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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

D2.8 (interim 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	31/10/2021
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[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)

[2] Nature of the deliverable: **R** = Report, **P** = Prototype, **D** = Demonstrator, **O** = Other

Version	Date	Author	Partner	Email	Comments[3]
0.0.1	30/09/2021	Sam Harrison	UKCEH	sharrison@ceh.ac.uk	Creation
0.0.2	12/10/2021	James Hanlon	IOM	James.Hanlon@iom-world.org	Drafted human exposure section
0.1.0	13/10/2021	Sam Harrison	UKCEH	sharrison@ceh.ac.uk	Drafted environmental section
0.1.1	15/10/2021	Apostolos Salmatonidis	LEITAT	asalmatonidis@leitat.org	Review and edits
0.1.2	18/10/2021	James Hanlon	IOM	James.Hanlon@iom-world.org	Edits after WP2 review
0.1.3	28/10/2021	James Hanlon	IOM	James.Hanlon@iom-world.org	Edits after SC and internal review
1.0.0	28/10/2021	Sam Harrison	UKCEH	sharrison@ceh.ac.uk	Final edits after SC and internal review

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

Deliverable abstract

In this deliverable, we discuss improvements required in existing release, fate and exposure models, with a particular focus on improvements that could be made to GUIDEnano. This deliverable is an interim and acts as a progress report for Task 2.2.

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 a number of potential improvements to GUIDEnano, such as the inclusion of default parameter sets, updated processes algorithms, and the inclusion of results from sensitivity/uncertainty analyses performed on other exposure models.

We discuss the progress to date for the improvements required in the human exposure models following on from M2.2. The improvements identified in MS2.2 included model assumptions, input parameters, algorithms and processes, uncertainty analysis and the inclusion of release rates. The main focus of our assessment to date has been in uncertainty analysis and we are currently developing methodology to improve the uncertainty analysis of the models. We also present the results to date and the work to be performed for the other improvements identified over the next year.

The results of improvements required in both environmental and human models will be presented in Deliverable 2.4 in October 2022.

Table of Content

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
NM	Nanomaterial
NP	Nanoparticle
OECD	Organisation for Economic Co-operation and Development
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
WP	Work Package
WWTP	Wastewater Treatment Plant

1. Scope

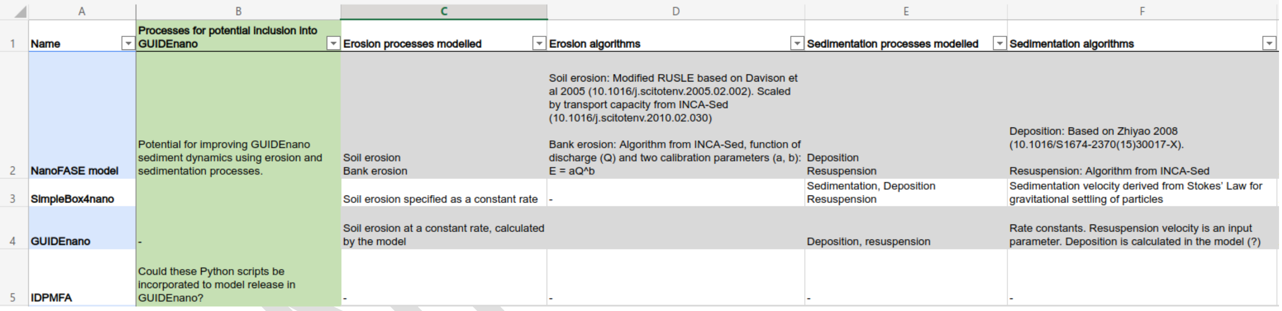
This deliverable acts as an interim deliverable for D2.4 (due M32) and serves to documents WP2's progress in assessing potential improvements required in existing release, fate and exposure models to make them more suited to SbD purposes. The work reported is largely part of Subtasks 2.2.3 (Streamlining 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.

2. Environmental release, fate and exposure models

2.1 Assessment methodology

The assessment of environmental release, fate and exposure models is being performed using the extended versions of the assessment spreadsheets used for D2.1, as detailed in MS2.2. 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 more suited to or relevant to SbD.



Name	Processes for potential inclusion into GUIDEnano	Erosion processes modelled	Erosion algorithms	Sedimentation processes modelled	Sedimentation algorithms
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
SimpleBox4nano		Soil erosion specified as a constant rate	-	Sedimentation, Deposition Resuspension	Sedimentation velocity derived from Stokes' Law for gravitational settling of particles
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 (?)
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 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, for example to increase realism or make data requirements more parsimonious.

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

2.2 Interim results

The assessment is ongoing and this interim deliverable serves to highlight the key findings so far. For environmental models, it is useful to consider release and fate/exposure models separately.

2.2.1 Release

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

Table 1. Environmental release models and tools selected for optimisation.

