This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 862419. This publication reflects only the author's views and the European Union is not liable for any use that may be made of the information contained therein.

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SAbyNA

H2020-NMBP-15-2020

Simple, robust and cost-effective approaches to guide industry in the development of safer nanomaterials and nano-enabled products

Start date of the project: 01/03/2020

Duration 48 months

D2.4 – Improvements required in existing models

WP	2	Streamlined methodologies, models and tools to facilitate release, fate & exposure assessment of NFs/NEPs for SbD purposes

Dissemination level[1]	PU	Due delivery date	31/10/2022
Nature[2]	R	Actual delivery date	30/11/2022

Lead beneficiary	UKCEH
Contributing beneficiaries	WP2 partners

[1] Dissemination level: **PU** = Public, **PP** = Restricted to other programme participants (including the JU), **RE** = Restricted to a group specified by the consortium (including the JU), **CO** = Confidential, only for members of the consortium (including the JU)
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Version	Date	Author	Partner	Email	Comments[3]
0.0.1	27/05/2022	Sam Harrison	UKCEH	sharrison@ceh.ac.uk	Creation
	25/7/2022	James Hanlon	IOM	James.Hanlon@iom-world.org.uk	Edits
0.1	8/11/2022	All WP2 partners			First draft
0.11	14/11/2022	Sam Harrison / James Hanlon / WP2 partners	UKCEH / IOM	sharrison@ceh.ac.uk / James.Hanlon@iom-world.org.uk	Final draft
1.0	30/11/2022	Ralph Vanhauten / SB / WP2 partners	-	-	Final version, including internal reviews

[3] Creation, modification, final version for evaluation, revised version following evaluation, final

Deliverable abstract

In this H2020 SAbyNA deliverable, we discuss suggested improvements in existing release, fate and exposure models, with a particular focus on improvements that could be made to GUIDEnano modules. This deliverable acts as an extension of the interim Deliverable 2.8 and documents work carried out in Task 2.2 (Optimization and usability improvement of data, methods and tools to estimate release, fate and exposure). The conclusions from this deliverable are being fed into WP6 to contribute to the creation of the SAbyNA Guidance Platform.

We report on our detailed assessment of environmental release, fate and exposure models, focussing on aspects such as processes and algorithms, input parameters, sensitivity/uncertainty analyses and scenarios/case studies. We identify several potential improvements to GUIDEnano, such as the inclusion of default parameter sets (e.g. for water composition, material phys-chem parameters and lifecycle scenarios), updated process algorithms and the inclusion of Specific Environmental Release Categories (SPERCs) to provide estimates of environmental release.

We discuss improvements required in the human exposure models and how these could be incorporated into GUIDEnano modules. The suggested improvements to GUIDEnano include providing default parameter sets, inclusion or improvement of specific processes (such as relative humidity and VOCs), read-across for exposure scenarios, whether a warning for exposure can be included and incorporating uncertainty assessment.

These suggestions are now being discussed for implementation with the GUIDEnano developers and WP6.

Table of Contents

Abbreviations

CB	Control Banding
CNT	Carbon Nanotubes
ECHA	European Chemical Agency
ENM	Engineered Nanomaterial
EUSES	EU System for the Evaluation of Substances
D	Deliverable
LCA	Life Cycle Assessment
M	Month
MFA	Material Flow Analysis
MS	Milestone
NEP	Nano Enabled Product
NF	Nanoform
NM	Nanomaterial
NP	Nanoparticle
NRV	Nano Reference Value
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
PEC	Predicted Environmental Concentration
RA	Risk Assessment
RMM	Risk Mitigation Measure
PCA	Principal Component Analysis
SbD	Safe(r) by Design
SME	Small and Medium Enterprise
SOP	Standard Operation Procedure
T	Task
WG	Working Group
WP	Work Package
WWTP	Wastewater Treatment Plant

1. Scope

This H2020 SAbyNA deliverable expands on the interim deliverable for D2.8 (submitted M20) and serves to document the optimisation of existing release, fate and exposure models to make them more suited to SbD purposes. The work reported is largely part of Subtasks 2.2.3 (Streamlining of environmental release and fate models) and 2.2.4 (Streamlining of human exposure models and tools), and is an extension of the model/tool assessment performed in D2.1 and MS2.2.

As discussed in MS2.2, GUIDEnano has been selected as the model which is most suited to SbD purposes. As such, the scope of this deliverable is largely on assessing how improvements to GUIDEnano could be made, potentially using elements from other models and tools. In the following, we refer to GUIDEnano as the central exposure, hazard and risk assessment model within the SAbyNA Guidance Platform, and thus many of our recommendations should be viewed in the context of the entire platform, as well as GUIDEnano and its constituent modules individually.

2. Environmental release, fate and exposure models

2.1 Assessment methodology

The assessment of environmental release, fate and exposure models was performed using the extended versions of the assessment spreadsheets developed for D2.1, as detailed in MS2.2. Links to these spreadsheets are provided in the Appendix, and an example shown in Figure 1. Over and above D2.1, they provide a more thorough template through which to assess the models, including detailed information on, for example, processes modelled and algorithms used. The goal of this is to identify elements of the models that could be incorporated into GUIDEnano, in particular those elements most suited to or relevant to SbD.

	A	B	C	D	E	F
1	Name	Processes for potential inclusion into GUIDEnano	Erosion processes modelled	Erosion algorithms	Sedimentation processes modelled	Sedimentation algorithms
2	NanoFASE model	Potential for improving GUIDEnano sediment dynamics using erosion and sedimentation processes.	Soil erosion Bank erosion	Soil erosion: Modified RUSLE based on Davison et al 2005 (10.1016/j.scitotenv.2005.02.002). Scaled by transport capacity from INCA-Sed (10.1016/j.scitotenv.2010.02.030) Bank erosion: Algorithm from INCA-Sed, function of discharge (Q) and two calibration parameters (a, b): E = aQ^b	Deposition Resuspension	Deposition: Based on Zhiyao 2008 (10.1016/S1674-2370(15)30017-X). Resuspension: Algorithm from INCA-Sed
3	SimpleBox4nano		Soil erosion specified as a constant rate	-	Sedimentation, Deposition Resuspension	Sedimentation velocity derived from Stokes' Law for gravitational settling of particles
4	GUIDEnano	-	Soil erosion at a constant rate, calculated by the model		Deposition, resuspension	Rate constants. Resuspension velocity is an input parameter. Deposition is calculated in the model (?)
5	IDPMFA	Could these Python scripts be incorporated to model release in GUIDEnano?	-	-	-	-

Figure 1. Example of the spreadsheets being used to assess environmental release and exposure models.

The spreadsheets are detailed fully in MS2.2, and here we provide a summary. The spreadsheets are split into four separate sheets:

- **Model descriptions:** General information about the model, mostly compiled during Task 2.1. Includes information on whether a sensitivity/uncertainty analysis has been completed, what materials the model has been used for, what spatial/temporal resolution it has, and the availability of input data.
- **Model parameters:** Key input and output parameters. Environmental release and exposure models generally have a large number of input parameters (even simpler models such as SimpleBox4nano can have hundreds of parameters), and so here we try to summarise the key input variables or variable groupings. The goal of capturing this information is to enable the linking of methods and data to model parameters, which will make it possible for GUIDEnano to recommend suitable methods and databases to source input parameters. At this stage, we have focussed on nano-specific parameters such as attachment efficiencies and dissolution rates.

- **Model environmental scenarios:** Here we collect information on the environmental scenarios the models have been run for. Depending on the spatial resolution of the model, this might be a local catchment or broader geographical regions (national, continental or global). The goal of this is to identify the availability of datasets for different geographical regions, which might be of use in GUIDEnano. Though GUIDEnano is not a catchment-based model (i.e., of a specific riverine catchment/watershed) and runs are not performed for specific geographical regions, certain environmental scenarios could be emulated through the use of input data. For example, a spatial region could be modelled by running GUIDEnano over a distribution of input parameters to mimic the environmentally-realistic range of a given parameter (e.g. water chemistry) within that spatial region.
- **Model algorithms and processes:** Detailed information on the processes included in the models and the algorithms used to model these is included on this sheet. This currently includes information on soil erosion, sedimentation, ENM aggregation, ENM dissolution, ENM chemical transformation (e.g. Ag sulphidation), atmospheric deposition/resuspension, wastewater treatment, subsurface/groundwater processes and release rates. The goal of collecting this information is to identify processes for potential inclusion into GUIDEnano kinetic fate module, for example to increase realism or make data requirements more parsimonious.

As GUIDEnano modules are the main focus for improvement, we will perform a more in-depth assessment of this model. This will include running the model for several scenarios that relate to the SAbyNA case studies.

2.2 Results

For environmental models, it is useful to consider release/grouping and fate/exposure models separately.

2.2.1 Release, grouping and others

As a recap of MS2.2 and D2.1, the release and grouping models selected for further assessment in T2.2 are shown in Table 1.

Table 1. Environmental release models and tools assessed for optimisation. Elements of these models are being considered for incorporation into GUIDEnano.

Model	Comments
LearNano	Web-based interface to predict ENM release rates. Links with MendNano.
ECETOC NanoApp	Web-based tool to help grouping of nanoforms based on phys-chem properties
LICARA NanoSCAN	Life-cycle assessment tool to predict benefits and risks of nanomaterials
IDPMFA	Dynamic probabilistic material flow analysis model which provides country-specific release rates to various compartments

Unfortunately, as of November 2022 the website that previously hosted LearNano has been down for over a year, and the original authors have been unresponsive to enquiries. We will keep LearNano on the list of tools as we see the benefits to its user-friendly interface, and its abilities to link with the MendNano model (also unavailable), but we have not been able to perform a full assessment.

ECETOC NanoApp is a web-based tool that helps with the grouping of nanoforms based on phys-chem properties. From a SbD perspective, grouping might be a useful way to tell whether certain material modifications are likely to make a given nanoform "safer". However, the tool does not make any indication on exposure nor hazard, rather the assumption is that if two nanoforms are considered similar to the applied criteria they will behave similar regardless of the context they are applied in and then can be registered within the same set. The similarity criteria used only leads to a match when all thresholds match the grouping and as such is very strict. Therefore, one can only state that an alternative SbD nanoform may not be grouped with the original nanoform when applying ECETOC NanoApp rules. Candidate nanoforms not grouped together with the original one can be both more or less hazardous and therefore this cannot be used as an indication for potential candidates as such.

In contrast, the grouping approach within the EU H2020 project GRACIOUS also includes exposure route and environmental compartment specific IATAs (Integrated Approaches to Testing and Assessment), which are used for the similarity assessment of candidate nanoforms, and is as such better suited to screening SbD candidates only leading to release and exposure in a certain context.

LICARA NanoSCAN covers the entire lifecycle of ENMs and considers human and environmental exposure, risk and benefits. The output is a series of scores, with lower scores (<0.3) indicating little risk, and higher scores (>0.8) indicating high risk. An arbitrary example is given in Figure 2. In order to obtain this output, users must answer a series of questions about the nanomaterial. The Swiss Precautionary Matrix is used for the environmental parts of the tool.

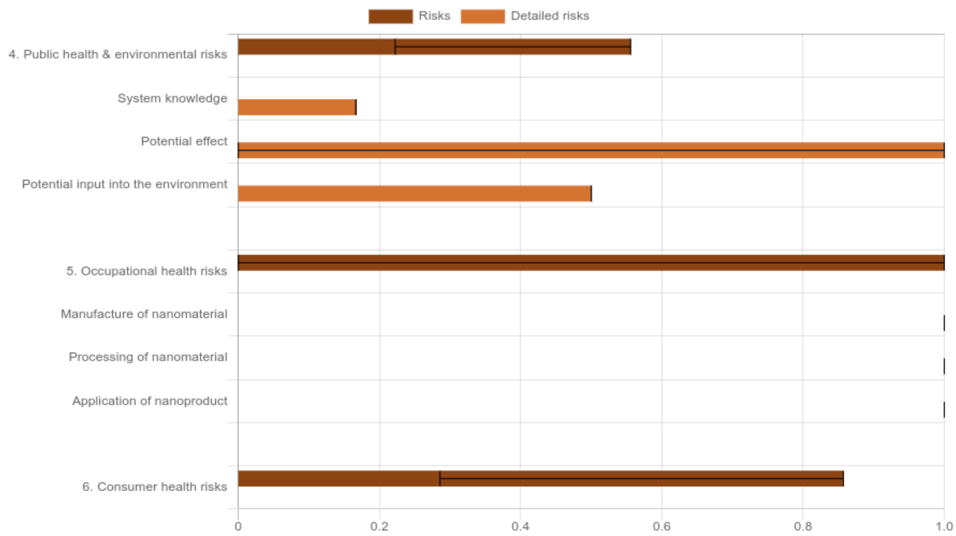

Figure 2. An example of the output of risk scores from LICARA NanoSCAN.

It is not a release or exposure tool in the strictest sense, in that the user must already have information on the likely release amount and pathway of their material. However, it provides an invaluable resource for SMEs in enabling them to qualitatively assess benefits and risks and communicate these to regulators and other stakeholders. As it is a screening level tool, it might be a useful resource for Part 1 of the SAbyNA Guidance Platform to link to.

IDPMFA models the environmental release of nanomaterials at country level, via an integrated dynamic probabilistic material flow analysis, for nano-Ag, nano-TiO2 and nano-ZnO. This model underpins a great deal of published literature on the environmental release of nanomaterials[4]. The model is open source and Python codes are provided via Zenodo, thereby making it an interesting candidate to further explore with relation to how and if it could be integrated with GUIDEnano at a later stage. However, as SAbyNA is more focussed on prospective exposure assessment taking into account SbD mitigations, the realistic release provided by IDPMFA are not so useful in the context of the project, and so its integration will not be explored further here.

[4] Adam *et al.* (2021): https://doi.org/10.1016/j.impact.2021.100312; Adam *et al.* (2018): https://doi.org/10.1016/j.envpol.2018.07.108

Specific Environmental Release Categories

Separate to the models/tools listed above, we are considering the use of Environmental Release Categories (ERCs) or Specific Environmental Release Categories (SPERCs)[5], which are often used to provide estimates of release rates (as fractional mass flows) for regulatory assessments. ERCs are 'use descriptors' defined from an environmental perspective, which include release factors that are conservative default values, assuming no specific risk management measures are in place. ERCs are designed to label the characteristics of a use based on different aspects relevant from the environmental perspective: the lifecycle stage at which a use takes place, the technical fate (destination) of the substance resulting from the use, the 'indoor or outdoor' use of a substance, and whether articles are used under release-promoting conditions. SPERCs correspond to sets of information describing specific good practice conditions of use and the corresponding release estimates to water, air, soil and waste. SPERCS are developed by sector groups of chemical industries and their downstream customer industries to refine the emission estimates obtained by using the ERCs' release factors, taking into account specific operational conditions and RMMs applied for the use in the sector. Such release rates might be useful in assessing exposure without the need for detailed experimental release work. Figure 3 shows the use of ERCs and SPERCs during screening level exposure assessments. While ERCs relate to lifecycle stage and to a broad spectrum of products, also considering the worst-case scenario (resulting in very conservative – and sometimes unrealistic - values), SPERCs refine these corresponding emission estimates by taking into account processes, sector specific products,[6] and RMMs applied. Therefore, they are inherently less conservative but more realistic than ERCs.

