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SimpleBox4nano: environmental fate modelling of nanomaterials *via* the Enalos Cloud Platform

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This work presents the development of a web application, freely accessible through the Enalos Cloud Platform (https://www.enaloscloud.novamechanics.com/insight/simplebox4nano/), that integrates the environmental fate model *SimpleBox4nano* and eliminates the complexities associated with the original Excel-based implementation. The web application replicates the full functionality of the original *SimpleBox4nano* model (version 4.03, released on 16 February 2024) and extends it further by including the option for dynamic simulations and advanced analyses of nanomaterial mass flows and chemical concentrations across multiple environmental compartments (air, soil, water and sediment) at regional, continental and global scales. Predefined nanomaterials and environmental landscape settings are included as defined in the original model, while users are also enabled to define custom nanomaterials by manually specifying their physicochemical properties. Users can add custom emission scenarios and environmental settings directly through the graphical user interface (GUI). Several model scenarios and case studies are presented to demonstrate the usability, reliability, and accuracy of the web application. A comparison functionality is integrated into the web application, enabling users to compare the predicted environmental mass distributions of multiple selected nanomaterials and a sensitivity exploration feature is integrated to support Safe and Sustainable by Design (SSbD)-oriented screening by identifying influential physicochemical properties through multi-run simulations. In addition, the web application incorporates a fate factor calculation module, a key parameter required for determining characterization factors in Life Cycle Impact Assessment (LCIA), to support the evaluation of both ecotoxicological and human health impacts. RESTful APIs have been integrated to ensure interoperability with external platforms.

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Sustainability spotlight

The *SimpleBox4nano* web-application is an open, user-friendly environmental fate model for nanomaterials that removes technical barriers to strengthen evidence-based governance (SDG 16) and enable responsible chemicals management (SDG 12). The dynamic simulations and comparative analyses provide critical insight for redesigning materials with reduced long-term accumulation and lower ecological burden supporting Safe and Sustainable by Design (SSbD). The integrated fate factor calculations enhance evaluation of potential impacts of nanomaterials on water, soil, and sediment systems, contributing to protection of water resources (SDG 6) and supporting proactive, climate-aligned environmental stewardship (SDG 13). Through FAIR and open access, and SSbD-oriented sensitivity analyses, the *SimpleBox4nano* web-application empowers researchers, regulators, and industry to co-create safer, more sustainable materials and strengthen global capacity for sustainable innovation.

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1 Introduction

Understanding the environmental behaviour, fate, and transport of nanomaterials is essential for assessing their potential exposure, ecological risks, and long-term sustainability. Nanomaterials are any organic, inorganic or mixed (organometallic) materials that exhibit distinct physicochemical and/or electrical properties arising from their ultrasmall size, typically ranging from 1 to 100 nm, and are characterized by a high surface area and enhanced reactivity compared with their bulk materials.[1] Based on their origin, nanomaterials are generally categorized into natural, incidental and engineered nanomaterials.[1–3] Natural nanomaterials occur without human intervention through geological, volcanic, or biological processes; for instance, mineral colloids, sea-spray aerosols, and magnetite nanoparticles produced by microorganisms.[4,5] Incidental nanomaterials, by contrast, are unintentionally generated during anthropogenic activities such as combustion, vehicle emissions, or metallurgical processes, producing nanoscale particles like soot or fly ash.[6] Engineered nanomaterials (ENMs) are intentionally designed and manufactured to exploit size-dependent optical, electrical, or catalytic properties that do not appear at the macroscale.[6] ENMs include materials such as titanium dioxide (TiO_2) and zinc oxide (ZnO) nanoparticles used in sunscreens and coatings, silver (Ag) nanoparticles for antimicrobial applications, cerium dioxide (CeO_2) in fuel additives, carbon-based nanomaterials like carbon nanotubes (CNTs), graphene and fullerenes for structural composites and electronics,[7–11] and emerging materials such as metal–organic frameworks (MOFs) and 2D transition metal carbides, nitrides, or carbonitrides (MXenes) which are widely used in energy capture and storage.[12,13] Fig. 1 presents the major nanomaterial categories grouped according to their structural configuration and composition. The five major categories include (i) carbon-based nanomaterials such as graphene, carbon nanotubes, and fullerenes; (ii) metal-based nanomaterials including metallic nanoparticles (Ag and Au) and metal oxides (Fe_3O_4 and CeO_2); (iii) polymeric/organic nanomaterials such as liposomes, dendrimers, nanogels and polymeric nanoparticles; (iv) composite/hybrid nanomaterials including nanocomposites, quantum dots, Janus nanoparticles, and core–shell hybrids that integrate multiple materials to achieve multifunctionality (MOFs and MXenes); and (v) biological/bioinspired nanomaterials such as protein-based nanoparticles, DNA nanostructures, and virus-like particles (VLPs) mimicking natural architectures.[14,15]

The key distinction of ENMs lies in their controlled synthesis, morphology, and surface functionalization, which determine aggregation, dissolution, and transformation pathways once released into the environment. However, these features complicate their environmental behavior. Once emitted, ENMs can undergo homoagglomeration, heteroagglomeration, sulfidation, dissolution, or eco-corona formation, processes that influence their mobility, persistence, and bioavailability across air, water, soil, and sediment compartments.[16,17] Specifically, in aquatic environments, the transport

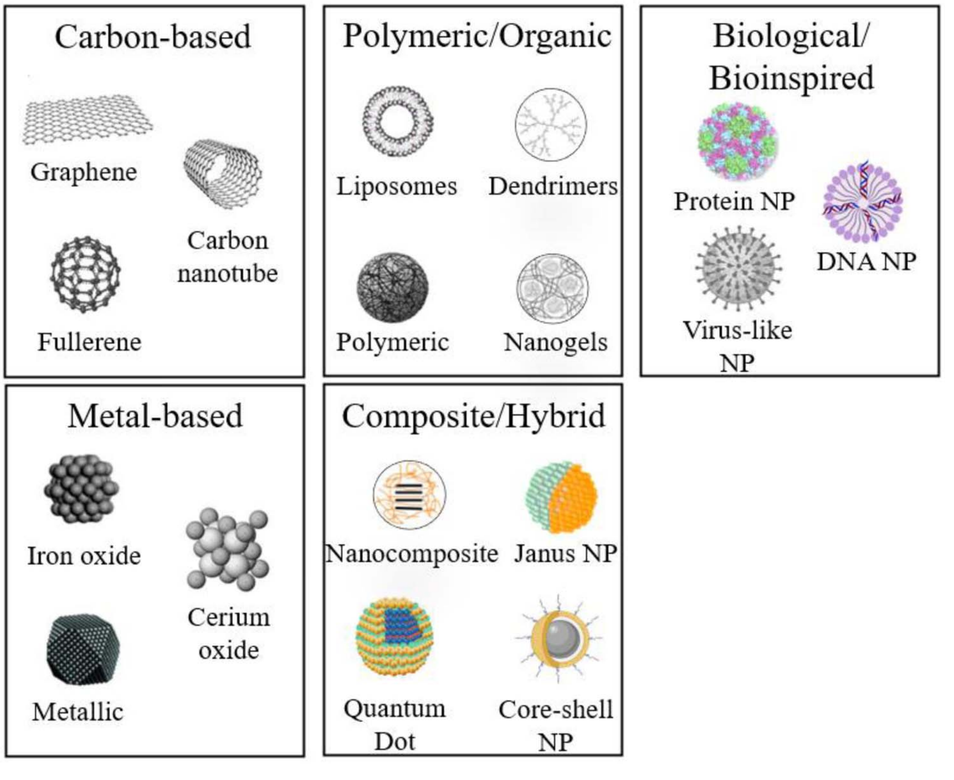

Fig. 1 Classification of nanomaterials into five major categories: carbon-based, metal-based, polymeric/organic, composite/hybrid, and biological/bioinspired nanomaterials.

and transformation processes for nanomaterials include aggregation, dissolution, advection, suspension, deposition, and burial, whereas in soils they involve water erosion, wind erosion, dissolution, runoff, aggregation and advection.[18] Within air environments, the transformation and transport processes encompass attachment, advection, aggregation, dry deposition, and wet deposition.[18] As direct measurements of ENMs in complex environmental matrices remain analytically challenging, predictive modeling of environmental concentrations has become increasingly important for exposure assessment and regulatory evaluation and forms the basis for life-cycle impact assessment (LCIA).[19,20] Analytical detection of ENMs in complex environmental matrices remains challenging.[21] Consequently, *in silico* models such as exposure assessment and environmental fate models have become essential tools for predicting environmental concentrations (PECs) when field measurements are unavailable. These *in silico* models can be broadly classified into (i) material flow analysis (MFA) models that estimate releases as inputs to fate models,[3,17,22–29] (ii) environmental fate models (EFMs) that link those releases into concentrations across environmental media (air, soil, water, sediment) and among species (free/pristine, aggregated/attached, and dissolved/ionic),[30–35] and (iii) spatial river/watershed models (SRWMs) that resolve spatiotemporal variability in hydrology and sediment transport.[21,36] The *SimpleBox4nano* (SB4N) environmental fate model has emerged as one of the most widely used and systematically evaluated frameworks for ENM exposure assessment[32,33] that extends the SimpleBox[37] chemical box-model approach to ENMs by representing three distinct ENM "species" (free/dispersed, hetero-aggregated to small particles, and attached to larger natural particles) and solving coupled first-order mass-balance equations across air, rain, freshwater, soil, and sediment.[32] Despite its strengths, SB4N has limitations as it assumes homogeneous environmental compartments and relies on first principle parameterization (*e.g.*, attachment efficiencies and transformation rates) which are not easily derived, *e.g.* based on laboratory studies with limited environmental representativeness. Moreover, while the dynamic option improves realism in relation to changes in emissions, it lacks spatial resolution and temporal variability of other processes, such as advection. If needed, other models such as nanoFate,[35] which simulates daily hydrometeorological forcing and sub-compartment heterogeneity, could be used. Nevertheless, SimpleBox and SB4N in particular have clear value as screening level multimedia fate models for ENMs making them key models for exposure estimation, uncertainty analysis, and life cycle impact assessment (LCIA).

