR exposure mu is very low (Figure 34b). Similarly, for RCR-exposure sigma and RCR effect mu, variations in RCR mu showed a linear trend with RCR exposure

sigma and RCR effect mu respectively (Figure 34 c and e) whereas a very low change was observed with RCR sigma (Figure 34 d and f). The sensitivity of the RCR mean and RCR sigma to RCR effect sigma is very low (Figure 34 g and h).

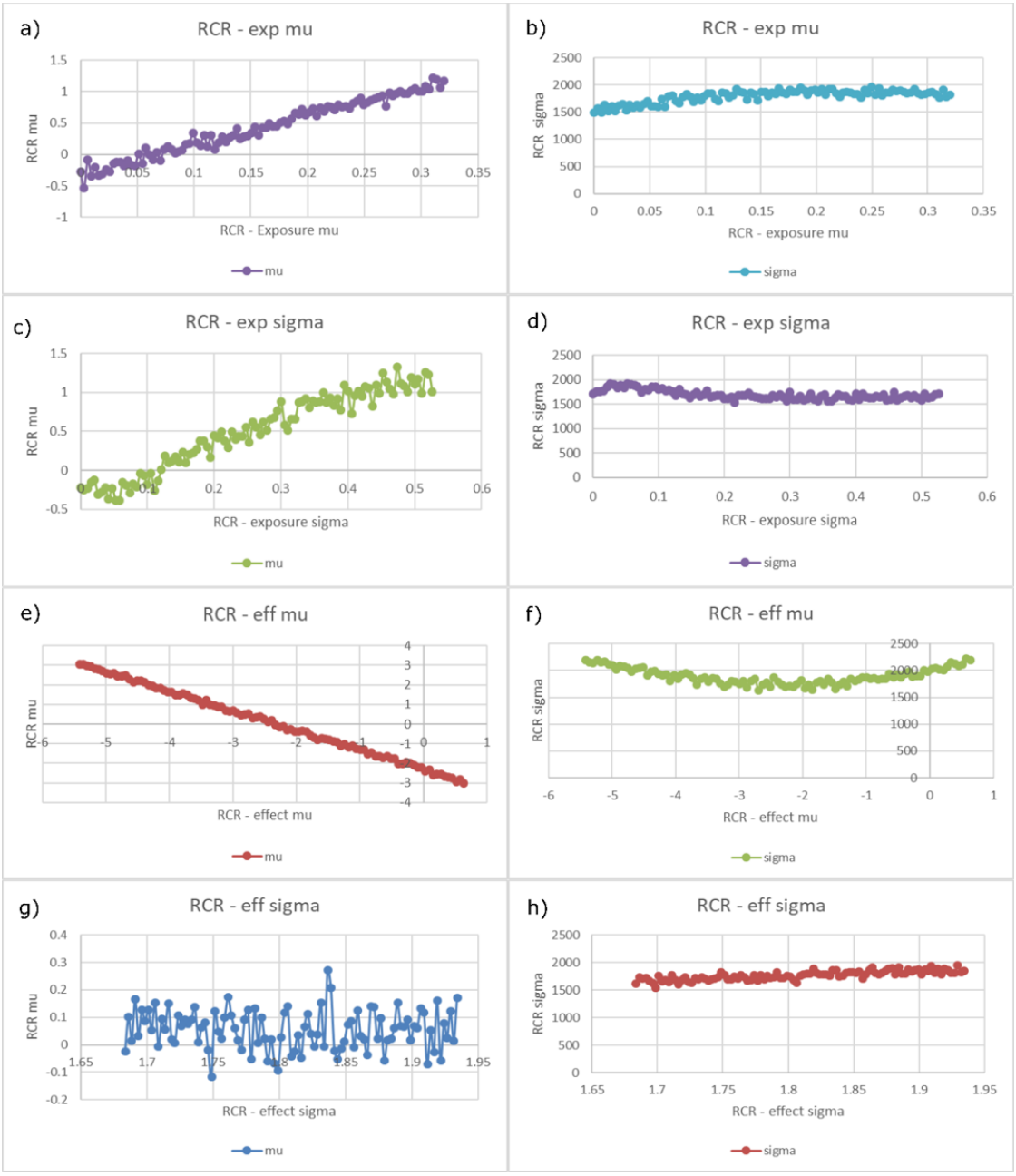


Figure 34. Output dependence on HH RCR – Exposure mu of SUNDS.

Note: a) mean and b) SD; RCR – Exposure sigma c) mean and d) SD; RCR- Effect mu e) mean and f) SD; and RCR – Effect sigma g) mean and h) SD.

Table 40. Most and least sensitive input parameters of SUNDS. Only for HH.

Most sensitive inputs	Least sensitive inputs
Life cycle stage distribution means	Variations in the other input parameters affect the output values, but their effect is significantly lower
Exposure mean	

4.2.12 ANSES tool

Method

234. The SA on the ANSES CB tool was performed by the diagnostic method, discussed in Section 4.1.5, and by the modified OAT method, discussed in Section 4.1.1, within the caLIBRAte project. For the diagnostic SA, the model runs 1 million times and for the modified OAT analysis, the model runs 4 million times.

Model outputs and inputs

235. The control, hazard and emission potential bands were used as output metrics. Model input parameters that were subjected to the SA are given in Table 41.

Table 41. List of input parameters and their possible responses of ANSES.

	Input name	Answer
Hazard	Does the product contain nanomaterials?	yes/no
	Is the nanomaterial already classified by a relevant authority?	yes/no
	Is the nanomaterial a biopersistent fibre?	yes/no
	Is there a preliminary hazard band of the bulk material?	yes/no
	Is there a preliminary hazard band of an analogous substance?	yes/no
	Is the product dissolution time longer than 1 hour?	yes/no
	Is there evidence that the reactivity of the product is not higher than that of the bulk or analogous material?	yes/no
Emission potential	Is the product a solid material, a liquid, a powder or an aerosol containing nanomaterials?	s/l/p/a
	Is the solid structure friable?	yes/no
	Is the liquid medium highly volatile?	yes/no
	Is the powder highly or moderately dusty?	yes/no
	Does the product release dust due to external forces while used?	yes/no
	Does the product melt while used?	yes/no

Results

236. Figure 35 shows the tool error rate in determining emission potential band as a function of the answer distribution and the probability of an error across input parameter relevant to the emission potential band. The default answer distribution is 80/20 and the error rate is 0%. As can be observed in Figure 35, no input parameter contributes significantly more than other parameters to the emission potential band. Three input parameters caused slightly higher amount of erroneous answers compared to others. These inputs are "*Does the product leave a powder when evaporated*", "*Is the liquid product sprayed*" and "Is *the powder product sprayed?*". Table 42 list the most and least sensitive parameters relevant to the emission potential band.

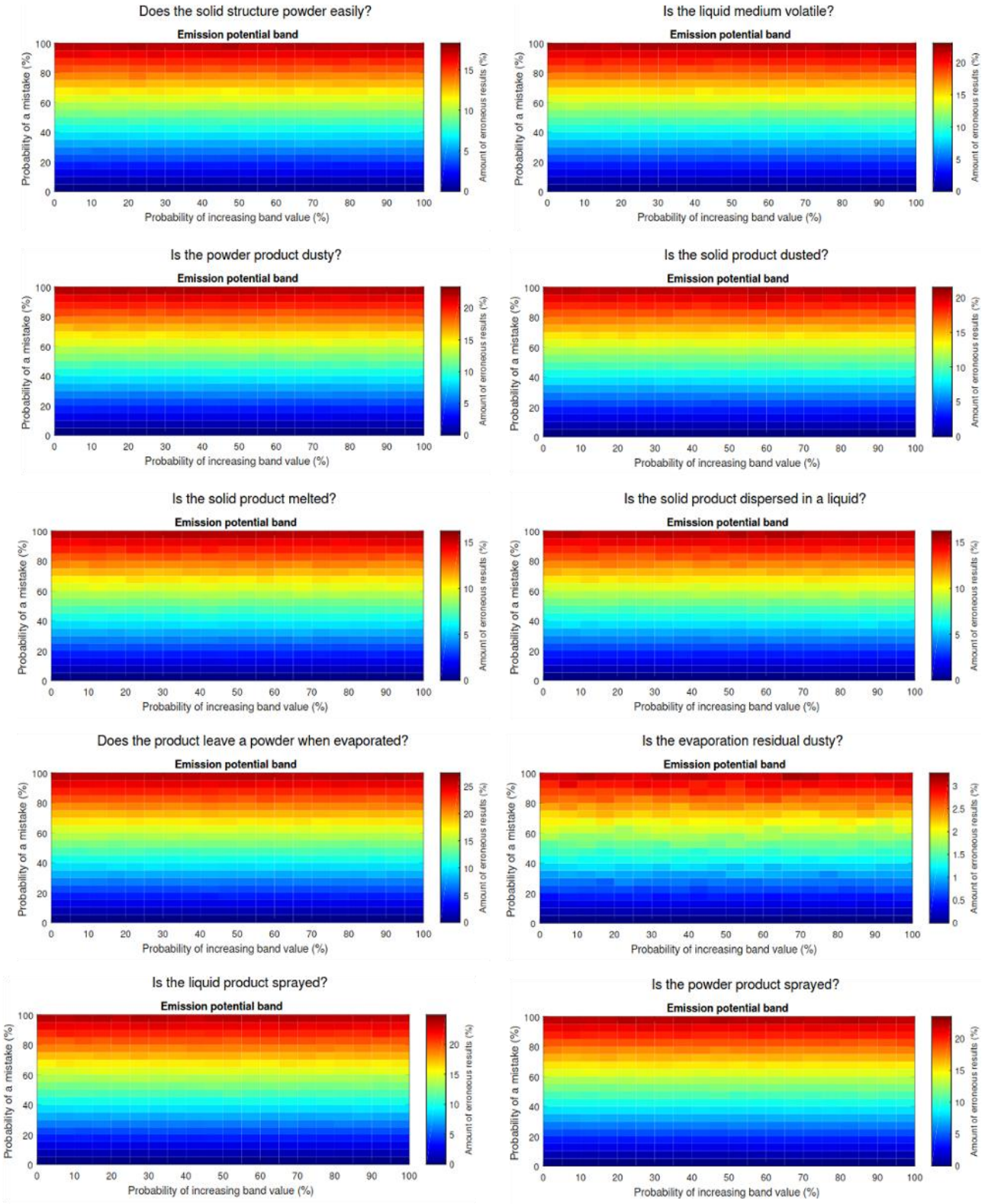


Figure 35. Answer distribution and error rate effects on the tool error across input parameters with 0 % default error rate and default 80/20 answer distribution of ANSES.

Table 42. Most and least sensitive parameters of ANSES CB Nanotool.

Most sensitive inputs	Least sensitive inputs
Almost equal sensitivity towards all input parameters, except the one listed in the next column	Is the evaporation residual dusty

4.2.13 Swiss Precautionary Matrix v3.0

Method

237. The OAT methodology, as described in Section 4.1, was selected to perform the SA testing in order to identify the most and least sensitive input parameters. Each input parameter was variated separately (number of runs = 26) and influence on output results was monitored. The worst-case scenario (highest score) was defined as the reference score to which all varied input parameters were compared because the input parameter "*nano-relevance*" acts as a knock-out criterion and would inhibit the analysis leading to overall scores of zero in a best-case scenario.

Model output and inputs

238. The model outputs are shown as scores for different output categories. A higher score is equal to a higher risk in the corresponding category. In total, eight different output categories were monitored throughout the analysis performed in caLIBRAte. However, five of the eight monitored outputs are related to the environmental part (named VUP; VUPSE; VUG,spez; VUGSE and VUG in Figure 36 and 37), which is out of the scope of the present report. Thus, this report will focus only on the output parameters "*Precautionary need for Workers; VA*", "*Precautionary need for Workers - worst case - ; VAWC*", and "*Precautionary need for Consumers; VV*". The same applies to the Input parameters, and those strictly related to the environment will not be considered. The output values combine the scores of the different spread sheets with the following equation:

$$V = N \times (W \times E + S)$$

239. In which, "*V*" is the output parameter (i.e. result), "*N*" is the score for the nano-relevance, "*W*" is the score for the hazard potential, "*E*" is the score for the exposure potential and "*S*" stands for the knowledge on the life cycle and material. Input parameters subjected to the SA for the Swiss Precautionary Matrix are given in Table 43. Input parameters not included in the SA and the justification for exclusion are provided in Table 44.

Table 43. Input parameters for SA of the Swiss Precautionary Matrix.

Input name	Minimum value	Medium value	Maximum value	Unit
N.X: Nano-relevance according to the precautionary matrix (i.e. contains nanoparticles and nanorods)				
N1a: Are the NPR agglomerates> 500nm?	0	N/A	1	[-]
N2A,V: Does deagglomeration of the agglomerates (or aggregates) to primary NPR or agglomerates <500nm occur under conditions in the body?	0	N/A	1	[-]
N2U: Is there a deagglomeration of the agglomerates (or aggregates) to primary NPR or agglomerates <500nm under the respective environmental conditions?	0	N/A	1	[-]
N2a: Are there agglomerates between 500nm and 10µm and can be absorbed by workers or consumers via the lungs?	0	N/A	1	[-]
S.X Specific framework conditions on the information status				
S1: Is the origin of the (nanoscale) starting materials known?	0	3	5	[-]
S2: Are the necessary data for filling the grid to be used for the nanoscale starting materials?	0	3	5	[-]
S3: Are the next users of the NPRs considered known?	0	3	5	[-]
S4: How accurate is the material system known or can disturbance factors (such as impurities) be estimated?	0	3	5	[-]
W.X Potential effect				
W1: Redox activity and / or catalytic activity of the NPR present in the nanomaterial	1	5	9	[-]
W2A,V: Stability (half-life) of the NPR present in the nanomaterial in the body	1	3	9	[-]
W2U: Stability (half-life) of the NPR present in the nanomaterial under environmental conditions	1	3	9	[-]
E1.X: Physical surroundings (this input parameter can be only selected as single choice)				
E1.1: Air	0	N/A	1	[-]
E1.2: Aerosol <10 µm	0	N/A	1	[-]
E1.3: Aerosol >10 µm	0	N/A	human: 0.1 environment: 1	[-]
E1.4: Liquid media	0	N/A	human: 0.1 environment: 1	[-]
E1.5: Solid matrix, not stable under conditions of use	0	N/A	human: 0.1 environment: 1	[-]
E1.6: Solid matrix, stable under conditions of use, NPR mobile	0	N/A	0.01	[-]
E1.7: Solid matrix, stable under conditions of use, NPR not mobile	0		0.0001	[-]
E2.X Maximum possible exposure of humans				
E2.1: Possible mass of NPR that a worker per day bypasses	1	5	9	[-]
E2.2: Possible mass of NPR with which a worker can come into contact in "worst case"	1	5	9	[-]
E2.3: Frequency with which a worker deals with the NPR	1	5	9	[-]
E2.4: Mass of NPR, which is used by a consumer per day across the product	1	5	9	[-]
E2.5: Frequency with which a consumer uses the product	1	5	9	[-]
E3.X Maximum possible input into the environment				
E3.1: Mass of NPR disposed of (waste water, exhaust air, waste) per year, which are not supplied to any specific disposal	1	5	9	[-]
E3.2: Mass of NPR in consumer products per year	1	5	9	[-]
E3.3: Mass of disposed NPR per year	1	5	9	[-]

Note: Maximum value = worst case (highest score) used as reference value.

Table 44. Input parameters excluded from SA of the Swiss Precautionary Matrix and justification for exclusion.

Input name	Justification for exclusion
Questions related to the spread sheet N (Nano-relevance)	The answers of this question act as a knock-out criterion meaning that in case of non-nanomaterial the result of this tool would be zero and therefore not applicable.
Complete spread sheet A	The sheet includes general questions concerning contact person, kind of material and aimed assessment category (workers, consumer and environment). Since it has no effect on the following sheets (except disregarding not selected assessment categories) it was omitted.