Model	Comments
LearNano	Web-based interface to predict ENM release rates. Links with MendNano.
NanoApp	Web-based tool to help grouping of nanoforms based on physchem 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, 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.

NanoApp is a web-based tool that helps with the grouping of nanoforms based on physchem properties. From a SbD perspective, grouping is a useful way to tell whether certain material modifications are likely to make a given ENM "safer": If a tool like NanoApp predicts that grouping of the original and modified ENM is possible, that is an indication that the modification will not produce an ENM that is significantly safer. On the contrary, if a modified ENM cannot be grouped with the original, then the modification might be a good candidate for SbD purposes. Of course, the actual effect of the modification on exposure must be considered to ensure it is not making the ENM less safe. We will explore the possibility for NanoApp to be linked with GUIDEnano to provide information on grouping to GUIDEnano. It should be noted that this tool is also being assessed in WP3. The EU Horizon 2020 project GRACIOUS is also studying the grouping of ENMs, and we will consider how work in that project could be useful for GUIDEnano.

LICARA NanoSCAN covers the entire life cycle 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.

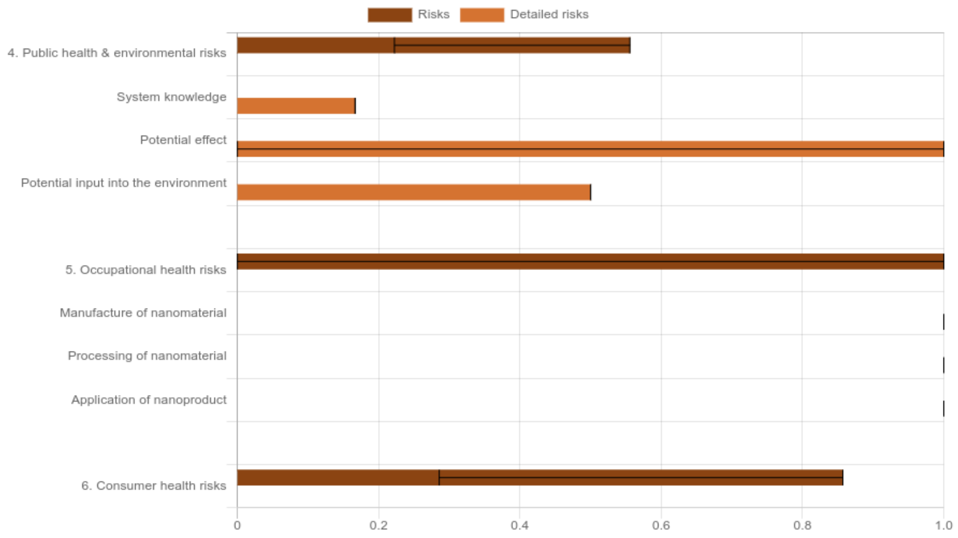


Figure 2. An example of the output of risk scores from LICARA NanoSCAN.

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. Hence, it might be a useful resource for GUIDEnano to link with to provide further functionality.

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.

Separate to the models/tools listed above, we will also consider 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 mass flows) for regulatory assessments. These group product uses into broad or specific categories and provide default release rates for products in these categories. Such release rates might be useful in assessing exposure without the need to perform detailed (and costly) release experiments. Figure 3 shows the use of ERCs and SpERCs during screening level exposure assessments. SpERCs take the broad release categories defined by ERCs and refine the corresponding emission estimates taking into account sector specific operational conditions and RMMs applied[6]. They are inherently less conservative but more realistic than ERCs. A potential improvement for GUIDEnano would be to provide a library of (Sp)ERCs for users to select from,

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[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

[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]. 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 an industrial use of paints and coatings, use of personal care products, and dispersive use of plant protection products. The fact that SpERCs are developed by industry bodies themselves presents a potential challenge in that there is no central database of SpERCs that have been developed (though tools like Chesar aim to integrate as many SpERCs as possible) and it is not trivial to find out which SpERCs concern ENMs.