Although SB4N is scientifically robust, its practical implementation has remained constrained by its dependence on Excel-based operation (https://doi.org/10.5281/zenodo.10671831) or more recently on scripting in R (https://doi.org/10.5281/zenodo.15348882), which limits user friendliness in terms of accessibility, scalability, and visualization capabilities. Running SB4N through Excel spreadsheets requires users to navigate across numerous worksheets, each containing parameter tables, intermediate calculations, and output summaries, making it difficult to visualize the model structure, interpret results holistically, or perform comparative analyses between scenarios and substances. Moreover, the spreadsheet format, with multiple sheets, becomes bulky while the absence of centralized visualization tools further restricts the ability to track model performance and outputs. This further complicates validation, restricts transparency, and limits its usage. In the European Union, SimpleBox forms the multimedia fate core of the European Union System for the Evaluation of Substances (EUSES) model,[38,39] which is used within the 'Chesar' tool under REACH for regulatory chemical risk assessment. However, these implementations focus on conventional chemicals, do not include the ENM-specific SB4N extension, and do not provide flexible, freely accessible use of the model

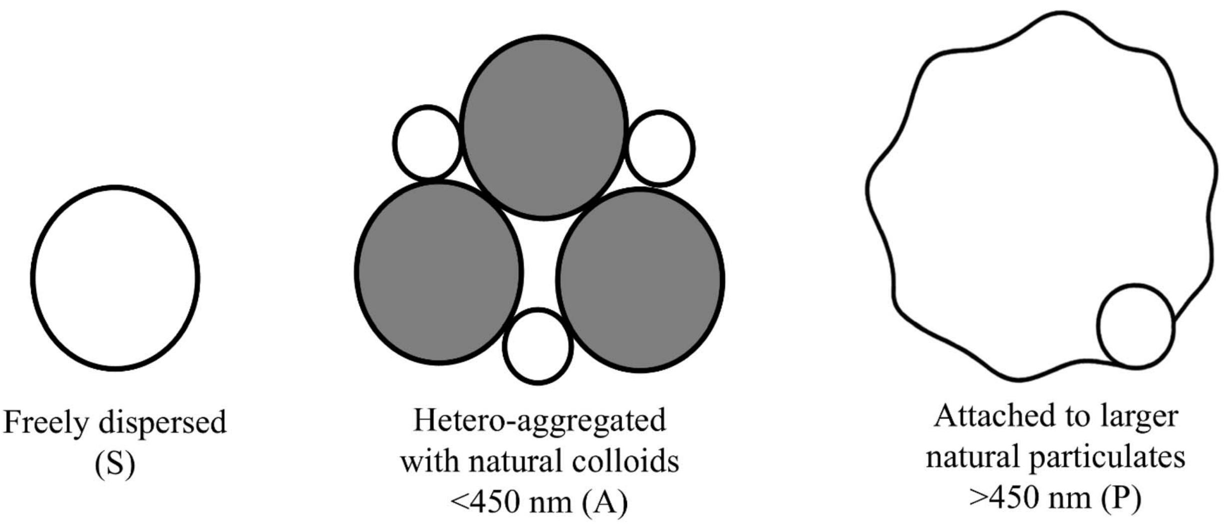

Fig. 2 Classification of ENP species as implemented within the SB4N model.

for broader research applications. On the other hand SimpleBox object oriented (https://doi.org/10.5281/zenodo.15348882) is a more modern implementation of the spreadsheet version, freely available for anyone to use, but requires R scripting knowledge which is a challenge for the average user. To address these challenges, the present work introduces the *SimpleBox4nano* web application, an online implementation, designed to provide an intuitive, interactive, and cloud-based interface for running SB4N simulations. The web application operates within the Enalos Cloud Platform,[40] which already hosts several nanoinformatics web tools, including NanoBioAccumulate,[41] LungDepo,[42] MicroPlasticFate,[43] and SimpleBox4Planet,[44] thereby offering users a unified digital environment for comprehensive environmental and exposure assessment.

The paper is structured as follows: Section 2 presents a brief description of the theoretical foundations of the SB4N model, the development of the web application and the statistical analysis methods used in this work. Section 3 demonstrates the application of the *SimpleBox4nano* web tool through a series of model execution workflows and use case studies that illustrate the core functionalities of the web application including its extensions. Finally, Section 4 presents the conclusions, summarizing the principal findings, emphasizing the advantages of the web-based implementation and outlining perspectives for future developments and integration of additional modelling capabilities.

2 Model principles and web application development

2.1 Model theory

The *SimpleBox4nano* (SB4N) model extends the classical SimpleBox multimedia fate framework to ENMs, to estimate their transport and concentrations across air, rain, surface water, soil, and sediment compartments as described by Meesters *et al.*[32] and is briefly summarized here. This adaptation involves three key extensions to account for nanospecific behavior: (i) SB4N models nonequilibrium colloidal behavior of chemical fate processes, instead of the equilibrium partitioning considered in other SimpleBox versions,[45,46] (ii) transformation between particulate species (such as aggregation) is not interpreted as a removal process, as the transformed material remains in the particulate mass balance as an altered species,[32] and (iii) dissolution into molecular or ionic forms is treated as a true removal pathway in all aqueous sub-compartments (rain, surface water, and pore water).[32] SB4N tracks three distinct ENM species within each compartment. The freely dispersed (S) species represent pristine or homo-aggregated ENMs (<100 nm), whose transport is primarily governed by advection and diffusion.[22] The hetero-aggregated (A) species consist of ENMs bound to natural colloids or organic matter (<450 nm). Finally, the attached (P) species are ENMs bound to larger natural particulates (>450 nm) that are susceptible to gravitational forces in aqueous media. The S and A species are considered to behave as colloids, while the P species are considered to behave as particulate matter. For atmospheric modeling, the air compartment is classified into dry air and rain to capture the specific rates at which airborne particles are collected within raindrops.[32,47] Fig. 2 presents the classification of ENMs as implemented within SB4N.

SB4N solves simultaneous mass-balance equations using first-order kinetics, where the time-dependent evolution of the compartmental masses is described as:

$$\frac{\mathrm{d}\mathbf{m}}{\mathrm{d}t} = \mathbf{Km} + \mathbf{e}$$

where $\mathbf{m}$ (kg) is the compartment mass, $\mathbf{e}$ (kg s^{-1}) is the emission vector and $\mathbf{K}$ (s^{-1}) is the system matrix of first-order rate constants for inter-compartment transport, loss from the system, hetero-aggregation/attachment, and removal process (*e.g.*, dissolution/degradation).[32]

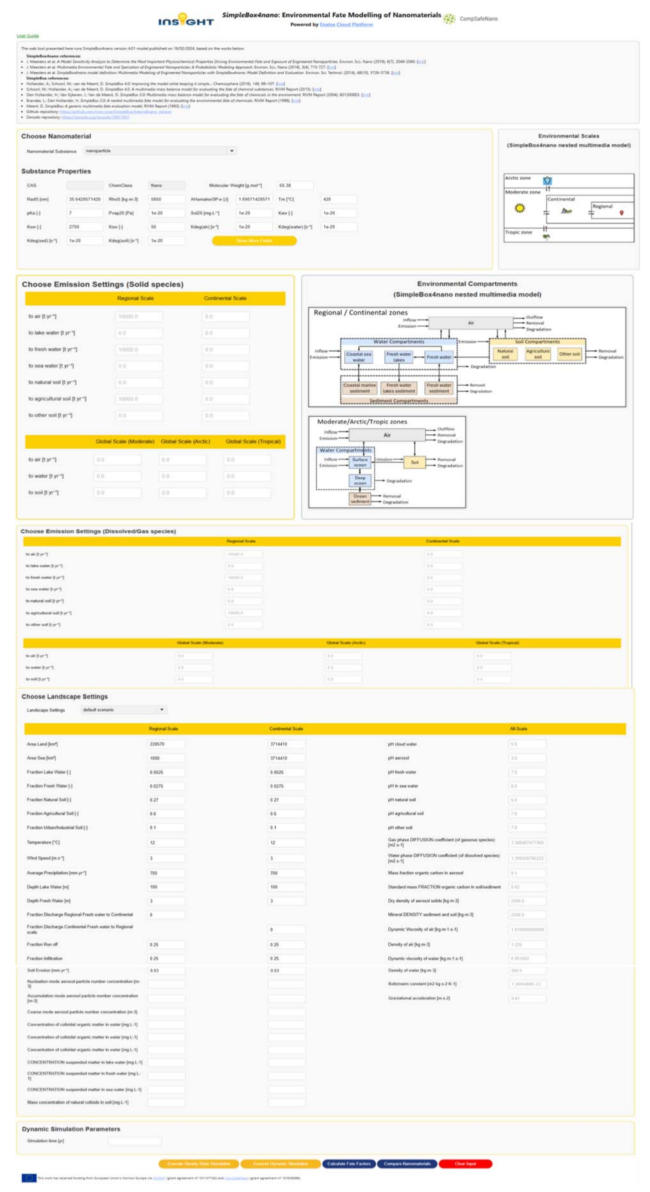

Fig. 3 Graphical user interface (GUI) of the *SimpleBox4nano* web application.

2.2 Web application development

2.2.1 UI/UX implementation. The backend of the *SimpleBox4nano* web application has been programmatically developed in Java for the backend, with the ZK Framework employed for the graphical user interface (GUI) and JavaScript used for dynamic chart rendering and interactivity. Cascading Style Sheets (CSS) and ZK User-Interface Markup Language (ZUL) define the layout and styling to ensure a modern and responsive design. The web application is deployed on the Enalos Cloud Platform and is freely accessible at https://www.enaloscloud.novamechanics.com/insight/simplebox4nano/index.zul. The user interface (UI) of the web application, presented in Fig. 3, has been designed to unify the entire workflow of SB4N (version 4.03, https://doi.org/10.5281/zenodo.10671831) within a single platform. It provides a structured layout that guides the user sequentially from the definition of the ENM and its physicochemical properties, through the configuration of emissions for solid and/or dissolved species, to the specification of the environmental landscape parameters that characterize the modeled system. In addition, the interface allows the user to define the temporal domain for dynamic simulations, specifying the number of years over which the residence time and mass evolution across compartments are to be computed. This design centralizes all model inputs and calculations within an intuitive and responsive web interface offering a unified, efficient, and transparent platform that enhances usability, facilitates parameter control, and enables seamless integration of the model setup, execution, and visualization.