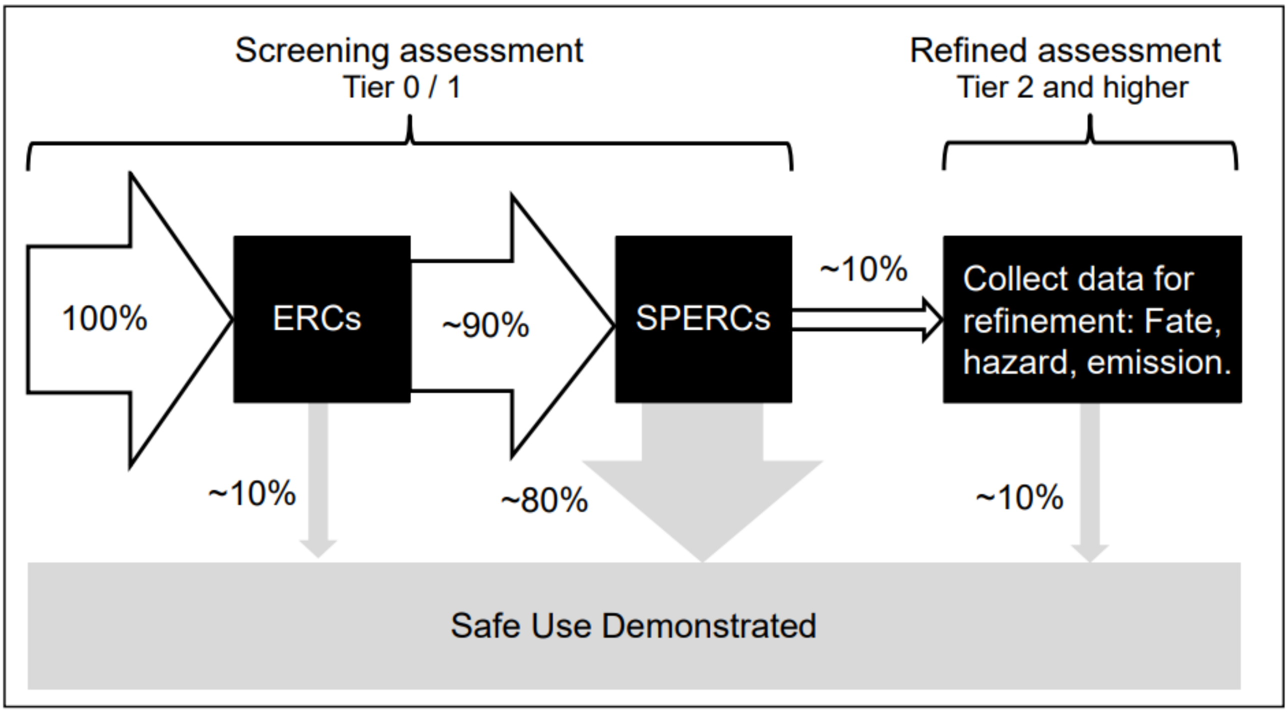

Figure 3. Illustrative scheme of the role of SpERCs as an element of a tiered approach to emission estimation. The width of the arrows is indicative of the portion of assessments that need refinement (horizontal) or pass the environmental exposure assessment.[5]

GUIDEnano already includes a list of ERCs as an option for providing release rates to the fate and exposure parts of the model. A potential improvement would be to provide a library of SPERCs for users to select from,

[5] ECHA, "SPERC Fact Sheet Format with Explanations": https://echa.europa.eu/documents/10162/15669641/sperc_factsheet_guidance_en.pdf/4c94f0fb-07dd-4e9f-842a-3f21a63bd3fe

[6] Reihlen et al (2015), "SPERCS – A tool for environmental emission estimation": https://doi.org/10.1002/ieam.1745

similarly to the Chesar tool[7]. The GUIDEnano infrastructure is already suitable for the incorporation of the emissions factors contained within SPERCs. The ECHA Use Maps Library and Table 1 in Reihlen et al, 2015[6] gives a useful overview of SPERC development activities by different sectors and trade bodies, covering uses such as industrial use of paints and coatings, use of personal care products, and dispersive use of plant protection products, among others. The fact that SPERCs are developed by industry bodies themselves presents a potential challenge in that there is no central database of SPERCs that is frequently updated (though tools like Chesar and libraries like the ECHA Use Maps Library aim to integrate as many SPERCs as possible) and it is not a trivial task to find out which SPERCs concern ENMs.

Although most of SPERCs do not consider nanomaterials themselves, some approximations/assumptions can be adopted to calculate the emissions of NMs to the environment, for example considering the % of the NM in a mixture or in a NEP (which allows estimation of the NM release on the basis of general released mass).

Also of note, since the interim deliverable D2.8, TNO have released a tool "Hot Spot Scan", which generates emissions data to environmental and occupational settings. It does so by providing users with a questionnaire that gathers information on the product's lifecycle and potential release pathways. A library of SPERCs is built into the tool.

In relation to the SAbyNA case study of additive manufacturing, although the EuPC (European Plastics Converters trade association) has developed an ECHA Use Map, no SPERC has been uploaded to the ECHA webpage. From SAbyNA consortium there is an ongoing contact with EuPC to clarify possible plans and timelines for the creation of any SPERC related with this sector (3D-printing).

[7] ECHA, Chesar tool: https://chesar.echa.europa.eu/

LCS (life cycle stage)	Location of use:	Specific formulation is known?	Coatings and inks	Solvent	Type of ingredient	Scale	General description	SPERC:
F (Formulation or re-packing)	Indoor	Yes	Liquid coatings and inks	Organic Solvent	volatile ingredients	Large scale (>1,000 tpa solvent use)	Formulation of organic solvent borne coatings and inks - large scale (>1,000 tpa solvent use) – volatiles	CEPE SPERC 2.1a.v2
						Small scale (<1,000 tpa solvent use)	Formulation of organic solvent borne coatings and inks - small scale (<1,000 tpa solvent use) - volatiles	CEPE SPERC 2.1b.v2
					non-volatile ingredients	-	Formulation of organic solvent borne coatings and inks - non-volatiles	CEPE SPERC 2.1c.v2
				Water	volatile ingredients	Large scale (>1,000 tpa solvent use)	Formulation of water borne coatings and inks - large scale (>1,000 tpa solvent use) - volatiles	CEPE SPERC 2.2a.v2
						Small scale (<1,000 tpa solvent use)	Formulation of water borne coatings and inks - small scale (<1,000 tpa solvent use) - volatiles	CEPE SPERC 2.2b.v2
					non-volatile ingredients	-	Formulation of water borne coatings and inks - non-volatiles	CEPE SPERC 2.2c.v2
			Powder coatings and inks	-	non-volatile ingredients	-	Formulation of powder coatings and inks – non-volatiles	CEPE SPERC 2.3a v.1
		No	Liquid coatings and inks (where specific formulation not known)	Organic Solvent or Water	volatile ingredients	Large scale (>1,000 tpa solvent use)	Formulation of organic solvent or water borne coatings and inks - large scale (>1,000 tpa solvent use) - volatiles	CEPE SPERC 2.4a.v2
						Small scale (<1,000 tpa solvent use)	Formulation of organic solvent or water borne coatings and inks - small scale (<1,000 tpa solvent use) – volatiles	CEPE SPERC 2.4b.v2
					non-volatile ingredients	-	Formulation of organic solvent or water borne coatings and inks - non-volatiles	CEPE SPERC 2.4c.v2

	Technique (application)	Location of use:	Type of ingredient	General description	SPERC:
IS (Use at industrial sites)	Spraying (incineration)	Indoor	volatile ingredients	Application - industrial - spraying - indoor use -	CEPE SPERC 4.1a.v2
	Spraying	Indoor	volatile ingredients	Application - industrial - spraying - indoor use -	CEPE SPERC 4.1b.v2
			non-volatile ingredients	Application - industrial - spraying - indoor use – non	CEPE SPERC 5.1a.v2
			powder	Application - industrial - spraying - indoor use -	CEPE SPERC 5.2a.v2
	Non-spray (incineration)	Indoor	volatile ingredients	Application - industrial – non-spray- indoor use - incineration - volatiles	CEPE SPERC 4.2a.v2
	Non-spray	Indoor	volatile ingredients	Application - industrial – non-spray- indoor use - volatiles	CEPE SPERC 4.2b.v2
			non-volatile ingredients	Application - industrial – non-spray- indoor use – non-	CEPE SPERC 5.3.v2
			powder	Application - industrial – non-spray- indoor use - powder	CEPE SPERC 5.4.v2
C: Consumer use	Brush/roller	Indoor	volatile ingredients	Application - consumer – brush/roller - indoor use -	CEPE SpERC 8a.1a.v2
			non-volatile ingredients	Application - consumer - brush/roller - indoor use –	CEPE SpERC 8c.1a.v2
		Outdoor	volatile ingredients	Application - consumer - brush/roller - outdoor use –	CEPE SpERC 8d.1a.v2
			non-volatile ingredients	Application - consumer - brush/roller - outdoor use –	CEPE SpERC 8f.1a.v2
PW: Widespread use by professional workers	Brush/roller	Indoor	volatile ingredients	Application - professional – brush/roller - indoor use -	CEPE SpERC 8a.2a.v2
			non-volatile ingredients	Application - professional - brush/roller - indoor use –	CEPE SpERC 8c.2a.v2
		Outdoor	volatile ingredients	Application - professional - brush/roller - outdoor use –	CEPE SpERC 8d.2a.v2
			non-volatile ingredients	Application - professional - brush/roller - outdoor use –	CEPE SpERC 8f.2a.v2
	Spraying	Indoor	volatile ingredients	Application - professional - spraying - indoor use -	CEPE SpERC 8a.3a.v2
			non-volatile ingredients	Application - professional - spraying - indoor use – non-	CEPE SpERC 8c.3a.v2
		Outdoor	volatile ingredients	Application - professional - spraying - outdoor use –	CEPE SpERC 8d.3a.v2
			non-volatile ingredients	Application - professional - spraying - outdoor use – non-	CEPE SpERC 8f.3a.v2

Figure 4. Summary of the existing paint-related SPERCs and their covered areas, including life cycle stage, location of use, application technique, solvent, production scale, etc. tpa = tonnes per anum.

Regarding the case study of paints, there are indeed developed SPERCs carried out by the European Council of the Paint, Printing Ink and Artists' Colours Industry (CEPE) since December 2020. Existing paint-related SPERCs are cepe_sperc_2.1, 2.2, 2.3, 2.4, 4.1+5.1+5.2, 4.2+5.3+5.4, 8.1, 8.2, and 8.3. Most of them include sub-SPERCs. Different SPERCs cover the general existing cases (as the life cycle of the paint, powder or liquid paints, organic- or water-based paints…) while the sub-SPERCs aim for the details inside each of these cases/

categories (large- or small-scale production, volatile and non-volatile compounds). A summary of the paints SPERCs is shown in Figure 4.

Paint-related SPERCs deliver several information and values:

- Use descriptors: LCS (lifecycle stage); SU (Sector of Use); PC (Product); ERC (Environmental Release Category); and PROC (Process) codes.
- Number of emission days per year (d/y).
- Typical maximum daily usage (kg/day), including the specific values for each of the components of the paints: pigment/extender/filler; binder; water; organic solvent/coalescent; and additives.
- Risk mitigation measures needed for reducing the release to outdoor air, water, and soil, and their efficiency.
- Release factors (% of release into the environmental compartment) to air, water, soil, and waste.
- Guidance of the required operational conditions (including information on technical strategies to achieve high raw material efficiency and waste disposal).

In addition, they also include some guidance to ease the process of categorizing a paint into a specific SPERC or to another. All the information contained in the paint-related SPERCs uploaded in the ECHA webpage has been collected and organized, and it can be found in Appendix 1.

2.2.2 Fate and exposure models

As a recap of MS2.2 and D2.1, the fate and exposure models selected for further assessment in T2.2 are shown in Table 2. Similarly to LearNano, the website for MendNano is currently unavailable.

Table 2. Environmental fate and exposure models selected for optimisation.

Model	Comments
NanoFASE	Spatiotemporal multimedia ENM exposure model
SimpleBox4nano	Screening level multimedia box model, based on SimpleBox, which underpins the EUSES tool
GUIDEnano	Web-based guidance tool to aid ENM risk assessment
MendNano	Dynamic multimedia box model, implemented with web-based interface. Links with LearNano.
nanoFate	Dynamic multimedia with some spatial resolution

Model algorithms and processes

Many of the models share equivalent or similar process algorithms, in part due to their chronological development. This includes GUIDEnano, whose algorithms share similarities with those from the NanoFASE project (which encompassed the NanoFASE and SimpleBox4nano models). However, there is potential room for improvement to process algorithms. Below, we summarise the evaluation of the fate and exposure models:

- Nanoparticle heteroaggregation to suspended particulate matter and attachment to the soil matrix is an important process governing nanomaterial fate. (Hetero)aggregation and attachment is not currently implemented in GUIDEnano, and we suggest this would be a useful addition to make. Due to the low concentrations of nanomaterials compared to suspended particulate matter, homoaggregation of nanoparticles to themselves is not considered an important process and could be excluded[8]. We suggest using the same attachment algorithms as implemented by most exposure models assessed, which use a collision frequency f_{coll} and attachment efficiency α (defined as the probably that a collision results in attachment/aggregation) to calculate an attachment rate $k_{\text{att}} = f_{\text{coll}}\alpha$. f_{coll} can be derived from fundamental physical processes (see Praetorius et al, 2012[8]) and is dependent on particle size, hence

[8] Praetorius, Scheringer, and Hungerbuhler (2012), "Development of Environmental Fate Models for Engineered Nanoparticles—A Case Study of TiO2 Nanoparticles in the Rhine River": https://doi.org/10.1021/es204530n

the importance of including size distributions in nanomaterial exposure modelling (which GUIDEnano already does). α is a semi-empirical parameter which could be obtained from literature for commonly-modelled materials.

- Deposition and resuspension should also include heteroaggregated nanomaterials. GUIDEnano calculates deposition from Stokes' Law, but does not include resuspension. A candidate algorithm for including resuspension is one based on river characteristics, also used by the NanoFASE model, from Lazar et al (2010)[9]. Stokes' Law is only strictly valid for non-turbulent flows, which excludes most realistic river systems. A modified method to calculate settling velocities is proposed by Zhiyao et al (2010), as used by the NanoFASE model, and this could be implemented in GUIDEnano. It is important to note that these modifications may not have a large impact on overall ENM fate, and so consideration should be given as to whether the time spent implementing them in GUIDEnano is justified.
- Dissolution and other chemical transformations (in particular, Ag dissolution and sulphidation) are identified as areas for improvement in all models assessed, including GUIDEnano. The NanoFASE model is currently being extended in the ASINA project to be able to model nano-Ag speciation, in part based on the model of Molleman and Hiemstra (2017)[10]. Elements of this Ag speciation model will be considered for improving GUIDEnano algorithms, in particular on the particle size-dependence of dissolution. Data from Molleman and Hiemstra could be used to verify GUIDEnano speciation predictions are in line with expected results.
- Few existing tools model wastewater treatment and groundwater. GUIDEnano contains the functionality to introduce a wastewater treatment plant as a system compartment, using the same processes as the aquatic compartment, and includes an aquatic zone in soils that could be used to model groundwater. There is room for further development of these compartments, but will require a review of models from other chemical domains, as none of the models we assessed included these compartments.