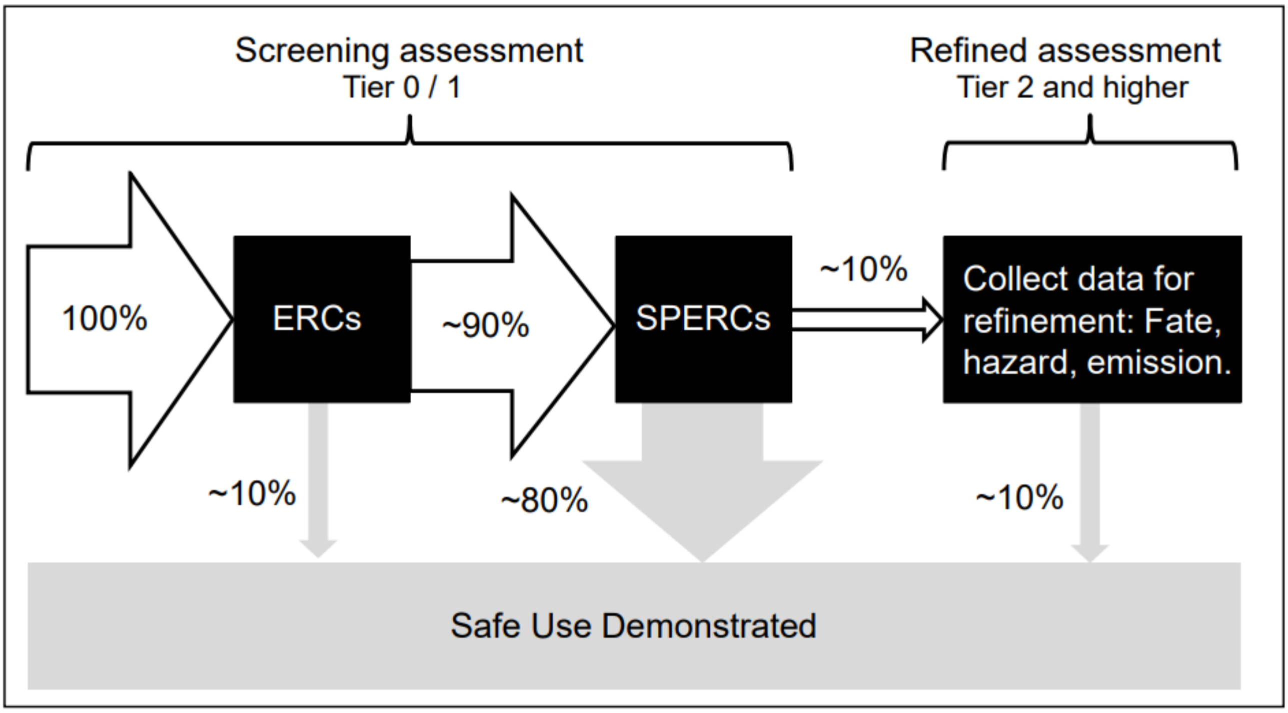

Figure 3. Illustrative scheme of the role of SpERCs as an element of a tiered approach to emission estimation. The width of the arrows is indicative of the portion of assessments that need refinement (horizontal) or pass the environmental exposure assessment.[5]

2.2.2 Fate and exposure

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

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

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 were based in part on 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:

- GUIDEnano includes resuspension as a rate constant and calculates deposition from Stokes' Law. Resuspension could be improved by calculating resuspension based on river characteristics, which the NanoFASE model does using resuspension algorithms from Lazar et al (2010)[8]. 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.
- Aggregation dynamics are modelled in equivalent or similar ways in all models.
- 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 Ag speciation, based partly on the work of Dale et al (2015)[9]. This work could provide dissolution and transformation dynamics to GUIDEnano.
- GUIDEnano already provides more sophisticated modelling of wastewater treatment and groundwater than any of the other assessed models.

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 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 may be able to explore the possibility 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 flows could be included via a seasonal variability factor (see MS2.2).

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[8] 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

[9] Dale et al (2015) " Stream Dynamics and Chemical Transformations Control the Environmental Fate of Silver and Zinc Oxide Nanoparticles in a Watershed-Scale Model": https://doi.org/10.1021/acs.est.5b01205

Model parameters

In general, the models require similar nano-specific parameters, such as attachment efficiencies, size distribution and material densities. They vary in the geographical parameters they require, with spatiotemporal models such as NanoFASE requiring complex spatiotemporal data. As detailed in the previous section, default phys-chem parameters for commonly used materials (e.g. TiO_2, Ag and ZnO) are available. We have begun to map model parameters to data sources and (standardised) methods in Task 2.2.

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)[10] 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, 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[11]. Example results are shown in Figure 4.
- 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 are performing a detailed assessment of exposure models, under the leadership of Environment and Climate Change Canada. This includes both uncertainty and sensitivity analyses on SimpleBox4nano and nanoFate (amongst others). This report is not publically available yet, but we will consider the results when it is.
- 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. For example, the critical ranges shown in Figure 4 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.
    - A probabilistic uncertainty analysis could be implemented in the environmental compartments to account for the natural variability in environmental parameters such as river flows and suspended sediment concentrations. Data from Meesters et al (2016)[11] could be used to support this.