Results

240. Output variation with input parameters is shown in Figures 36, 37 and 38. The variation of the input parameters S1- S4 (Specific framework conditions on the information status) had an effect slighter than one percent on the overall scoring (Figure 36), suggesting a low sensitivity of these input parameters regarding the overall results. The reason for the low impact of the variation is the additive relation of these parameters in the score equation.

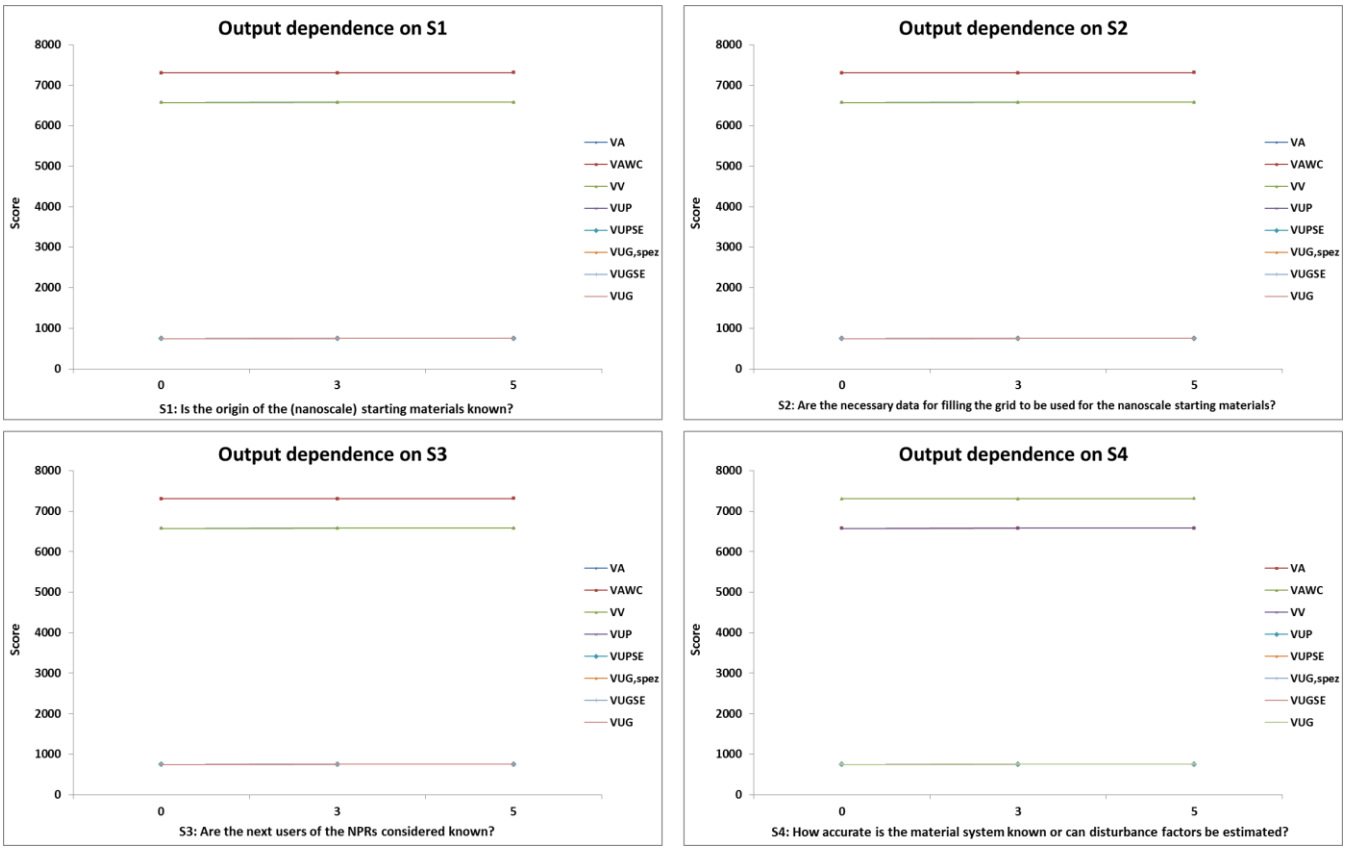


Figure 36. SA of the input parameters of the Swiss Precautionary Matrix S1-S4 and their influence on the output results.

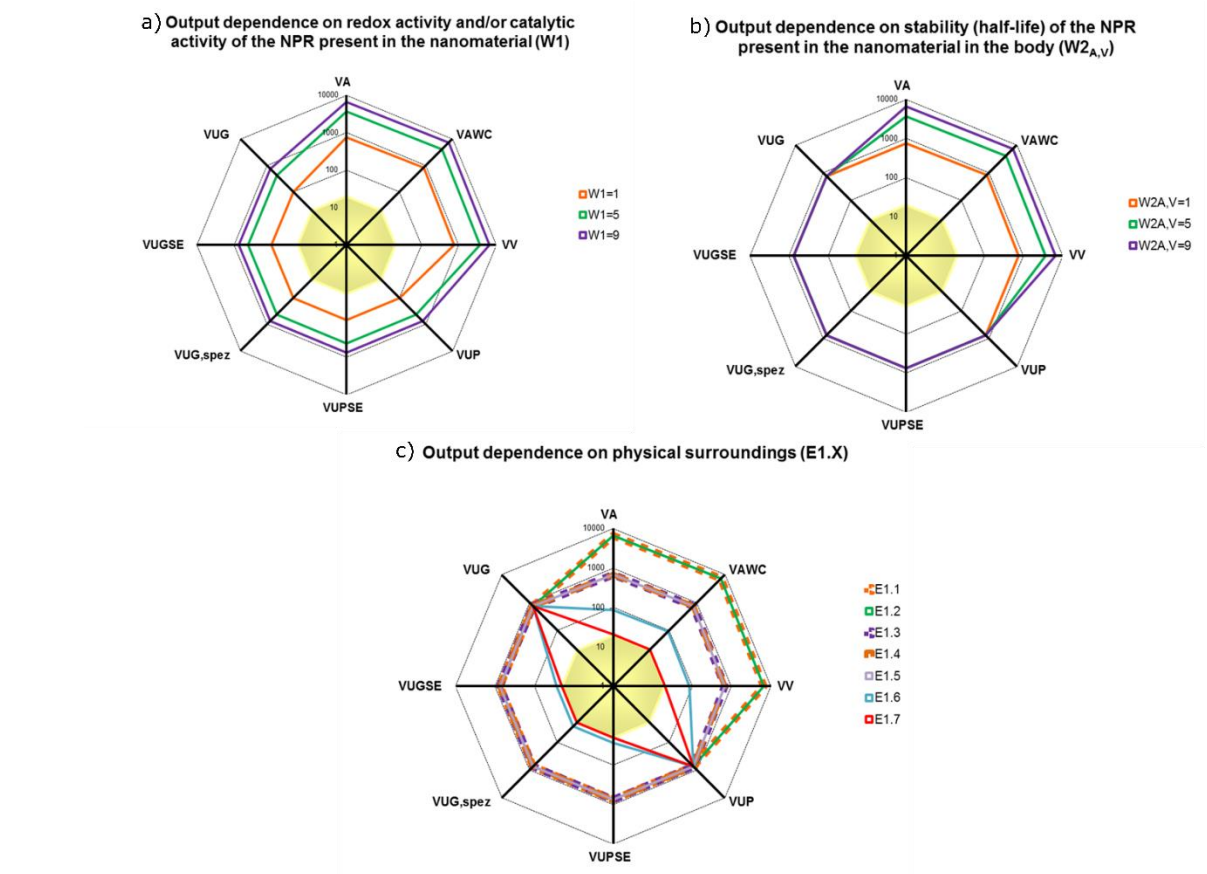


Figure 37. Radar chart of the SA for the input parameters of the Swiss Precautionary Matrix.

Note: a) W1; b) W2A,V; and c) E1.X.

241. Variation of outputs with the input parameter W1 (redox and/or catalytic activity) illustrated in Figure 37 a, show the highest variation between the highest (9) and lowest (1) score for workers and consumers (VAWC, VA, VV) with decreases up to 88.6%. Similarly, for the input parameter W2A,V (Stability (half-life) of the NPR present in the nanomaterial in the body), represented in Figure 37 b, the maximal decrease is approximately 88% when comparing the highest and lowest scores for the worker and consumer outputs.

242. Input parameters E1.1-E1.7 related to the physical surroundings define the exposure, attribute the highest score to air released materials, and the lowest score to non-mobile nanomaterials embedded in a solid matrix. Consequently, the parameters have different strong influences on the overall scores as shown in Figure 37 c. The input parameters E1.3 – E1.5 decreases the scores for the worker and consumer output parameters considerably by 89.7%. In contrast, a slighter effect is observed for the input parameters E1.6-E1.7. Conversely, E3.1-E3.3 related to input material into the environment (data not shown) do not have any influence on worker and consumer output.

243. Input parameters E2.1 and E2.3, related to the amount of material handled and how often a worker comes into contact with a nanomaterial, influence on score variation up to 88.6% (Figure 38 a and c). Conversely, E2.2 (mass contact in a worst-case scenario), changed only with approximately nine percent and remains at a high score of 6662 out of 7310 points, which is also reasonable due to the fact of a worst-case consideration (Figure 38 b). With the input parameters E2.4 (mass used by a consumer) and E2.5 (exposure frequency of consumers), the potential consumer exposure is regarded (Figure 38 d and e). For both inputs, variation on consumer output is similar, with a decrease up to 88.6% when compared to the

reference scores. In Table 45 a summary of most sensitive (organized from the highest to lowest change on score) and least sensitive input parameters is presented.

Table 45. Most and least sensitive input parameters of Swiss Precautionary Matrix.

Most sensitive inputs	Least sensitive inputs
Nano-relevance according to the precautionary matrix (N.X)	Origin of the nanomaterial (S1)
Solid matrix, stable under conditions of use, NPR not mobile (E1.7)	Data availability (S2)
Solid matrix, stable under conditions of use, NPR mobile (E1.6)	Downstream user (S3)
Solid matrix, not stable under conditions of use (E1.5)	Purity of the material system (S4)
Redox activity and/or catalytic activity of NPR present in the nanomaterial (W1)	
Stability (half-life) of the NPR present in the nanomaterial in the body (W2,A,V) or under environmental conditions (W2,U)	

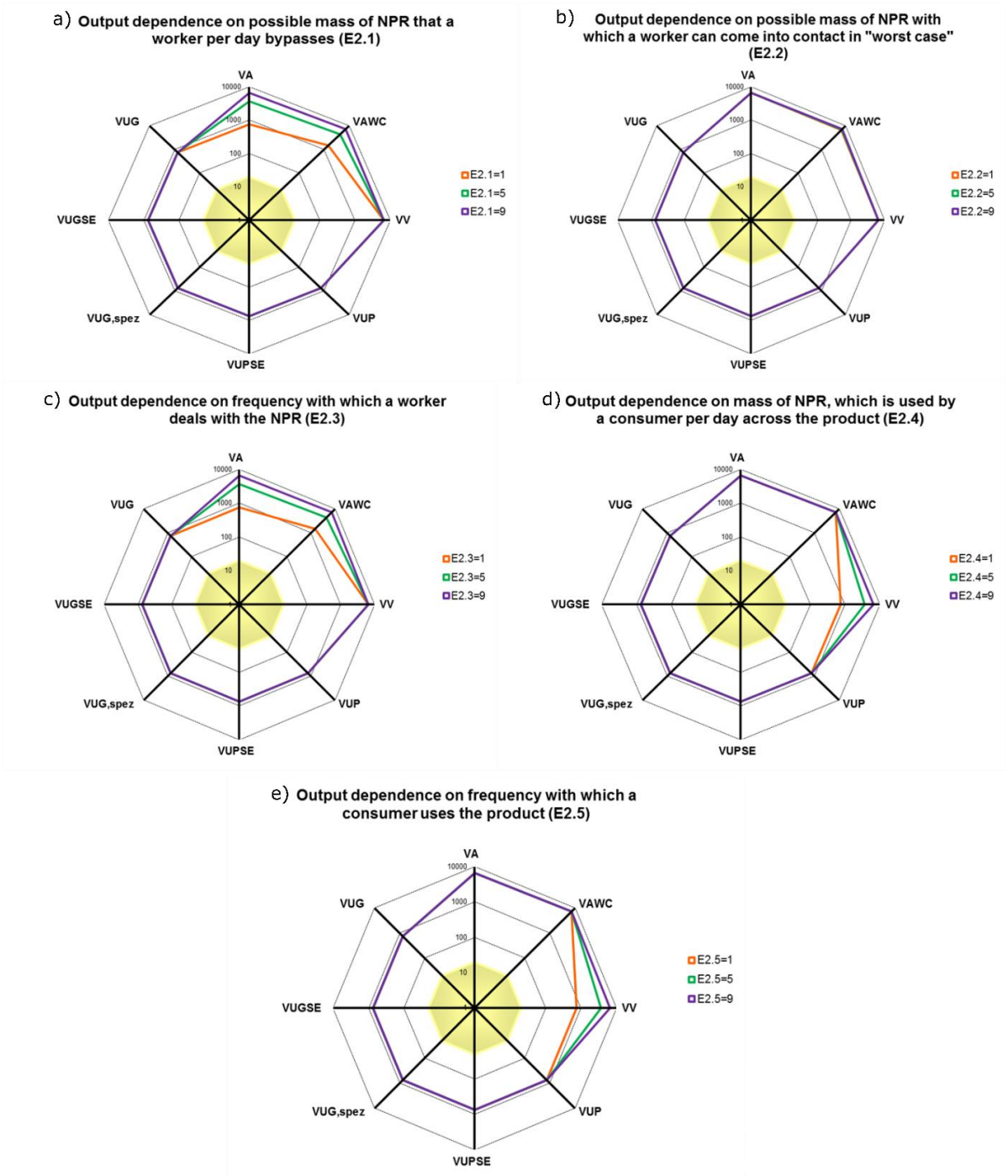


Figure 38. Radar chart of the SA for the input parameter of the Swiss Precautionary Matrix.

Note: a) E2.1; b) E2.2; c) E2.3; d) E2.4; and e) E2.5.

4.2.14 Stoffenmanager nano v1.0

Method

244. The SA of this tool was carried out using statistical design of experiments to define the input values and linear regression methodology to sort the input parameters in decreasing order of their influence on the tool's output. The Stoffenmanager Nano tool includes dependent questions (may or not be asked depending on answer in previous question) as well as independent questions (asked in all cases). Questions for inhalation exposure and hazard characterization were considered separately. In addition, to reduce the complexity of the SA for the inhalation exposure, the dependent questions were separated from the independent obtaining two subsets. On the first subset, all independent questions were considered, an average outcome was used for the dependent questions (9 questions with 580608 different combinations of answers from which 120 were selected allowing the identification of the relative contribution of each independent question). For the second subset, dependent questions were taken into account whereas an average outcome was used for the independent questions (1665 combinations of answers based on the 13 dependent questions). In total, 199 800 models runs were performed. A regression model was then fitted to each subset to estimate the contribution of each question to the variety in the exposure scores. Finally, the contributions of the questions in each subset were rescaled to allow for comparisons across the subsets. Contribution of independent and dependent questions to the inhalation exposure estimation variation are shown in Table 46.

Table 46. Contributions of independent and dependent questions to variation in the inhalation exposure estimates of Stoffenmanager nano.