The *SimpleBox4nano* web application provides both curated and fully customizable inputs to balance reproducibility with scenario flexibility. For ENMs, users may select from predefined substances already encoded in the *SimpleBox4nano* Excel spreadsheet (*vs.* 4.03-nano) such as nano-TiO_2, nano-Ag, and nano-ZnO which come with consistent physicochemical defaults and rate parameters retrieved from the literature[32,33,48] or switch to a 'Custom' selection to supply material specific values. Emissions can be specified from the UI directly for solid and/or dissolved species at the desired compartment and scale zone. Landscape configuration follows the same design philosophy: standard scenarios (*e.g.*, the EUSES[38] regional setup) are available for rapid, harmonized assessments, while

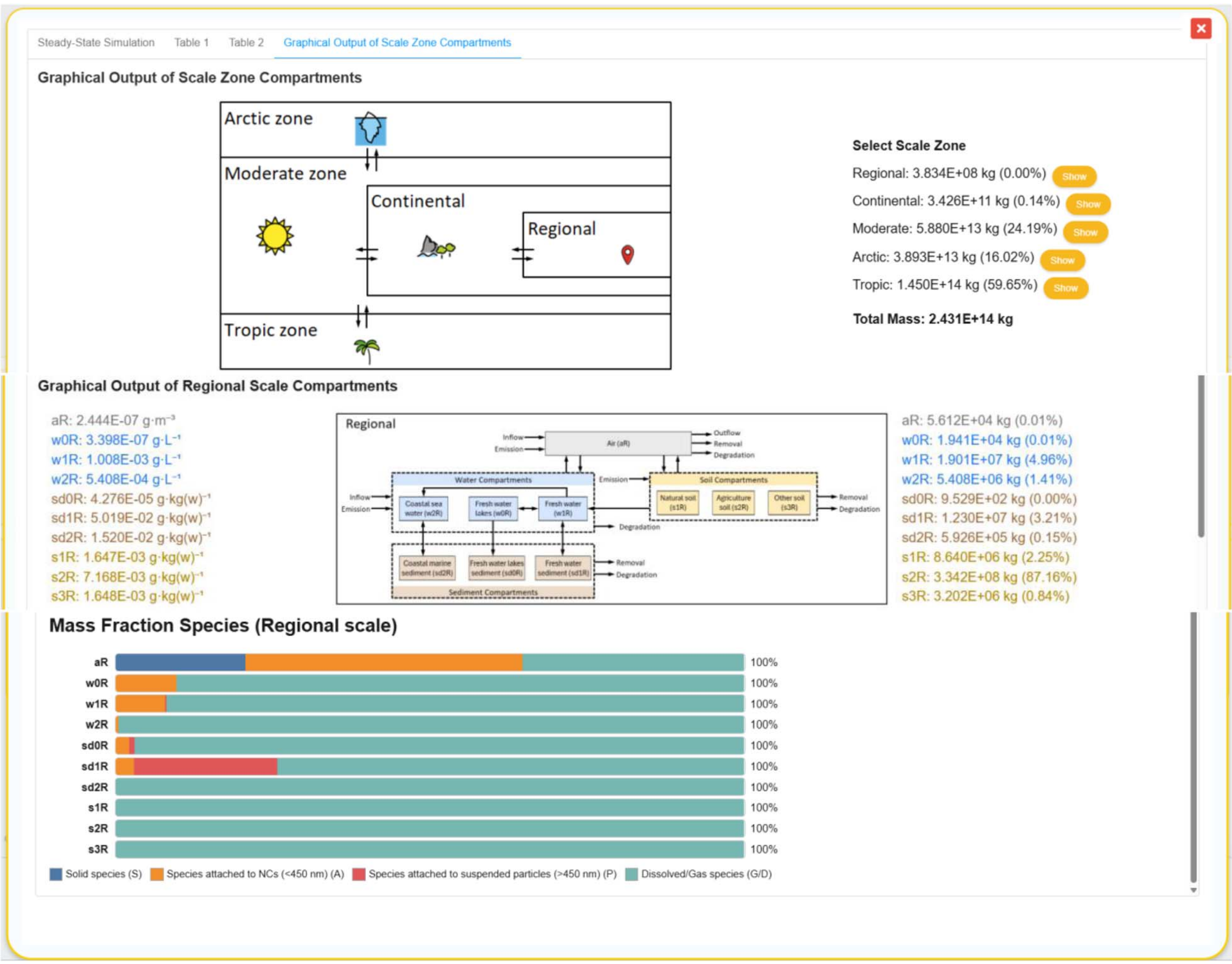

Fig. 4 Graphical output of the *SimpleBox4nano* web application showing the steady-state mass and concentration distributions and mass fraction species across environmental compartments for a selected scale zone (regional, continental, moderate, arctic and tropic) after selecting the 'Execute Steady-State Simulation' button shown in Fig. 3.

all environmental descriptors remain editable by the user directly from the UI or through a 'Custom' selection. Notably, for user-defined custom scenarios temporary session files are created to execute simulations and are automatically deleted upon page refresh or session termination. No long-term retention or cross-user access to custom input data is implemented in the current cloud deployment, supporting transparent and responsible data handling aligned with United Nations Sustainable Development Goal 16 (SDG 16). In addition, the UI design, through clearly sectioned layouts, consistent labelling, and visual cues such as colour-coded groupings and input validation, implements good practice in scientific modelling workflows by guiding users through a logical and transparent parameterization process. This user experience (UX)-oriented design reduces cognitive load, discourages inconsistent input configurations, and facilitates efficient scenario definition and rerunning, thereby supporting more robust, reproducible, and user-consistent model applications.

2.2.2 Steady-state simulations. Once the ENM, emission, and landscape parameters have been defined, the user can use the 'Execute Steady-State Simulation' button to compute compartmental masses, concentrations, and fugacities at steady-state, displayed in both tabular and graphical forms. As shown in Fig. 4, the total mass across scale zones (regional, continental, moderate, arctic and tropic) is graphically presented along with the mass fractions of the modeled species, classified as solid species (S), hetero-aggregated species attached to natural colloids (<450 nm) (A), species attached to suspended particles (>450 nm) (P), and dissolved/gaseous species (G/D). The complete output windows generated after selecting the 'Execute Steady-State Simulation' button are provided in Section S4 of the SI, while detailed quality checks for assessing accuracy and reliability of the steady-state calculations are presented in Sections S1 and S2 of the SI.

2.2.3 Dynamic simulations. To capture transient accumulation and decay, the *SimpleBox4nano* web implementation employs a two-phase dynamic simulation: (i) a build-up phase under constant emissions and (ii) a decay phase where emissions are set to zero. Integration is performed numerically using an implicit (backward) Euler scheme on a uniform time grid Δt (years):

$$\mathbf{m}_{k+1} = (\mathbf{I} - \Delta t\mathbf{K})^{-1}(\mathbf{m}_k + \Delta t\mathbf{e})$$

where $\mathbf{I}$ is the identity matrix that ensures dimensional consistency of the discrete-time operator. This formulation ensures numerical stability for stiff systems and preserves the non-negativity of masses. The solver is implemented in Java using Apache Commons Math ODE libraries.

Once the user specifies the simulation time (in years) within the interface (see Fig. 3) and selects the 'Execute Dynamic Simulation' option, the application produces a plot of the normalized mass evolution ($m(t)/m_{\text{steady-state}}$) over time, as shown in Fig. 5. The resulting curves display two distinct phases: a build-up phase under constant emissions and a decay phase where emissions are set to zero, both computed for each environmental compartment. The example shown in Fig. 5 corresponds to the regional scale, illustrating the temporal dynamics of ENM accumulation and removal. This functionality enables users to visualize and interpret the time required for an ENM to approach steady-state conditions, thereby offering insight into the timescales of environmental accumulation and potential long-term persistence within each compartment. Similarly to the steady-state validation, a thorough comparison

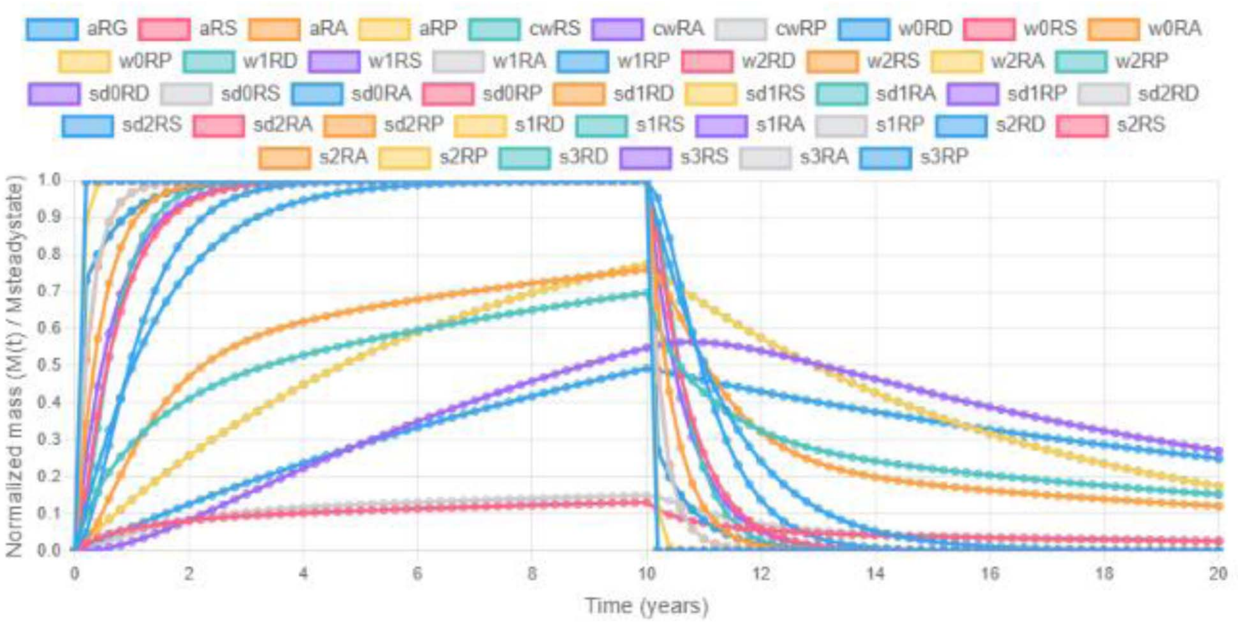

Fig. 5 Normalized dynamic simulation results ($m(t)/m_{\text{steady-state}}$) of the *SimpleBox4nano* web application for the regional scale zone, showing the time evolution of mass accumulation and decay across environmental compartments. Each curve represents a compartment-specific species.

was conducted to verify the accuracy and reliability of the dynamic simulation implementation in the web application. The results, presented in Section S3 of the SI, compare the time-resolved outputs from the web application with those generated by the original Dynamic R-shell implementation, showing excellent agreement between the two, as expected. The complete graphical output window produced upon selecting 'Execute Dynamic Simulation' from the user interface is presented in Section S5 of the SI.