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[10] 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

[11] Meesters et al (2016), “Multimedia environmental fate and speciation of engineered nanoparticles: a probabilistic modeling approach”: https://doi.org/10.1039/C6EN00081A

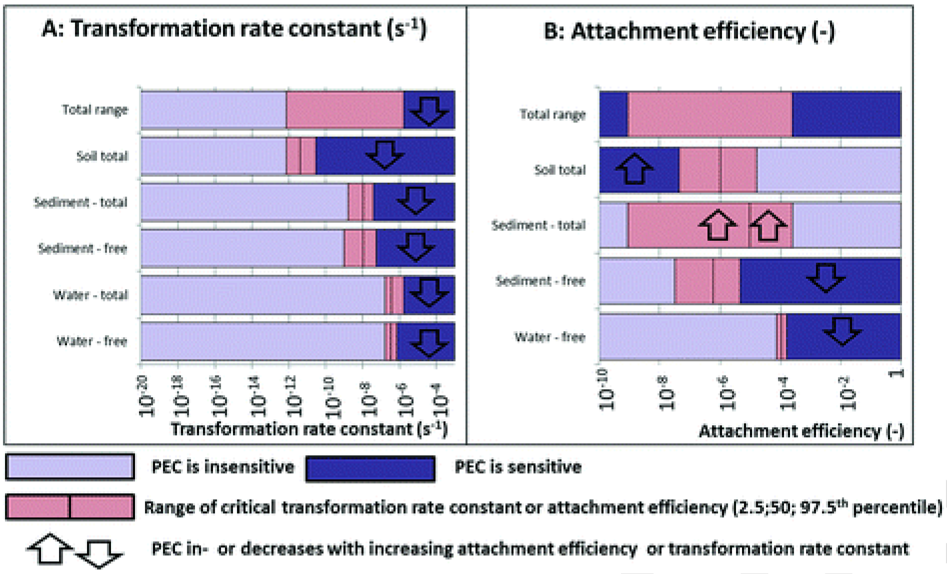

Figure 4. Critical ranges for transformation rate constants and attachment efficiencies in SimpleBox4nano.

2.2.3 GUIDEnano

The previous sections detail potential improvements for GUIDEnano. For clarity, these are summarised here. It should be noted that this list is not yet exhaustive and our assessment is ongoing.

- GUIDEnano could provide a link to NanoApp to enable users to provide information on grouping.
- A link to LICARA NanoSCAN could be provided to point SMEs to a tool through which they can qualitatively assess the benefits and risks of their product development.
- GUIDEnano could provide a library of (Sp)ERCs for users to select from, similar to the Chesar tool[12].
- There is 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.
- Improved nano-Ag and Cu dissolution and transformation dynamics could be implemented in GUIDEnano using algorithms currently being developed for the NanoFASE model in the ASINA project.
- 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 or the probabilistic approach mentioned below.
- 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.
- Results from uncertainty and sensitivity analyses performed on other models, in particular SimpleBox4nano, could be used to either provide guidance to users on critical parameter ranges, or to account for natural variability in environmental parameters by implementing a probabilistic approach in environmental compartments.

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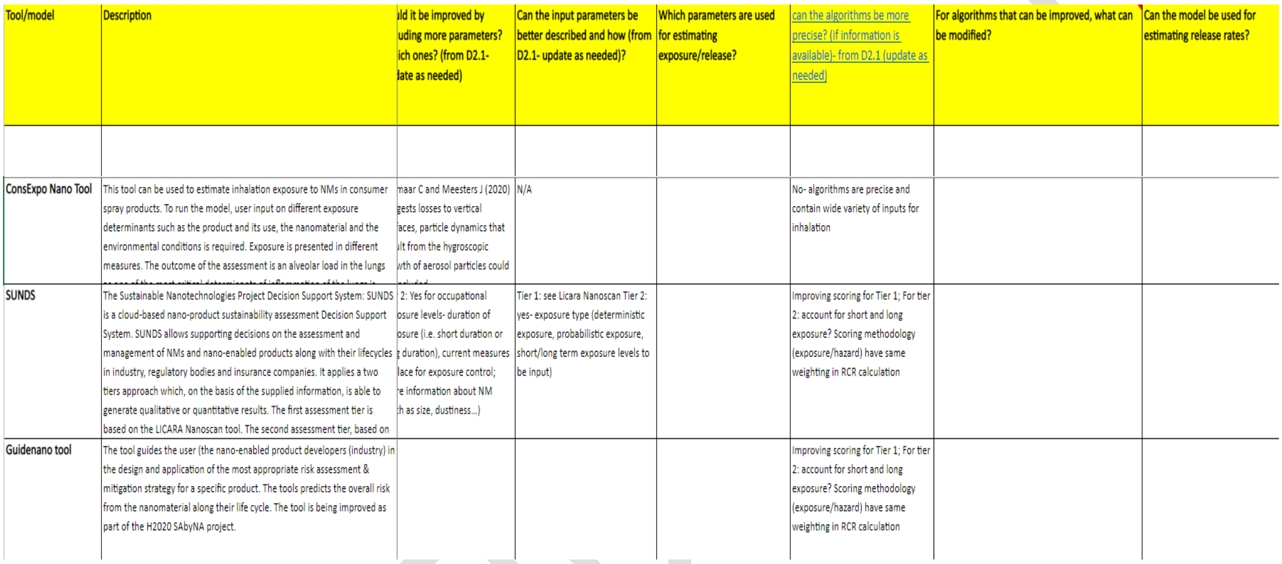
[12] ECHA, Chesar tool: https://chesar.echa.europa.eu/

3. Human release, fate and exposure models

3.1 Assessment methodology

The assessment of the human exposure models is being 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 5 and a link to the spreadsheet in available in the Appendix. In D2.1, a shortlist of models was devised and a number of aspects for improvement for these models were identified in MS2.2. 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 is to streamline and improve the identified models and also identify aspects of models that could be incorporated into GUIDEnano.