Scenarios and case studies

The goal of studying scenarios and case studies is to ascertain whether scenario parameter sets could be made available in GUIDEnano to make it easier for end users to define cases in GUIDEnano.

- Most models have been used to model TiO_2, and some Ag, ZnO, CeO_2 and CuO. SimpleBox4nano has an intuitive system for using pre-defined material cases, and could be a basis for default parameters. The data for each of these cases is easily available and referenced within the model spreadsheet.
- GUIDEnano has the ability to show example case studies that other users have created. Users can duplicate these and so they can act as default parameter sets that can be modified by end users.
- Generally, models don't explicitly include detailed phys-chem information, such as presence of a coating or use of additives, as this is generally considered too detailed to be useful with data that is widely available. This information must be included implicitly in other parameters such as attachment efficiencies. This makes the models difficult to assess with regard to the impact of SbD measures, where the goal might be to make modifications to the chemistry of an ENM of a given material. GUIDEnano and NanoFASE are the most advanced in this regard, allowing for the specification of ENMs made up of multiple constituents.
- The range of geographical and temporal scenarios modelled is large. GUIDEnano provides a nice balance between being simple enough to parameterise without complex spatiotemporal datasets, but also providing some spatial resolution through the use of nested and chained compartment boxes. Temporal resolution is flexible.
    - We will explore the feasibility of extending the transport model of GUIDEnano to allow a degree of temporal variability, to better quantify the highly dynamic nature of natural watercourse. For example, seasonal variability in meteorology (rainfall) and hydrology (flows) could be included via a seasonal variability factor (see MS2.2).

[9] Lazar et al (2015), "An assessment of the fine sediment dynamics in an upland river system: INCA-Sed modifications and implications for fisheries": https://doi.org/10.1016/j.scitotenv.2010.02.030
[10] Molleman and Hiemstra (2017), "Time, pH, and size dependency of silver nanoparticle dissolution: the road to equilibrium". https://doi.org/10.1039/c6en00564k

- A potential improvement to GUIDEnano could be giving users the option to select from a list of pre-defined lifecycle scenarios (covering manufacturing, use, disposal and potential releases during each of these), to save them having to create and link multiple (environmental) compartments manually. This also applies to human exposure modelling setups.

Model parameters

In general, the models require similar nano-specific parameters, such as attachment efficiencies (for those that model aggregation – not GUIDEnano), size distribution and material densities. They vary in the geographical parameters they require, with spatiotemporal models such as NanoFASE requiring complex spatiotemporal data. For example, attachment efficiencies may depend on the environmental medium in which the ENM resides. As detailed in the previous section, default phys-chem parameters for commonly used materials (e.g. TiO_2, Ag and ZnO) are available.

Uncertainty and sensitivity analyses

Few ENM exposure models have had uncertainty or sensitivity analyses performed. The large number of input parameters and potentially large spatiotemporal variability in these parameters makes this a particularly complex and onerous task.

- Meesters et al (2019)[11] performed a sensitivity analysis on SimpleBox4nano to determine the most important phys-chem properties driving ENM fate and exposure. This defined critical ranges for given parameters, within which ENM PECs were most sensitive to changes in that parameter. They varied five phys-chem parameters (diameter, transformation rate constant (e.g. Ag → Ag_2S rate), attachment efficiency, density and Hamaker constant) over ranges that hypothetical covers all types of ENMs. To account for environmental variability, they also used probability distributions for variables pertaining to the environmental system[12]. Example results are shown in Figure 5.
- A sensitivity analysis of the NanoFASE model is in process at the moment, but the results are not yet available.
- The OECD Working Party on Manufactured Nanomaterials performed a detailed assessment of exposure models[13], under the leadership of Environment and Climate Change Canada. This includes both uncertainty and sensitivity analyses on SimpleBox4nano and nanoFate (amongst others).
- A full uncertainty or sensitivity analysis on GUIDEnano is unfeasible due to the large number of input parameters and segmented nature of the model. Two options for improvement could be considered:
    - Results from other sensitivity analyses (e.g. SimpleBox4nano) could be used to provide guidance to users of GUIDEnano and the SAbyNA Guidance Platform. For example, the critical ranges shown in Figure 5 could be shown to users so that they can prioritise efforts to obtain the parameters to which ENM fate is most sensitive in the realistic ranges of the material they are assessing.
    - Environmental heterogeneity could be accounted for by giving users the option to choose from a selection of pre-defined environmental compartment compositions. For example, in the aquatic compartments, a dropdown box could be presented for users to select from a variety of pre-defined water compositions (with varying e.g. pH, flow, temperature). These options should be selected to represent a broad variety of water compositions encountered in Europe or globally.

[11] Meesters et al (2019), “A model sensitivity analysis to determine the most important physicochemical properties driving environmental fate and exposure of engineered nanoparticles”: https://doi.org/10.1039/C9EN00117D
[12] Meesters et al (2016), “Multimedia environmental fate and speciation of engineered nanoparticles: a probabilistic modeling approach”: https://doi.org/10.1039/C6EN00081A
[13] OECD, “Evaluation of Tools and Models Used for Assessing Environmental Exposure to Manufactured Nanomaterials Functional Assessment and Statistical Analysis of Nano-Specific Environmental Exposure Tools and Models”: https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-CBC-MONO(2021)23%20&doclanguage=en

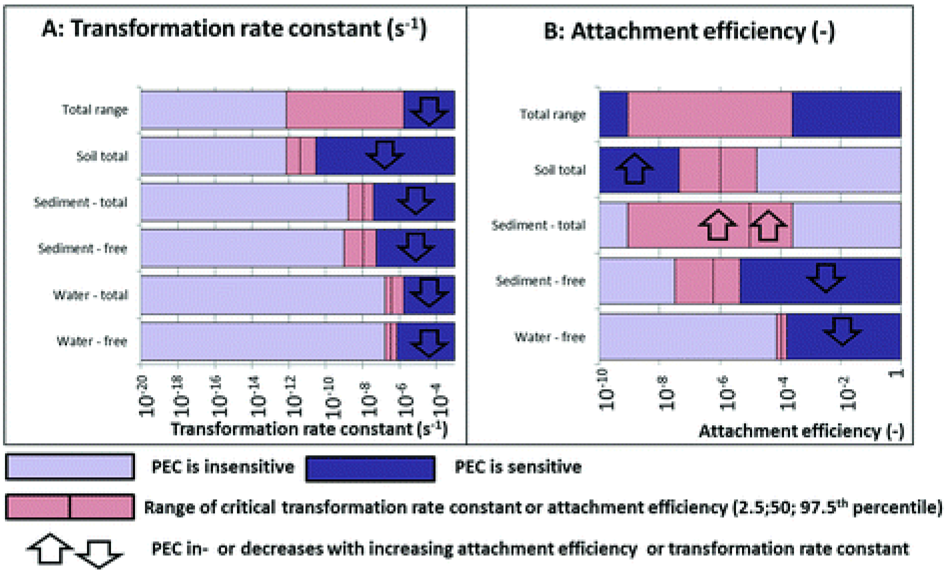

Figure 5. Critical ranges for transformation rate constants and attachment efficiencies in SimpleBox4nano. The red areas of the range in which the calculated PECs are most sensitive to the given parameter (i.e. a small change in the input parameter results in a relatively significant change in the PEC).

2.2.3 GUIDEnano: Summary of recommended improvements

The previous sections detail potential improvements for GUIDEnano for inclusion in the user-friendly industry Guidance Platform that SAbyNA is developing. For clarity, the key recommended improvements are summarised here. We will work alongside the GUIDEnano developers and WP6 in the remainder of the project to help implement these suggestions in GUIDEnano.

- GUIDEnano could provide a library of SPERCs for platform users to select from, similar to the Chesar tool and TNO Hot Spot Scan. The list of SpERCs could be based on the ECHA Use Maps library, with potential additions relevant to the SAbyNA case studies based on ongoing discussions with EuPC.
- GUIDEnano fate processes in environmental compartments could be updated to also include attachment/heteroaggregation in soils and surface waters. Sedimentation and resuspension of heteroaggregated particles should be modelled.
- There is further scope for improving sedimentation dynamics in GUIDEnano using modified resuspension and deposition algorithms, though the effect of this might not be large enough to warrant the effort required to make this modification.
- There is scope for improving dissolution and transformation algorithms, particular for nano-Ag, based on implementation of nano-Ag speciation in the NanoFASE model as part of the ASINA project. In particular, the size dependence of dissolution could be considered.
- Temporal dynamics, in particular seasonal variances in flow rates, could be a potential improvement to allow GUIDEnano to account for seasonal variances in PECs. This could be implemented via seasonal factors.
- Default parameter sets for commonly modelled materials, such as TiO_2, Ag and ZnO, could be implemented using GUIDEnano cases. Data are available from other models, such as SimpleBox4nano. Where data are not available, GUIDEnano should point to methods/SOPs (as identified within Task 2.2) that can be used to determine given parameters.
- A selection of lifecycle scenarios from which users can choose, via a dropdown menu, would enable them to quickly set up commonly used scenarios without having to manually link compartments.
- Similarly, a selection of water compositions could be provided to users, with the goal of representing likely water compositions encountered in Europe (or globally). This would be a useful way of taking into account environmental heterogeneity without using probabilistic approaches.

3. Human release, fate and exposure models

3.1 Assessment methodology

The assessment of the human exposure models has been performed using an extended spreadsheet based on the spreadsheet created in D2.1, which is detailed in MS2.2. A snapshot of the spreadsheet is shown in Figure 6 and a link to the spreadsheet in available in Appendix 1.

Tool/model	Description	ıld it be improved by uding more parameters? ich ones? (from D2.1- date as needed)	Can the input parameters be better described and how (from D2.1- update as needed)?	Which parameters are used for estimating exposure/release?	can the algorithms be more precise? (if information is available)- from D2.1 (update as needed)	For algorithms that can be improved, what can be modified?	Can the model be used for estimating release rates?
ConsExpo Nano Tool	This tool can be used to estimate inhalation exposure to NMs in consumer spray products. To run the model, user input on different exposure determinants such as the product and its use, the nanomaterial and the environmental conditions is required. Exposure is presented in different measures. The outcome of the assessment is an alveolar load in the lungs	maar C and Meesters J (2020) gests losses to vertical faces, particle dynamics that ılt from the hygroscopic wth of aerosol particles could	N/A		No- algorithms are precise and contain wide variety of inputs for inhalation		
SUNDS	The Sustainable Nanotechnologies Project Decision Support System: SUNDS is a cloud-based nano-product sustainability assessment Decision Support System. SUNDS allows supporting decisions on the assessment and management of NMs and nano-enabled products along with their lifecycles in industry, regulatory bodies and insurance companies. It applies a two tiers approach which, on the basis of the supplied information, is able to generate qualitative or quantitative results. The first assessment tier is based on the LICARA Nanoscan tool. The second assessment tier, based on	2: Yes for occupational osure levels- duration of osure (i.e. short duration or g duration), current measures lace for exposure control; re information about NM h as size, dustiness...)	Tier 1: see Licara Nanoscan Tier 2: yes- exposure type (deterministic exposure, probabilistic exposure, short/long term exposure levels to be input)		Improving scoring for Tier 1; For tier 2: account for short and long exposure? Scoring methodology (exposure/hazard) have same weighting in RCR calculation		
Guidenano tool	The tool guides the user (the nano-enabled product developers (industry) in the design and application of the most appropriate risk assessment & mitigation strategy for a specific product. The tools predicts the overall risk from the nanomaterial along their life cycle. The tool is being improved as part of the H2020 SAbyNA project.				Improving scoring for Tier 1; For tier 2: account for short and long exposure? Scoring methodology (exposure/hazard) have same weighting in RCR calculation		

Figure 6. Example of the spreadsheets being used to assess human exposure models.

In D2.1, a shortlist of models was devised and a number of aspects for improvement for these models were identified in MS2.2. As a recap of MS2.2 and D2.1, the human exposure models selected for further assessment in T2.2 are shown in **Error! Reference source not found.**. LICARA NanoSCAN has been added to the shortlist since the submission of D2.1, as the newer version of the model has been released. The selection process for the models is outlined in D2.1. The analysis of GUIDEnano is specifically discussed in section 3.2.7.

Table 3. Human exposure tools and models selected for optimisation.

Name	Route of exposure considered
ART	Inhalation
ConsExpo Nano Tool	Inhalation
Control Banding Tool	Inhalation
GUIDEnano	Inhalation, dermal
LICARA NanoScan	Inhalation, dermal, oral
Nanosafer CB	Inhalation
Precautionary Matrix for NMs	Inhalation
Stoffenmanager Nano	Inhalation

Name	Route of exposure considered
SUNDS	Inhalation, oral, dermal (included, but not possible to use)

This has been further developed in the spreadsheet, for example including information on model algorithms and processes, input parameters and uncertainty. The goal of this task has been to identify opportunities for streamlining and to improve the identified models and also identify aspects of models that could be incorporated into GUIDEnano, in particular those elements more suited to or relevant to SbD.

The spreadsheets are described in M2.2, and here we provide a summary of the spreadsheets. The spreadsheets are split into five separate sheets which will continue to be improved and modified during the course of Task 2.2. The sheets are as follows:

- **Model assessment:** This contains general information collected for the models, which were mostly complied from D2.1 such as life cycle stage the model is covering spatial resolution for exposure and the assessed exposure route(s). This also includes the summary of the results of the assessment being undertaken in T2.2 and will be used to identify improvements that can be made to existing route. For example, this includes inclusion of further model assumptions, improving model algorithms and processes, improvements to the input parameters and the parameters used for estimating exposure/release. We have also identified the potential uses of the models within the SAbyNA platform.
- **Model algorithms and processes:** This includes detailed information on the processes which are included in the models and the algorithms which are used to model these processes. This includes information on worker exposure processes and algorithms, consumer exposure processes and algorithms, activity processes and algorithms and process from the model which could potentially be included into GUIDEnano.
- **Model parameters:** This builds on the work performed in the caLIBRAte project in which the input parameters for human exposure models were identified. These have also been grouped by category. The human exposure models generally contain a large number of input parameters which can be time consuming for the user.
- **Uncertainty analysis:** In some of the models, there is no uncertainty analysis for the human exposure assessment, whilst in others the uncertainty analysis is included (such as the Precautionary Matrix). This could potentially be improved and/or included in GUIDEnano. This sheet collates the detailed uncertainty analysis performed for the shortlisted models. This includes:
    a. assessing the relationship between the output and input parameters
    b. assessing if measurement data can be included in the model as measurements can help to evaluate uncertainty
    c. if uncertainty contributions can be associated with input parameters in the model (and which ones are more critical)
    d. establishing if the model allows the overall uncertainty to be quantified.