The *SimpleBox4nano* web application also integrates the computation of the Fate Factor (FF)[49] as shown in Fig. 3, which represents the cumulative environmental residence time of a substance per unit emission. For each compartment j, the FF is obtained by integrating the time-dependent mass $m_j(t)$ as shown below:

$$FF_j = \frac{1}{e_{\text{tot}}}\int_0^{\infty} m_j(t)\mathrm{d}t = \frac{1}{e_{\text{tot}}}\left[-\mathbf{K}^{-1}e\right]_j$$

where $e_{\text{tot}} = \sum_i e_i$ is the total emission rate (kg s^{-1}). Within the web application, the integration is defined by the user rather than being fixed to infinity. This enables the assessment of time-limited or scenario-specific fate factors by truncating the integral at a finite simulation time T:

$$FF_j(T) \approx \frac{1}{e_{\text{tot}}}\int_0^{T} m_j(t)\mathrm{d}t = \frac{1}{e_{\text{tot}}}\sum_K m_j(t_k)\Delta t$$

where T is the user-defined time (years) and Δt is the simulation time step. This flexibility allows the user to analyze short-, medium-, or long-term accumulation and persistence of ENMs in specific environmental compartments, without the assumption of full equilibrium. The FF expresses how long a unit mass of a released substance remains in the environment and how it is distributed among compartments before removal. High FF values indicate prolonged residence or slow removal, implying stronger environmental persistence or delayed recovery following emission cessation. In contrast, low FF values correspond to rapid dissipation or efficient removal mechanisms (*e.g.*, sedimentation, dissolution, or degradation).[49] It is important to note that in order to perform the FF calculation, the user must specify a single emission input in one compartment only within the continental scale. An error message is automatically displayed if multiple emission sources or incompatible compartments are selected. The complete graphical output window, including the input panel where users can specify the simulation duration and the corresponding FF results expressed in days for each receiving compartment within the continental scale, is provided in Section S6 of the SI.

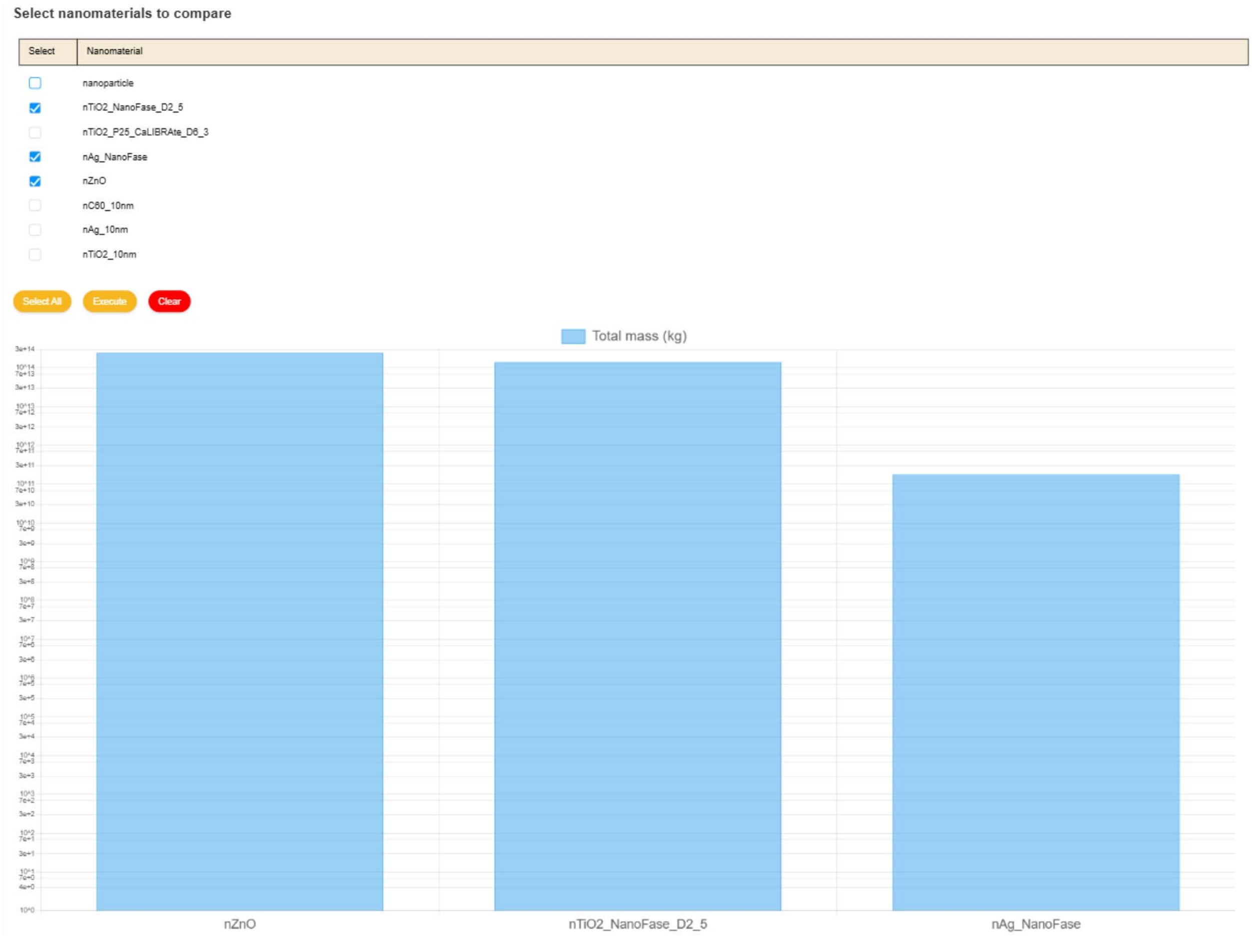

Fig. 6 Comparative output of the *SimpleBox4nano* web application showing the total steady-state mass distributions across environmental compartments for selected ENMs under identical emission and landscape conditions.

2.2.4 Comparative analysis. To facilitate comparative analysis among ENMs, the *SimpleBox4nano* web application incorporates a dedicated comparison function, accessible through the 'Comparison Nanomaterials' button in the interface (see Fig. 3). This feature enables users to directly compare the total environmental mass accumulated or distributed across compartments for multiple ENMs under identical emission and landscape conditions already defined within the user interface. As illustrated in Fig. 6, the resulting output presents the comparative results as total mass (kg) for each selected ENM across the modeled environmental scales. This functionality not only enhances interpretability but also supports sensitivity-type analyses, allowing users to explore how intrinsic physicochemical differences such as particle size, density, or dissolution rate translate into distinct environmental distributions. Such side-by-side visualization of outcomes promotes transparent evaluation of ENM-specific behaviors and can assist in identifying ENMs or nanoforms that exhibit higher persistence or potential for compartmental accumulation under comparable exposure scenarios.

2.2.5 Sensitivity exploration. In addition, the *SimpleBox4nano* web application integrates a 'Sensitivity Exploration' functionality (button) that enables the systematic evaluation of multiple input scenarios by varying 13 physicochemical properties while keeping emission and landscape settings fixed as defined in the UI. For each scenario, steady-state masses (kg) are computed for the modeled species and reported by form: solid (S), hetero-aggregated to natural colloids (<450 nm) (A), attached to suspended particles (>450 nm) (P), and dissolved/gaseous (G/D). Scenarios can be entered manually or imported *via* a CSV file, allowing exploration of the ENM radius, density, acid dissociation constant, melting temperature, partitioning properties (K_{aw}, K_{ow}, K_{sw}, P_{vap} and Sol), Hamaker constant, kinetic parameters (transformation, degradation and dissolution constants) and attachment efficiency. The Sensitivity Exploration window is shown in Fig. 7. The output can be downloaded in Excel format. This functionality enables structured sensitivity screening and comparative assessment of how key ENM physicochemical assumptions influence the total mass of species, thereby supporting evidence-based prioritization of material properties relevant to Safe-and-Sustainable-by-Design (SSbD) development of new ENMs.

2.2.6 Application programming interface (API) configuration. The *SimpleBox4nano* web application also implements a RESTful API to enable programmatic communication, data interoperability, and large-scale automation across computational tools. The API provides a POST endpoint (https://enaloscloud.novamechanics.com/insight/apis/simplebox4nano/results/), which accepts JSON-formatted requests containing the ENM properties and emission configurations and returns structured simulation results, including steady-state masses, concentrations and fugacities. Two GET endpoints, https://enaloscloud.novamechanics.com/insight/apis/simplebox4nano/substance and https://enaloscloud.novamechanics.com/insight/apis/simplebox4nano/scenarios, are implemented to retrieve the predefined ENM library and landscape settings, respectively. Swagger/OpenAPI documentation is available *via* the Enalos Cloud Swagger user interface (UI) (https://enaloscloud.novamechanics.com/insight/swagger-ui/index.html#/) using the OpenAPI specification (https://enaloscloud.novamechanics.com/insight/apis/swagger.json). API access does not require specific user registration, and no rate limits are applied. This communication protocol allows seamless data exchange between the *SimpleBox4nano* web application and other web-based modeling services. The functionality and validation of the POST and GET endpoints are demonstrated in Section S7 of the SI.