Tool/model	Description	ıld it be improved by uding more parameters? ich ones? (from D2.1- late 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 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 5. Example of the spreadsheets being used to assess human exposure models.

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 used, 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 for 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 are also identifying the potential uses of the models with in 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 currently 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. Due to the differing nature of the models, the columns will be further defined and modified as the assessment progresses.
- **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. Here, we will identify if it is possible for minimum parameters required for a

meaningful output to be defined. This will allow us to identify potential streamlining of input parameters and building on D2.1, which will also allow us to link key parameters with the test methods identified in D2.1.

- **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 analysis of uncertainty which has been the current focus of T2.2 to date. This includes:
    a. assessing the relationship between the output and input parameters
    b. assessing if measurement data can be included in the model which can reduce uncertainty
    c. if uncertainty contributions can be associated with input parameters in the model (and which ones are important for uncertainty)
    d. establishing if the model allows the overall uncertainty to be quantified.
- **GUIDEnano detailed analysis**: As part of the assessment, IOM and LEITAT are also performed a detailed analysis of the latest version of GUIDEnano under development (version 4). This includes assessing the exposure aspects and identifying potential streamlining and improvement.

3.2 Interim results

The assessment is ongoing and this interim deliverable serves to highlight the key findings so far. The main focus, since the submission of M2.2 has been on the uncertainty analysis for the shortlisted models.

3.2.1 Shortlisted models

As a recap of MS2.2 and D2.1, the human exposure models selected for further assessment in T2.2 are shown in Table 3. LICARA NanoSCAN has been added to the shortlist the submission of D2.1, as the new version of the model has been released. The selection process for the models is outlined in D2.1.

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

Name
ART
ConsExpo Nano Tool
Control Banding Tool
GUIDEnano
LICARA NanoScan
Nanosafer CB
Precautionary Matrix for NMs
Stoffenmanager Nano
SUNDS

The potential improvements to the models are outlined in section 3.1 and also in MS2. These are described in more detail in the following sections. The models are planned to be used in Part 2 of the SAbyNA platform.

3.2.2 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) could be limited. For example, no information was available for Stoffenmanager Nano, limited information was available for the Precautionary Matrix (no protective measures are in place); whilst for ConsExpo Nano the assumptions for spraying are well described (including spraying distance and dispersion).

As part of T2.2, the model assumptions are being updated for the shortlisted models where this information is available. Where the information for the model assumptions is known, further model assumptions for potential inclusions will also be identified. This will allow us to identify potential streamlining of the shortlisted models and also potential assumptions which could be used in GUIDEnano.

3.2.3 Model algorithms and processes

As discussed in section 3.1 and M2.2, information is being collated for the algorithms and processes modelled in the shortlisted models. Some of this information was collated as part of D2.1 and is being further elaborated. This includes information on the algorithms and processes for worker exposure, consumer exposure, scoring used by the models and activities used in the models. This analysis will allow us to identify algorithms and process which can be streamlined and also those that could be included into GUIDEnano. An example of some of the information collected to date for algorithms and process is described in Table 4.

Table 4. Model algorithms and processes

Model	Worker exposure algorithms	Consumer exposure algorithms
Precautionary Matrix for NMs	E_a= $E1_{a,v}$ • E2.1 • E2.3; for worst case: E_a^{WC} = $E1_{a,v}$ • 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 = $E1_{a,v}$ • E2.4 • E2.5 where $E1_{a,v}$: type of carrier material, E2.4: amount of NM the consumer comes into contact, E2.5: frequency with 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
ConsExpo Nano	N/A	Exposure described in Delmaar et al., (2005) for the spray model. For a custom scenario: A_{inh}= Q_{inh}•C_{air}•T Where Q_{inh} is the inhalation rate (volume per time), T the exposure duration, and C_{air} is the air concentration

3.2.4 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, such as by material properties, environmental/room properties, process and the number of exposed employees. A similar task will also performed for the ART model.

As described in MS2.2, the assessment of the model input parameters is split into a number of different tasks. These are described in the following sections.

Identifying the minimum parameters that are required for a meaningful output

This will involve analysing the shortlisted models and identifying the minimum parameters that are required for each model. This will in turn, 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 on the shape, size, dustiness, room properties, ventilation and duration/frequency of exposure. Input parameters for specific models include dustiness (Control Banding tool, Nanosafer CB and GUIDEnano), ventilation rate (Stoffenmanager Nano, GUIDEnano 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 (link is in the appendix).