In terms of these shortlisted models (Table 3), as discussed in Deliverable 2.1 the available models are mostly for inhalation exposure. The lack of dermal exposure models for nanomaterials has also been identified as a knowledge gap in deliverable 2.1 and this is still the case at the time of this deliverable. Some of models (i.e. Licara Nanoscan) consider dermal exposure, but not in any depth of detail. SUNDS has an option for calculating dermal exposure, however this option is not able to be selected at the present time. Dermal exposure models which are not nano-specific are available, such as ConsExpo (consumer exposure), Risk of Derm (for filling, mixing or loading, spraying, dispersion and mechanical treatment), and the ECOTOC-TRA tool. Oral exposure was not considered within deliverable 2.1, however this should now be considered for the SAbyNA case studies. In the shortlisted models, inadvertent oral exposure is considered in SUNDS.

3.2 Results for human exposure models

3.2.1 Model assumptions

For the assumptions used by the models, information was collated as part of D2.1. As part of D2.1, it was found that in some cases, publicly available information (such as user manuals and published literature) is limited in many cases. As part of this deliverable, these model assumptions have been updated and are described in the accompanying Excel spreadsheet. For suggesting possible improvements to model assumptions due to limited information this has only been identified for one model. In the case for the Precautionary Matrix, the potential for the user to add any protective measures which are already used for occupational and/or consumer exposure would be beneficial.

3.2.2 Model algorithms and processes

For the shortlisted models, information has been collated for the algorithms and processes modelled for worker exposure, consumer exposure, scoring used by the models and activities used in the models. This has been collected for potential streamlining of these models into GUIDEnano and the SAbyNA platform and also to investigate which potential exposure scenarios could be integrated into the platform. This information is also collated to see if any potential streamlining of algorithms for these shortlisted could also be performed.

Worker exposure algorithms and consumer exposure algorithms

Information on worker exposure and consumer exposure algorithms varies depending on the model and these are described in Table 4. In the case of Stoffenmanager Nano, Nanosafer CB, and SUNDS this information is not publicly available.

For the Precautionary Matrix, information is available for both the worker exposure and consumer exposure algorithms. The Precautionary Matrix could potentially be linked in Part 1 of the SAbyNA platform, as the output is a score that specifies to the user if action is needed to be taken for the NF/NEP. In the case of the Control Banding Tool, information is limited; however, this tool assigns a control banding score for the NF/NEP and recommends possible RMMs. In the case of Nanosafer CB and SUNDS, no information is publicly available. For ConsExpo Nano, information is available on the algorithms used within the spray model. These algorithms could potentially be incorporated into GUIDEnano or a link provided to the model, as discussed further in section 3.2.7. Information is available for the algorithms of ART, however it is also worth noting that this is not NF/NEP specific.

In conclusion, in many cases there is limited or no information available on the algorithms which has meant limited potential improvements have been identified. These improvements include improving the scoring methodology for LICARA NanoScan, the RCR weighing for exposure and accounting for short term/long term exposure in SUNDS, and improvement in the Precautionary Matrix for worker exposure. ConsExpo Nano could potentially be streamlined into the SAbyNA platform from the available information for the spray model.

Table 4. Model algorithms and processes for worker and consumer exposure

Model	Worker exposure algorithms	Consumer exposure algorithms	Exposure scenarios modelled
Precautionary Matrix for NMs	$E_a = E1_{a,v} \cdot E2.1 \cdot E2.3$; for worst case: $E_a^{WC} = E1_{a,v} \cdot E\ 2.2$ where: $E1_{a,v}$: Carrier material, E2.1: Amount of NM which the worker comes into contact per day, E2.2: Amount of NM which the workers comes into contact in the worst case, E2.3: Frequency with which a worker comes into contact with NMs.	$E_v = E1_{a,v} \cdot E2.4 \cdot E2.5$ where $E1_{a,v}$: type of carrier material, E2.4: amount of NM the consumer comes into contact, E2.5: frequency with	N/A- user defined

Model	Worker exposure algorithms	Consumer exposure algorithms	Exposure scenarios modelled
		which consumer comes into contact with NM Carrier material: $E1_{a,v}$ = predefined values used; distinction made between possible exposure of lungs ($E1_{a,v}$ =1) and other target organs ($E1_{a,v}$ =0.1) in air and liquid media	
Control Banding Tool	Risk level = severity score • probability score	N/A	Activity classifications available: working with nanomaterials in liquid media (also during pouring and mixing or agitation), generating nanoparticles in gas phase, handling nanoparticles in powder form, maintaining equipment and processes used to produce or fabricate nanomaterials, clean up of spills or waste material, cleaning of dust collection systems used to capture nanoparticles; machining, sanding, drilling or other mechanical disruptions of materials containing nanoparticles, other activities that can result in potential exposure to nanomaterials

Model	**Worker exposure algorithms**	**Consumer exposure algorithms**	**Exposure scenarios modelled**
Stoffenmanager Nano[14]	$B = [(C_{nf} + C_{ff} + C_{ds}) \cdot \eta_{imm} \cdot \eta_{ppe} \cdot t_h \cdot f_h]$ $C_{nf} = E \cdot H \cdot \eta_{lcnf} \cdot \eta_{gvnf}$ $C_{ff} = E \cdot H \cdot \eta_{lcff} \cdot \eta_{gvff}$ $C_{ds} = E \cdot a$	N/A	Source-receptor-approach, the same activity is conducted using the same substance in the far field as in the near field
LICARA NanoScan	Inhalation: Input from Stoffenmanager which is based on the source-receptor approach[15] Dermal: Input from Stoffenmanager which is based on Risk of Derm[16]	Unclear: questions are asked on knowledge, effects and release for public health effects	N/A
Nanosafer CB	N/A	N/A	N/A
ConsExpo Nano	N/A	Exposure described in Delmaar et al., (2005)[17] for the spray model. For a custom scenario: $A_{inh}= Q_{inh} \bullet C_{air} \bullet T$ Where Q_{inh} is the inhalation rate (volume per time), T the exposure duration, and C_{air} is the air concentration	For paints: pneumatic spraying, spray can and user defined
SUNDS	For inhalation: Two box model, adapted from Ganser et al.[18] For consumer exposure: as per ConsExpo Nano		Contains 161 activities with release rates; deterministic and

[14] Birgit Van Duuren-Stuurman, Stefan R. Vink, Koen J. M. Verbist, Henri G. A. Heussen, Derk H. Brouwer, Dinant E. D. Kroese, Maikel F. J. Van Niftrik, Erik Tielemans, Wouter Fransman, Stoffenmanager Nano Version 1.0: A Web-Based Tool for Risk Prioritization of Airborne Manufactured Nano Objects, The Annals of Occupational Hygiene, Volume 56, Issue 5, 2012, 525–541

[15] (a) Hans Marquart, Henri Heussen, Maaike Le Feber, Dook Noy, Erik Tielemans, Jody Schinkel, John West, Doeke Van Der Schaaf, 'Stoffenmanager', a Web-Based Control Banding Tool Using an Exposure Process Model, The Annals of Occupational Hygiene, Volume 52, Issue 6, August 2008, Pages 429–441 (b) John W. Cherrie, Thomas Schneider, Validation of a New Method for Structured Subjective Assessment of Past Concentrations, The Annals of Occupational Hygiene, Volume 43, Issue 4, May 1999, Pages 235–245

[16] H. A. Goede, S. C. H. A. Tijssen, H. J. Schipper, N. Warren, R. Oppl, F. Kalberlah, J. J. Van Hemmen, Classification of Dermal Exposure Modifiers and Assignment of Values for a Risk Assessment Toolkit, The Annals of Occupational Hygiene, Volume 47, Issue 8, November 2003, Pages 609–618

[17] J.E. Delmaar, M.V.D.Z. Park, J.G.M. van Engelen. RIVM report 320104004/2005. ConsExpo 4.0 Consumer Exposure and Uptake Models Program Manuel

[18] Ganser GH, Hewett P. Models for nearly every occasion: Part II - Two box models. J Occup Environ Hyg. 2017 Jan;14(1):58-71. doi: 10.1080/15459624.2016.1213393. Erratum in: J Occup Environ Hyg. 2017 Aug;14(8):D139.

Model	Worker exposure algorithms	Consumer exposure algorithms	Exposure scenarios modelled
	For oral exposure: adapted from Gorman et al.[19]		probabilistic exposure throughout the life cycle
Licara NanoSCAN	As for Stoffenmanager Nano	As for the NanoRiskCat Project	see NanoRiskCat project
ART	Overall Exposure is:[20] $Ct = \frac{1}{t\ total} \sum(t\ exposure \cdot (Cnf + Cff + Su))$	N/A	Source–receptor model takes into account the contribution from near-field and far-field sources

3.2.3 Model Input Parameters

Following on from D2.1, using outputs from caLIBRAte as starting point we have further developed the input parameters and have grouped the input parameters into categories for the shortlisted exposure models into different categories. These categories are as follows and are described in more detail in the accompanying Excel spreadsheet:

- Material/particle properties
- Environmental/room properties
- Properties of the processes
- Number of exposed employees
- Protective equipment applied
- Limit values/ Toxicity of the nanomaterial / Derived no effect level (DNEL)
- Other parameters

As discussed in section 3.1, the focus of the shortlisted models is on the inhalation route of exposure. Inhalation exposure is the focus of discussion in this section.

Identifying the minimum parameters that are required for a meaningful output

This task has involved analysing the shortlisted models and identifying the minimum parameters that are required for each model. This in turn, could allow potential streamlining of the models to be performed. For many of the models, a large number of input parameters are required. Input parameters that can be required by the models include input on the shape, size, dustiness, room dimension, ventilation and duration/frequency of exposure. Input parameters for specific models include dustiness (Control Banding tool, Nanosafer CB, ART

[19] Gorman Ng M, Semple S, Cherrie JW, Christopher Y, Northage C, Tielemans E, Veroughstraete V, Van Tongeren M. The relationship between inadvertent ingestion and dermal exposure pathways: a new integrated conceptual model and a database of dermal and oral transfer efficiencies. Ann Occup Hyg. 2012 Nov;56(9):1000-12
[20] Jody Schinkel, Wouter Fransman, Patricia E. McDonnell, Rinke Klein Entink, Erik Tielemans, Hans Kromhout, Reliability of the Advanced REACH Tool (ART), The Annals of Occupational Hygiene, Volume 58, Issue 4, May 2014, Pages 450–468, https://doi.org/10.1093/annhyg/met081

and GUIDEnano), ventilation rate (Stoffenmanager Nano, GUIDEnano, ART and ConsExpo Nano) and room dimensions (Stoffenmanager Nano, NanoSafer CB, ConsExpo Nano and GUIDEnano). The input parameters for each of the models is detailed in the model parameters sheet in the model assessment spreadsheet and is further detailed in deliverable 2.1.

Regarding sensitivity analysis, this has previously been performed in caLIBRAte using One-at-a-Time (OAT) analysis. From this analysis, the most and least sensitive parameters for the models were identified (published by the OECD[21]) and are described in Table 5. The drawback to OAT analysis is that this approach can be too simplistic and can also be misleading depending on the situation. For example, in ConsExpo Nano, the two least sensitive parameters were those associated with ventilation rate and the room volume, which can be correct when the consumer is in the near field. However, in a workplace setting these two parameters are key determinants of dispersion and exposure.

Table 5. Sensitivity analysis of the shortlisted models (OECD, 2021Error! Bookmark not defined.)

Model	Most sensitive parameters	Least sensitive parameters
Precautionary Matrix for NMs	Nano-relative according to the precautionary matrix; Solid matrix, stable under conditions of use, NPR not mobile; Solid matrix, stable under conditions of use, NPR mobile; Solid matrix, not stable under conditions of use; Redox activity and/or catalytic activity of NPR present in the nanomaterial; Stability (half-life) of the NPR present in the nanomaterial in the body or under environmental conditions	Origin of the nanomaterial, data availability, downstream user, purity of the material system
Control Banding Tool	Estimated maximum amount of chemical used in one day, dustiness, number of employees with similar exposure, operation duration (per shift)	Frequency of operation (annual)
Nanosafer CB	OEL nano and bulk, material density, specific surface area, amount of material used in cycle, dustiness, duration of work cycle, room size	Activity level, process energy level, ACH, number of work cycles per day, pause between work cycles, coating, amount of material used per activity in work cycle, duration of activity in work cycle, solubility in water
Stoffenmanager Nano	Process domain, daily cleaning, monthly inspection, concentration, handling in the worker breathing zone, viscosity, appearance, frequency of handling	Duration of handling, room volume, room ventilation, local control measures, product type, dustiness, moisture content, dilution and handling (activity)
ConsExpo Nano	Aerosol diameter, inhalation rate, weight fraction nano material in product, mass generation rate, spray duration, airborne fraction	Ventilation rate, room volume
Licara NanoSCAN	Stoffenmanager's hazard and exposure score (product manufacturing, product processing, product application), occupational health risks	N/A

[21]https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-CBC-MONO(2021)27%20&doclanguage=en

Model	Most sensitive parameters	Least sensitive parameters
SUNDS (Human Health only)	Life cycle stage distribution means, exposure mean	Variations in other input parameters have an effect on the output values, but the effect is significantly lower
GUIDEnano	Not performed	
ART	Not performed	

Following on from this work, for identifying the minimum parameters that are required for a meaningful output to be supplied by the model, Principal Component Analysis (PCA) on the model input parameters has been performed to establish the minimum parameters required for a meaningful output. PCA is a mathematical algorithm that involves the identification, independent and recurring modes of variations through data reduction.[22] The process performed for the PCA analysis has been as follows:

- Identifying the relevant exposure parameters to be analysed and those that could be excluded
- Preparing an input file for the PCA analysis in Stata and values to be used for PCA for each model parameter (such as minimum and maximum values for each parameter, possible values that can be entered by the user for each input parameter etc. using input from case studies and OECD OAT analysis)
- Running the PCA analysis in Stata to identify the following:
    - Correlations between the different input parameters, for example if the input parameters are weakly correlated, moderately correlated, moderately to strongly correlated or strongly correlated
    - Explaining variances by the different possible component, such as the 1st component, 2nd component, 3rd component etc.
    - Identifying the principal components
    - Identifying if some parameters could potentially be excluded from the model input parameters.

PCA analysis for the shortlisted models

The results of the PCA analysis for the shortlisted models for the exposure input parameters are presented in Table 6. One limitation of PCA analysis that affects the analysis as that where the required input for the parameter is not number based (such as selecting a text option from a drop-down menu). In these cases, arbitrary values (i.e. 1, 2, 3 etc.) have been assigned for the possible options and are indicated by a * in the table. This is particularly the case for Stoffenmanager Nano and for some of the input parameters in ART.