Source		Percentage
Independent Questions (IQ)	Explained	21.9 %
	Unexplained	0.1 %
Dependent Questions (DQ)	Explained	16.3 %
	Unexplained	0.7 %
Interactions (IQ x DQ)		61.0 %
Total		100 %

Model output and inputs

245. Stoffenmanager Nano provides two outputs, hazard characterization and inhalation exposure. However, the present report focuses only on the SA conducted for the inhalation exposure output. Input parameters considered for the SA of the Stoffenmanager nano inhalation exposure part are not given.

Results

246. Most and least sensitive input parameters are summarized in Table 47.

Table 47. Most and least sensitive input parameters of Stoffenmanger nano.

Most sensitive input	Least sensitive input
Process domain	Duration of handling
Daily cleaning	Room volume
Monthly inspection	Room ventilation
Concentration	Local control measures
Handling in the worker breathing zone	Product type
Viscosity	Dustiness
Appearance	Moisture content
Frequency of handling	Dilution and handling (activity)

247. While the process domain does not directly lead to an exposure estimate, it was identified as a sensitive parameter due to the high dependency of the follow-up questions. Furthermore, for the independent questions, the duration of handling, the room volume, room ventilation, local control measures and PPE had a low sensitivity. For the dependent questions the product type, dustiness, moisture content, dilution and handling (activity) had a low sensitivity. A possible explanation for this might be that all answers lead to relatively low exposures (and this did not influence the model depending on the answer chosen). No unexpected behaviours were detected during the SA of Stoffenmanager nano.

4.2.15 ConsExpo nano

Method

248. The SA on this tool was performed using the MC AAO method, discussed in Section 4.1.3, within the caLIBRAte project. This method was applied for a specific scenario, representing the use of a hypothetical nanomaterial in a deodorant spray. A number of specific assumptions to describe the situation was used in the analysis. Spraying towards exposed person and a reduced personal volume (cloud volume) were assumed. Other scenarios may show a somewhat different sensitivity to various parameters.

249. For MC sampling, the distributions for the parameters were determined as follows: the base scenario was taken from the ConsExpo fact sheet on Cosmetics (Bremmer et al. 2006). In the fact sheet scenario, input parameters are specified relatively conservative. Minimum and maximum values for the parameter were estimated from the ConsExpo fact sheet default, and then the parameter value of the base scenario was taken as the most likely value. A MC simulation was performed taking 10,000 random samples from the specified distributions and calculating the output of model from each sample, giving samples of a distribution of output as a result. Scatter plots of the output of the model versus single parameters over the range of their values were created. For the analysis of the global sensitivity for the different model parameters, a Standardised Regression Coefficient (SRC) was calculated using the following equation:

$$SRC_i = \frac{\sigma_{X_i}}{\sigma_Y} \times b_i$$

250. where σ_{X_i} and σ_Y are the standard deviations of the studied parameter and the output of model respectively, and b_i is constant coefficient taken from the linear regression of the output of the model on the studied parameter. The SRC derived in this way expresses sensitivity of the model to parameter changes in a way that allows direct comparison between different parameters. A higher (absolute) value of the SRC for a particular parameter implies a higher (global) sensitivity of the model to changes in this parameter. As a rule of thumb, an SRC > 0.2 signifies a high global sensitivity, for an SRC between 0.1 and 0.2 sensitivity is less pronounced but still significant. For SRCs smaller than 0.1 the model is regarded as insensitive.

Model outputs and inputs

251. As output metric, the deposited mass of the inhaled nanomaterial is used. Model input parameters that were analysed for sensitivity are given in Table 48. It should be noted that the parameter ranges defined based on the base scenario reflect a plausible set of uncertainties in parameters values, but not necessarily the whole range of variability. Other ranges could influence the results of the SA. Thus, no generalized conclusion should be drawn from the results. A list of inputs that were not tested is given in Table 49, with justification for the exclusion.

Table 48. Input parameters for SA of ConsExpo nano.

Input name	Most likely value	Minimum value	Maximum value	Unit
Exposure duration	4	2	6	min
Weight fraction nano material in aerosol	0.5	0	1.0	[-]
Aerosol diameter	6	2	10	µm
Mass generation rate	0.4	0.2	0.6	g/s
Airborne fraction	0.75	0.5	1.0	[-]
Spray duration	9	6	12	sec
Cloud volume	0.1	0.01	10	m^3
Room volume	11	8	14	m^3
Room height	2	1	3	m
Ventilation rate	3	0	6	1/h
Density nano material	10	8	12	g/cm^3
Diameter (spherical) nano material	20	10	30	nm
Inhalation rate	2.8	0.5	5.0	m^3/h
Weight fraction nano material in product	0.05	0.01	0.1	[-]
Dissolution rate	0.01	0.001	0.1	per day

Note: Most Likely Value = mean of distribution for AAO-MC

Table 49. Input parameters excluded from SA of ConsExpo nano.

Input name	Justification for exclusion
Aerosol coefficient of variation	The aerosol was modelled as a mono-disperse distribution to clarify the effect of the aerosol diameter on the model results. This could become unclear when using a distribution of aerosol size rather than a single size
Exposure frequency	As an output, the deposited dose during a single exposure event was selected. Exposure frequency only impacts the time dependent, long term alveolar load, but is irrelevant for the deposited dose.
Shape of the nano material	The deposited mass depends only on the shape, size and density of the aerosol and is independent (in the model) of the shape of the nano material
Simulation duration	Affects only the long term alveolar load, not the deposited dose in the single exposure event
Body weight	The deposited dose is (in the model) independent of the body weight

Results

252. Figure 39 shows the variation in the output of the tool across the changes in the input parameters with the corresponding SRCs, which in turn indicates that all input parameters have an influence on the output of the model.

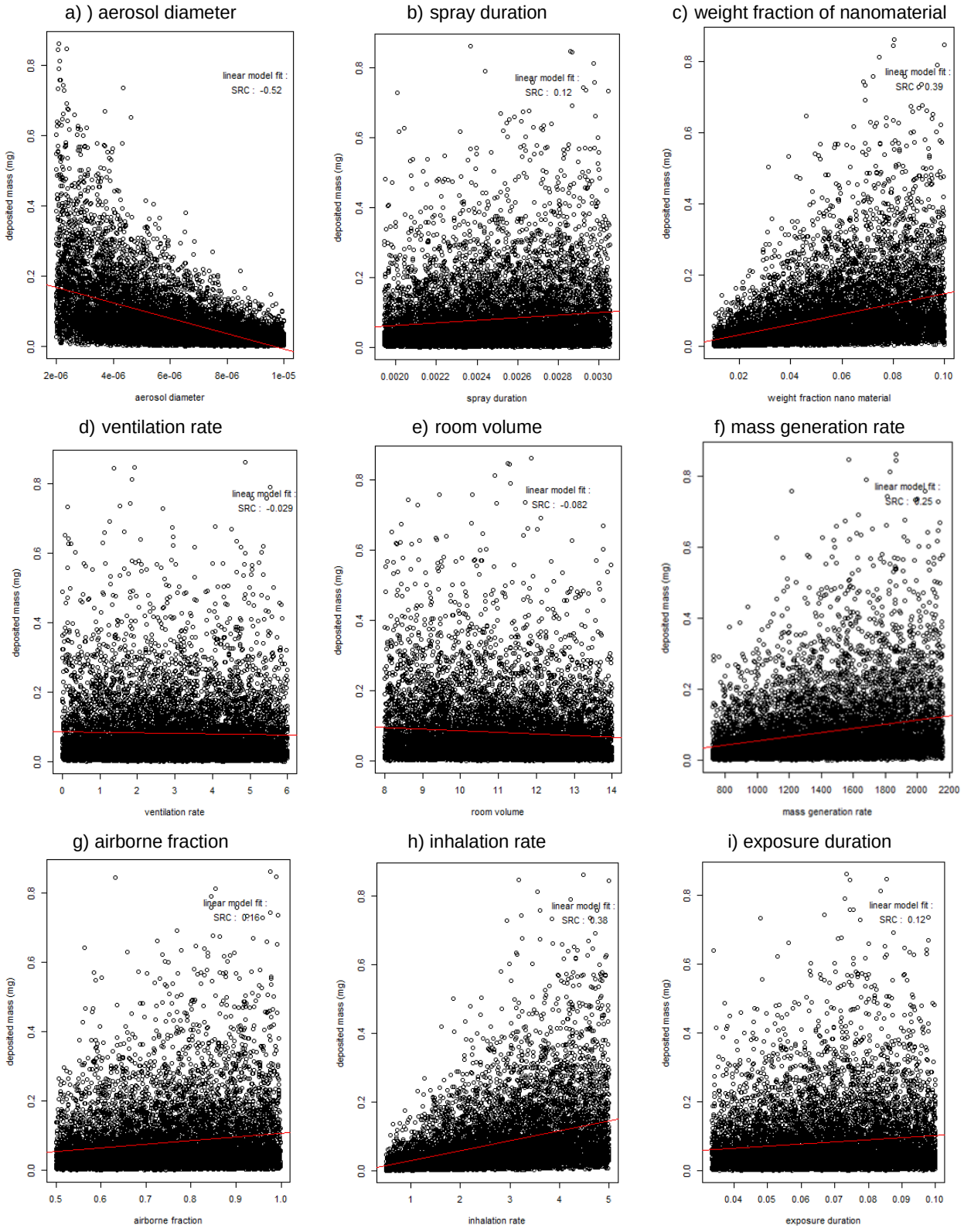


Figure 39. Variations on ConsExpo nano estimated deposited mass.

Note: Variations with changes of a) aerosol diameter, b) spray duration, c) weight fraction of nanomaterial, d) ventilation rate, e) room volume, f) mass generation rate, g) airborne fraction, h) inhalation rate, and i) exposure duration.

253. The aerosol diameter, inhalation rate, weight fraction of nano material in product, mass generation rate, spray duration and airborne fraction have a strong influence on the output of the tool. This behaviour can be understood. The weight fraction of the nano material in the product determines directly how much material is available for inhalation after use of the spray. The spray duration in the case of 'on-person' spraying (in the deodorant spray scenario chosen as the base scenario) determines both the amount of aerosol released and the time a small 'personal volume' around a person is assumed in the model. The mass generation rate, used as an input independently from the spray duration in the model, determines directly how much material is produced per second of spray use. The airborne fraction directly determines the amount that becomes airborne after use of a spray on a surface. The aerosol diameter and inhalation rate determine directly the amount inhaled and deposited from indoor air. Overall, in the investigated scenario, for the mass generation rate, the airborne fraction, inhalation rate, the weight fraction of the nano material, and the spray duration, a change of x% in input value of each of these parameters (while keeping other input values constant) will lead a change of x% in the model output. For other parameters, such as ventilation rate and room volume, the sensitivity was much lower. This is probably due to the specific scenario used (deodorant spray application) for which a 'personal volume' is assumed during use of the spray. In the period of use of the spray, the release is limited to the personal volume and is independent of the room volume. The ventilation rate determines the removal of the substance from the indoor environment (room volume) and as in the considered base scenario of a deodorant spray, a personal volume is assumed during use of the spray, the ventilation rate has a minor effect on the personal volume assumed. The exposure duration determines how long a person is exposed to exposure after the spray is released. The influence of this parameter on exposure will depend on ventilation, sedimentation, and the length of the exposure. For long exposure durations, changes in this parameter are not expected to have a high influence. In the considered scenario, the exposure duration has a moderate influence on the model output. The most and least sensitive parameters are summarized in Table 50.

Table 50. Most and least sensitive input parameters of ConsExpo nano.

Most sensitive inputs	Least sensitive inputs
Aerosol diameter	Ventilation rate
Inhalation rate	Room volume
Weight fraction nano material in product	
Mass generation rate	
Spray duration	
Airborne fraction	

4.2.16 Advanced REACH Tool v1.5

Method

254. The ART tool combines a source-receptor approach with independent MFs, and the ability to update the estimates with the user's own data to estimate by means of a quantitative output worker inhalation exposure from solids and liquids (Fransman et al., 2011[40]). The SA was performed by OAT methodology as described in section 4.1. A total of 69 input parameters were tested for SA and only "*activity coefficient*", "*chemical name*", "*CAS*" and "*other processes*" were excluded from sensitivity analysis. Only the drop down options were considered for the SA except for "*task time*" and "*vapour pressure*" for which drop down options are not available and the user is required to introduce a value.

Model output and inputs

255. The tool provides an estimate of the exposure mass concentration with a confidence interval for full-shift or long term exposure. For the estimated mass the user can select between median, 75, 90, 95 and 99th percentiles and for the confidence interval between inter-quartile, 80, 90 and 95%. 90th and 90% percentile and confidence interval were used for the SA.

256. The total number of input questions that the user is required to answer are variable as the tool has independent and dependent questions/input parameters, which may or not be asked depending on answers in previous questions (e.g. "*activity description*" options will depend on type of material previously selected). Independent input parameters are task duration, product type, weight fraction, emission source distance to the worker, containment, local controls (primary and secondary options), enclosure and cleaning routine, site size, and ACH. Dustiness and moisture information are only required for solids and paste/wet powders, whereas temperature, vapour pressure and viscosity is needed to conduct exposure assessments for liquids and solids dissolved in liquids. Personal enclosure and segregation are only required if emission source is located outside of the worker breathing zone. General base values and emission source type used per product are described in Table 51 and Table 52.

257. Other inputs related to the emission source, which are dependent on product type, are required such as amount of material handled, type of handling or type of powder coating. Description of base values used to characterise emission source type depending on the product type are provided in Table 53 and Table 54. Base options/values were selected according to most likely option and the rest of the range options were tested for variation. In the case of "*task duration*" and "*vapour pressure*" the base values and ranges considered for SA were selected according to what would be physically possible in an occupational exposure scenario (e.g. for time duration 15, 60, 240 and 480 min were tested).

Table 51. ART base values for general independent input parameters.

Input parameter	Type of product				
	Powders	**Solids**	**Paste or wet powder**	**Liquids**	**Powders in liquids**
Task duration (min)	60	60	60	60	60
Weight fraction	Main component (50-90%)	Main component (50-90%)	Main component (50-90%)	Main component (50-90%)	Main component (50-90%)
Emission source in breathing zone?	Yes	Yes	Yes	Yes	Yes
Containment	Reduced	Reduced	Reduced	Reduced	Reduced
Local controls	No	No	No	No	No
Enclosure and cleaning routine	No enclosure and regular cleaning	No enclosure and regular cleaning	No enclosure and regular cleaning	No enclosure and regular cleaning	No enclosure and regular cleaning
Site	Indoor-100m^3	Indoor-100m^3	Indoor-100m^3	Indoor-100m^3	Indoor-100m^3
ACH (h^{-1})	3	3	3	3	3
Other processes	No	No	No	No	No

Table 52. ART base values for general dependent input parameters.

Input parameter	Type of product				
	Powders	Solids	Paste or wet powder	Liquids	Powders in liquids
Dustiness	Coarse dust	n/a	Coarse dust	n/a	n/a
Moisture	Dry (<5%)	Dry (<5%)	n/a	n/a	n/a
Temperature	n/a	n/a	n/a	Room T	Room T
Vapour pressure (Pa)	n/a	n/a	n/a	3000	3000
Viscosity	n/a	n/a	n/a	n/a	Low
Personal enclosure	No	No	No	No	No
Segregation	No	No	No	No	No

Table 53. ART Emission source base selection per product type.