From a broader perspective the web tool presented here can take a critical position as a bridge between nanospecific

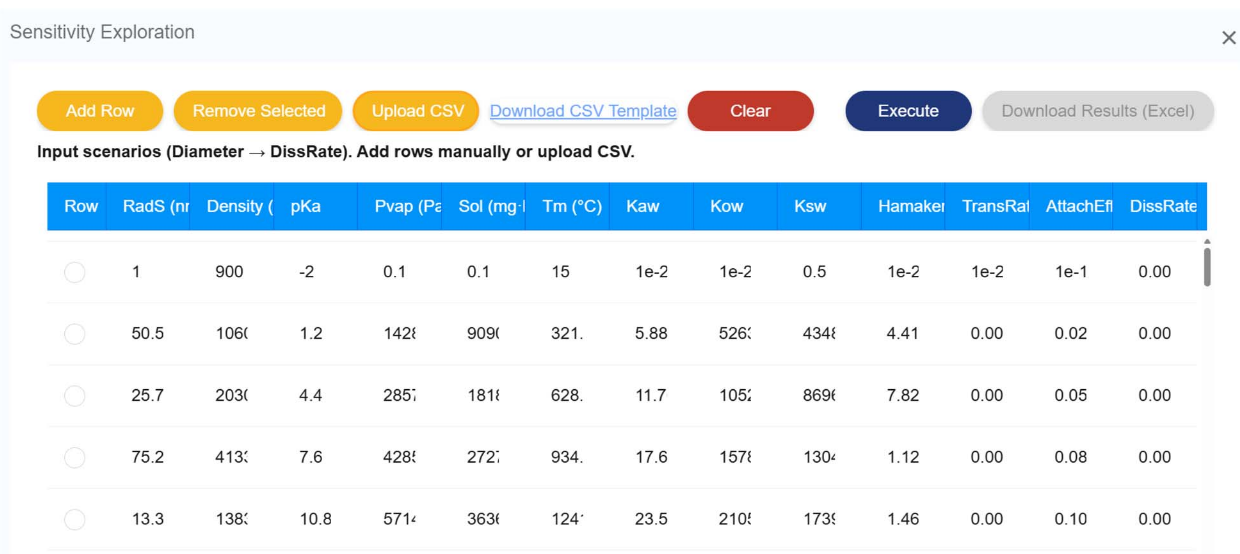

Fig. 7 Sensitivity exploration interface of the *SimpleBox4nano* web application, illustrating the definition of multiple input scenarios through variation of physicochemical properties.

environmental fate modeling and broader sustainability evaluation systems. Its standardized and interoperable architecture allows direct integration with Life Cycle Impact Assessment (LCIA) workflows, supporting the quantitative linkage between emissions, environmental fate, and potential impacts. From a policy and regulatory standpoint, this alignment is particularly significant, as the SimpleBox model family already serves as the multimedia fate module of EUSES and constitutes a cornerstone of EU REACH's chemical safety and exposure assessment.[37]

The *SimpleBox4nano* web application is freely accessible and requires no prior programming experience or theoretical background, enabling regulators, researchers, and industry professionals to perform advanced environmental modeling through an intuitive graphical interface. This open-access, no-code design reflects the overarching philosophy of the INSIGHT project (funded under the Horizon Europe programme) which aims to promote the digitalization, accessibility, and interoperability of nanosafety data and modeling infrastructures. Importantly, *SimpleBox4nano* supports the principles of SSbD by providing quantitative metrics that enable early-stage identification of ENMs with lower environmental persistence or reduced exposure potential providing an evidence-based, predictive component to the SSbD decision-making process, linking mechanistic environmental fate modeling with sustainability-by-design strategies. The web application presented here also exemplifies a Findable, Accessible, Interoperable, and Reusable (FAIR)-by-design digital tool in environmental and nanosafety informatics. Its REST-based architecture ensures that all data products and model results are fully aligned with the FAIR principles,[50] thereby advancing open, transparent, and reproducible environmental modeling.

A concise comparative feature table is provided in Table 1, summarizing the key capabilities of the original Excel implementation (*vs.* 4.03-nano), the scripting-based (such as R-shell) implementation and the new web application. The comparison includes steady-state visualization, quasi-dynamic modeling, automated Fate Factor (FF) calculation, API interoperability, multi-material comparison functionality, and high-throughput sensitivity exploration within the SSbD framework, thereby clarifying the functional advances and interoperability improvements introduced by the web-based deployment. In addition, Table 1 explicitly contrasts practical aspects related to accessibility and deployment (web-based access without local installation), required user expertise (no programming required), and workflow reproducibility (guided and standardized UI-driven execution).

2.3 Statistical analysis

The statistical analyses presented in Section 3 make use of multiple input scenarios generated by varying the 13 ENM physicochemical properties within the 'Sensitivity Exploration' functionality. Scenario sets were constructed using a Halton sequence sampling design, and the relative importance of the 13 ENM physicochemical properties was quantified using Pareto-based factor importance ranking. All statistical analyses were performed using the Isalos Analytics Platform.[51,52]

2.3.1 Halton design. A Halton sequence-based sampling design was employed to explore the 13-dimensional ENM physicochemical parameter space across 10 000 input scenarios. A Halton sequence is a deterministic low-discrepancy (quasi-random) sequence defined for a given dimension d using mutually prime bases $b_1, b_2, \ldots, b_d$. For a given index n, the d-dimensional Halton point $\mathbf{h}_n$ is constructed as

$$\mathbf{h}_n = (\phi_{b_1}(n), \phi_{b_2}(n), \ldots\phi_{b_d}(n))$$

where $\phi_b(n)$ is the radical inverse function in base b, defined as

$$\phi_b(n) = \sum_{k=0}^{\infty} a_k b^{-(k=1)}$$

with $n = \sum_{k=0}^{\infty} a_k b^k$ representing the base-b expansion of n. Each quasi-random point was subsequently scaled to the predefined

Table 1 Comparative summary of the functional capabilities and usability features of the Excel (v4.03-nano), the scripting-based, and the web-based (Enalos Cloud) implementations of *SimpleBox4nano*

Feature	Excel version implementation of *SimpleBox4nano* (v4.03-nano)	Scripting-based implementation	Web application implementation of *SimpleBox4nano* (Enalos Cloud)
Steady-state mass calculations	✓	✓	✓
Graphical visualization of results	Limited/manual	Limited/manual	✓ Interactive, integrated UI plots
Quasi-dynamic simulations	✓ (requires additional scripting for automation)	✓	✓ (Integrated, no external scripting required)
Automated Fate Factor (FF) calculation	Limited/manual	Limited/manual	✓
API access for interoperability	✗	✗	RESTful API (POST + GET endpoints)
User-friendly GUI input handling	Limited (spreadsheet-based)	✗	✓
Multi-material comparison feature	Limited/manual	Limited/manual	✓
High-throughput sensitivity exploration (13 physicochemical properties)	Limited/manual	Limited/manual	✓
Accessibility/deployment	Local file (desktop)	Local scripts (desktop/HPC)	Web-based (online access *via* a browser)
No coding expertise required	Partial (basic spreadsheet skills)	✗	✓
Reproducible workflow/guided UI	Limited (user-dependent)	Limited (user-dependent)	✓ Guided workflow with standardized inputs/outputs

lower and upper bounds of the corresponding physicochemical property.

A Halton sequence was selected instead of classical Monte Carlo sampling because quasi-random designs provide significantly more uniform coverage of high-dimensional parameter spaces and achieve faster convergence rates with fewer sample points.[53] Unlike Monte Carlo, which produces clustered random draws, Halton sequences dramatically improve uniform coverage of the 13-dimensional parameter space, capture nonlinearities and interactions more efficiently, reduce noise in regression models, improve the stability of environmental fate predictions and avoid oversampling requirements inherent to Monte-Carlo.[54]

2.3.2 Pareto-based importance ranking. To identify which ENM properties and property combinations most strongly influence the steady-state model outputs, a Pareto analysis was performed using the Isalos Analytics Platform. The approach is grounded in the Pareto (80/20) principle, which states that approximately 80% of the variability in a system response can often be attributed to around 20% of the input factors. For each output response Y (*e.g.*, total mass of S-, A- and P species), a second-order regression model was fitted to the results from the 10 000 Halton-sampled scenarios:

$$Y = \beta_0 + \sum_{i=1}^{p} \beta_i X_i + \sum_{i=1}^{p} \beta_{ii} X_i^2 + \sum_{i=1}^{p-1} \sum_{j=i+1}^{p} \beta_{ij} X_i X_j + \varepsilon$$

where $p = 13$ denotes the number of ENM physicochemical properties, X_i are the (coded or normalized) inputs, β_i are main-effect coefficients, β_{ii} are quadratic (curvature) coefficients, β_{ij} are two-factor interaction coefficients for all unique pairs $i < j$, and ε is the residual error term. For each effect k (main, quadratic, or interaction), the estimated coefficient $\widehat{\beta}_k$ and its standard error $\mathrm{SE}(\widehat{\beta}_k)$ were obtained from the fitted model. The standardized effect used for Pareto ranking was the absolute t-statistic:

$$E_k = |t_k| = \left| \frac{\widehat{\beta}_k}{\mathrm{SE}\left(\widehat{\beta}_k\right)} \right|$$

The Pareto plots presented in Section 3 display the ENM physicochemical properties on the y-axis and their corresponding standardized effect magnitudes on the x-axis. A reference threshold line corresponding to a critical t-value is superimposed:

$$E_k \geq t_{a/2,v}$$

where $t_{a/2,v}$ is the two-sided critical value of the t-distribution at significance level a and v degrees of freedom. Effects exceeding this threshold are interpreted as statistically influential within the explored parameter ranges, while effects below the threshold are considered secondary contributors under the same modelling assumptions. Overall, this second-order Pareto framework provides a computationally efficient and interpretable way to rank the relative importance of ENM physicochemical drivers, potential nonlinearities and pairwise interactions.