From these results, it is generally the case that the input parameters are correlated with each other and none of the input exposure parameters dominates over another input exposure parameter (although there are small differences for each of the input parameters in the PCA analysis). From this analysis, it is not possible to reduce the number of input exposure parameters that are required for a meaningful output at this stage.

Table 6. PCA results

Model	Results for input exposure parameters	Parameters excluded from analysis
Precautionary Matrix for NMs	All input exposure parameters approximately equal (no input parameter dominates over the other)	General information parameters (free text)

[22] (a) Rigner M. What is principal component analysis? Nature Biotechnology, 2008, 26(3), 303-304 (b) Eder B et al. Incorporating principal component analysis into air quality evaluation. Atmospheric Environment, 2014, 82, 307-315.

Model	Results for input exposure parameters	Parameters excluded from analysis
Control Banding Tool	All input exposure parameters approximately equal (no input parameter dominates over the other)	N/A
Nanosafer CB	OEL parameters dominate over the other parameters (which are approximately equal)	Required input parameters: Material name, Optional input parameters
Stoffenmanager Nano	All input parameters equal*	Name risk assessment (free text)
ConsExpo Nano	Input Exposure parameters approximately equal, however cloud volume is a dominant parameter	Name of scenario, scenario type, name or description of nanomaterial
Licara NanoSCAN	For Exposure: as per Stoffenmanager Nano	N/A
SUNDS (inhalation exposure only)	Mean inhalation use dominates; other parameters approximately equal	N/A
ART	All input parameters equal*. When parameters that require numerical input are only analysed, these are approximately equal	N/A

When input parameters are changed, can the changes in result be viewed in "real time"?

Ideally as part of SbD, when the user changes the values of an input parameter, the effect of this change can be viewed in "real time" such as an updated exposure viewing. From the shortlisted models, only two of the models allow changes to the input parameters to be viewed in real time. These are:

- Control Banding Tool: If an exposure input parameter is changed, the relevant outputs (probability score, probability bans, overall risk level without controls, recommended engineering control based on risk level, and/or upgrade engineering control) changes accordingly. However, it is worth noting that this tool is an Excel spreadsheet.
- Licara NanoSCAN: Input parameters can be changed for the environmental benefits, public health and environmental risks, occupational health risks, and consumer health risks for exposure. However, the input for occupational health risks is from Stoffenmanager Nano. When any of the input parameters are changed then the results will change in "real time" and be presented to the user. This allows the user to see which parameters could be changed, for example to reduce the public health risks from exposure to the NF/NEP.

Within Stoffenmanager Nano, it is possible to change an input parameter within the same assessment (without creating a new risk assessment). However, after changing the relevant input parameter, the user still needs to select the risk assessment (step 6) to view the results (such as the effect on exposure score).

The Precautionary Matrix for NMs, Nanosafer CB, ConsExpo Nano, SUNDS, and ART require a new assessment to be run if an input parameter is modified.

Parameters used for estimating exposure/release for dermal and oral exposure

As discussed in section 3.1, there is a gap for models that assess dermal exposure for NFs/NEPs, with no models identified for quantitative dermal exposure to NF/NEPs. For oral exposure, SUNDS provides quantitative inadvertent oral exposure. These parameters were not previously analysed by OAT analysis and have not been analysed by PCA analysis. The input parameters required by SUNDS for inadvertent oral exposure are as follows:

- Body weight (in kg)

- Surface contact area between hand and mouth (cm^2).
- Geometric mean of finger moisture (µs)
- Geometric standard deviation of finger moisture
- Minimum value of hand loading (ng)
- Maximum value of hand loading (ng)
- Estimate of the number of hand-mouth contacts (Yes/No)
    - If yes is selected, the following input parameters are required:
        - Number of hand to mouth contacts per hours
        - Number of simulations to be performed
    - If no is selected, the following input requirements are required:
        - Are gloves worn (Yes/No)
        - Are gloves worn for more than 75% of the shift (Yes/No)
        - Is RPE worn for more than 50% of the shift (Yes/No)
        - Typical worker time spent during a normal shift (job profile 1 or job profile 2)
        - Number of simulations to be performed

Default values are also provided for the following input parameters for inadvertent oral exposure in SUNDS, for example:

- Surface contact area between hand and mouth (cm^2). This is around one for a single finger and up to ten for the whole hand
- Geometric mean of finger moisture (µs). The default value is for high moisture, with a value of 1000 supplied

How easy/difficult is it for the user to provide information for the input parameters

An additional aspect that is beneficial to consider is the quantity/type of information that is required to be input by the user for the input parameters. In terms of this information, this includes the ease/difficulty of providing this information and also the cost associated with collecting this information.

An initial assessment has been performed on some of the input parameters for some of the shortlisted models (Precautionary Matrix for NMs, Control Banding Tool, Nanosafer CB, Stoffenmanager Nano and SUNDS (for Tier 2 of the model). This work is ongoing (further discussed in Appendix 2) and will be discussed in upcoming deliverables, for example it may be possible to verify the ease/difficult of the data requested by the parameters and any cost implications (such as the data required to be supplied by the user) with the SAbyNA industrial partners for the two sectors (paints and 3D printing). For these models assessed, to date the following initial conclusions can be drawn:

- Precautionary Matrix for NMs and Control Banding Tool: For some of the input parameters, this may require the user to consult other information sources/perform potential testing, however there is an option for “not known” to be selected and no numerical input is required by the user.
- Nanosafer CB: For some of the input parameters, these require numerical input from the user (such as amount of nanomaterial and the workroom properties). These may also require the user to consult other information sources and this model is more data intensive than the Precautionary Matrix for NMs and the Control Banding Tool.
- Stoffenmanager Nano: The input parameters provide a couple of options for the user to select for the answer for each of the relevant input parameters. However, these input parameters may require the user to consult other information sources/perform potential testing (such as dustiness).
- SUNDS (Tier 2 assessment for inhalation and oral exposure). This model requires the user to enter numerical values for the input parameters, apart from the activity generating the release rate which supplies a drop down menu. This model may be data intensive for the user, requiring the user to consult other information sources/perform potential testing. This could also have cost implications for the user.

Can the input parameters be better described, if so how?

As part of the assessment, an analysis has been performed on which input exposure parameters could be better described, as misunderstanding of what is required could lead to incorrect inputs by the user, Improvements have been identified for four of the models, and potential improvements for these models (Precautionary Matrix for NMs, SUNDS, LICARA NanoSCAN, and ART) are described in Table 7.

Table 7. Input parameters description

Model	Potential improvements for parameter description
Precautionary Matrix for NMs	Rephrasing carrier material such as to matrix
SUNDS	Exposure type (deterministic exposure, probabilistic exposure, short/long term exposure levels to be input) could be redefined
LICARA NanoSCAN	Some better description of the input parameters could be addressed as misunderstanding of the questions asked can lead to user variability
ART	Potential improvement could be possible on the terminology used for the input parameters

Parameters used for estimating exposure/release

Within the accompanying Excel spreadsheet, we have identified those parameters (such as dustiness) that are used for release rates in the shortlisted models, where this information is available. For example, in the Precautionary Matrix the parameters which are used for release/exposure include the amount of NF handled daily and the amount in a "worst case" scenario and the frequency of exposure. Nanosafer CB considers dustiness, room dimension, air change rates, mass used and frequency of the task for estimating release, whereas Stoffenmanager Nano uses dustiness and moisture content as key parameters for release rates. SUNDS which calculates the probabilistic and deterministic exposure in the near field and far field uses default release rates (presumed this is wt. %, however this is not stated) from 161 activities (see the following figure), but dustiness is not included as a key parameter for exposure determination.

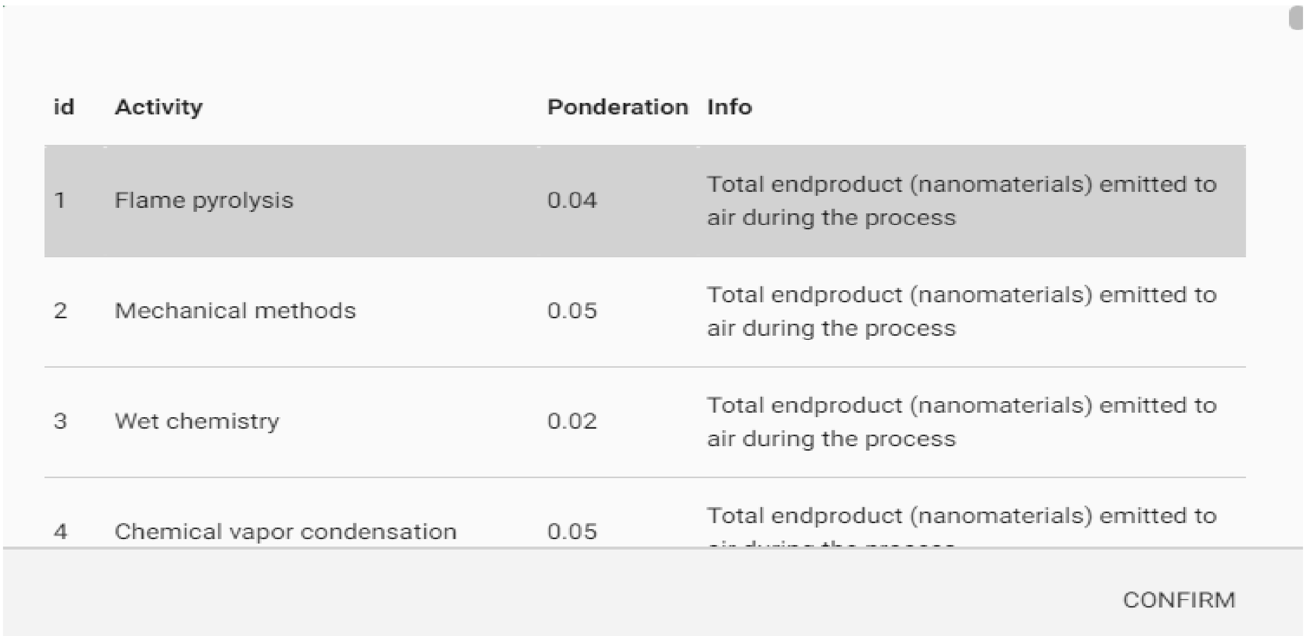

Figure 7. Snapshot of the release rates provided by SUNDS

3.2.4 Uncertainty analysis

Introduction to uncertainty for exposure assessment

Uncertainty is an aspect which needs to be improved in the current tools and models as previously discussed in Deliverable 2.1. ECHA, as part of performing a chemical safety assessment provide guidance for performing uncertainty analysis as part of the assessment[23]. ECHA provide three types of uncertainty to be assessed:

- Model uncertainty – relating to simplifications the model makes. This is primarily based on extrapolation (such as using the model in a domain which it was not developed for), errors in modelling and dependence errors);
- Parameter uncertainty – relating to individual model parameters/values/measurements;
- Scenario uncertainty – user dependent. This could be an important contributor to uncertainty, such as the user incorrectly entering incomplete scenario(s) information.

Within our uncertainty analysis, we have assessed the model uncertainty and parameter uncertainty as appropriate. Scenario uncertainty is an important contributor of uncertainty; however, at this time it has not possible to evaluate this. This is described in the following sections.

Uncertainty in existing exposure models

In the shortlisted models in Deliverable 2.1 (Precautionary Matrix for NMs, Control Banding Tool, Stoffenmanager Nano, Nanosafer CB, ConsExpo Nano, SUNDS, LICARA Nanoscan, ART, and GUIDEnano), one aspect that was identified for potential improvement and streamlining was the consideration of uncertainty analysis within the models. Within GUIDEnano, for uncertainty the number of parameters to be analysed is dynamic and is dependent on the scenario configuration.

Aspects of uncertainty analysis which are important include the inclusion of measurement data (which is beneficial for uncertainty analysis, however this data must correspond to the parameters and scenarios entered by the user in the models, such as room volume, RMMs, and amount of NF) and the measurement scales used in the model. The Monte Carlo method is typically used for uncertainty analysis in exposure models and is used for the Control Banding Tool, ConsExpo Nano and SUNDS.

For each of the shortlisted models, an analysis of how uncertainty is included in the models has been performed along with potential improvements to the uncertainty analysis for the models has been performed. The aspects that have been assessed for uncertainty are as follows:

- Description of the output of the model. This is intended as the sole quantity to be measured/estimated without uncertainty, for example if the output of the model is a score/exposure band then this is more difficult to assess for uncertainty.
- Is the relationship (mathematical model) between the output and the various inputs well known (e.g. explicit)?
- Are measurements involved in the assessment? If measurements are involved, this is beneficial for uncertainty analysis if these measurements are reflecting the same conditions as entered by the user.
- Is it possible to include the uncertainty contributions associated with the input parameters?
- Can the overall uncertainty (e.g., expanded uncertainty) be quantified?
- What input parameters are important for uncertainty
- What are the major contributions of uncertainty?

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[23] ECHA 2012. Guidance on information requirements and chemical safety assessment Chapter R.19: Uncertainty analysis. https://echa.europa.eu/documents/10162/13632/information_requirements_r19_en.pdf/d5bd6c3f-3383-49df-894e-dea410ba4335

- Model assumptions uncertainty.
- Which information about uncertainty is missing?

An additional aspect that should also be considered for uncertainty is training the user on the different exposure models. This would involve training the user on entering the correct information, such as the ensuring all relevant activities, scenarios, and compartments are entered into the model to reduce potential uncertainty from the user.

Input parameters uncertainty

As discussed above, as part of the uncertainty analysis the input parameters in the shortlisted exposure models have been assessed. This assessment has involved the potential improvement and streamlining for input parameters uncertainty. The following aspects have been assessed and the results are described in Table 8:

- In**put parameters, which are important for uncertainty**. Those input parameters which are important of uncertainty have been identified from the results of the sensitivity analysis from the caLIBRate project which has been published by OECD[24]. It is important that the important parameters of uncertainty are known, so that these are investigated for potential improvement/streamlining.
- **Inclusion of uncertainty contributions:** In the models, it has also been assessed if uncertainty contributions related to the input parameters could be evaluated. This is not possible in the Precautionary Matrix, Control Banding Tool, Stoffenmanager Nano and also individually in ART. This is possible for ConsExpo Nano and is included for LICARA NanoSCAN (this only includes the uncertainty bars, indicating the possible minimum or maximum scores resulting from the ambiguity caused by unanswered questions) and SUNDS.
- **Inclusion of measurement data in the input parameters:** Including measurement data is beneficial for uncertainty evaluation. For the models this is possible, however this varies between models as some models (such as ART) allow values to be entered, whereas other models (such as the Control Banding Tool) do not allow measurements to be entered. For those models that do not allow measurement data to be entered, these data can be used to guide the user to select the correct input option provided by the model. For example, in Stoffenmanager Nano the user can use measured dustiness values to select one of the following options for the dustiness input parameter: very high (>500 mg/kg), high (>150-500 mg/kg), medium (50-150 mg/kg), and low (<50 mg/kg).