Work 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 (this work is not yet published). 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.

For identifying the minimum parameters that are required for a meaningful output to be supplied by the model, we are planning to perform Principal Component Analysis (PCA) on the model parameters 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.[13] Another possible method that could be used is latent class analysis which involves grouping and analysing variables based on similar patterns. Depending on the results from Principal Component Analysis, latent class analysis may be investigated further.

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". As part of the assessment, we will identify which models allow input parameters to be changed and the result to be viewed in "real time". For example, the Precautionary Matrix does not allow this, whereas the updated version of LICARA NanoSCAN updates some results as values for input parameters are entered.

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

As part of D2.1, an initial analysis was performed on whether the input parameters could be better described. This is being further developed during this stage of the assessment. Some initial results are presented in Table 5. As part of this task, additional parameters that could be added to the models and for inclusion into GUIDEnano are being described.

Table 5. Input parameters description (initial results)

Model	Potential improvements for parameter description
Precautionary Matrix for NMs	Rephrasing carrier material
SUNDS	Exposure type could be redefined
LICARA NanoSCAN	Some better description of the input parameters could be addressed
ART	Potential improvement could be possible

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[13] (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.

Parameters used for estimating exposure/release

As part of the assessment, we are establishing how required parameters such as release rates can be generated. This will involve relating dustiness indexes (and key parameters) to release rates and information on the parameters used for estimating release/exposure. 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. Due to the nature of the models, some of these do not provide release rates as outputs, such as the control banding models.

3.2.5 List of activities and process relevant for SAbyNA case studies

In addition to the improvements required to the existing models identified in M2.2, we are also going to identify the activities and process which are relevant for worker and consumer exposure for the SAbyNA paints and 3D printing case studies (in collaboration with WG4 and WP7). This will involve identifying activities and processes which are commonly performed and whether it is possible to provide default values and/or ranges for the required input parameters for the models.

As part of this task, we will continue on the work on grouping from GRACIOUS (this is also underway in WG4) and also on read-across of exposure scenarios. We will also use the framework for read-across of worker inhalation data proposed by Franken et al. which is based on using ECHA PROC codes.[14] Grouping and read-across of exposure scenarios will be assessed for implementation in the models. The results of this task may also be used for refining default values and/or ranges for exposure.

3.2.6 Uncertainty analysis

As part of the assessment, one aspect that could potentially be improved in the shortlisted models is the uncertainty evaluation. Aspects of uncertainty analysis which are important include the inclusion of measurement data (which is beneficial for uncertainty analysis) and the measurement scales used in the model.

As part of the uncertainty analysis, 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. Information has been collected on the following aspects for uncertainty as described in M2.2:

- 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.
- Is it possible to include the uncertainty contributions associated with the input parameters?
- Can the overall uncertainty (e.g., expanded uncertainty) be quantified?
- What are the major contributions of uncertainty?
- Model assumptions uncertainty.
- Which information about uncertainty is missing?

The Monte Carlo method is typically used for uncertainty analysis and is used for the Control Banding Tool, ConsExpo Nano and SUNDS. Potential improvement and streamlining for the uncertainty analysis have been identified, which includes the following aspects, these are highlighted in Table 6:

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[14] 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

- **Inclusion of measurement data in the input parameters:** As previously discussed, including measurement data is beneficial for uncertainty. 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).
- **Inclusion of uncertainty contributions:** In the models, it has also been assessed if uncertainty contributions could be included with input parameters. 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.
- **Quantifying the overall uncertainty**: We have also assessed if the overall uncertainty can be quantified within the model. This is the case for ConsExpo Nano, SUNDS and ART. However, this is currently not possible for the Control Banding Tool and there is not enough information for the Precautionary Matrix, to determine if this is also the case for this model.
- **Missing information:** We have identified for each model, additional information that could be used to improve the uncertainty analysis. This generally is the inclusion of uncertainty contributions.

Table 6. Selected uncertainty aspects for human exposure models

Model	Potential inclusion of measurement data	Inclusion of uncertainty contributions for input parameters	Can the overall uncertainty be quantified?	Missing information
Precautionary Matrix for NMs	Potentially for two exposure parameters (amount of NM and frequency). Unable to enter measurements	Not possible in the model	Not enough information supplied for the model	Uncertainty contributions; information on the scales used
Control Banding Tool	Potentially, but unable to enter measurements	Potentially for Monte Carlo analysis	Not possible	Mathematical model and probability distribution of the inputs for Monte Carlo
Stoffenmanager Nano	Potentially (such as dustiness), but unable to enter measurements	Not possible in the model. Contributions could potentially be quantified	Does not provide this in the output. Potentially could be quantified.	Input uncertainty contributions
Nanosafer CB	Could be, such as amount of NM	Not possible in the model. Contributions could potentially be quantified.	Does not provide this in the output. Potentially could be quantified.	Input uncertainty contributions

