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ENVESOME: The Environmental Exposome and Health

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Abstract

ENVESOME addresses the impact of air pollution, noise, light, and hazardous waste on non-communicable diseases through the development of an integrative exposome framework. The project combines advanced human biomonitoring and new approach methodologies (NAMs) (in vitro systems, multi-omics, computational toxicology) to elucidate adverse outcome pathways (AOPs) linking complex pollutant mixtures to disease. We collect detailed external exposure data (ambient sensors, wearables, remote sensing) and biological measurements (genomics, epigenomics, proteomics, metabolomics, cytokine panels) in population cohorts and experimental models. A physiologically based biokinetic (PBBK) modelling platform combined with Bayesian inversion methods links external exposures to internal doses and back-calculates realistic in vitro test concentrations via quantitative in vitro–in vivo extrapolation (QIVIVE). Machine learning and advanced statistics map high-dimensional omics signatures onto health endpoints and derive exposure–effect dose-response relationships (Benchmark Doses). Parallel in vitro studies (human cell/organoid models of liver, brain, immune, cardiac, respiratory systems) characterize mechanistic toxicity pathways for real-life chemical mixtures. These mechanistic insights and omics-based biomarkers are integrated with socio-behavioral data (agent-based models of activity patterns, socioeconomic context) to account for vulnerability. The project conducts interventional case studies in Urban and Waste contexts: co-designing and testing exposure-reduction strategies (e.g. traffic mitigation, green infrastructure, waste management) via Urban Living Labs with stakeholders. Continuous exposure and health monitoring (wearables, questionnaires, biomarkers) evaluate intervention efficacy. Finally, project findings are translated into practical tools. These include updated exposure limit values derived from pathway-based dose–response analysis; a city-scale Decision Support System (DSS) for policy simulation that integrates air quality, noise, light, and waste exposure models with population data; a user-focused mobile application (for education, exposure tracking, and health coaching) with an integrated chatbot to communicate risks and promote healthy behaviors; and a fuzzy-logic risk stratification engine that combines multifactorial data for personalized prevention. Overall, ENVESOME employs a systems-level exposome approach that merges detailed exposure assessment, multi-omics profiling, computational modeling, and stakeholder engagement to uncover causal links between environmental stressors and health across the life course. It delivers targeted, science-driven interventions for public health protection.

1 INTRODUCTION

Human health is shaped by complex mixtures of environmental stressors rather than isolated pollutants. Individuals are exposed to combinations of chemicals (including ultrafine particles, black carbon, emerging contaminants) and non-chemical factors (noise, artificial light, psychosocial stress) that vary across space, time and social context [1]. Traditional single-pollutant assessments fail to capture these real-life scenarios, prompting a shift to the exposome paradigm – the totality of exposures over the life course [2, 3]. The exposome approach seeks to link external exposures with internal biological responses through longitudinal monitoring and molecular profiling (Rappaport et al., 2014). In practice, this requires harmonizing longitudinal exposure and health data, wearable sensors, and high-throughput

omics analyses (genomics, epigenomics, transcriptomics, proteomics, metabolomics) to reveal cumulative and synergistic effects [4, 5].

However, integrating such diverse data streams poses major challenges. Modern sensors (wearables, IoT) can provide high-resolution air pollution, noise and light measurements [6], but fusing these with geographical and temporal models remains difficult due to gaps and biases [7, 8]. Similarly, moving from measured exposures to biological impact requires internal biomarkers; classical single-analyte biomarkers (e.g. blood lead) often miss interactive effects of mixtures [9]. Multi-omics profiling can capture broad pathway perturbations under exposure [10], but the resulting data are complex and demand advanced analytics [11]. Machine learning and statistical techniques are increasingly applied to reveal patterns and dose–response relationships in omics data [5]. Organizing these findings under mechanistic frameworks is aided by Adverse Outcome Pathway (AOP) models, which link molecular initiating events to higher-level key events and endpoints [12]. AOPs provide a scaffold for interpreting how mixtures of pollutants trigger disease pathways, but require sophisticated computational tools to handle heterogeneous datasets and interactions [13].

Socioeconomic factors further modulate exposures and health. Lower income, education, or housing quality often correlate with higher pollution burdens and reduced resilience [14]. Agent-based models of individual behaviors and demographics can simulate how daily activities and built environments shape personal exposures [15, 16]. Including these social determinants is essential to design equitable interventions.

Regulatory standards still largely focus on single agents and generic thresholds. However, there is growing recognition that exposure limit values should incorporate mechanistic dose–response evidence and account for mixture toxicity [17]. Policymakers also require agile tools, such as decision-support systems and mobile platforms, to integrate the latest science with local data [18]. While advances in artificial intelligence and data science (e.g. natural language processing and semantic knowledge graphs) offer new ways to synthesize large bodies of literature and data [19], these tools must remain transparent and firmly grounded in domain expertise [20].

ENVESOME is explicitly designed to meet these challenges by integrating cutting-edge exposomic methods, multi-omics technologies, and computational toxicology within co-created Urban Living Labs. By merging multi-scale exposure data with mechanistic toxicological insights, the project aims to generate robust evidence of how complex environmental mixtures cause disease and to translate this knowledge into targeted policies and interventions. In doing so, ENVESOME bridges research and application, advancing a systems-based framework for environmental health protection.

2 ENVESOME methodology

2.1 Key methodological elements

ENVESOME's methodological framework spans three linked pillars: (a) comprehensive exposure assessment and internal effect modeling, (b) application in intervention case studies, and (c) translation into policy tools (guidelines, DSS, apps), as illustrated in Fig. 1.