Powders	Solids	Paste, slurry or wet powder	Liquids	Powders in liquids
Transfer of powders-Falling	Wood, fracturing and abrasion	Handling of contaminated object/paste	Spray application of liquids-surface spraying	Spray application of liquids-surface spraying

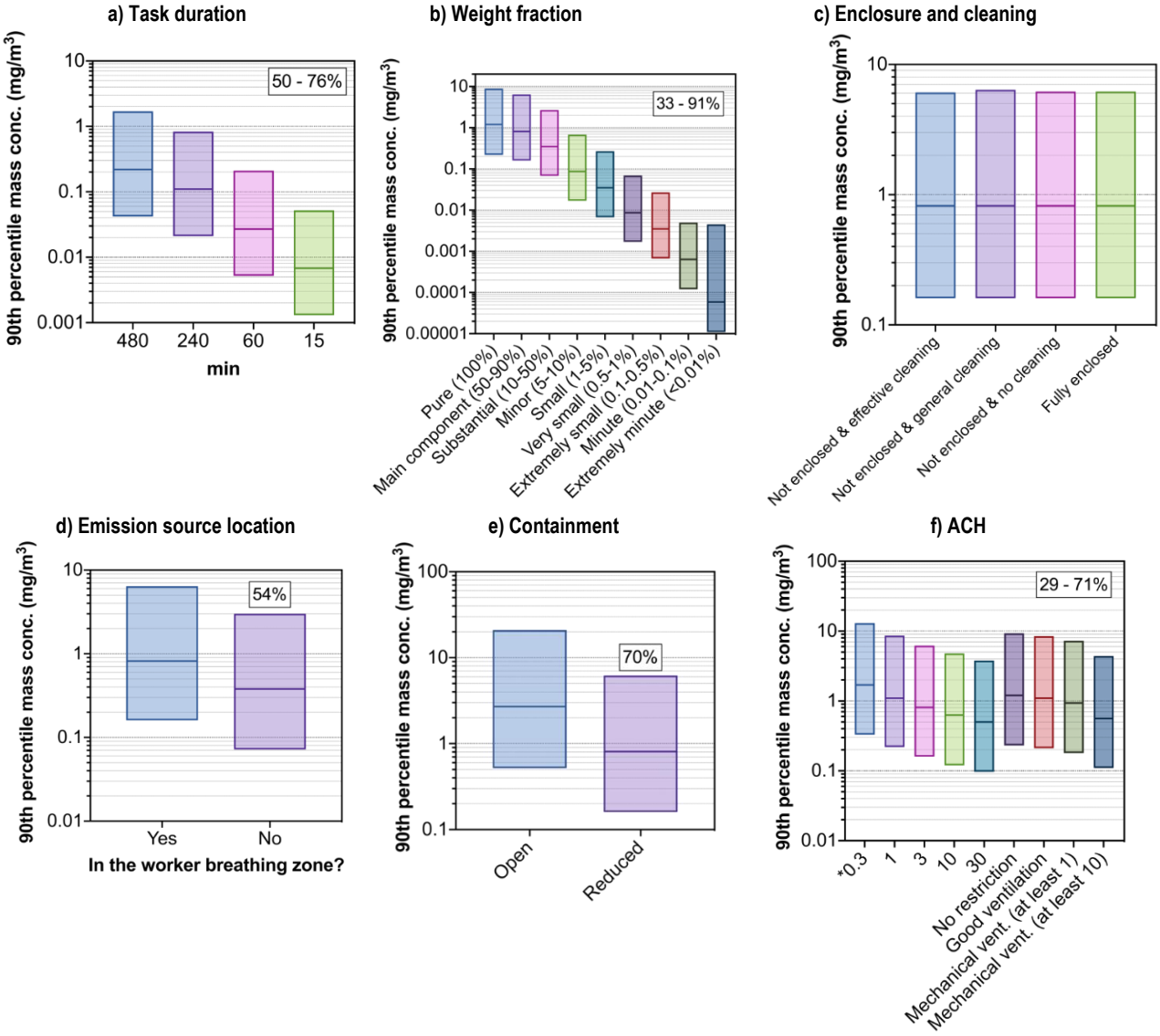
Table 54. ART base values for emission source dependent input parameters.

Input parameter	Base option	Units
Powders, granules or pelletized materials		
Transfer of powders-Falling		
Activity description	10-100	[Kg/min]
Type of handling	Routine transfer	[-]
Drop height	<0.5	[m]
Transfer of powders-Vacuum transfer		
Activity description	10-100	[Kg/min]
Impaction on contaminated objects		
Activity description	Impact on substantially and visibly contaminated objects	[-]
Type of handling	Normal impaction	[-]
Handling of contaminated objects		
Activity description	Handling of substantially and visibly contaminated objects	[-]
Type of handling	Normal handling	[-]
Spray application of powders		
Activity description	Powder coating	[-]
Spray direction	Any direction	[-]
Movement and agitation of powders		
Activity description	10-100	[Kg]
Level of agitation	Application of compressed air	[-]
Compressing of powders		
Activity description	10-100	[Kg/min]
Fracturing powders		
Activity description	10-100	[Kg/min]
Solids		
Fracturing and abrasion		

Input parameter	Base option	Units
Material	Wood	[-]
Activity description	Mechanical sanding/abrasion of large amounts or resulting in large amounts	[-]
Abrasive blasting		
Material	Wood	[-]
Activity description	Abrasive blasting of large surfaces	[-]
Type of abrasive blasting	Dry abrasive blasting	[-]
Abrasive blasting direction	Any direction	[-]
Paste, slurry or clearly wet powder		
Handling of contaminated solid object or paste		
Activity description	Handling of substantially and visibly contaminated objects	[-]
Type of handling	Normal, regular work	[-]
Liquids & Powders in liquids		
Spray application of liquids-surface spraying		
Activity description	High application rate (>3)	[l/min]
Spraying direction	Any direction	[-]
Spray technique	High compressed air	[-]
Spray application of liquids-spray liquid in a space		
Activity description	Large scale	[-]
Activity with open liquid-undisturbed & agitated surfaces		
Activity description	Open surface >3	[m^2]
Handling of contaminated objects		
Activity description	Activities with treated/ contaminated objects surface >3	[m^2]
Object contamination	>90	[%]
Spreading of liquids		
Activity description	Spreading liquids at surfaces >3	[m^2]
Application of liquids in high speed		
Activity description	Large-scale high speed movements	[-]
Transfer of liquids-bottom		
Activity description	>1000	[l/min]
Transfer of liquids-falling		
Activity description	>1000	[l/min]
Type of loading	Splash	[-]

Results

258. As shown in Figure 40, from the general independent input variables, the only input parameter, which did not show any variation, was enclosure and cleaning (Figure 40c). Variation in mass concentration changed accordingly with time decrease and weight fraction. Thus, a variation of x% in the input value (while keeping other input values constant) will lead a change of x% in the model output (Figure 40a and 40b). Conversely, mass concentration variation due to changes in ACH, and site size were independent of the % of variation of the input parameter (Figure 40f and 40h), with variations for the values tested ranging between 29-71% and 20-90%, respectively. The presence of the emission source in the worker breathing zone or not, and of containment measures or not, implied variations in the mass concentrations of 54 and 70%, respectively (Figure 40d and 40e), and the different local controls had reduction effects in mass concentrations between 30 and 100% when comparing to no local controls applied (Figure 40g).


a) Task duration
90th percentile mass conc. (mg/m3)
50 - 76%
480
240
60
15
min
b) Weight fraction
33 - 91%
Pure (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%)
c) Enclosure and cleaning
Not enclosed & effective cleaning
Not enclosed & general cleaning
Not enclosed & no cleaning
Fully enclosed
d) Emission source location
54%
Yes
No
In the worker breathing zone?
e) Containment
70%
Open
Reduced
f) ACH
29 - 71%
*0.3
1
3
10
30
No restriction
Good ventilation
Mechanical vent. (at least 1)
Mechanical vent. (at least 10)

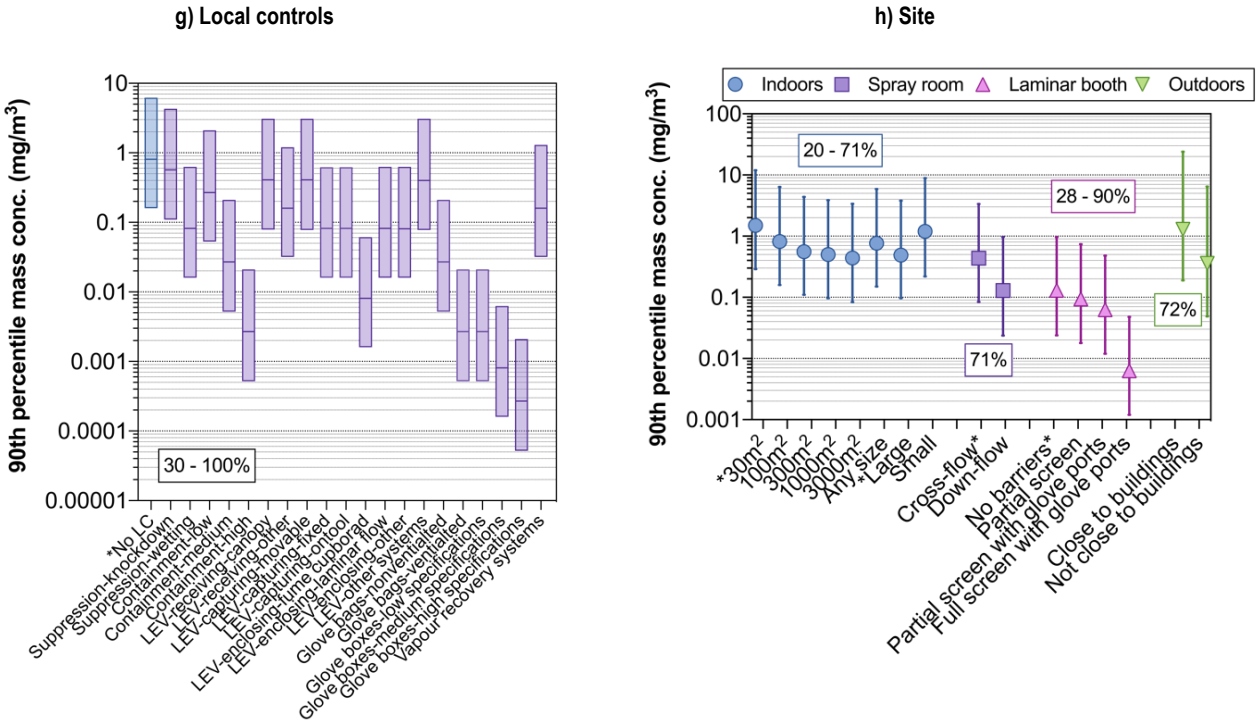


Figure 40. ART general independent input parameters SA.

259. Influence of general dependent input parameters in output mass concentration is represented in Figure 41. Gradual variations between 66 and 90 % were identified for dustiness, moisture and viscosity variations (Figure41 a, b and d). Segregation and enclosure had reduction effects of 32-90% when compared to not using any type of measures (Figure 41 c). Vapour pressure values between 800 and 80000 Pa did not had an impact in mass concentrations, which remained constant at the maximum concentration value of 10000 mg/m^3. For values between 800 and 30 Pa, gradual variations of 23-73% were observed. Similarly, no effects in mass concentrations were observed from process temperature variations (Figure 41 f). It is not sure whether the lack of sensitivity of these two input parameters it is due to a lack of sensitivity from the specific input parameter or to the different input parameters selected. Mass concentrations variations with changes on material specific dependent input parameters are represented in Figures 42, 43, 44 and 45. Overall, gradual mass concentrations variations between 65-72% were detected for the different material and activity specific input parameters, with gradual threefold increases and decreases. However, in some cases, activity description input parameter implied mass concentrations variations up to 99% (Figure 42 a, b and e; Figure 43 b, c and d; and Figure 45 b) or on the contrary no variations (Figure 43 b, 44 d, 45 e). In three activity descriptions for powders in liquid, spreading, bottom transfer and handling of contaminated objects, no sensitivity at all was detected (Figure 45 c, d and g).

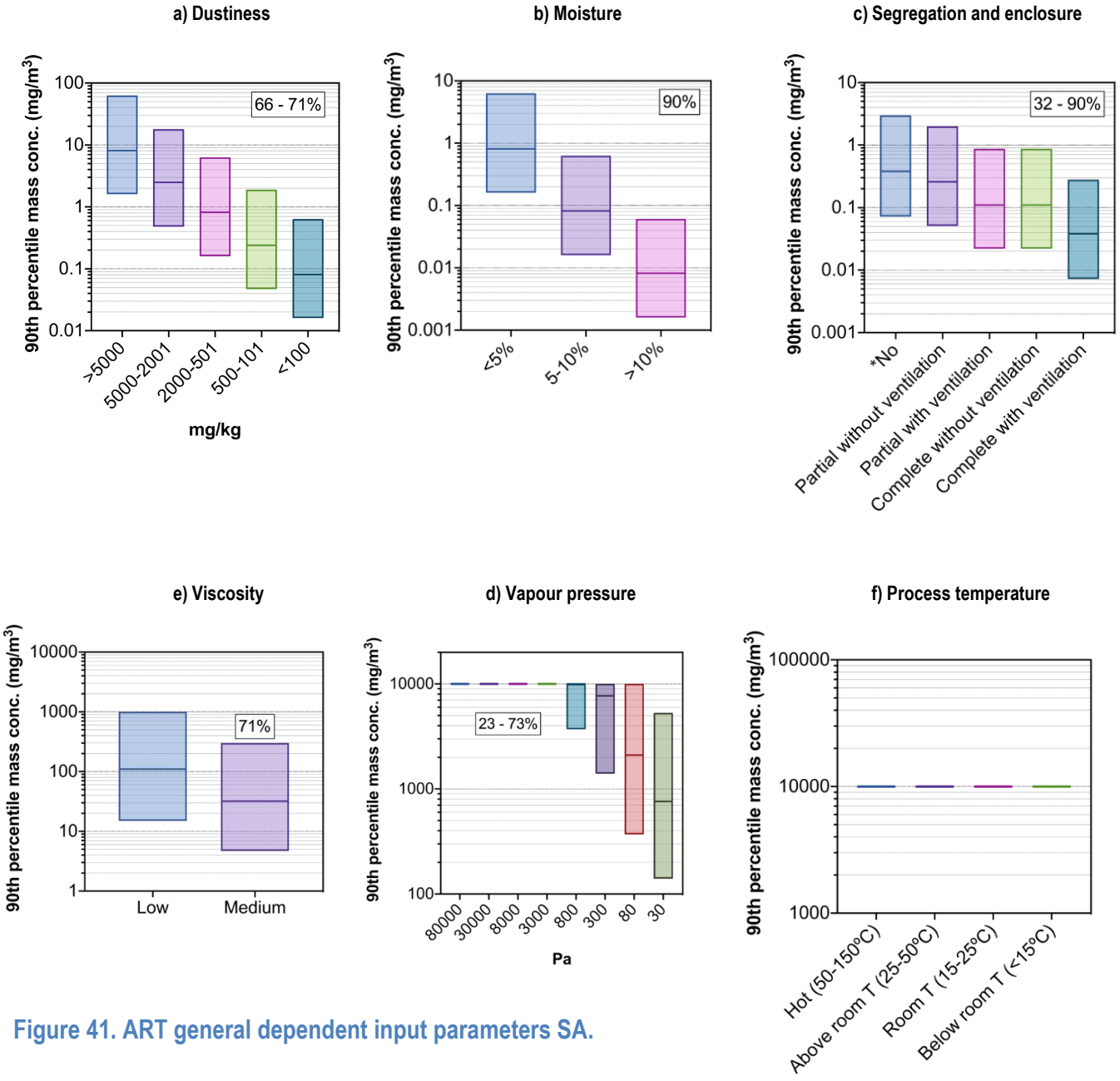


Figure 41. ART general dependent input parameters SA.