3 Results and discussion

Within this section, several modelling scenarios and case studies are presented to showcase and critically evaluate the robustness and capabilities of the *SimpleBox4nano* web-tool developed herein. The objective here is not to draw new scientific conclusions from the simulated outputs, but to illustrate how the current web app implementation can be applied in practice and what type of scenario can be explored using the web-based workflow developed. Section 3.1 presents the environmental fate of one of the default ENMs available in *SimpleBox4nano*, quantifying its distribution across environmental compartments under three solid-species emission scenarios to air, water, and soil in the moderate (global-scale) zone, and FF calculations over a 100-year horizon for three solid-species emission scenarios at the continental scale (emission to continental air, continental seawater, and continental natural soil). Although the *SimpleBox4nano* web-tool supports emissions modelled as either dissolved or solid species, all the analyses presented here in this section are restricted to solid-species emissions. This focus is adopted because explicit solid-species treatment represents a key extension introduced by the SB4N model relative to the original SimpleBox framework which considers emissions only as dissolved species and which has already been implemented as a web-tool through *SimpleBox4-Planet*.[44] Section 3.2 examines the robustness of the web implementation through a global sensitivity analysis using a 10 000 point Halton design, demonstrating high-throughput execution of 10 000 scenarios and quantifying the influence and statistical significance of 13 key ENM physicochemical properties on the environmental fate of the default ENM available in *SimpleBox4nano*, using the total mass of solids (S + A + P) as the response under three solid-species emission scenarios to air, water, and soil in the moderate (global-scale) zone. All simulations are conducted using the default landscape configuration available in *SimpleBox4nano*.

3.1 Environmental fate modeling of an ENM

Under the three (pristine) solid-species emission scenarios (1000 t year^{-1} released to a single compartment of the moderate-zone/global scale, *i.e.*, air, surface water, or soil), a highly consistent large-scale fate pattern is obtained (Fig. 8 for air emission; Fig. S14 for water emission; Fig. S16 for soil emission), with the chosen emission magnitude being representative of high-volume ENMs for which global production has been estimated to be on the order of 10^3–10^5 t year^{-1} and annual environmental releases are typically in the hundreds to thousands of tonnes, depending on pathways.[26,55] In all three cases, the steady-state mass is predicted to be dominated by the tropical zone (∼60%), followed by the moderate zone (∼24%) and the arctic zone (∼16%), while the continental and regional contributions remain negligible, indicating that, for a fixed emission in the moderate (global) zone, the long-term

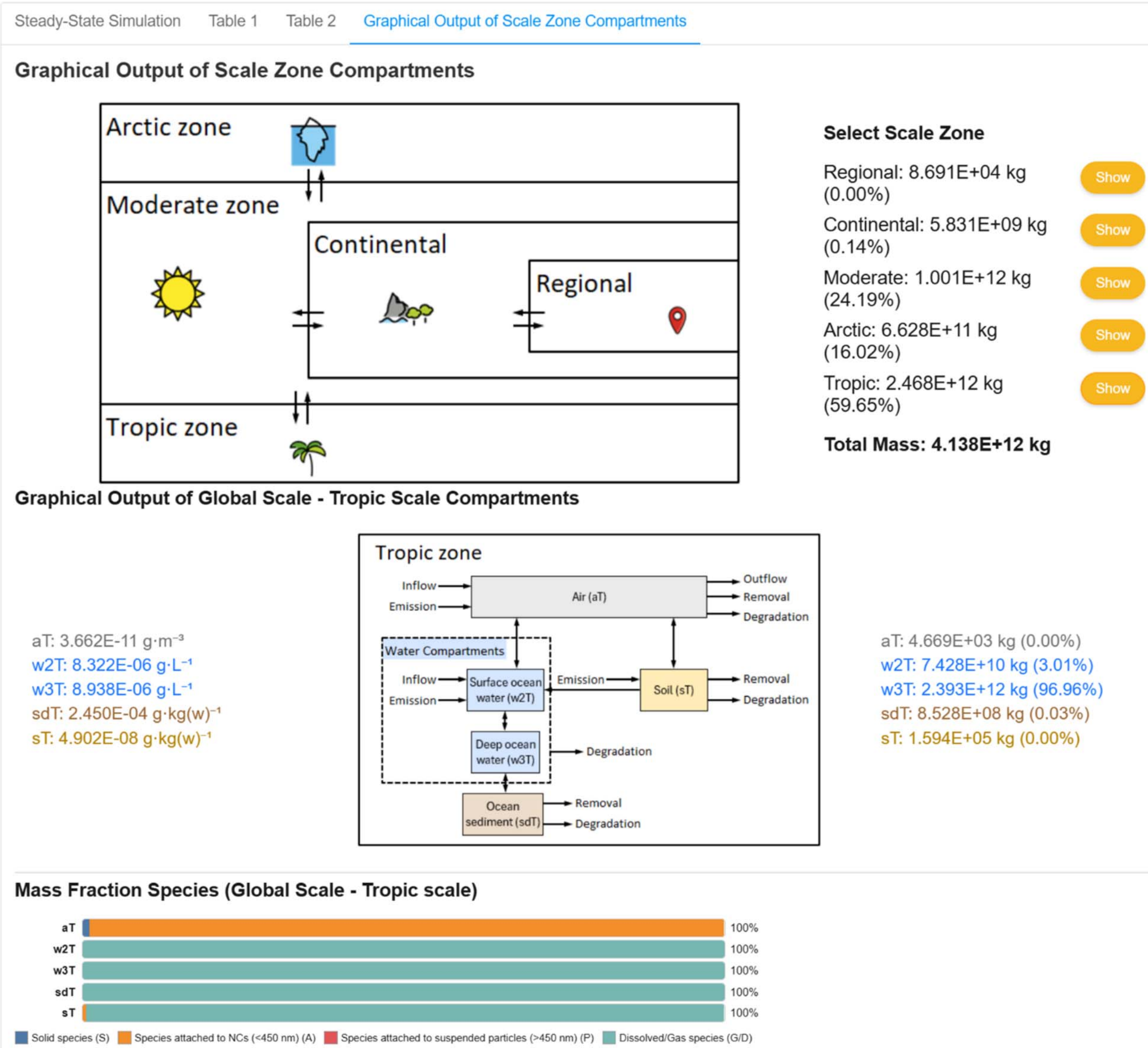

Fig. 8 Graphical output of the steady-state mass of ENM as generated from the *SimpleBox4nano* web application per scale zone for solid-species emission to air (1000 t year^{-1}) applied in the moderate (global-scale) zone. The figure reports (top) the steady-state mass distribution across scale zones, (middle) the corresponding mass distribution among tropic-zone compartments (aT, w2T, w3T, sdT, and sT) together with the associated compartmental concentrations, and (bottom) the mass fraction of species (S, A, P, and G/D) at the tropical scale.

distribution is largely insensitive to whether the ENM is initially released to air, water, or soil and is instead governed by large-scale interzonal transport and mixing. Consistently, within the tropical zone the ENM burden is concentrated in the oceanic water compartments, with the deep ocean water (w3T) retaining the overwhelming fraction of mass (~96.96%) and surface ocean water (w2T) contributing ~3.01%, whereas ocean sediment (sdT) remains minor (~0.03%) and the tropic air/soil compartments are negligible in terms of total mass (Fig. 8, S14 and S16). This behavior is consistent with earlier multimedia environmental fate modeling studies, which also reported deep-ocean-dominated burdens for slowly degrading substances and ENMs.[33,44,56,57] Importantly, the mass-fraction species panels (Fig. 8, S14 and S16) reveal that, in the tropical air compartment (aT), hetero-aggregated forms (A) constitute the dominant fraction in all three solid-emission scenarios, with the contribution of freely dispersed solids (S) being highest for the case where solids are emitted to the moderate-zone soil compartment. By contrast, the water and sediment compartments are predicted to be sustained almost entirely in the dissolved/gas species (G/D), implying that, regardless of whether pristine solids are initially released to air, water, or soil, the atmospheric burden remains largely solid-associated, while the global steady-state mass is nevertheless driven towards the ocean, where dissolution and subsequent partitioning dominate.

The Fate Factor (FF, days) is next computed for the default ENM (available in the *SimpleBox4nano* web application) to evaluate how the emission compartment at the continental scale modulates where mass is retained over the 100-year horizon, as shown in Fig. 9 (solid-species emission to

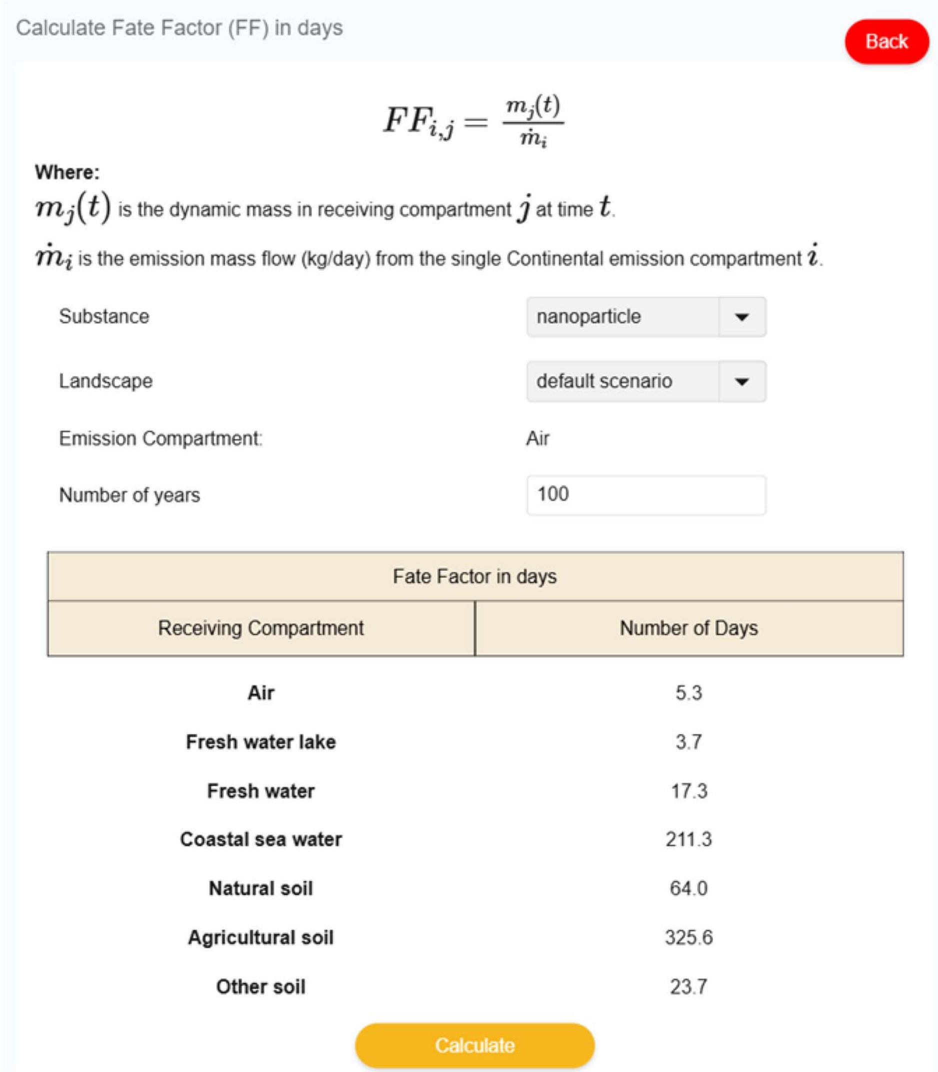

Fig. 9 Fate factor (FF, days) graphical output generated using the *SimpleBox4nano* web application for the default ENM, calculated over a 100-year simulation horizon for solid-species emission to continental air (1000 t year^{-1}). The interface reports the compartment-specific FFs (in days) for receiving compartments (air, freshwater lake, freshwater, coastal seawater, natural soil, agricultural soil, and other soil).