Table 8. Input parameters uncertainty aspects for human exposure models

Model	Input parameters important for uncertainty	Inclusion of uncertainty contributions for input parameters	Potential inclusion of measurement data
Precautionary Matrix for NMs	Nano-relevance; solid matrix stable under conditions of use, nanomaterial not mobile; solid matrix, stable under conditions of use, nanomaterial mobile; solid matrix, not stable under conditions of use	Not possible in the model	Potentially for two exposure parameters (amount of NM and frequency). Unable to enter measurements

[24] OECD 2021. Evaluation of Tools and Models for Assessing Occupational and Consumer Exposure to Manufactured Nanomaterials. https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-CBC-MONO(2021)27%20&doclanguage=en

Model	Input parameters important for uncertainty	Inclusion of uncertainty contributions for input parameters	Potential inclusion of measurement data
Control Banding Tool	Almost equal sensitivity towards all input parameters	Potentially for Monte Carlo analysis	Potentially, but unable to enter measurements
Stoffenmanager Nano	Process domain, daily cleaning, monthly inspection, concentration, handling in the breathing zone, viscosity, appearance, frequency of handling	Not possible in the model. Contributions could potentially be quantified	Potentially (such as dustiness), but unable to enter measurements
Nanosafer CB	OEL nano and bulk, material density, specific surface area, amount used in cycle, dustiness, duration of work cycle, room size	Not possible in the model. Contributions could potentially be quantified.	Could be, such as amount of NM
ConsExpo Nano	Aerosol diameter, inhalation rate, weight fraction of nanomaterial in the product, spray duration, aerosol fraction	Yes, possible for input parameters	Model allows measurement data to be included
SUNDS	Life cycle stage distribution means	Requires the user to input uncertainty estimates	Measurement data can be used
LICARA NanoSCAN	Exposure score (from Stoffenmanager Nano), occupational health risks, consumer health risks	Only included via the precautionary approach	Potentially (such as dustiness), but unable to enter measurements
ART	Not available	Not individually (distributions for multipliers for each modifying factors of the mechanistic model are not already assigned).[25] Variance components are taken into account in the Bayesian model.	Model allows measurement data to be included

[25] Fransman W et al. Advanced Reach Tool (ART): Development of the Mechanistic Model." *Annals of Occupational Hygiene*, 2011, 55 (9): 957–79. doi:10.1093/annhyg/mer083

Description of output and the relationship between the outputs and inputs

For the shortlisted models, the outputs have been investigated and also if the relationship for the mathematical model between the outputs and input parameters are meaningful as described in Table 9. For this, the following aspects have been assessed:

- **Description of the output**: This is intended as the sole quantity to be measured/estimated without uncertainty. This describes what the final output of the model, such as a score for potential exposure, exposure band or an estimated exposure concentrations.
- **Is the relationship (physical/mathematical model) between the outputs and inputs known**: For physical models and mathematical models, the general approach does not change. We have assessed if this is known in the exposure models, where this information is available. This relationship is known for the Precautionary Matrix, Stoffenmanager Nano, ConsExpo Nano, SUNDS, LICARA NanoSCAN and ART. For the Control Banding Tool and Nanosafer CB it has not been possible to fully conclude if the relationship between the outputs and input is known from the information available.

An additional aspect that could be considered (not considered here) is the potential for a more precise description of the exposure (such as eight-hour exposure in the near field) that is estimated by the model as part of the description of the output. However, for control banding tools that use the ordinal scale this is not possible due to the information provided by the scale.

Table 9. Outputs/inputs uncertainty aspects for human exposure models

Model	Description of the output*	Relationship (mathematical model) between the outputs and inputs known?
Precautionary Matrix for NMs	Potential exposure (score). The final output is an estimation of the need for precautionary measures (score)	Yes
Control Banding Tool	Risk level (score)	Yes for deterministic model; unclear for Monte Carlo model
Stoffenmanager Nano	Partial output: the exposure score is assigned to an exposure band on the logarithmic scale. The final output is a risk priority band (score)	Yes for exposure
Nanosafer CB	Partial output: Exposure score Final output: Risk level	Potentially
ConsExpo Nano	Outputs in regards to dose	Yes
SUNDS	Partial output: exposure value or the probabilistic distribution of exposure Final output: Risk Characterisation Ratio (dimensionless)	Yes
LICARA NanoSCAN	As per Stoffenmanager Nano for occupational exposure	As per Stoffenmanager Nano for occupational exposure

Model	Description of the output*	Relationship (mathematical model) between the outputs and inputs known?
ART	Exposure level (concentration estimate)	Yes

Overall uncertainty and missing uncertainty information

As part of the uncertainty assessment, we have assessed if the overall uncertainty of the models is able to be quantified and also what information is missing from the models and could be used for improving the uncertainty (Table 10). More specifically this has involved the following:

- **Quantifying the overall uncertainty**: We have also assessed if the overall uncertainty can be quantified within the model. This can be quantified for ConsExpo Nano, SUNDS, and ART. LICARA NanoSCAN takes uncertainty into consideration as uncertainty bar on the total result, it does not use quantitative uncertainty estimation techniques (e.g. Monte Carlo simulation). The overall uncertainty could potentially be quantified for Stoffenmanager Nano and Nanosafer CB, however this is not provided within the output. For the Precautionary Matrix and Control Banding Tool, this is not enough information available to investigate if this is possible.
- **Missing information:** We have identified for each model, additional information that could be used to improve the uncertainty analysis.
- For example, Stoffenmanager Nano and Nanosafer CB could be improved by the inclusion of input uncertainty contributions. For ConsExpo Nano and SUNDS, no missing information for uncertainty was identified.

Table 10. Overall uncertainty and missing information for human exposure models

Model	Can the overall uncertainty be quantified?	Missing information
Precautionary Matrix for NMs	Not enough information supplied for the model	Uncertainty contributions; information on the scales used
Control Banding Tool	Not enough information supplied for the model	Mathematical model and probability distribution of the inputs for Monte Carlo
Stoffenmanager Nano	Does not provide this in the output. Potentially could be quantified.	Input uncertainty contributions
Nanosafer CB	Does not provide this in the output. Potentially could be quantified.	Input uncertainty contributions
ConsExpo Nano	Yes (distribution)	N/A
SUNDS	Estimated in the model by Monte Carlo	N/A
LICARA NanoSCAN	Uncertainty bars included indicating minimum/maximum scores for unanswered questions	The uncertainty contributions are not only due to unanswered questions

Model	Can the overall uncertainty be quantified?	Missing information
ART	Quantified by confidence intervals	Uncertainty contributions associated with the input parameters

3.2.5 Case studies- Control Banding Tools

Case studies have been performed for uncertainty analysis on the Precautionary Matrix for NMs, the CB Nanotool and Stoffenmanager Nano. In this deliverable, the case study for the Precautionary Matrix for NMs is presented.

Methodology

For uncertainty analysis, the methodology to be used for assessing uncertainty in control banding tools is as below and is illustrated in Figure 8:

- The scoring scale is the first part to be assessed as part of an uncertainty analysis. The scale is a classification proposed in order to describe the nature of information contained within the numbers assigned to objects or subjects, so therefore within the variable.[26] Stevens developed the known classification with four scales, which are nominal, ordinal, interval and ratio.[27]
- The second step is defining the allowed basic operations and permissible statistics for each scale, which are defined from the Theory of Scales of Measurement (S.S. Stevens).[27] This allows to see if the uncertainty contributions of a single input parameter can be defined according to GUM (Guide to the expression of uncertainty in measurement). If uncertainty contributions are not able to be defined, then potential improvements can alternatively be suggested.
- The third step then involves checking that the mathematical model which specifies the output to identify any drawbacks/limitations for the input parameter scales. If this is the case, then potential improvements can be suggested for the second step and this step could then be repeated.
- The fourth step involves the evaluation of the overall uncertainty, taking into account the possible improvements identified in the second step.

An operating procedure has also been developed for evaluating uncertainty. This is supplied in Appendix 3.

[26] Kirch, Wilhelm, ed. (2008). "Level of Measurement". *Encyclopedia of Public Health*. **2**. Springer. pp. 851–852. doi:10.1007/978-1-4020-5614-7_1971.

[27] S. S. Stevens, "On the theory of scales of measurement" Science, vol. 103, no. 2684, pp. 677–680, Jun. 1946.

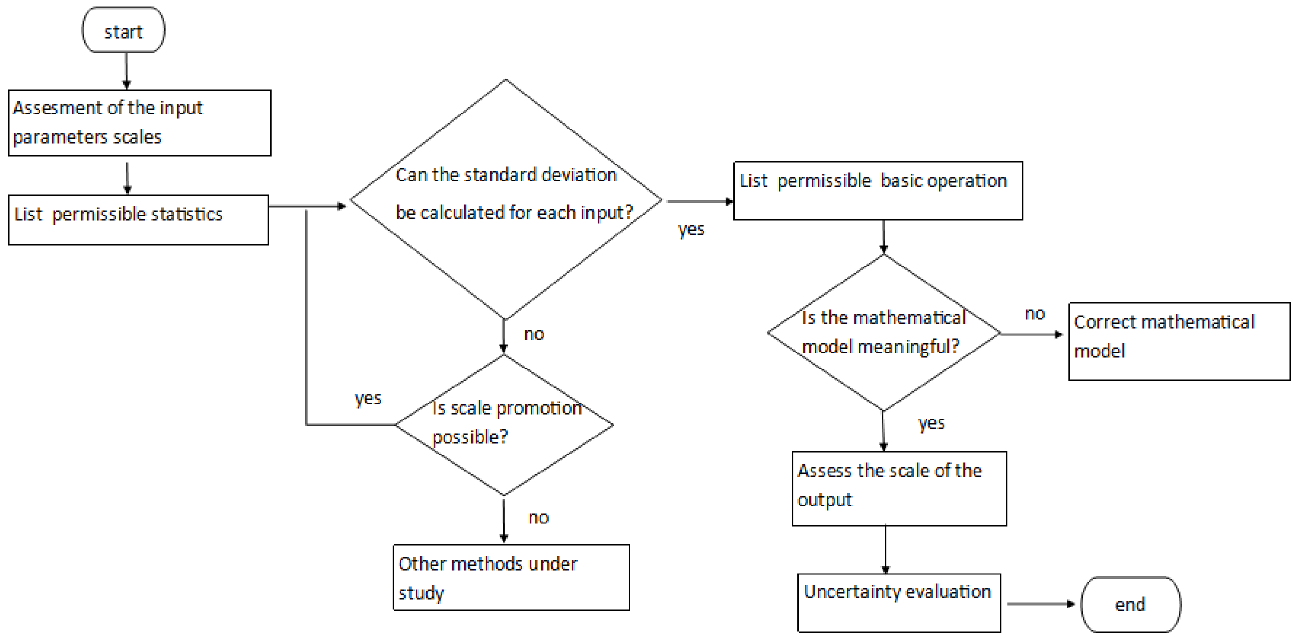

Figure 8. Flowchart for improving uncertainty in human exposure models.

Precautionary Matrix Uncertainty Case Study

Using the methodology described in the previous section, a case study has been performed on the Precautionary Matrix.

In the Precautionary Matrix, three parameter groups are used for human exposure. These parameters are as follows:

- Carrier material, specific for the "workers/consumers" target groups ($E1_{A,V}$)
- Amount of nanomaterial with which a worker/consumer comes into contact (E2.1 per day for worker, E2.2 in the worst case for worker, E2.4 per day for consumer)
- Frequency with which a worker/consumer comes into contact with nanomaterials (E2.3 for worker, E2.5 for consumer)

The scoring used for these groups is provided in Table 11.

Table 11. Scoring for Precautionary Matrix

Parameter Group	Parameter	Scoring
Carrier Material	Air, aerosols <10 µm (intake into lungs; possible input into environment)	1
	Air, aerosols >10 µm (intake into upper respiratory tract and gastrointestinal tract (GIT); possible input into environment)	0.1
	Liquid media (intake through GIT and skin; possible input into environment)	0.1
	Solid matrix, not stable under process conditions or conditions	0.1

Parameter Group	Parameter	Scoring
	of use (intake through lungs, GIT and skin; possible input into environment)	
	Solid matrix, stable under process conditions or conditions of use, nanomaterial mobile (low exposure for people and input into environment)	10^{-2}
	Solid matrix, stable under process conditions or conditions of use, nanomaterial not mobile (human exposure and input into environment unlikely)	10^{-4}
Amount of nanomaterial	Amount of nanomaterial with which a worker/consumer comes into contact per day	<1.2 mg: 1 (low); <12 mg: 5 (medium); >12 mg: 9 (high); Unknown: 9
	Amount of nanomaterial with which a worker could come into contact in the "worst case"	<12 mg: 1 (low); <120 mg: 5 (medium): >120 mg: 9 (high); Unknown: 9
Frequency Parameter Scoring	Frequency with which a worker/consumer handles the nanomaterial	Monthly: 1 (low); Weekly: 5 (medium); Daily: 5 (high); Unknown: 9

The scores presented in Table 11 are then combined through a mathematical model to give rise to the following equations:

- Potential exposure of workers: $E_A = E1_{A,V} \cdot E2.1 \cdot E2.3$ and in the "worst case": $E_A{}^{WC} = E1_{A,V} \cdot E2.2$
- Potential exposure of consumers: $E_v = E1_{A,V} \cdot E2.4 \cdot E2.5$

Following on from this, the scoring scales have been assessed following the methodology approach described in the previous section. The scoring are all on the ordinal scale as they do not have an absolute zero point, the distance between any two adjacent attributes is not always equal and the function is strictly monotone. This means that multiplication is not a permissible operation (Stevens, 1946). For the Precautionary Matrix, it can be concluded that it is not possible to evaluate the conventional quantitative uncertainty contributions. Further work is ongoing on an alternative assessment.

However, potential improvements for improving the uncertainty assessment of the Precautionary Matrix. These are as follows:[28]

- For the carrier material there is a possibility that if the maximum release for the material can be established, then uniform distribution could be used (similar to that for frequency)
- For the frequency parameter, an improvement can be the use of a ratio scale. It is assumed that the annual number of working days is 240 days, which correspond to the maximum frequency and 12 days

[28] Nebbia, Rebecca (2022) Work-Related Risks: Assessment, Management and Quality impact. Doctoral Thesis

is the minimum frequency (as the number of months during the year). Since the only available information is a lower limit a = 12 and an upper limit b = 240 with a < b, then, according to the principle of maximum entropy, a uniform (i.e. rectangular) distribution R(a, b) over the interval [a, b] would be assigned to the quantity (i.e. frequency) (JCGM 101:2008). The uniform distribution is adopted when nothing is known about the behaviour of the uncertainty factor within its variability range, as it is difficult to determine the frequency with which a worker/consumer comes into contact with nanomaterials. However, this would be only a convention, the best solution remains the measurement/ knowledge of the parameter.

- For the amount of nanomaterial parameter, an improvement is for the measurement of the amount of nanomaterial with which a worker/consumer comes into contact. Using measurements (ratio scale) instead of scores would bring the benefit of enabling the evaluation of the expanded uncertainty of this parameter. This would be achieved by using experimental data.