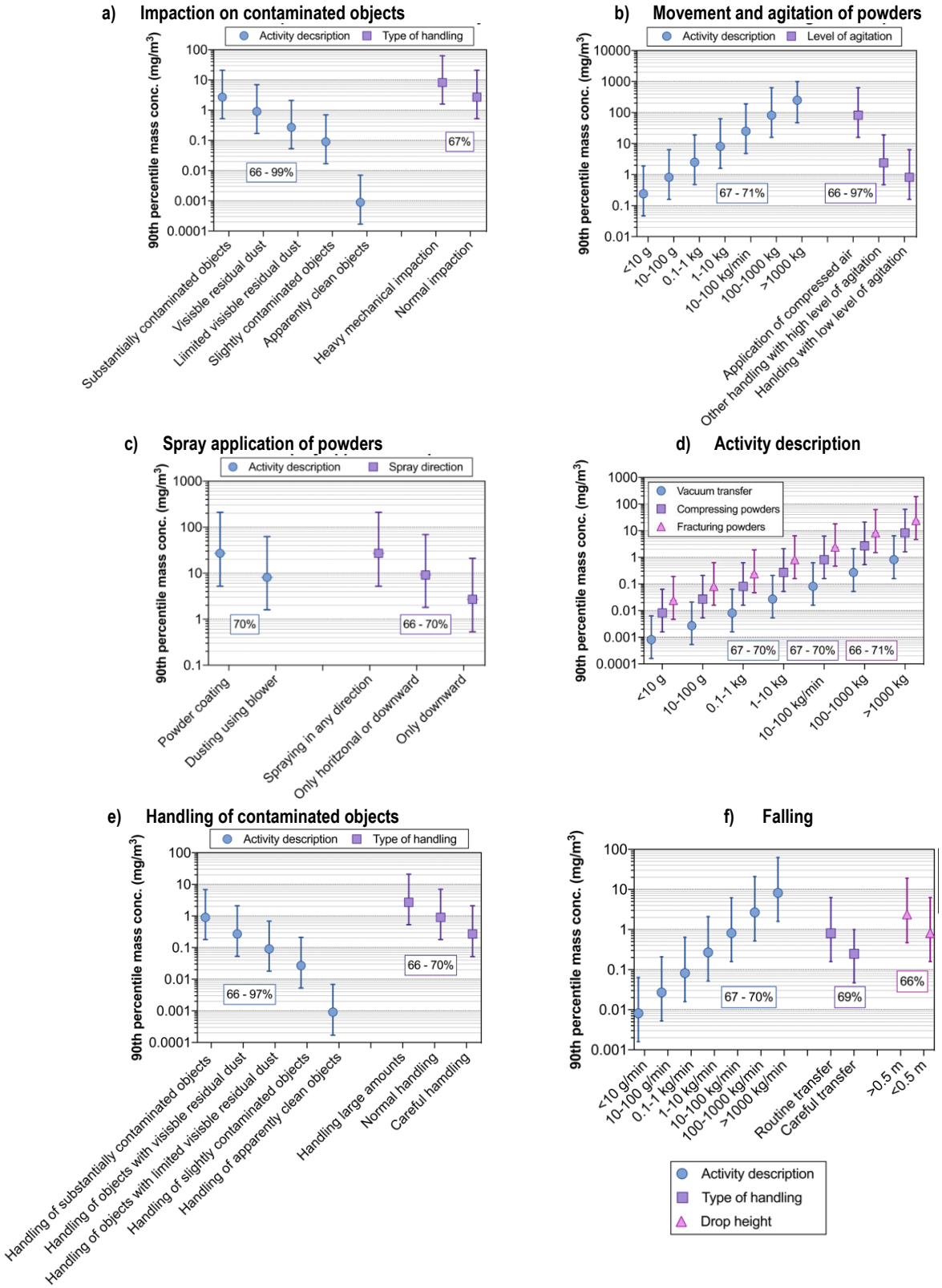


Figure 42. ART powder specific dependent input parameters SA.

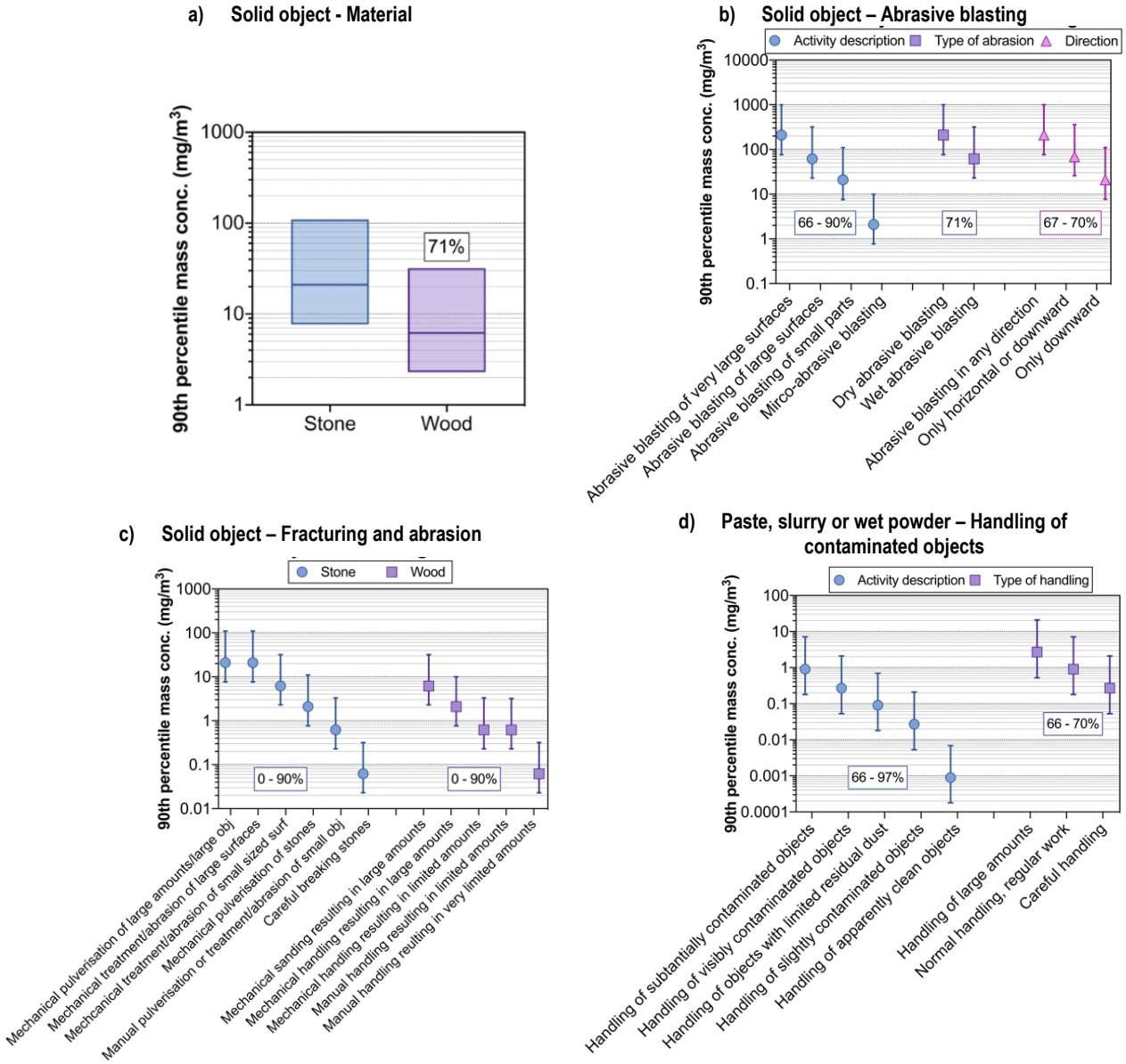


Figure 43. Solid object, and paste, slurry or wet powder specific dependent input parameters SA of ART.

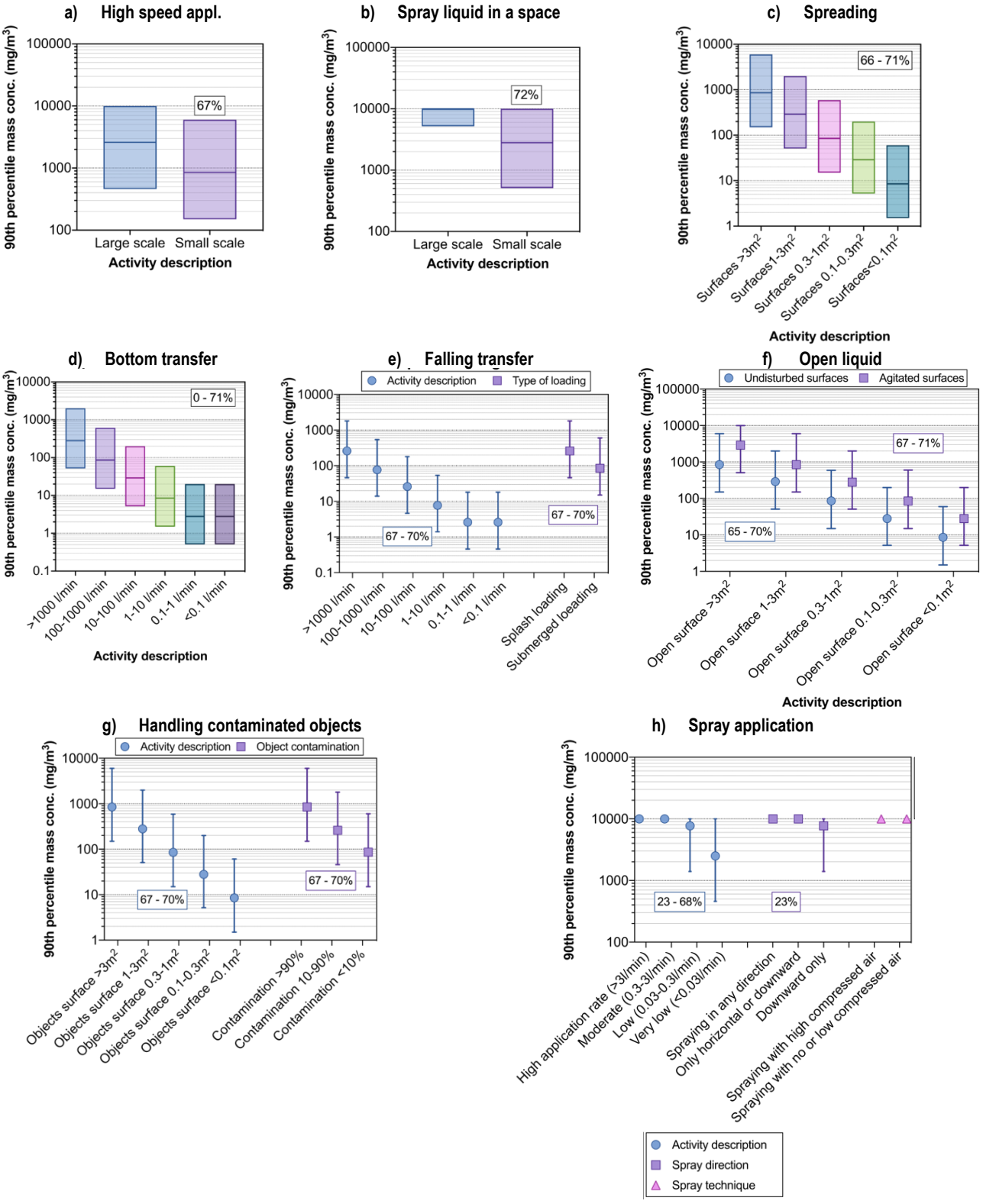


Figure 44. Liquids specific dependent input parameters SA of ART.

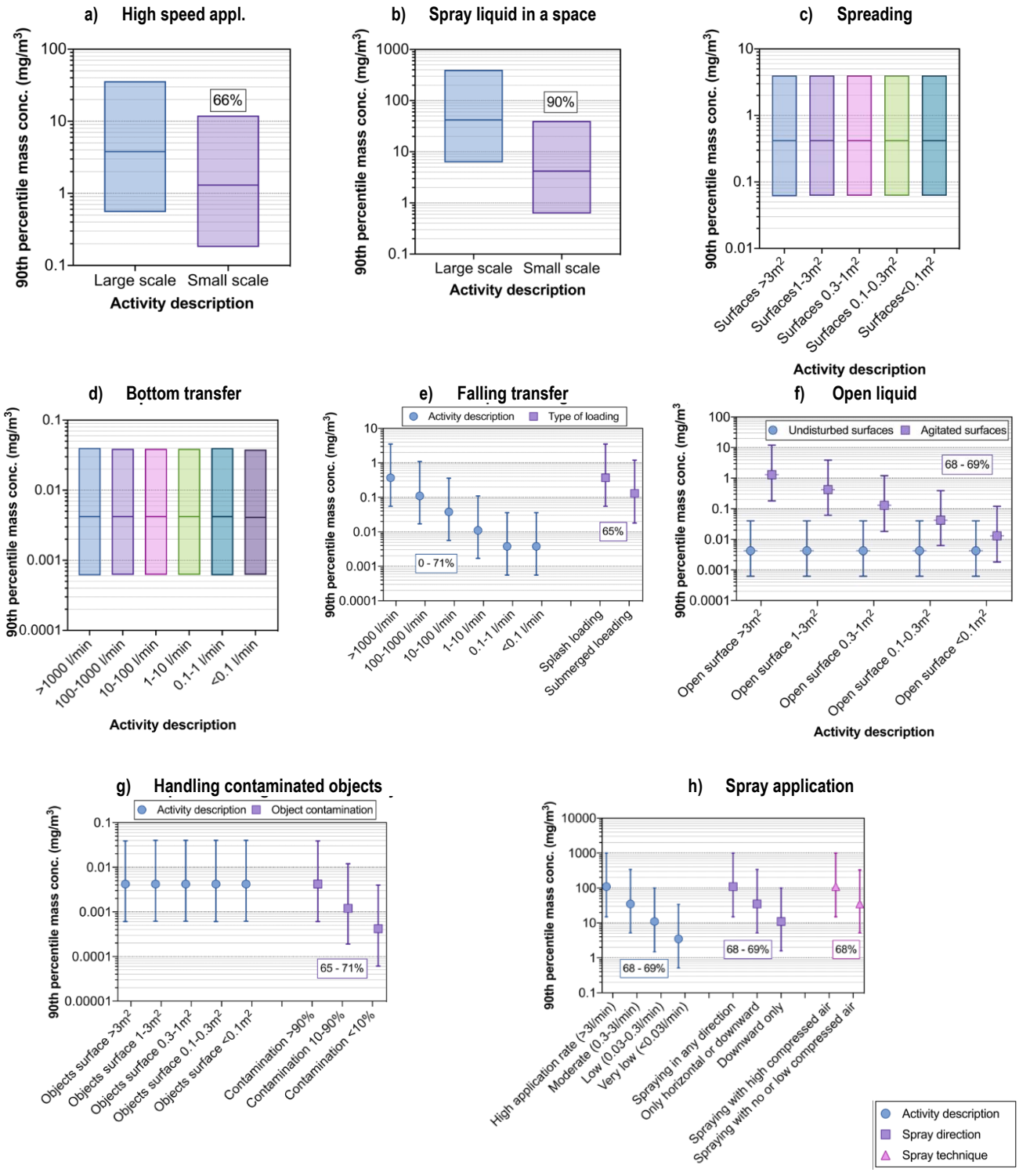


Figure 45. Powder in liquid specific dependent input parameters SA of ART.

260. Comparison of the impact on mass concentration due to changes on activity type for powders, liquids and powder dissolved in liquid is represented in Figure 46. The comparison was made by selecting worst case scenario for each specific activity. The type of activity selected implied variations of 62-100% when compared to the activity with highest exposure mass concentrations.