continental air), Fig. S15 (solid-species emission to continental seawater), and Fig. S17 (solid-species emission to continental natural soil). For solid-species emissions (1000 t year^{-1}) to the air continental compartment non-zero FFs are obtained in all receiving media, indicating efficient transfer from the atmosphere to both waters and soils: the longest residence time is predicted in agricultural soil (325.6 days) and coastal seawater (211.3 days), with smaller yet non-negligible values in natural soil (64.0 days), freshwater (17.3 days), other soil (23.7 days) and a comparatively short atmospheric residence time (air 5.3 days), pointing to rapid deposition and cross-compartment redistribution. In contrast, for solid-species emissions (1000 t year^{-1}) directly to the coastal seawater continental compartment, the FF is essentially confined to that compartment (437.8 days) with all other compartments reported as 0.0 days at the given precision, implying that the solid material, once introduced into seawater, remains largely in the marine environment over the modelled period. For solid-species emissions to the natural soil continental compartment, the largest FF is obtained in natural soil (2311.8 days), indicating very long persistence in the emission compartment, while non-zero FFs in freshwater (155.8 days) and coastal seawater (424.6 days) show that a fraction of the emitted solids is exported to aquatic systems *via* runoff/leaching (Fig. 9). These observations are consistent with SB4N-USEtox FF analysis of nano-TiO_2 conducted by Salieri *et al.*,[58] who reported the highest persistence for soil emissions ($FF_{s,s} = 2.9 \times 10^5$ days), intermediate persistence for water emissions ($FF_{w,w} = 128$ days), and a short atmospheric residence time ($FF_{a,a} = 3.3$ days). Overall, these results confirm that air emissions are characterised by short atmospheric residence time but the broadest cross-media redistribution, sea-water emissions exhibit intermediate residence times that remain strongly localised in the marine compartment, and soil emissions are dominated by very long-term retention in soil with secondary contributions to fresh and coastal waters.

Table 2 Lower and upper bounds of the 13 ENM physicochemical parameters used to define the multidimensional design space for the simulations conducted using the *SimpleBox4nano* web application

Radius primary ENMs (nm)	Density (kg m^{-3})	pK_a (−)	P_{vap} (Pa)	Sol (mg L^{-1})	T_m (°C)	K_{aw} (−)	K_{ow} (−)	K_{sw} (−)	Hamaker constant (J)	Transformation rates (s^{-1})	Attachment efficiency (−)	Dissolution rates (s^{-1})
1	900	−2	0.1	0.1	15	1×10^{-20}	1×10^{-20}	0.5	1×10^{-21}	1×10^{-20}	1×10^{-10}	1×10^{-6}
100	30 000	14	1 000 000	1 000 000	4000	100	10 000 000	100 000	1×10^{-19}	0.001	1	0.001

3.2 Sensitivity exploration of ENM properties

The *SimpleBox4nano* web application is next used to explore how ENM properties control environmental fate. A multidimensional design space is defined for 13 key ENM (physicochemical) parameters, as shown in Table 2. As discussed in Section 2, the SB4N model extends the conventional SimpleBox framework[37] to describe speciation, hetero-aggregation, dissolution and transformation of ENMs across environmental compartments.[32,33,48] The lower and upper bounds are selected to span the properties of a broad set of realistic ENMs and their molecular or ionic transformation products. These include metal oxides such as TiO_2, ZnO and CeO_2, silver and iron nanoparticles, carbon nanotubes, fullerenes, and polymeric nanomaterials.[17,23,24,59] A detailed justification for the selected parameter ranges is provided in Section 9 of the SI, based on literature data. A Halton design (Section 2.3.1) is applied using the Isalos Analytics Platform to generate 10 000 design points that systematically sample combinations within the range of each of the 13 ENM physicochemical properties in Table 2, enabling screening of nonlinear responses and potential interaction structures. The 'Sensitivity Exploration' feature of the *SimpleBox4nano* web tool is then used to execute 10 000 steady-state simulations and generate the corresponding outputs for the modelled species (S, A, P and G/D). The 10 000 scenarios are imported *via* a CSV (Comma-Separated Values) file within ∼2–3 seconds, while execution of a 10 000-scenario batch on the cloud platform required on average ∼8–9 minutes to complete, demonstrating the computational efficiency of the implementation and its practical suitability for high-throughput scenario and sensitivity analyses. This workflow is repeated for three solid-emission scenarios of 1000 t $year^{-1}$ released to the air, water, or soil compartment, respectively in the moderate-zone (global scale), resulting in a total of 30 000 simulations.

Section S10 of the SI presents scatter plots of the total mass of each modelled species from the 10 000 simulations for the three different emission scenarios. Fitted second-order polynomial curves are included to provide an initial visual indication of nonlinear trends. However, since scatter plots alone do not quantify parameter influence, standardized main effects, two-factor interactions, and quadratic terms are computed using the Isalos Analytics Platform through Pareto plots (Section 2.3.2), which rank the relative contribution of each physicochemical parameter to the variability in the model outputs. The D-species are not discussed, since all three scenarios consider only solid-species emissions with no direct release of dissolved or gaseous forms. In addition, as shown by the Pareto plots in Section S11 of the SI, none of the 13 ENM physicochemical parameters exceeds the statistical significance for the D-species under any of the three emission scenarios.

The Pareto analysis for solid-species emissions of 1000 t $year^{-1}$ to the air compartment of the moderate (global-scale) zone (Fig. 10) shows that the variability in the total solid-associated mass (S + A + P) is controlled by only a small subset of the 13 ENM physicochemical parameters. In the main-effects Pareto chart, the standardized effects of transfer rate

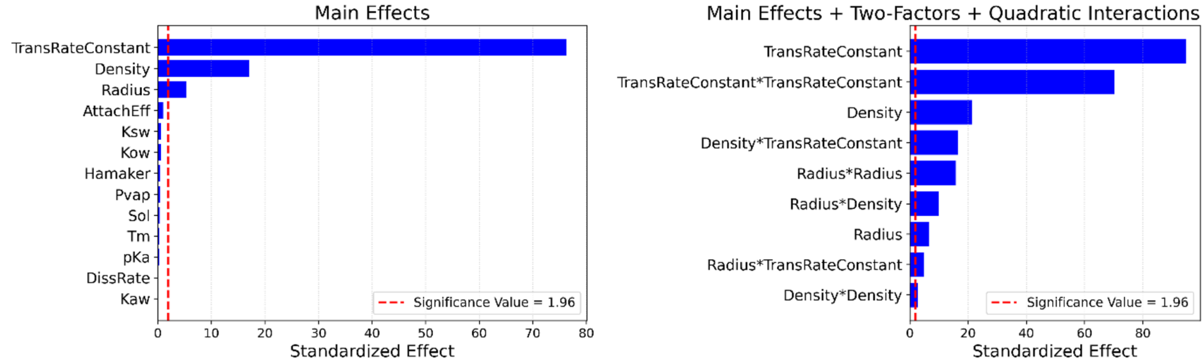

Fig. 10 Pareto charts of standardized effects for the total solid-associated mass (S + A + P) under a solid-species emission of 1000 t year^{-1} to the air compartment of the moderate (global scale) zone. Left: the main-effects Pareto chart for all 13 ENM physicochemical parameters. Right: Pareto chart including main, two-factor interaction, and quadratic terms for the three influential ENM properties observed in the left chart. The vertical red dashed line in both charts denotes the statistical significance threshold.

constant, density, and radius clearly exceed the significance threshold, while all remaining parameters (including the Hamaker constant, attachment efficiency, partition coefficients, solubility, vapour pressure, pK_a, and dissolution rate) lie well below it. The Pareto chart including main effects, two-factor interaction, and quadratic terms for these three influential properties, reveals that the dominant contribution arises from the main effect of transfer rate constant, followed by its quadratic term and then the main effect of density. Additional, smaller but still significant contributions arise from the quadratic terms of radius and density and from interaction terms such as radius × density and density × transfer rate