3.2.6 Suggested improvements for GUIDEnano for SbD

As previously identified in D2.1, GUIDEnano is the most promising model for SbD for human exposure. As part of the SAbyNA platform, selected GUIDEnano modules are being used with further refinements for inclusion into the SAbyNA platform for the human exposure module for SbD purposes and the two SAbyNA case studies on 3D printing and paints.

As part of this deliverable, a number of potential improvements have been identified for GUIDEnano and these are discussed in more detail in this section. In summary, these are:

- Allowing changes to exposure input parameters and for these changes in the result to be viewed “real time”
- An exposure scenarios read-across
- Default input exposure parameter values, such as for paints which are provided in ConsExpo Nano and also release rates for activities which are provided in SUNDS
- Inclusion of a warning for exposure
- Inclusion of ConsExpo Nano
- Inclusion of VOCs into the kinetic fate model
- Linking and/or inclusion for other exposure models
- Mitigation factors for specific risk management measures for specific scenarios
- Modelling outdoor paints exposure
- Performing One at a Time (OAT) analysis
- Uncertainty assessment
- Validation and inclusion of a ‘check’ scenario

Within this section, the suggested improvements have been divided between the relevant routes of exposure (inhalation, dermal, oral, and potentially multiple/all exposure routes).

Inhalation exposure

Default input exposure parameter values – consumer exposure

As is the case for environmental exposure, default parameter values could be provided. Within ConsExpo Nano, default parameter values are provided for pneumatic spraying and spray can. These values are provided in Table 12. These parameters are not specific to any NF/NEP and are specifically for the exposure scenario with a nano-enabled paint product. For additional consumer default input parameter values, ConsExpo also contains fact sheets that can be used for default parameters, however these are not nano specific. The inclusion of default input parameters is also being developed as part of the development of activity cards in WG4. For release rates, the default rates for release to the air from SUNDS could also be used.

Table 12. ConsExpo Nano default parameters

Exposure scenario	Default parameters
Pneumatic spraying	**Scenario:** Exposure duration (min): 25 minutes; **Aerosol:** Mass median aerosol diameter: 15.1 µm, Arithmetic coefficient of variation:1.2; Maximum aerosol diameter: 10 µm; **Spray**: Mass generation rate: 0.5 g/s; Airborne fraction: 0.14; **Usage**: Spray duration: 798 secs; **Room**: Room volume: $34m^3$; Room height: 2.25m; Ventilation rate: 1.5 per hour; **Nanomaterial**: Type of dispersion: Monodisperse; Shape nano particle: Sphere; **Simulation**: Exposure Pattern: repeated; Exposure frequency: 2 per year; Simulated duration: 365 days; Inhalation rate: 1.4 m^3/h
Spray can	**Scenario:** Exposure duration (min): 20 minutes; **Aerosol:** Mass median aerosol diameter: 15.1 µm, Arithmetic coefficient of variation:1.2; Maximum aerosol diameter: 10 µm; **Spray**: Mass generation rate: 0.45 g/s; Airborne fraction: 0.7; **Usage:** Spray duration: 900 secs; **Room**: Room volume: $34m^3$; Room height: 2.25m; Ventilation rate: 1.5 per hour; **Nanomaterial**: Type of dispersion: Monodisperse; Shape nano particle: Sphere; **Simulation**: Exposure Pattern: repeated; Exposure frequency: 2 per year; Simulated duration: 365 days; Inhalation rate: 1.4 m^3/h

Default input exposure parameter values – occupational exposure

In SUNDS for the activity generating the release rate input parameter a library of 161 activities is provided with default release rates to the air provided. These activities cover the synthesis and use of NF/NEPs and could potentially be used within the SAbyNA platform. An example of some of the activities and the provided release rates are described in .

Table **13.**

Table 13. Examples of occupational release rates provided by SUNDS for activity input parameter

Activity	Release Rate (wt. %)	Information
Use at industrial site leading to inclusion into/onto article	0.1	Percentage of NF from the input that is released to air
Mixing	0.025	Percentage of the powders which have as gone airborne from mixing
Weighing	0.0085	Percentage of the powders which have as gone airborne from mixing
Spraying of paints by pneumatic spraying	0.025	Percentage of the paints which do not result the surface because of overspraying and becoming airborne
Spraying of paints by spray can	0.0085	Percentage of the paints which do not result the surface because of overspraying and becoming airborne
Sanding	0.2	Percentage which is related to the trested surface and the NF amount which is incorporated at that surface

Inclusion of ConsExpo nano

ConsExpo Nano is of relevance to SAbyNA as it assesses consumer exposure to sprays. Within ConsExpo Nano, there are four separate models for estimating the time dependent alveolar load which are: 1) Model for estimating the concentration and inhaled mass of the sprayed aerosol; 2) Model for estimating the deposition in the alveoli from the aerosol diameter and the mass density; 3) Model for simulating the clearance of the material from the alveoli. This assumes the non-soluble particle load in the alveoli; and 4) Kinetic model which accounts for the dissolution of the material. This uses information on the dissolution rate of the material in the alveoli using information which is user-specific. ConsExpo Nano uses the ConsExpo spray tool (within ConsExpo model) and combines this with the ICRP deposition and clearance model for the estimation of inhaled and deposition doses. Within the model, two exposure scenarios are available that can loaded by the user. These are exposure from pneumatic spraying and from using a spray can.

Information on the algorithms and input parameters used by ConsExpo Nano is available ((see section 3.2.2 and the Excel file) and the accompanying Excel file). ConsExpo Nano is also well documented, with other details such as information on the nanomaterial exposure models, calculation of the dose metrics and the assumptions used by the model publicly available.

Within the kinetic fate model of GUIDEnano, it could be possible to include the spray model from ConsExpo Nano. If this is not possible, then a link to ConsExpo Nano could be provided to the user. Within GUIDEnano, the inclusion of these models from ConsExpo Nano may be required to be included at the human receptor site rather than at the system compartment site,

Inclusion of a warning for exposure

Within Part 1 of the SAbyNA platform, flags are considered for the NF entered by the user. For those NFs with OELs, a flag is raised with the user informing about the OELs and NRVs (Nano-reference values) (Table 14 and

Table 15). Within Part 2 of the platform and GUIDEnano, a warning could be indicated to the user when the exposure concentration is close to/over these values for when the user enters an exposure concentration from another model (as within the platform, SbD solutions will be suggested).

Table 14. NFs with OELs

NF	OEL	Source
TiO_2	0.3 mg/m^3	NIOSH[29]
	0.8 µg/m^3; short term: 4 µg/m^3	ANSES[30]
Carbon nanotubes, carbon nanofibres	1 µg/m^3 (elemental carbon)	NIOSH[31]
Carbon nanotubes	0.01 fibres/cm^2	Van Broekhuizen et al., 2012[32]**Error! Bookmark not defined.**

Table 15. NFs with NRVs

NF	NRVs	Source
Ag, Fe, Au, Pb, La, TiO_2, CeO_2, ZnO, SiO_2, CoO, nanoclay,	20,000 particles/cm^3	Van Broekhuizen et al., 2012[32]
C60, Carbon black, TiN, Sb_2O_5, polymers, polystyrene, dendrimers	40,000 particles/cm^3	

Inclusion of VOCs into the kinetic fate model

The emission of Volatile Organic Compounds (VOCs) occurs during 3D printing. This has been observed from the literature review of 3D printing performed in Deliverable 7.1 and from the initial 3D printing measurement campaign performed at LEITAT3D Hub. During this campaign, no free or protruding Carbon Nanotubes (CNTs) were observed from samples collected during printing using PC-CNT filaments. However, VOCs emissions were observed from printing. The emission of VOCs can be related to the process parameters (such as printing temperature) and also filament composition.

[29] https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf
[30] https://www.anses.fr/en/content/recommended-occupational-exposure-limits-titanium-dioxide-nanoparticles
[31] https://www.cdc.gov/niosh/docs/2013-145/pdfs/2013-145.pdf
[32] Van Broekhuizen et al. Exposure Limits for Nanoparticles: Report of an International Workshop on Nano Reference Values. Ann Occup Hyg, 2012, 56, 515-524

Within GUIDEnano, the emission of VOCs are not currently considered. VOCs when emitted are in the gas phase. The DustEx model, which is used for assessing exposure to semi-volatile substances (SVOCs) in products, assesses SVOCs in their kinetic source to dose model as follows[33]:

- Evaporation from the product to the gas phase and emission of SVOCs
- The SVOCs then partition to airborne particulate matter
- Inhalation exposure is possible from SVOCs in the gas phase and bound to particles

It is being investigated on the inclusion of VOCs into the kinetic fate model of GUIDEnano. Within the model, it is not possible to model separate VOCs, so Total Volatile Organic Compounds (TVOCs) will be modelled. Within the kinetic fate model, the average properties of TVOCs (i.e., such as concentration) is required. The modelling of emissions of VOCs could be linked to the filament composition, such as usage of filament in terms of mass and linking to emission of TVOCs. The consideration of the movement of TVOCs in the kinetic fate model (in the gaseous state) will also need to be considered within the model.

Modelling outdoors paints exposure

A potential improvement concerns the paints case study and outdoor painting activities. The outdoor use of paints is relevant for consumer exposure and also occupational exposure. Within GUIDEnano a multi-box model is used, for example this could contain multiple near fields within the far field. The near field is currently a cubic shape with no fixed size (a size of $8m^3$ (2m*2m*2m) is preferred). The near field is also fixed around the point of release. However, in the case of spray activities, where the nozzle (for example, from the spraying can) is moving, the near field is considered to also move along.

For indoor paint exposure scenarios such as spray painting in an enclosed booth, this model can be used with the near field around the worker in the booth and the far field being the rest of the room. However, for outdoor paint scenarios, there are other factors that need to be considered. These are the size of the far field, the movement of the consumer/worker whilst undertaken painting activities (such as spray-painting a fence) and environmental factors that could affect exposure (such as the effect of wind on exposure in the far field). For the movement of the worker/consumer during the painting activities, one potential addition could be introducing a third box within the model for the object being painted. This is being further investigated.

Dermal exposure

As previously discussed in section 3.1, there is a lack of dermal exposure models for nanomaterials. SUNDS has an option for estimating dermal exposure, however this is currently not possible to be selected/run. We will continue to monitor any developments for dermal exposure models for nanomaterials for aspects that could be incorporated within the GUIDEnano modules.

Currently, within GUIDEnano there are currently models for 'instant application', 'release contact rate', 'rubbing of', 'migration', and 'diffusion'. The drawback is these are not specific to NFs/NEPs. Presently, due to the lack of dermal exposure models to NFs/NEPs, it is not possible to provide further suggestions for improvements for dermal exposure only for SbD purposes within the GUIDEnano modules.

Oral exposure

Inclusion of SUNDS (oral exposure)

Inadvertent oral exposure is considered within SUNDS for occupational exposure. The outputs provided by SUNDS for oral exposure is the exposure lower confidence limit and the exposure upper confidence limit in mg/kg_bw/day for probabilistic exposure and deterministic exposure.

[33] https://www.rivm.nl/en/consumer-exposure-to-chemical-substances/exposure-models/DustEx

The model that is used for calculating the exposure in SUNDS is based on that in the IEAT (Ingestion Exposure Assessment Tool) package (the conceptual model is presented in figure 1 of the reference).[34] The IEAT model estimates the hand/object landing from information supplied by the user for estimating inadvertent oral exposure, however it is not specifically designed for nanoparticles.[35] For example, within IAET the model parameters are not designed for use with nanomaterials, as smaller particles could have different transport properties to those materials which are micron-sized.[36]

However within SUNDS it is stated that the inadvertent oral exposure is based on the nanoIEAT model. For the nanoIEAT model, detailed information is not currently available (further work is being undertaken to see if information is available). The required input parameters for inadvertent oral exposure in SUNDS are described in section 3.2.3. This model could be further investigated for possible inclusion within the GUIDEnano modules for oral exposure, or a link provided to the model that the user can access for assessing oral exposure.

All exposure routes

Allowing changes to exposure input parameters and for these changes in the result to be viewed "real time"

The feasibility of allowing changes to exposure input parameters (such as changing room dimensions, humidity, ventilation etc.) and for the results to be viewed in "real time" allowing the user to compare the effect of changing parameters of exposure has been investigated. This is not feasible, as each modification on an exposure input parameter would have an effect on other parameters, for example changes for the near field will have an effect on the exposure concentrations on the far field and vice versa. One potential option could be to have an option for the user to copy scenarios to allow comparisons to be undertaken.

Exposure scenario 'read across'

Franken et al. have developed a framework for the read-across of worker inhalation data based on ECHA PROC codes and read read-across factors from the ART exposure model and the ECETOC TRA model.[37] This is a framework based on read-across factors developed based on read-across factors from the ART exposure model and also the ECETOC TRA model. For using read-across, this framework calculates read-across factors which are based in other substances and/or the work situation. The existing data is first assessed for its quality and then mapped for the difference or similarity with either another substance and/or with the work situation. However, it is advised that good quality data is required for this read-across framework. Potential read-across for ECHA PROC codes are for PROC 8a (Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities), PROC 8b (Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities), PROC 9 (Transfer of substance or preparation into small containers (dedicated filling line, including weighing), and PROC 26 (Handling of solid inorganic substances at ambient temperature).[37]

It could be further investigated to assess the feasibility of this read-across framework and its potential application for NF/NEPs within the GUIDEnano modules. It could also be investigated if using this read-across approach

[34] Gorman Ng M, Semple S, Cherrie JW, Christopher Y, Northage C, Tielemans E, Veroughstraete V, Van Tongeren M. The relationship between inadvertent ingestion and dermal exposure pathways: a new integrated conceptual model and a database of dermal and oral transfer efficiencies. Ann Occup Hyg. 2012 Nov; 56(9):1000-12.

[35] http://www.sun-fp7.eu/wp-content/uploads/2017/01/SUN_Deliverable_5_2.pdf#page=9

[36] Derk H. Brouwer, Suzanne Spaan, Martin Roff, Anne Sleeuwenhoek, Ilse Tuinman, Henk Goede, Birgit van Duuren-Stuurman, Francesca Larese Filon, Dhimiter Bello, John W. Cherrie. Occupational dermal exposure to nanoparticles and nano-enabled products: Part 2, exploration of exposure processes and methods of assessment, International Journal of Hygiene and Environmental Health, 291(6), 2016, 503-512

[37] Franken R et al. Extrapolating the Applicability of Measurement Data on Worker Inhalation Exposure to Chemical Substances, *Annals of Work Exposures and Health*, 2020, 64(3), 250–269, https://doi.org/10.1093/annweh/wxz097

could be made sensitive for SbD purposes. Caution is also required for read-across, for example for read-across for ECHA PROC codes.

Linking and/or inclusion for other exposure models

Within the platform, it could be possible to provide linkages to other models. Within the current version of GUIDEnano, there is an option for users to enter experimental data and also exposure estimates from other models.