Model	**Potential inclusion of measurement data**	**Inclusion of uncertainty contributions for input parameters**	**Can the overall uncertainty be quantified?**	**Missing information**
ConsExpo Nano	Model allows measurement data to be included	Yes, possible for input parameters	Yes (distribution)	N/A
SUNDS	Measurement data can be used	Requires the user to input uncertainty estimates	Estimated in the model by Monte Carlo	N/A
LICARA NanoSCAN	Potentially (such as dustiness), but unable to enter measurements	Only included via the precautionary approach	Uncertainty bars included indicating minimum/maximum scores for unanswered questions	The uncertainty contributions are not only due to unanswered questions
ART	Model allows measurement data to be included	Not individually (distributions for multipliers for each modifying factors of the mechanistic model are not already assigned).[15] Variance components are taken into account in the Bayesian model.	Quantified by confidence intervals	Uncertainty contributions associated with the input parameters

As part of the uncertainty analysis, an in-depth case study is being performed for the Precautionary Matrix uncertainty analysis. Based on these findings, this could be used to: (i) as a guide for performing uncertainty analysis for the models and used as guidance in the platform (ii) identify improvements which could be applied and (iii) used for potentially inclusion for uncertainty in GUIDEnano. This in-depth analysis is currently being performed and the results will be described in Deliverable 2.4. Initial findings on the methodology to be employed are provided here.

Precautionary Matrix Uncertainty Analysis Case Study - Methodology

For this analysis, only the human exposure parameters are being considered. These are specifically the following parameters for the Precautionary Matrix:

- Carrier material, specific for the "workers/consumers" target groups ($E1_{A,V}$)

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[15] 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

- 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)

These parameters are then used for the scoring for the potential exposure of workers and consumers, which are:

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

Each of these three groups is assessed from a different scoring scale, whilst within each group the parameters in the group are evaluated within the same scoring scale. For uncertainty analysis, a five-step analysis is performed as illustrated in Figure 6:

- 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.[16] The scale types are nominal, ordinal, interval and ratio.
- 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).[17] This allows to see if the uncertainty contributions of a single input parameter can be defined. 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 expanded uncertainty, taking into account the possible improvements identified in the second step.

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[16] 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.