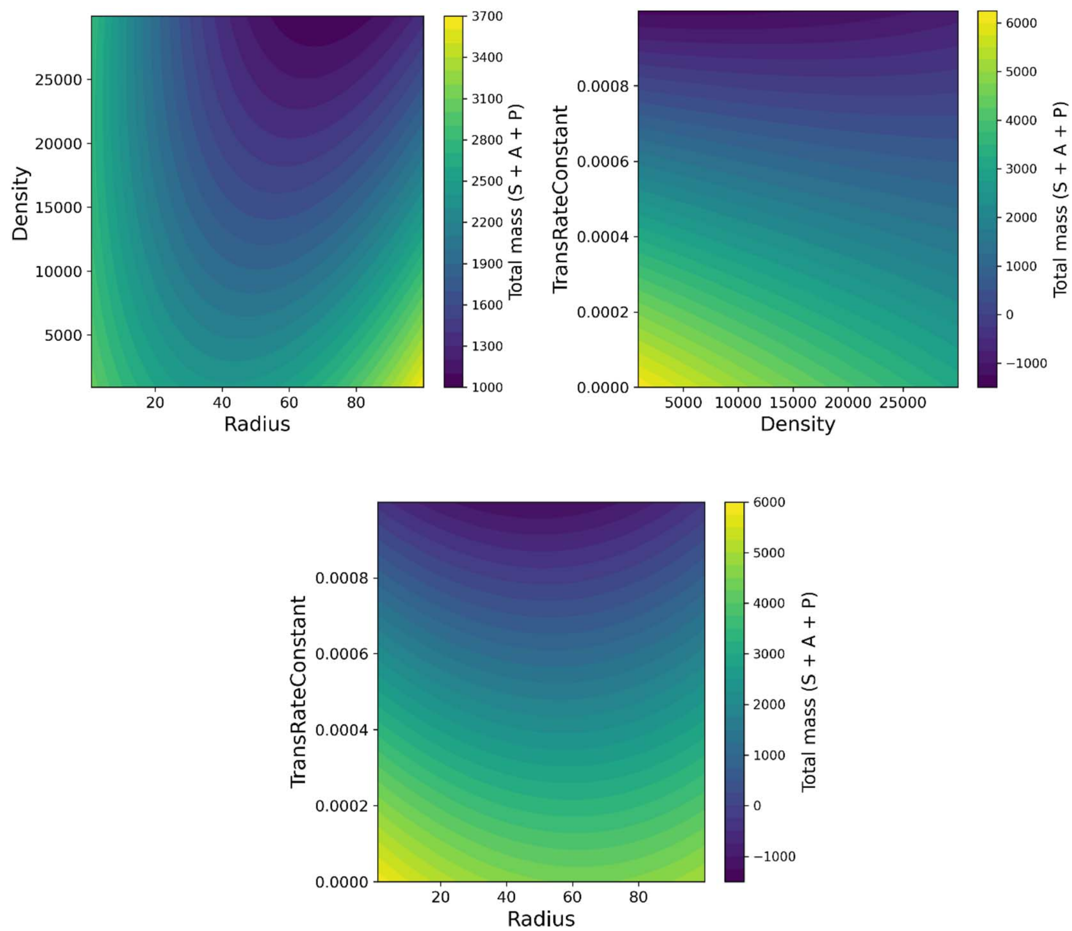

Fig. 11 Two-factor response surfaces (heat maps) of the predicted total solid-associated mass (S + A + P) for the default ENM under a solid-species emission of 1000 t year^{-1} to the air compartment of the moderate (global-scale) zone. The colour scale indicates the steady-state total mass of S + A + P (kg), with cooler colours (blues) corresponding to lower values.

constant. To further investigate the combined influence of the three key properties, two-factor response surfaces were constructed from the fitted second-order model (Fig. 11). The heat map for radius × density shows a clear non-linear pattern, with the lowest total solid mass (S + A + P) occurring at intermediate radii and high densities, whereas large, low-density ENMs yield the highest burdens. The density-transfer rate constant surface is almost planar, indicating that increasing both density and transformation rate monotonically decreases the total solid mass, consistent with faster transfer out of the particulate pools. In the radius × transfer rate constant plot, the response again exhibits curvature in radius but a strong monotonic decrease with increasing transformation rate, suggesting that, within the explored ranges, fast-transforming ENMs of intermediate size are associated with the smallest S + A + P burden.

Section S12 of the SI presents the corresponding Pareto and response-surface analyses for solid-species emissions of 1000 t year^{-1} ENMs into the soil and water compartments of the moderate (global) zone. For the soil emission scenario, the main-effects Pareto chart shows that only the dissolution rate and transfer rate constant exceed the significance threshold, indicating that the total solid-associated mass (S + A + P) is controlled almost entirely by the balance between dissolution and transformation, with all other ENM physicochemical parameters playing a negligible role. The Pareto chart including main effects, two-factor interaction, and quadratic terms for these three influential properties confirms that their linear and quadratic terms dominate and that interaction effects are comparatively minor. In contrast, for the water emission scenario the response is governed by a richer set of drivers: the dissolution rate is by far the most influential parameter, followed by the transfer rate constant, and then radius and attachment efficiency, with several quadratic and interaction terms contributing significantly to the variance. The associated heat maps for the water scenario reveal strongly non-linear response surfaces: low total S + A + P masses are obtained for combinations of a high dissolution rate with low attachment efficiency, for intermediate radii at a high dissolution rate or high transfer rate constant, and for simultaneously a large dissolution rate and transfer rate constant, whereas slowly dissolving, highly attaching, large ENMs yield the highest burdens in water. Overall, across all three emission scenarios, the sensitivity patterns consistently indicate that modifying a small set of ENM properties, primarily the dissolution rate, transformation (transfer) rate constant, particle size and density, and, for direct water releases, attachment efficiency, provides clear SSbD design levers for reducing the steady-state particulate load (S + A + P) in the environment. These findings are consistent with those of previous studies, which identified dissolution, transformation, size-related properties and attachment/aggregation behaviour as the dominant controls on ENM fate and speciation.[32,33,48,56,58]

4 Conclusion

The development of the *SimpleBox4nano* web application presented in this work provides a user-friendly, cloud-based (hosted on the Enalos Cloud Platform, accessible at https://www.enaloscloud.novamechanics.com/insight/simplebox4nano/index.zul) alternative to the original Excel implementation of the SB4N multimedia fate model. By integrating all model inputs, computations and visualisations within a single graphical interface, the web implementation removes much of the fragmentation, limited scalability and cell-level manipulation that are intrinsic to spreadsheet workflows, while preserving full compatibility with the SB4N model definition and parameterisation. Relative to the Excel version, which is restricted to steady-state calculations, the web application explicitly integrates quasi-dynamic simulations for time-resolved fate, a Fate Factor module, an ENM-comparison feature, and a sensitivity-exploration mode that can execute thousands of simulations by systematically varying ENM physicochemical properties and exposes these capabilities *via* a no-code user interface and RESTful APIs. All inputs and outputs are defined on a single, well-structured page, supported by clearly sectioned layouts, consistent labelling, colour-coded groupings and input validation, which implement good practice in scientific modelling workflows by guiding users through a transparent parameterisation process and reducing opportunities for inconsistent configurations. This User Experience (UX)-oriented and FAIR-by-design implementation lowers the entry barrier for regulators, researchers and industry users and provides a robust digital backbone for ENM-specific exposure assessment and SSbD decision support.

The case studies conducted in this work using the *SimpleBox4nano* web application collectively demonstrated that, for realistic high-volume releases of pristine solid ENMs (1000 t year^{-1}) to air, water or soil in the moderate (global) zone, an ocean-dominated ultimate fate is observed, with the tropical deep ocean (w3T) acting as the principal global sink and surface ocean water (w2T) contributing only a few percent of the total mass, while continental and regional zones retain negligible ENM fractions. The speciation outputs revealed that near-field behaviour remains strongly compartment dependent, with the tropical air compartment (aT) exhibiting an appreciable solid-associated species load (dominated by hetero-aggregates) whereas oceanic water and sediment contain almost entirely the dissolved/gas (D) species. FF analyses over a 100-year horizon further showed that solid-species emissions to continental air generate the broadest cross-media redistribution (with non-zero FFs in all receiving compartments and the longest residence time in agricultural soils and coastal seawater), whereas emissions directly to coastal seawater produce FFs essentially confined to the marine compartment with intermediate residence times, and emissions to natural soil are dominated by very long residence times in the emitting soil, with secondary contributions to fresh and coastal waters. Finally, the global sensitivity and response-surface analyses based on 30 000 simulations indicated that only a small subset of ENM physicochemical properties, primarily the transformation (transfer) rate constant, dissolution rate, particle size and density, and, for direct water releases, attachment efficiency, control the variability in the total solid-associated mass (S + A + P), with other parameters making negligible contributions within the tested ranges. The fitted second-order models highlighted pronounced non-linear and interaction effects and suggested ENM-property regions (*e.g.*, high dissolution and transformation rates, intermediate radii, and reduced attachment efficiencies) that minimise the steady-state particulate burden. These findings show that the *SimpleBox4nano* web application can move beyond single-scenario fate predictions to support property-based optimisation of ENMs and provide directly usable structure-fate insights for SSbD strategies aimed at reducing environmental solid-phase ENM loads without compromising functionality.

The *SimpleBox4nano* web application provides a strong foundation for future expansion and development towards fully integrated LCIA workflows. Future integration will include the implementation of effect factor (EF) calculations for ecotoxicity and human toxicity, enabling direct computation of characterisation factors (CFs) and complete impact assessment within the same web environment. This will be achieved through an integrated species sensitivity distribution (SSD) module supported by curated ecotoxicity datasets for freshwater, marine, and terrestrial species, from which effect (hazard) concentrations (*e.g.*, E C_{20} or E C_{50}) will be derived to enable EF and, subsequently, CF and impact score calculations. Such an extension will build on earlier work in which SB4N outputs were harmonised with USEtox.[58,60] The novel SimpleBox Object Oriented version in R could be coupled with the web app allowing for easily including improvements and updates of the original model in a user friendly way. In addition, coupling these environmental fate models with automated ENM property-prediction workflows (*e.g.*, QSAR/QSPR, machine learning and quantum-chemical calculations) would further streamline parameterisation and enhance predictive power. Collectively, these future developments would transform *SimpleBox4nano* into a next-generation, FAIR-compliant environmental fate and impact modelling ecosystem capable of supporting regulatory evaluation, design of SSbD materials development, and comprehensive life-cycle assessments across diverse classes of particulate pollutants.

Author contributions

Conceptualization, D. M. and A. A.; methodology, D. M; software, D. M, S. K., and A. T.; supervision, G. M, J. Q., J. M., I. L, and A. A.; writing-original draft preparation, D. M.; writing-review and editing, D. M., S. K., P. K., A. T., G. M., J. Q., J. M., I. L., and A. A; funding acquisition, I. L. and A. A.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information (SI). Supplementary information: providing a comprehensive analysis of the outcomes generated by using the *SimpleBox4nano* web-tool. See DOI: https://doi.org/10.1039/d6su00092d.

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