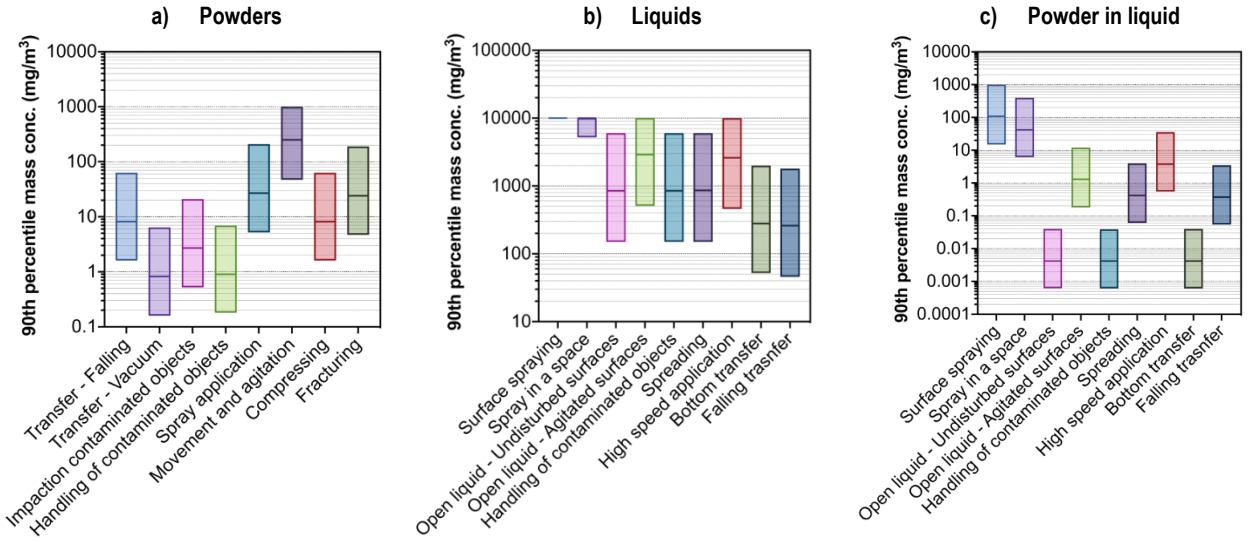


Figure 46. Activity type SA variation for material type a) powder, b) liquid and c) powder in liquid of ART.

261. To sum up, most of the input parameters showed a similar behaviour with gradual increases/decreases between 65-71% (threefold). Up to 90% variations were detected for moisture content, segregation and enclosure, and activity description for impact on contaminated objects, handling of contaminated objects, abrasive blasting, fracturing and abrasion, spray of a liquid in a space, and level of agitation for movement and agitation of powders. Activity type implied variations of up to 100%.

262. Conversely, least sensitive input parameters, showing no effect on mass concentration were enclosure and cleaning, process temperature, and activity description for spreading, bottom transfer and handling of contaminated objects for powders in liquids.

4.2.17 Multiple-Path Particle Dosimetry Model (MPPD)

Method

263. The SA on this tool was performed using the OAT method discussed in Section 4.1.1. A human lung model, Yeh-Schum 5-Lobe model, with consumer upright scenario was used for the analysis. In OAT range scanning, for numerical input parameters except for the GSD and pause fraction parameters, reference values were varied from -50% to +50% with an increment of 10%. The reference value of the GSD parameter was varied from 10% to 100% with an increment of 10%, as the tool does not allow GSD < 1. The reference value of the pause fraction was varied up to 0.9, as the sum of pause and inspiratory fractions must be between 0 and 1. For breathing scenario and type of diameter parameters, reference values were varied based on the values provided by the tool. The reference values of numerical input parameters were chosen from the work of Christian et al., who quantified exposure to airborne nanoparticles released by consumer spray products.

Model outputs and inputs

264. The deposited mass predicted by the tool was used as an output metric. Model inputs that were subjected to the SA are given Table 55. It should be noted that the parameter ranges defined below reflect a plausible set of uncertainties in parameters values, but not necessarily the whole range of variability. Other ranges could influence the results of the SA. Thus, no generalized conclusion should be drawn from the results.

Table 55. Input parameters for SA of MPPD.

Input name	Most likely value	Minimum value	Maximum value	Unit	Multiple choice
Air concentration	0.0858	0.0429	0.1287	mg/m³	N/A
Tidal volume	1000	500	1500	ml	
GSD	1	1	2		
Particle diameter	25	12.5	37.5	nm	
Particle density	10.49	5.245	15.735	g/cm³	
Inspiratory fraction	0.5	0.25	0.75	[-]	
Pause fraction	0	0	0.9	[-]	
URT volume	50	25	70	ml	
FRC volume	3300	4950	1650	ml	
Breathing frequency	19	9.5	28.5	1/min	
Diameter type				N/A	CMD/MMD/MMAD
Breathing scenario					Nasal/ Oral-normal Augmenter/ Oral-mouth-breather/ Endotracheal

Note: Most Likely Value = default value for OAM.

Results

265. Figure 47 shows the variation in the output of the tool across the changes in 12 input parameters, indicating that all input parameters, except for particle density, have an influence on the output of the model. The particle air concentration, the tidal volume, and the particle diameter have a high influence on the model output whereas the inspiratory fraction, the breathing scenario, URT and FRC volumes have a low influence on the model output. As shown in Figure 53, the model output increases linearly with increasing the particle air concentration and tidal volume whereas it decreases with increasing the particle diameter. These parameters directly determine the deposition in the respiratory tract. Overall, in the investigated scenario, for the particle air concentration and tidal volume, a change of x% in input value of each of these parameters (while keeping other input values constant) will lead a change of x% in the model output. Table 56 lists the most and least sensitive input parameters.

Table 56. Most and least sensitive input parameters of MPPD.

Most sensitive inputs	Least sensitive inputs
Tidal volume	Inspiratory fraction
Air concentration	Breathing scenario
Particle diameter	Type of diameter
GSD	URT volume
	FRC volume

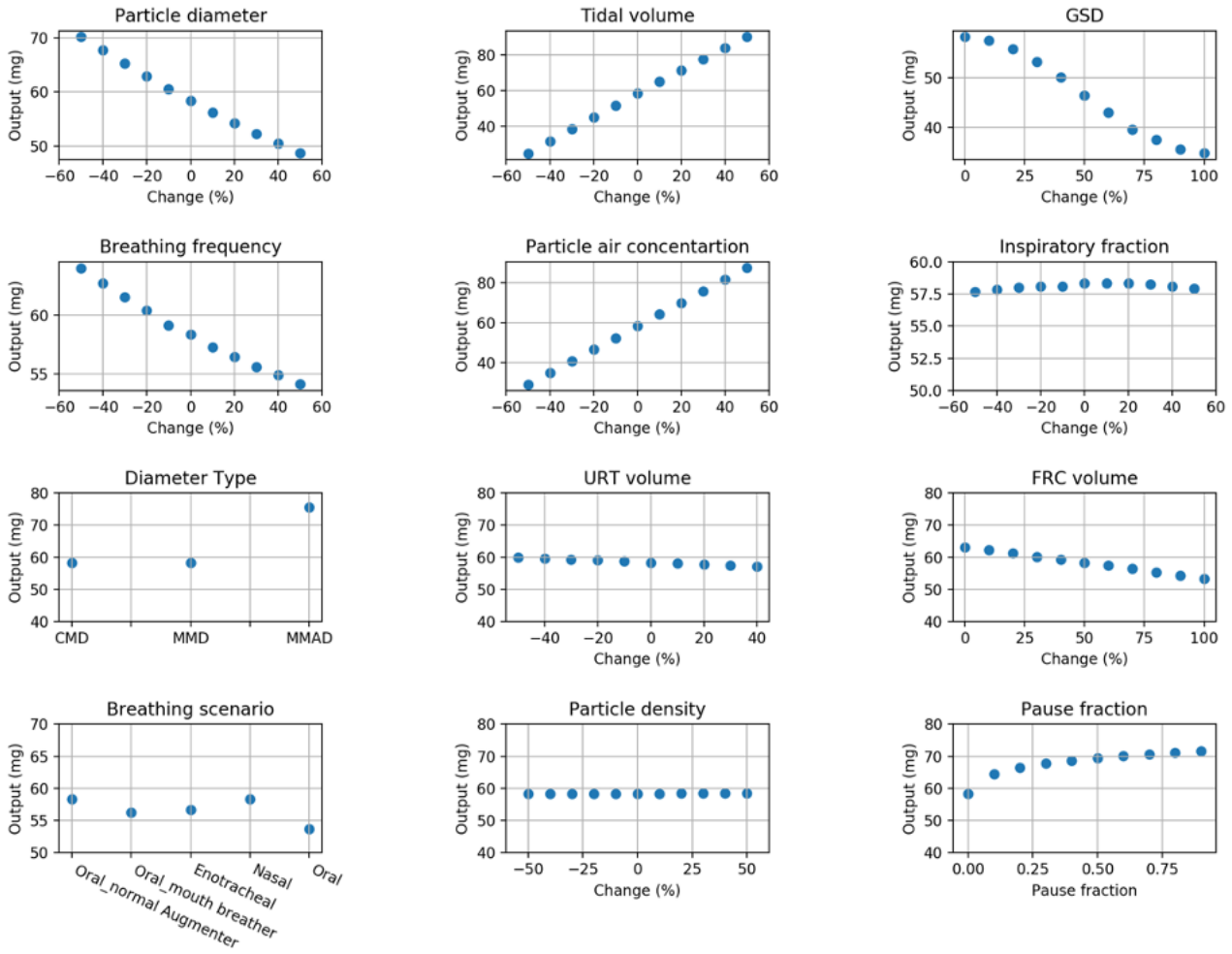


Figure 47. Variation in the output of MPPD model as function of changes in input parameters.

4.2.18 Boxall et al. 2007

Method

266. The SA on this model was performed using the MC AAO method discussed in Section 4.1.3. A specific scenario, the use of a hypothetical nanomaterial in a deodorant spray, was used for the analysis. This ensures that the parameters refer to the same scenario and prevents unphysical combinations of input parameters. For MC sampling, the distributions for the parameters were determined as follows: the base scenario was taken from the ConsExpo fact sheet on Cosmetics (Bremmer et al. 2006). In the fact sheet scenario, input parameters are specified relatively conservative. Minimum and maximum values for the parameter were estimated from the ConsExpo fact sheet default, and then the parameter value of the base scenario was taken as the most likely value. A MC simulation was performed taking 10,000 random samples from the specified distributions and calculating the output of model from each sample, giving samples of a distribution of output as a result. Scatter plots of the output of the model versus single parameters over the range of their values were created. For the analysis of the global sensitivity for the different model parameters, a Standardised Regression Coefficient (SRC) was calculated using the following equation:

$$SRC_i = \frac{\sigma_{X_i}}{\sigma_Y} \times b_i$$

267. where σ_{X_i} and σ_Y are the standard deviations of the studied parameter and the output of model respectively, and b_i is constant coefficient taken from the linear regression of the output of the model on the studied parameter. Computed in this way, The SRC determines sensitivity of the model to parameter changes in a way that allows direct comparison between different parameters. A higher (absolute) value of the SRC for a parameter represents a higher sensitivity of the model to the parameter.

Model outputs and inputs

268. The cumulative exposure predicted by the model was used as an output metric. Model input parameters that were subjected to the SA are given Table 57. It should be noted that the parameter ranges defined based on the base scenario reflect a plausible set of uncertainties in parameters values, but not necessarily the whole range of variability. Other ranges could influence the results of the SA.

Table 57. Input parameters for SA of Boxall et al. (2007).

Input name	Most likely value	Minimum value	Maximum value	Unit
Amount of product used	1.6	0.8	2.4	g
Proportion of nano in product	0.05	0.01	0.1	-
Room volume	11	8	14	m^3
Exposure time	4	2	6	min
Escape fraction	0.75	0.5	1	-
Air change rate	3	0	6	1/h

Note: Most Likely Value = mean of distribution for AAO-MC.

Results

269. Figure 48 shows the variation in the output of the model across the changes in the input parameters with the corresponding SRCs, which in turn indicates that all input parameters have an influence on the output of the model. The amount of product used, the weight fraction of nano material in product, the escape fraction, the exposure time, and the room volume have a strong influence on the output of the tool whereas the ventilation rate has a low influence on the model output. This behavior can be understood from the equation of the model:

$$E = \int_0^T \frac{f \times Q \times \rho}{V} e^{-kt}\, dt,$$

270. where e^{-kt} accounts for dilution due to the air change rate (k), E is the cumulative exposure, Q is the amount of product used, ρ is the proportion of MNM in product, f is a fraction of product escaping as aerosol, V is the room volume, and t is the time. The integration is from time t=0 (when product is used) to time T when the consumer leaves exospore area. The model assumes that the air concentration of MNM diminishes exponentially with the time and air change rate. As reported by Boxall et al 2007, if T is a short time (e.g., 10 minutes), dilution with air change can be ignored and consequently the above equation is reduced to:

$$E = \frac{f \times Q \times \rho}{V} \times T$$

271. Considering the question above, for the amount of product used, the weight fraction of nano material in product, the escape fraction, and the exposure time, a change of x% in the input value of each of these parameters (while keeping other input values constant) will lead a change of x% in the model output. The amount of product used and the weight fraction of nano material in product determine directly how much material used in an application. The escape fraction determines the amount that becomes airborne after use of a spray. The exposure duration determines how long a person is exposed to exposure after the spray is released. The most and least sensitive input parameters are given in Table 58.

Table 58. Most and least sensitive input parameters of Boxall et al. (2007).

Most sensitive inputs	Least sensitive inputs
Fraction of nano in product	Ventilation rate
Escape fraction	
Exposure time	
Amount of product used	
Room volume	

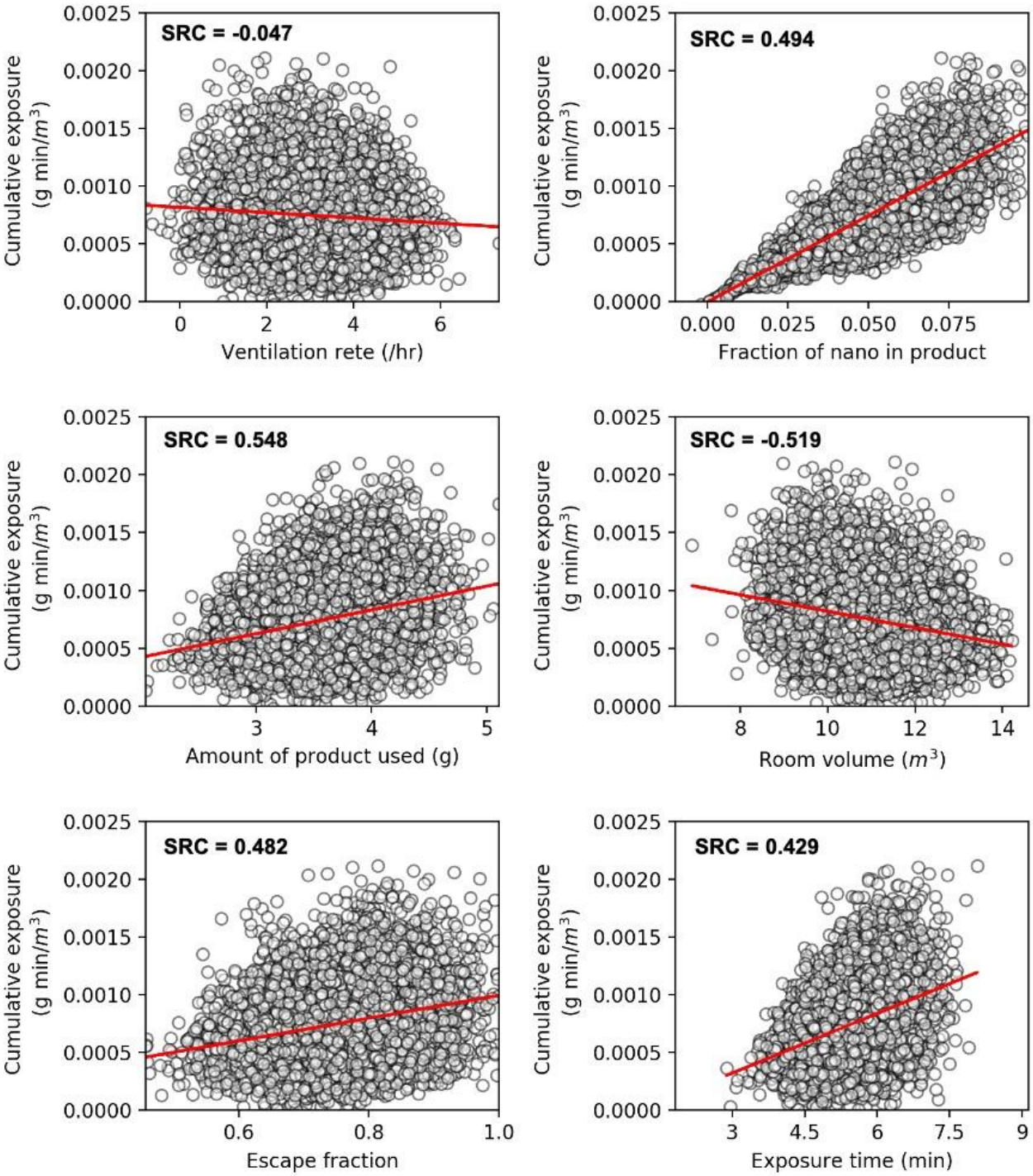


Figure 48. Scatter plots of the output of Boxall et al. (2007) as function of changes in input parameters with corresponding SRCs.