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

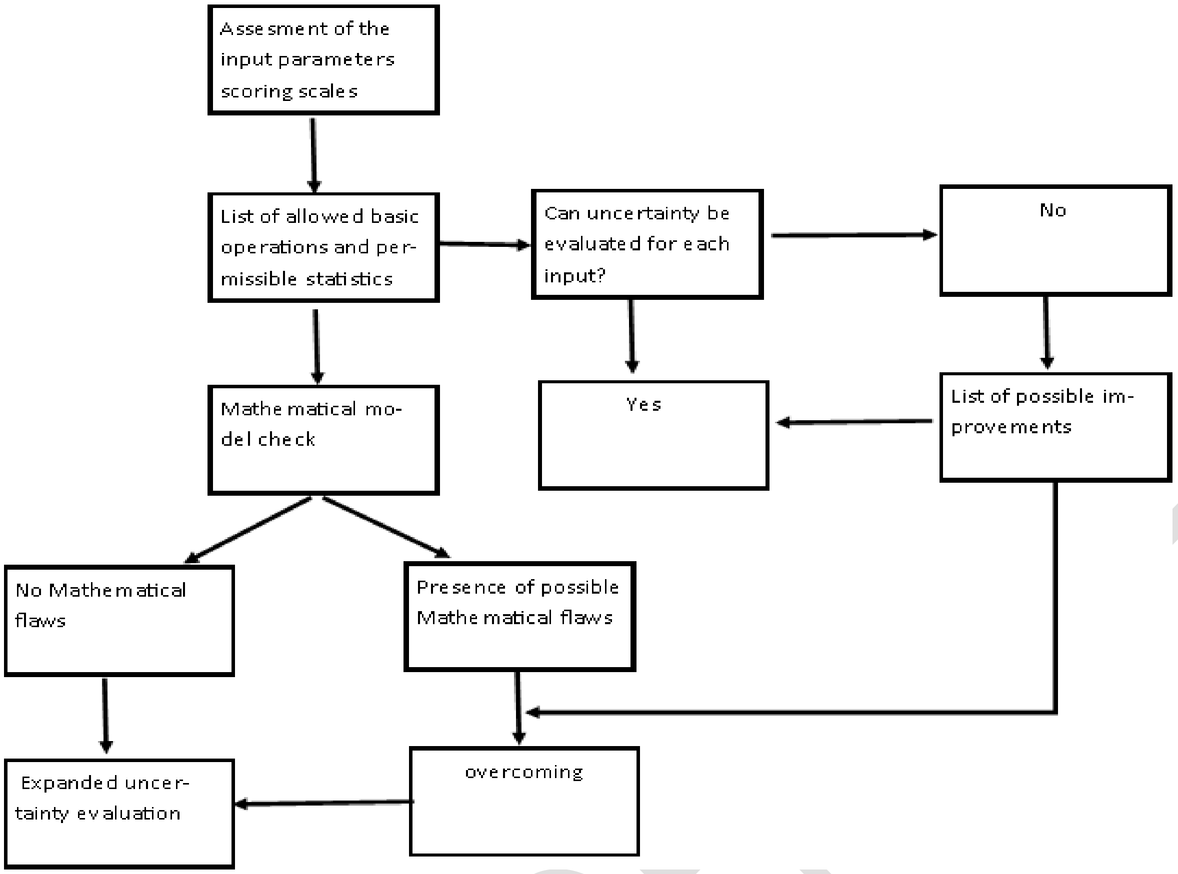

Figure 6. Flowchart for improving uncertainty in human exposure models.

3.2.7 GUIDEnano

As discussed in M2.2, a specific focus of T2.2 will be identifying and implementing improvements for human exposure in GUIDEnano. The GUIDEnano model is the most promising model for SbD purposes. Over the coming months, GUIDEnano will be of particular focus for the assessment. As part of this assessment, we are using the latest development version of GUIDEnano (v4), and this will be assessed by each member of the review team at IOM and LEITAT using selected case study scenarios. A detailed analysis is also being performed on each exposure aspect for GUIDEnano. This includes, for example list of activities and release rates, compartments, available protection controls, exposure paths, exposure scenario(s) and any other relevant human exposure information. Also as part of the assessment of the models, we are identifying aspects of the others models which could be included in GUIDEnano.

Below, is a list of potential improvements for GUIDEnano. This list is net yet exhaustive and the assessment is ongoing.

- Inclusion of background data for the exposure assessment into GUIDEnano. This is an area of current focus for the assessment.
- A link to SUNDS and LICARA NanoSCAN could be provided to point SMEs to a tool through which they can qualitatively assess the benefits and risks of their product development.
- Potential streamlining of ConsExpo Nano and inclusion into GUIDEnano. ConsExpo Nano is particularly relevant for the paints case study as it assesses consumer exposure to sprays.
- Default input parameters values for the relevant exposure input parameters could be provided in GUIDEnano for common materials (such as SiO_2 and CNTs which are relevant for the case studies).
- We are also investigating the parameters that are required for a meaningful output in GUIDEnano. This could allow refinement of the input parameters.

- Inclusion of uncertainty analysis for the exposure assessment. This could be by using uncertainty analysis performed by other models (such as ART or ConsExpo Nano) with any appropriate improvements or developing an uncertainty analysis based on the methodology being developed in section 3.2.6 or using a similar approach for hazard assessment currently included in GUIDEnano (use of multiplication factors). If this is not possible, guidance could also be provided to the user for performing uncertainty analysis and the results of this entered by the user into GUIDEnano.
- Development of activity cards into GUIDEnano for exposure. This is being developed in WG4.
- GUIDEnano requires quantitative information on the emission rate, which may not be available. Other models consider emission rates (such as LICARA NanoScan) consider emission rates, this will be investigated further to see if aspects of emission from other models could be incorporated into GUIDEnano.

4. Next steps

For both the environmental release and exposure and human exposure models, we will continue with the assessment of the potential identified improvements outlined in this deliverable. The final results of this assessment will be presented in Deliverable 2.4 due in October 2022. A particular focus over the coming months, will be on identifying aspects of models which could be included in GUIDEnano and potential improvements to GUIDEnano to allow WP6 to develop GUIDEnano. For potential improvements already outlined in this deliverable, we will liaise closely with WP6 and the GUIDEnano developers to assess the feasibility and desirability of these suggestions.

5. Conclusions

Here, we have detailed progress made in optimising and scoping improvements to models/tools for environmental and human exposure assessment. We are performing a detailed assessment of models shortlisted in D2.1 and MS2.2, with a particular focus on elements of models that could help improve GUIDEnano. In this deliverable, we have detailed our interim findings from this assessment, and discussed potential improvements to GUIDEnano. We have 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. This deliverable is the interim version of D2.4, due M32.

6. Deviations from the workplan

No deviations to be reported.

Appendix - links to assessment spreadsheets

Environmental release and expose models assessment spreadsheet: https://acondicionamiento.sharepoint.com/sites/P-SAbyNA/_layouts/15/Doc.aspx?OR=teams&action=edit&sourcedoc={DB89A35C-2522-4BB5-8782-B96174032984}

Human expose models assessment spreadsheet: https://acondicionamiento.sharepoint.com/sites/P-SAbyNA/_layouts/15/Doc.aspx?OR=teams&action=edit&sourcedoc={894DB437-9708-4EBA-8187-A70751C6E5EF}