Within the platform, linkages to other models could be provided (i.e. ConsExpo Nano and SUNDS) with information supplied to the user on what input parameters are required to be input (these are described in the accompanying Excel file) by the user, possibly as a pictorial representation. Links could also be provided for the other shortlisted models listed in Table 3**Error! Reference source not found.**. Even though these models are not suited for SbD and limited optimisation has been identified, aspects of these models could be used by the user; for example the Control Banding Tool for RMMs and activities and Stoffenmanager Nano.

SUNDS could also be linked to GUIDEnano, in that it considers probabilistic and deterministic exposure in the near field and far field throughout the life cycle. Amongst the exposure parameters used are the room volume, air changes per hour, used mass, task duration, duration of the generation phase, density, particle diameter, and the activity generating the release rate. SUNDS also contains an activity library which provides release rates for the total end product (nanomaterials) emitted to the air during the process and could be used for release rates to be provided to the user for the relevant activities.

Mitigation factors for specific risk management measures for specific scenarios

Within Part 1 of the SAbyNA platform, the ECEL library for RMMs developed by TNO[38] and the GUIDEnano RMM library have been updated for specific scenarios. This work needs to further developed (led by WP5 with relevant WP2 input) for the platform.

One at a time (OAT) analysis

Within the updated GUIDEnano modules, it could be possible to identify the most sensitive parameters. This would involve identifying the most important parameters and then modifying each parameter one by one and identifying changes in the output.

Uncertainty assessment

Within the ECHA chemical safety assessment guidance for uncertainty analysis[23], the following aspects are considered for uncertainty:

- Model uncertainty – relating to simplifications the model makes. This also includes possible dependent errors and also the application of the model out with of the validity domain
- Parameter uncertainty – relating to individual model parameters/values/measurements. This includes potential measurement uncertainties such as measurement errors, the uncertainty in data section including the default values used and the exposure concentration used, extrapolation for data, such as for read-across across exposure scenarios, and also the data variability such as the behaviour variation related to the exposure potential
- Scenario uncertainty – user dependent. This includes the adequacy of the assumptions used for the exposure scenario. Aspects that are major sources for uncertainty for this include the emission sources, the exposed population, the exposure event (both the frequency and magnitude, exposure route(s) and also missing/incorrect information from the user (such as the exclusion of processes and activities in a scenario).

Within the previous version of GUIDEnano, uncertainty for human exposure is not considered. Even though a review has been performed for each of the shortlisted human exposure models (Precautionary Matrix for NMs,

[38] https://www.tno.nl/en/newsroom/2020/10/tno-launches-risk-management-measures/

Control Banding Tool, Stoffenmanager Nano, Nanosafer CB, ConsExpo Nano, SUNDS, LICARA NanoSCAN, and ART), it is worth noting that the uncertainty assessment is model-specific.

For SbD aspects and GUIDEnano, the most encouraging model for uncertainty assessment is Stoffenmanager Nano. However, a number of potential improvements were identified for Stoffenmanager Nano. This includes that the overall uncertainty is not quantified in the output (this could be potentially quantified) and also that input from uncertainty contributions is not currently considered. For the consideration of including an uncertainty assessment for human exposure, the aspects which are highlighted above (considered by ECHA) would need to be taken into account. Due to these limitations and the complexity of performing an uncertainty analysis for human exposure, an assessment of uncertainty for human exposure will not be added to GUIDEnano within the SAbyNA platform. Adding an uncertainty assessment may be misleading for the user, for example basing on Stoffenmanager Nano.

It is proposed that to address uncertainty for human exposure, a qualitative output is provided to the user explaining the following could be used:

- Uncertainty is not considered for human exposure within GUIDEnano
- Uncertainty in human exposure can be considered and assessed separately by the user
- References are provided to the user for further information for performing an uncertainty analysis. This includes reference to ECHA Chapter R.19: Uncertainty analysis[39] and also to the SOP developed for assessing uncertainty (Appendix 3 of this deliverable)

Validation of exposure part and the inclusion of a 'check' scenario

With the updates and improvements being performed for the human exposure part (such as the improvements for the kinetic fate model), there is a requirement for validation of the updates/improvements. This would involve comparing the exposure concentration derived by the modelling and the measured exposure concentrations. It is proposed that for validation, that experimental exposure data generated within the SAbyNA project for 3D printing and paints is used. This would ensure that where additional data is needed, this could be obtained from the relevant project partners. Amongst the experimental data that could be used for validation could be the obtained exposure measurement data is filament production, 3D printing, and end of life studies (such as shredding).

In deliverable 2.1, the inclusion of a 'check' scenario has been suggested. This involves including a scenario in which the user could use and check they are using the model correctly. This will be further investigated during validation of the human exposure part, such as using the validation exposure scenarios for this. For this possible 'check' scenario, caution will need to be used.

4. Next steps

In this deliverable, we have identified several tangible improvements that could be made to GUIDEnano to help the safe-by-design production of nanomaterials and nano-enabled products. We will continue liaising closely with WP6 to help take these suggestions forward towards implementation in GUIDEnano. Where work is ongoing on scoping potential improvements, this will continue in parallel with implementing improvements in GUIDEnano. Particular areas for continued work include generating new SPERCs relevant to the SAbyNA case studies, considering the importance of end-of-life scenarios and their inclusion in GUIDEnano, potential developments in models for dermal exposure and investigating read-across. We will also focus on using GUIDEnano to provide exposure assessments of the SAbyNA case studies, using this as an opportunity to assess whether further improvements could be made.

[39] https://echa.europa.eu/documents/10162/13632/information_requirements_r19_en.pdf/d5bd6c3f-3383-49df-894e-dea410ba4335

5. Conclusions

Here, we have detailed progress made in optimising and scoping improvements to models/tools for environmental and human exposure assessment. We have identified several tangible improvements to our chosen exposure tool, GUIDEnano. This includes suggestions focussed on elements such as model processes/algorithms, availability of sensitivity/uncertainty analyses, use of scenarios/case studies, availability of input parameters, and methods to provide release rates to exposure models. We will continue to work closely with WP6 to implement these suggestions.

6. Deviations from the workplan

No deviations to be reported.

Appendix 1 – Links to assessment spreadsheets

A snapshot of the assessment spreadsheets used within WP2 is archived on Zenodo: https://doi.org/10.5281/zenodo.7380141. This includes:

- Environmental release and exposure model assessment spreadsheet
- Human exposure model assessment spreadsheet
- SPERCs assessment for the SAbyNA paints case study

Appendix 2 – Level of information required for input parameters

Table 16. Information required for input parameters for some of the shortlisted human exposure models

Model	Input Parameter	Information required for the user and cost considerations
Precautionary Matrix for NMs	Parameter E2.1 (Carrier material). The potential options to the user are: • Air, Aerosols <10 µm • Air, Aerosols >10 µm • Liquid media • Solid matrix, not stable under relevant process conditions or conditions of use • Solid matrix, stable under relevant process conditions or conditions of use, nanomaterial mobile • Solid matrix, stable under relevant process conditions or conditions of use, nanomaterial not mobile	For this parameter, the user is only required to select one option, with no additional user input required beyond this. However, to select the correct option the user may be required to collect additional information to answer this question, for example by reviewing the literature (such as safety data sheets) or by performing experimental tests, such as for establishing the matrix stability, which would add costs to the user.
	Parameter E2.2 (Amount of nanomaterial with which a worker comes into contact in the “worst case”). The potential options to the user are: • Up to 12 mg • 12 – 120 mg • Over 120 mg • Not known	For these parameters, the user is only required to select one option, with no additional user input required beyond this. To select the correct option, the user may need to consult with other persons/information sources to correctly answer (such as checking with the people involved in formulation).
	Parameter E2.3 (Frequency with which a worker handles the nanomaterial). The potential options to the user are: • Monthly • Weekly • Daily • Not known	
	Parameter E2.4 (Amount of nanomaterials which a consumer handles daily through the utility product). The potential options to the user are: • Up to 1.2 mg • 1.2 – 12 mg • Over 12 mg • Not known	For these parameters, the user is only required to select one option, with no additional user input required beyond this. To select the correct option, the user may need to consult with other persons/information sources to correctly answer.
	Parameter E2.5 (Frequency with which a consumer uses the utility product). The potential options to the user are: • Monthly • Weekly	

Model	Input Parameter	Information required for the user and cost considerations
	• Daily • Not known	
Nanosafer CB	The following parameters provide a drop down menu for the response: • Energy level.- drop down menu • Activity level in the work room	For the energy level, the user is provided with a drop down menu with activities. This parameter does not require any more information to be provided by the user.
	The following parameters require input from the user (i.e. a value needs to be entered by the user): • Total amount of nanomaterial used per cycle at the workstation • How long does it take to perform one cycle at the workstation • Minutes pass between each work cycle • Times work cycle is repeated daily • Mass handled in the work cycle • Time required to pour one scoop etc. in the work cycle • Length of workroom • Width of workroom • Height of workroom	These parameters require information to be provided by the user, so could be data intensive for the user (with the associated cost implications). To select the correct option, the user may need to consult with other persons/information sources to correctly answer.
	Air Exchange in the work room	This parameters may require information to be provided by the user, however a drop down menu is available with a list of locations.
SUNDS (Tier 2- inhalation parameters)	In tier 2 (assessment), the following input parameters are required for the exposure assessment: • Particle diameter • Density • Percentage of pure NM • Used mass • Task duration • Duration of the generation phase • Number of repetitions • Room volume • Air changes • Activity generating the release rate	The activity parameter allows the user to select an activity from a drop down menu. The other input parameters require numeric input from the user. These parameters may require the user to perform to consult with other persons/information sources to correctly answer. It could also be the case that testing may be required (such as density and particle diameter) if this information is not available. These parameters may be data intensive for the user to supply with potential cost implications.

Appendix 3 – Operating procedure for evaluating the uncertainty of control banding tools

1. Scope

This operating procedure applies to the Control Banding tools that have been assessed within the SAbyNA project (Precautionary Matrix for NMs, Control Banding Tool, Stoffenmanager Nano, and Nanosafer CB). The aim of this procedure is to describe general rules to allow uncertainty considerations that are otherwise unusual in risk ranking[40] (Burgman, 2005).

This operating procedure is designed to be a quick guide for evaluating uncertainty. For more detailed information, the user is recommended to consult Good Practice Guide No.11 on uncertainty by Bell.[41]

2. Terms and definitions

The terms and definitions used in this operating procedure are as follows:

- *Scale of measurement of a variable*: This is a classification proposed in order to describe the nature of information contained within numbers assigned to objects or subjects, therefore within the variable;
- *Mathematical model*: This is the relationship between the input and the output parameters;
- *Expanded uncertainty*: This is the quantity defining an interval about the result of a measurement that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the measurand (the quantity intended to be measured);
- *Combined standard uncertainty:* This is the standard uncertainty of the result of a measurement when that result is obtained from the values of a number of other quantities, equal to the positive square root of a sum of terms, the terms being the variances or covariance's of these other quantities weighted according to how the measurement result varies with changes in these quantities.

3. **Procedure**

The first step to be undertaken is to identify all of the input relevant parameters within the Control Banding tool.

The next stage is to assess the scale of measurement (Kirch et al, 2008[42]) of each parameter in accordance with the Theory of Scales of Measurement (Stevens, 1946[43]) as set out in the following table.

Table 17. Checklist for uncertainty

Checklist Item	Yes	No	Measurement Scale	Allowable basic operations	Permissible statistics
1. The numbers/symbols serve only as labels or tags for			Nominal	Equivalence	Mode, chi square

[40] Burgman, M. A. 2005. *Risks and Decisions for Conservation and Environmental Management*. Cambridge, UK: Cambidge University Press.
[41] Bell S. Good Practice Guide No.11. The Beginner's Guide to Uncertainty of Measurement. National Physical Laboratory. https://www.npl.co.uk/special-pages/guides/gpg11_uncertainty.pdf
[42] Level of Measurement. In: Kirch W. (eds) Encyclopedia of Public Health (2008). Springer, Dordrecht. https://doi.org/10.1007/978-1-4020-5614-7_1971
[43] Stevens, S. S. (7 June 1946). "On the Theory of Scales of Measurement". Science. **103** (2684): 677–680. doi:10.1126/science.103.2684.677

Checklist Item	Yes	No	Measurement Scale	Allowable basic operations	Permissible statistics
identifying and classifying objects					
2a. A ranking scale in which numbers are assigned to objects to indicate the relative extent to which the objects possess some characteristic. 2b. Can determine whether an object has more or less of a characteristic than some other object, but not how much more or less 2c. Strictly (monotone) increasing transformations of scale are permissible.			Ordinal	Equivalence, order	Mode, chi square, median, percentiles
3a. Numerically equal distances on the scale represent equal values in the characteristic being measured. 3b. It permits comparison of the differences between objects. 3c. The location of the zero point is not fixed. Both the zero point and the units of measurement are arbitrary. 3d. Any positive linear transformation of the form $\Phi(x) = a + b \cdot x$ (with $b>0$) will preserve the properties of the scale.			Interval	Equivalence, order, addition, subtraction	Mode, chi square, median, percentiles, Mean, standard deviation, correlation, regression, analysis of variance
4a. Possesses all the properties of the previous scales. 4b. It has an absolute zero point (generally corresponding to the absence of manifestation of the characteristic being measured). 4c. Only proportionate transformations of the form $\Phi(x) = b \cdot x$, where b is a positive constant, are allowed.			Ratio	Equivalence, order, addition, subtraction, multiplication, division	All statistical techniques can be applied to ratio data

If the answer to all the items contained in a row is “yes” then the corresponding measurement scale is that listed in the third column (nominal, ordinal, interval, or ratio).

Following on from this, the following should then be performed:

- Based on the measurement scale, each input parameter should be assessed for the allowable basic operations discussed in column 5 of the table (i.e. equivalence, order etc.) and for the permissible statistics (i.e. mode, chi square etc.) of the last column of Table 17.
- Each input parameter should then be evaluated for uncertainty. Conventional quantitative uncertainty can only be evaluated for interval and ratio scales as standard deviation is not a permissible statistic for ordinal and nominal scales. Use Bell[44] as guide for conventional quantitative uncertainty evaluation.
- Check the maths used in the mathematical model. This is dependent on the allowable basic operations. For example, if the scale of the input parameters is ordinal, it is not meaningful to perform addition, subtraction, multiplication, and division between them.
- If the input parameters are interval or ratio scales (cardinal scales), the measurement units should be checked.
- Assess the measurement scale of the output and also the permissible statistics. This is useful to understand if the overall uncertainty can be quantified, Indeed for the ratio scale, it is required for calculating the expanded uncertainty and confidence intervals.
- Evaluate the overall uncertainty. It may be necessary to provide an interval about the measurement result that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the quantity subject to measurement, so an expanded uncertainty U is obtained by multiplying the combined standard uncertainty u_c by a coverage factor k (JCGM, 2008[45]). Expanded uncertainty can be evaluated using Bell as guide.

[44] Stephanie Bell. **Good Practice Guide No. 11.** The Beginner's Guide to Uncertainty of Measurement. National Physical Laboratory

[45] JCGM 100:2008. Evaluation of measurement data — Guide to the expression of uncertainty in measurement.