4.2.19 Nazarenko et al. 2012 & 2014

Method

272. The SA on this model was performed using the MC AAO method discussed in Section 4.1.3. A specific scenario, the use of a nano material in a deodorant spray, was used for the analysis, which ensures that the parameters refer to the same scenario. For MC sampling, the normal distributions for the parameters were determined as follows: the base scenario was taken from the work of Park et al. who studied airborne manufactured nano-objects released from a deodorant spray product. The parameter values of the base scenario were adjusted to the most likely values taken as the mean values of the distributions. The standard deviations of the normal distributions are defined as 20% of the associated means. Minimum and maximum values for the parameter were estimated from the associated mean and standard deviations values. A MC simulation was performed taking 10,000 random samples from the specified distributions and calculating the output of model from each sample, giving samples of a distribution of output as a result. Scatter plots of the output of the model versus single parameters over the range of their values were created. For the analysis of the global sensitivity for the different model parameters, a Standardised Regression Coefficient (SRC) was calculated using the following equation:

$$SRC_i = \frac{\sigma_{X_i}}{\sigma_Y} \times b_i$$

273. where σ_{X_i} and σ_Y are the standard deviations of the studied parameter and the output of model respectively, and b_i is constant coefficient taken from the linear regression of the output of the model on the studied parameter. Computed in this way, The SRC determines sensitivity of the model to parameter changes in a way that allows direct comparison between different parameters. A higher (absolute) value of the SRC for a parameter represents a higher sensitivity of the model to the parameter.

Model outputs and inputs

274. The inhaled dose predicted by the model was used as an output metric. Model input parameters that were subjected to the SA are given Table 59. It should be noted that the parameter ranges defined below reflect a plausible set of uncertainties, but not necessarily the whole range of variability. Other ranges could influence the results of the SA.

Table 59. Input parameters for SA of Nazarenko et al. (2012 & 2014).

Input name	Most likely value	Minimum value	Maximum value	Unit
Air concentration	300	120	480	µg/m³
Proportion of nano in product	0.1	0.04	0.16	[-]
Exposure time	10	4	16	min
Body weight	65	25	100	Kg
Inhalation rate	0.60	0.21	0.96	m³/h
Particle diameter	250	100	400	nm

Note: Most Likely Value = mean of distribution for AAO-MC.

Results

275. Figure 49 shows the variation in the output of the model across the changes in the input parameters with the corresponding SRCs, which in turn indicates that all input parameters have an influence on the output of the model. The air concentration, the weight fraction of nano material in product, the body weight,

the exposure time, inhalation, have a strong influence on the output of the tool whereas the particle diameter rate has a low influence on the model output. This behavior can be understood from the equation of the model.

$$ID = f_{nano} \times IF \times C_{air} \times Q_{inh} \times T_{contanct}/Bw$$

$$IF = 1 - 0.5\left(1 - \frac{1}{1+0.00076\, d_p^{2.8}}\right),$$

276. where ID is inhaled dose of particulate matters per application (ng/kg bw/application), Q_{inh} is the inhalation rate for a given gender (L/min), $T_{contanct}$ is duration of contact per application (min), Bw is the body weight, f_{nano} is the mass fraction of MNM in the product, C_{air} is the mass concentration of particulate matter in air, IF is inhalability fraction, and $d_p^{2.8}$ is particle diameter. Considering the equation above, for the inhalation rate, the weight fraction of nano material in product, the air concentration, and the exposure time, a change of x% in the input value of each of these parameters (while keeping other input values constant) will lead a change of x% in the model output. The inhalation rate, air concentration, and exposure time determine directly the amount of product inhaled. The weight fraction of the nano material in the product determines directly how much nanomaterial is available for inhalation after use of spray. The most and least sensitive input parameters are given in Table 60.

Table 60. Most and least sensitive input parameters of Nazarenko et al. (2012 & 2014).

Most sensitive inputs	Least sensitive inputs
Fraction of nano in product	Particle diameter
Air concentration	
Body weight	
Exposure time	
Inhalation rate	

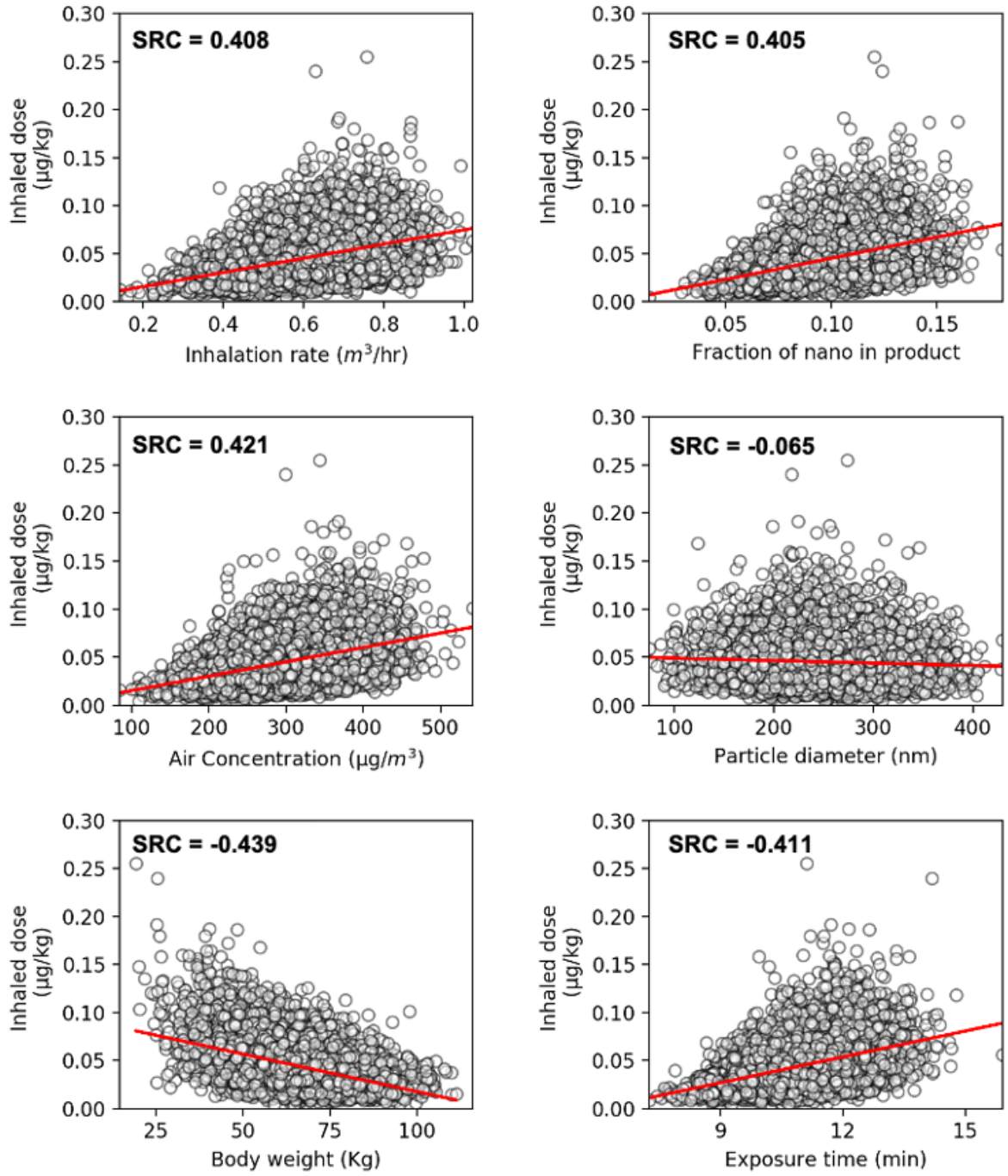


Figure 49. Scatter plots of the output of Nazarenko et al. (2012 & 2014) as function of changes in input parameters with corresponding SRCs.

5 Performance testing

277. In total, 15 tools (10 nanospecific and 5 conventional chemical) and 7 nanospecific tools were selected for the performance testing under the occupational and consumer projects, respectively. The 15 models/tools selected for the performance testing for occupational exposure are ISO, BIORIMA Occupational exposure section, RISKOFDERM, MEASE, EMKG, Stoffenmanager, ENAE-CPSC, LiCARA nanoSCAN, NanoSafer, GUIDEnano, SUNDS, Swiss Precautionary Matrix, Stoffenmanager Nano, ConsExpo nano and ART. The 7 models/tools selected for the performance testing for consumer exposure include ConsExpo nano, Stoffenmanager Nano, Swiss Precautionary Matrix, GUIDEnano, NanoSafer, Boxal et al. (2007), and ENAE-CPSC.

278. EGRET and ECETOC TRA were discarded after the assessment of the scope of the tools. Even though, ECETOC TRA is a ECHA recommended tool, both tools were not considered for further testing as they are limited to the exposure to liquids (cleaning agents, coating products, textiles and sprays). I-NANO and dART were discarded, as no user interface is yet available. SprayExpo, CB nanotool and ANSES were discarded after SA, as unexpected behaviours, which require of further analysis for full understanding, were detected as detailed in sections 4.2.3, 4.2.8 and 4.2.12. NanoRiskCat was discarded, as the tool has only one input parameter, and ConsExpo was also not considered for further testing as the tool has a nano version (ConsExpo nano) which is considered for performance testing. The models MPPD and Nazarenko et al. (2012 & 2014) were discarded for further performance testing despite not showing unexpected behaviors due to lack of data. Finally, the tools DREAM, CEM, E-FAST, ERDEM and WPEM were not considered, as in the consumer project, it was decided that only nanospecific tools would be considered although the initial compilation list included non nanospecific tools. A summary of the selection process and steps is available in Table 60.

279. The results of the performance testing are provided in two separate documents for the occupational and consumer exposure assessment.

- Annex 1 – Part II: Performance testing results for occupational exposure tools/models ENV/CBC/MONO(2021)28
- Annex 2 – Part III: Performance testing results for consumer exposure tools/models ENV/CBC/MONO(2021)29

6 Conclusions and recommendations

280. To evaluate the suitability of tools and models for assessment of occupational and consumer exposure of MNMs, 32 tools/models were compiled through an extensive literature review of peer reviewed publications, the outcomes from recent international projects and inventories, and consultation with OECD WPMN. A summary of the tested tools and obtained results is presented in Table 61.

281. The complied tools/models include 17 nano-specific, given in Category 1 of the inventory, and 15 non-nano-specific, given in Category 2 of the inventory. Considering the tier classification, 14 of the tools are classified as Tier 1 or 2, 4 as tier 2-3 and 14 as Tier 3. Most of the tools are classified as Control Banding (10) or Quantitative Exposure Assessment tools (17), whereas just a few (5) are designed for risk benefit, risk categorisation, risk management and risk assessment.

282. All the inventoried tools/models except the non-nanospecific consumer models (5 tools) were subjected to the scope analysis and accessibility and support examination. The scope analysis provided information on their intended use in terms of scenarios and routes of exposure, output of the models/tools, assumptions considered by models/tools, and input parameters required by models/tools. The accessibility and support examination addressed the user-interface of each model/tool and availability of input parameters required by the models/tools.

283. Regarding input parameters, category 1 (nanospecific) tools require particle molecular structure, morphology, surface chemistry, density or diameter. Conversely, category 2 tools only require information regarding the material CAS, state (solid, liquid, vapour), and density in some cases. Regardless of the category, the most common required input parameters are the description of the type of activity, amount of product used, fraction of MNM in the product, dustiness index of the powder material (as a quantitative or qualitative value), release rate as well as information regarding the activity/exposure duration, number of repetitions, room size and ventilation rate. Other frequently required input parameters are purity or concentration of active substance, solubility and volatility, vapour pressure, LEV and worker protection. Besides that, some tools require specific input parameters such as particle deposition, number of employees exposed or whether the source is located in the breathing zone of the worker or not. For tools including hazard assessment, information regarding toxicity, risk phrases and OEL values are needed. In general, all the input parameters required by models/tools are relatively easy to obtain from available literature, SDS or manufactures information. However, for some models/tools gathering all the required parameters is more complex. In many cases, tools provide guidance (e.g. ACH in the room, PROCs) or databases in order to estimate values (e.g. deposition by ENAE-CPSC exposure model). With regards to user-interface, 13 tools/models are web-based, 8 are download tools, and 5 are protocols or guidance documents. The difficulty score ranged from 1 for ConsExpo up to 4.2 for Nazarenko et al., (2012 & 2014). Most of the tools difficulty score ranged between 1.4 – 2.4 (BIORIMA, MEASE, EMKG, Stoffenmanager, ENAE-CPSC, CB nanotool, LiCARA nanoSCAN, NanoSafer, GUIDEnano, SUNDS, Swiss PM, Stoffenmanager nano, ConsExpo nano, ART, ECETOC TRA and MPPD). The difficulty score was 3.4 for NanoRiskCat, 3.6 for the ISO CB nanotool and ANSES, and 3.8 for Boxall et al., (2007).

284. Following the scope analysis, and accessibility and support examination, the 15 models/tools were subjected to the SA. The SA addressed the sensitivity of models/tools against changes in input parameters. This testing allowed identification of unexpected behaviours and the most and least sensitive parameters of models/tools.

Table 61. List of models tested and summary of the assessments conducted and obtained results.

Model nº	Model and version	Model Type (category)	Application domain	Scope analysis (Yes/No)	Accessibility and support (Yes/No)	Sensitivity analysis method used	Pass the selection process?	Reason for selection/discard for further performance testing	Project
1	ISO/TS 12901-2:2014 CB nanotool v1.0 (Part 2)	CB (category 1)	Work	YES	YES	Diagn	YES (but unexpected behaviour registered)	Nanospecific CB tool. Unexpected behaviour was due to precautionary principle	Occupational
2	BIORIMA Occupational exposure section	QEA (category 1)	Work	YES	YES	OAT	YES	New nano specific tool with no unexpected behaviours other than no sensitivity to number of repetitions	Occupational
3	SprayExpo model 2.3	Physical modelling, QEA, (category 2)	Cons/Work	YES	YES	OAT and MC AAO	NO (extremely low sensitivity to parameters and unexpected behaviour)	Not nanospecific and SA not conclusive	Occupational
4	RISKOFDERM (ECHA recommended)	QEA (category 2)	Work	YES	YES	OAT	YES	ECHA recommended dermal chemical conventional tool with no unexpected behaviours detected	Occupational
5	MEASE 2.2.0 (ECHA recommended)	CB (category 2)	Work	YES	YES	OAT	YES	ECHA recommended chemical conventional tool with no unexpected behaviours	Occupational
6	EMKG Expo tool 2.0 (ECHA recommended)	CB (category 2)	Work	YES	YES	OAT	YES	ECHA recommended chemical conventional tool with no unexpected behaviours	Occupational
7	EGRET 2.0	QEA (category 2)	Cons/work	YES	YES	NOT TESTED (non-suitable)	NO	Non-suitable after scope analysis assessment	Occupational
8	Dermal Advanced Reach Tool (dART)	QEA (category 2)	Work	YES	YES	NOT TESTED (no user interface)	NO	No user interface	Occupational
9	Stoffenmanager 8.3 (ECHA recommended)	CB / RM (category 2)	Work	YES	YES	NOT TESTED (= Stoffenmanager nano tested)	YES	ECHA recommended chemical tool. Only Stoffenmanager nano tested and showed no unexpected behaviours	Occupational

Model nº	Model and version	Model Type (category)	Application domain	Scope analysis (Yes/No)	Accessibility and support (Yes/No)	Sensitivity analysis method used	Pass the selection process?	Reason for selection/discard for further performance testing	Project
10	Engineered Nanoparticle Airborne Exposure (ENAE) Tool (CPSC ENP Model) v1.0	QEA (category 1)	Cons/work	YES	YES	OAT	YES	Nanospecific tool with no unexpected behaviours detected	Occupational and consumer
11	Control Banding (CB) Nanotool v2.0	CB (category 1)	Cons/Work	YES	YES	OAT	NO (almost equal sensitivity towards all input parameters)	Nanospecific tool with unexpected behaviours detected (equal sensitivity to all input parameters)	Occupational and Consumer
12	LiCARA nanoSCAN v1.0	Risk Benefit (category 1)	Env / Cons / Work	YES	YES	OAT	YES	Nanospecific tool with no unexpected behaviours detected	Occupational and Consumer
13	NanoSafer v1.1β	CB / RM (category 1)	Work	YES	YES	OAT	YES	Nanospecific tool with no unexpected behaviours detected	Occupational and Consumer
14	GUIDEnano tool	RA / RM (category 1)	Env / Cons / Work	YES	YES	NOT TESTED (model too complex)	YES	Nanospecific tool with high complexity	Occupational and Consumer
15	The SUN Decision Support System (SUNDS)	Combination of multiple approaches, RA / RM (category 1)	Env / Cons / Work	YES	YES	OAT	YES	Nanospecific tool with no unexpected behaviours detected	Occupational and Consumer
16	ANSES tool	CB (category 1)	Work	YES	YES	Diagn and modified OAT	NO (extremely low sensitivity to parameters)	Nanospecific tool with unexpected behaviours detected (extremely low sensitivity to input parameters)	Occupational and Consumer
17	Swiss Precautionary Matrix v3.0	Risk Cat (category 1)	Env / Cons / Work	YES	YES	OAT	YES	Nanospecific tool with no unexpected behaviours detected	Occupational and Consumer
18	Stoffenmanager Nano v1.0	CB / RM (category 1)	Work	YES	YES	Statistical design of experiments and linear regression methodology	YES	Nanospecific tool with no unexpected behaviours detected	Occupational and Consumer
19	ConsExpo Nano	Physical modelling,	Cons	YES	YES	Global uncertainty – AAO MC	YES	Nanospecific tool with no unexpected behaviours detected	Occupational and Consumer

Model nº	Model and version	Model Type (category)	Application domain	Scope analysis (Yes/No)	Accessibility and support (Yes/No)	Sensitivity analysis method used	Pass the selection process?	Reason for selection/discard for further performance testing	Project
		QEA (category 1)							
20	ConsExpo	Physical modelling, QEA (category 2)	Cons	YES	YES	NOT TESTED (= ConsExpo nano tested)	NO	Conventional chemical tool with a nano version available. Only the nano version is addressed in this project	Occupational and Consumer
21	Advanced REACH Tool v1.5 (ECHA recommended)	QEA (category 2)	Work	YES	YES	OAT	YES	ECHA recommended chemical conventional tool with no unexpected behaviours	Occupational and Consumer
22	ECETOC TRA v3.1 (ECHA recommended)	CB (category 2)	Cons/Work	YES	YES	NOT TESTED (non-suitable)	NO	Non-suitable after scope analysis assessment	Occupational and Consumer
23	NanoRiskCat	Risk Cat (category 1)	Cons/Work	YES	YES	NOT TESTED (one input parameter)	NO	Nanospecific tool with only one input parameter	Occupational and Consumer
24	Multiple-Path Particle Dosimetry Model (MPPD)	QEA (category 1)	Cons/Work	YES	YES	OAT	NO (no measurement data)	No measurement data was available for performance testing	Consumer
25	I-NANO	QEA (category 1)	Cons/Work	YES	YES	NOT TESTED – (no user interface)	NO (no user interface)	No user interface	Consumer
26	Boxall *et al*. 2007	QEA (category 1)	Cons	YES	YES	AAO MC	YES	Nanospecific tool with no unexpected behaviours	Consumer
27	Nazarenko *et al*. (2012 & 2014)	QEA (cat 1)	Cons	YES	YES	AAO MC	NO (no measurement data)	No measurement data was available for performance testing	Consumer
28	DREAM	CB (category 2)	Work	No (Non-nanospecific)	No (Non-nanospecific)	NOT TESTED (non-nanospecific)	NO	Not nanospecific. Under the consumer project it was decided that only nanospecific tools would be considered	Consumer
29	Consumer Exposure Model (CEM)	QEA (category 2)	Cons	No (Non-nanospecific)	No (Non-nanospecific)	NOT TESTED (non-nanospecific)	NO	Not nanospecific. Under the consumer project it was decided that only nanospecific tools would be considered	Consumer

Model nº	Model and version	Model Type (category)	Application domain	Scope analysis (Yes/No)	Accessibility and support (Yes/No)	Sensitivity analysis method used	Pass the selection process?	Reason for selection/discard for further performance testing	Project
30	E-FAST	QEA (category 2)	Cons	No (Non-nanospecific)	No (Non-nanospecific)	NOT TESTED (non-nanospecific)	NO	Not nanospecific. Under the consumer project it was decided that only nanospecific tools would be considered	Consumer
31	Exposure Related Dose Estimating Model (ERDEM)	QEA (category 2)	Cons	No (Non-nanospecific)	No (Non-nanospecific)	NOT TESTED (non-nanospecific)	NO	Not nanospecific. Under the consumer project it was decided that only nanospecific tools would be considered	Consumer
32	Wall Paint Exposure Model (WPEM)	QEA (category 2)	Cons/Work	No (Non-nanospecific)	No (Non-nanospecific)	NOT TESTED (non-nanospecific)	NO	Not nanospecific. Under the consumer project it was decided that only nanospecific tools would be considered	Consumer

Note: Yes/No indicates whether tool/model are examined for scope analysis and accessibility and support. (Abbreviations: Env - environmental, Cons - consumer, CB – Control Banding, RA - Risk Assessment, RM – Risk Management, QEA - Quantitative Exposure Assessment, Risk Cat - Risk Categorization, OAT - One-at-a-time, Diagn - Diagnostic, MC - Monte Carlo, AAO – All at once).

285. The least and most sensitive parameters are different between models/tools, which is mostly attributed to the different application domains of the models/tools and potential differences in their hard-coded parametrisation. It should be noted that the results of the SA are based on input ranges defined in this work, which were mainly defined based on a specific case scenario or tried to consider all physically possible range of input options. For ConsExpo nano, MPPD, Boxall et al. (2007), Nazarenko et al. (2012 & 2014), the input ranges are defined based on the different specific exposure scenarios, which could influence the results. Thus, cautions should be taken when interpreting the results and no generalized conclusions on influential parameters should be drawn from the analysis. In general, using an exposure scenario limits the range of parameter values used in the analysis, as the entire possible space of input for parameters is not covered. However, this ensures that the parameters are correlated in the sense that they refer to the same scenario and prevents unphysical combinations of input values.

286. The most sensitive parameters shared between the tools/models include the presence of nanomaterials in the production (ANSES, Swiss Precautionary Matrix), releases amount/release rate (ConsExpo nano, Stoffenmanager nano, ENAE-CPSC, SprayExpo), fraction of MNMs in product (Boxall *et al.,* 2007, Nazarenko *et al.,* 2012 & 2014, SprayExpo and ConsExpo nano), air concentration of particle (Nazarenko *et al.,* 2012 & 2014, MPPD), inhalation rate (Nazarenko *et al.,* 2012 & 2014, ConsExpo nano), activity duration (ConsExpo nano, Nanosafer), and exposure time (Nazarenko *et al.,* 2012 & 2014, Boxall *et al.,* 2007, ENAE-CPSC). The least sensitive parameters shared between the tools/models include origin of nanomaterial / product type (Swiss Precautionary Matrix, Stoffenmanager nano) and activity level/handling activity (NanoSafer CB, Stoffenmanager nano). In addition, there are a few input parameters showing high sensitivity in one tool/model, but low sensitivity in another tool/model. These parameters include room volume, room ventilation rate, OEL values, duration of handling/work cycle, particle diameter and dustiness. These parameters are of primary interest, as the difference in the sensitivities point to underlying differences in the models, in the metrics used in the SA, and in the assumptions of base scenarios from which the analysis was performed

287. The ANSES CB Nanotool, CB nanotool and ISO/TS 12901 CB tool are simple control banding based models, which either follow a decision tree by answering questions or in case of CB nanotool assume a discrete score on each question. The CB nanotool showed similar sensitivity on almost all of its parameters. Regarding ISO/TS CB tool, the applied testing method did not enable comparison of individual parameters.

288. In the cases of ConsExpo nano, Nazarenko *et al.,* 2012 & 2014, and Boxall *et al.,* 2007, MC AAO method, in which normal distribution is defined for input parameters, was used to perform the SA, and SCR was calculated as measure of sensitivity. The calculated SCR allows direct comparison between different parameters for each of these models/tools. However, while the AAO method considers the direct influence of a parameter on model/tool as well as the joint influence of parameters on model due to interactions between input parameters, the SCR could not analyse interactions between specific combinations (pairs, triples, etc.) of input parameters and provide detailed insights. Without such analysis, cautions should be taken when drawing conclusion. Moreover, The SCRs assumes a linear model response towards changes of parameters, which is not the case for some parameters of these models/tools. A similar case is the one from SprayExpo, for which OAT and AAO-MC methods were used. Using these methodologies, interdependency of some parameters could not be fully addressed, and some unexpected behaviours, for which no other explanation was found, were observed. To address these issues, as an alternative approach, variance-based sensitivity analysis will be recommended for future activities in order to further investigate the sensitivity of some tools.

289. It can be noted that harmonization on choosing input ranges and SA methods could make the direct comparison of the results between models/tools more meaningful. Such a harmonization can be achieved using a unified SA method and input ranges. However, this would only be applicable to models/tools that consider similar conditions, and here, this was generally not the case. Thus, different SA methods are justified in this work. This is the case, for instance, of ConsExpo nano and

Stoffenmanager nano, which have high difference in their application domain. Similarly, harmonization on input ranges can be done only to some extent due to the varying application domain of the models/tools. While the differing SA method limits the direct comparison of the results between models/tools, the SA methods fitting for the specific model make the results on parameter sensitivities more tangible.

290. Along with the most and least sensitive parameters, the unexpected behaviour of the models was analysed. A number of 10 models were found to have non sensitive parameters, which was the most common unexpected behaviour in the models (Table 62).

291. Overall, the result of the SA can indicate the values of which input parameters need to be measured or estimated more accurately. High-accurate data of highly sensitive parameters can significantly reduce uncertainty resulted from these parameters in models/tools output. As such, the user should pay particular attention in choosing values for the highly sensitive parameters. It should be noted that low sensitive parameters could also induce uncertainty in models/tools output as model outcomes are not only influenced by changes of parameters but also due to the uncertainty of the parameters itself. Therefore, the fact that a parameter is categorised as a low sensitive parameter does not mean it can be discarded from the tool, the user still needs to determine the values of these parameters as accurate as possible when using models/tools.

Table 62. Overview on the unexpected behaviour of the models.

Model/Tool	Non sensitive parameters
ISO/TS 12901-2:2014 CB nanotool v1.0 (Part 2)	
BIORIMA (Occupational exposure section)	X
SprayExpo model 2.3	X
RISKOFDERM	
MEASE 2.2.0	
EMKG Expo tool 2.0	
EGRET 2.0	Not tested
Dermal Advanced Reach Tool (dART)	Not tested
Stoffenmanager 8.3	Not tested
Engineered Nanoparticle Airborne Exposure (ENAE) Tool (CPSC ENP Model) v1.0	
Control Banding (CB) Nanotool v2.0	X
LiCARA nanoSCAN v1.0	
NanoSafer v1.1β	X
GUIDEnano tool	Not tested
The SUN Decision Support System (SUNDS)	X
ANSES tool	X
Swiss Precautionary Matrix v3.0	X
Stoffenmanager Nano v1.0	X
ConsExpo Nano	X
ConsExpo	Not tested
Advanced REACH Tool v1.5	X
ECETOC TRA v3.1	Not tested
NanoRiskCat	Not tested
Multiple-Path Particle Dosimetry Model (MPPD)	
I-NANO	Not tested
Boxall *et al*. (2007)	
Nazarenko *et al*. (2012 & 2014)	

Note: The condition marked with X implicates presence of that behaviour.

292. Following the sensitivity analysis, 15 of the 23 occupational models/tools (10 nanospecific and 5 chemical conventional) and 7 of the 15 models/tools compiled for assessing consumer exposure to MNM were selected for performance testing. Final tools selected for performance testing as well as a summary of results obtained is shown in Table 61. The 15 models/tools selected for the performance testing for occupational exposure are ISO, BIORIMA Occupational exposure section, RISKOFDERM, MEASE, EMKG, Stoffenmanager, ENAE-CPSC, LiCARA nanoSCAN, NanoSafer, GUIDEnano, SUNDS, Swiss Precautionary Matrix, Stoffenmanager Nano, ConsExpo nano and ART. The 7 models/tools selected for the performance testing for consumer exposure include ConsExpo nano, Stoffenmanager Nano, Swiss Precautionary Matrix, GUIDEnano, NanoSafer, Boxal et al. (2007), and ENAE-CPSC. Models/tools not selected for performance testing and the reasons are 1) unexpected behaviour detected during sensitivity analysis (SprayExpo, ANSES and CB Nanotool), 2) not suitable for MNM exposure assessment (ECETOC TRA, ConsExpo and EGRET), 3) no user interface for performance (dART, NanoRiskCat, and I-NANO), and 4) lack of measurement data on internal dose of MNMs (Nazarenko et al. 2012 & 2014 and MPPD). The results of the performance testing are provided in two separate documents. It is important to note that the available measurement data for consumer exposure is generally lower than for occupational exposure, making the performance testing for consumer exposure scenarios limited to a few case studies. The low availability of measurement data on consumer exposure scenarios and the general lack of internal dose data demonstrate the importance and need to generate these types of data for use in evaluation and implementation of models/tools to estimate exposure to MNMs.

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Annex 1

The results of the performance testing for Occupational exposure are provided in a separate document:

- Part II: Performance testing results for occupational exposure tools/models ENV/CBC/MONO(2021)28

Annex 2

The results of the performance testing for Consumer exposure are provided in a separate document:

- Part III: Performance testing results for consumer exposure tools/models ENV/CBC/MONO(2021)29

Annex 3

The inventory of models/tools compiled for the occupational and consumer exposure assessment of MNM and the calculated difficulty score are given in the Excel file - *Exposure Models Inventory.xlsx.*