The approach harmonizes **external exposome** measurements (environmental monitoring, sensors, models) with **internal exposome** data (biomonitoring, omics) and computational analysis to establish exposure–health linkages.

- **Cohort data**: The validity of the ENVESOME methodology relies on its application to diverse human populations. The project leverages a massive repository of data from existing cohorts while establishing new, targeted case studies to test interventions. The project harmonizes data from over 12 legacy cohorts, creating a pan-European database of exposure and health profiles. The key existing cohorts integrated into ENVESOME are presented in Table 1.
- **Integrated Exposure Assessment**: We compile the best available environmental and personal data (from EU cohorts and new measurements) and utilize the INTEGRA multimedia model. INTEGRA, an integrated multimedia exposure model, combines fixed-site air monitoring data, remote sensing outputs, and personal sensor measurements (wearable air pollution monitors, the NoiseCapture app for noise, and the CloudClip device for personal light exposure) to reconstruct individual exposure profiles under real-life conditions. A particle deposition model (MPPD) is used to estimate the lung retention of ultrafine particles and aeroallergens. In addition, an agent-based simulation incorporates socioeconomic factors (e.g. housing conditions and commuting patterns) into individualized exposure scenarios to reflect real-world behavior. In parallel, a physiologically based biokinetic (PBBK) model links external exposure concentrations to internal tissue doses (including a multi-compartment brain model for the central nervous system). Bayesian data-fusion techniques (e.g., Markov Chain Monte Carlo simulations) integrate monitoring records, model outputs, and longitudinal trends (e.g., socioeconomic datasets) to infer lifetime multi-stressor exposures while handling data gaps. To identify internal exposure biomarkers, ENVESOME employs non-targeted and suspect screening of biospecimens using high-resolution mass spectrometry (LC-QTOF-MS and GC-QTOF-MS), which can reveal both known and novel compounds in blood or urine. Key exposure biomarkers are then quantified with validated targeted assays. Network analysis of co-exposure profiles is also performed to detect common pollutant combinations in individuals. This holistic pipeline links external measurements, internal biomonitoring data [21], and personal behavior information to build comprehensive "exposure fingerprints" that can be associated with health outcomes. Network analysis of co-exposure profiles is also performed to detect common pollutant combinations in individuals [22]. This holistic pipeline links external measurements, internal biomonitoring data [23], and personal behavior information [16] to build comprehensive "exposure fingerprints" that can be associated with health outcomes [24].
- **Multi-Omics Analysis**: We apply layered omics on cohort and in vitro samples to reveal molecular responses to exposures. Key components include:

- *Epigenomics*: Genome-wide DNA methylation (850K CpG beadchip) and microRNA profiling from extracellular vesicles. Top differentially methylated sites and EV-miRNAs are statistically associated with exposure metrics and health indicators, then validated by targeted sequencing or qPCR.
- *Transcriptomics*: RNA sequencing (Ion AmpliSeq NGS) quantifies gene expression shifts, including alternative splicing. Standard pipelines (edgeR, DESeq2) normalize and identify differentially expressed genes; pathway enrichment (GSEA, Bioinfominer) highlights impacted biological processes.
- *Proteomics*: Label-free, data-independent acquisition LC–MS^n runs (DIA-NN analysis) quantify global proteome changes. Peptides are filtered by false discovery rate; candidate protein biomarkers are validated by sensitive targeted assays.
- *Metabolomics*: High-resolution UPLC-QToF-MS (with complementary GC–MS or NMR) captures small-molecule changes in biofluids and cell media. Multiple chromatographic/ionization methods detect diverse metabolite classes. Metabolites are identified via databases and standards. Both targeted and untargeted analyses (including gut-microbiome metabolites) elucidate disrupted metabolic pathways.
- *Cytokines*: Multiplex immunoassays (Luminex xMAP) measure panels of inflammatory and immune markers (up to 80 analytes). Generalized linear models (adjusted for covariates) test for exposure-related differences; bioinformatics links cytokine patterns to immunotoxic and cardiometabolic pathways.

Table 1
Key existing cohorts integrated into ENVESOME

Cohort Name	Country	Focus Area	Key Biomonitoring Data	Sample Size (Approx.)
HEALS-EXHES	GR, ES, SI, PL	General Exposome (Pregnancy/Childhood)	Phthalates, Metals, Phenols	~ 1,750 (Mothers/Children)
URBANOME	GR, SI, DK, IT, ES	Urban Health & Wellbeing	Sensor-based exposure, Mental health	~ 1,000+
CROME	GR, SI, IT, ES	Chemical Exposome (Southern EU)	HBM (Children, Teens, Adults)	600
REPRO_PL	Poland	Longitudinal Mother-Child Health	Phthalates, Heavy Metals, Cotinine	~ 1,200 (Phase I)
HERACLES	Greece	Waste Management Impact	Metals, Plasticizers, Dioxins	~ 350 Children
ECHOES	Spain	Petrochemical Exposure	Silicone Wristbands (PAHs, PCBs)	~ 218 Children
INMA	Spain	Birth Cohort (Env. Factors)	Organochlorines, Metals, Pesticides	~ 3,000+
B4FOX	Portugal	Occupational (Firefighters)	Smoke toxicants, Stress markers	Not Specified
EDIA-N-Cog	Greece	Neurodegeneration Registry	Clinical markers (Dementia)	Registry-based
CDDA	Greece	Cognitive Disorders Database	Neuropsychological profiles	~ 2,000 Patients

These omics layers are integrated using custom bioinformatics workflows. Single-omics results (per tissue and matrix) feed into computational models and multi-view analyses. Functional annotation and network analysis (e.g. qAOP construction) map how exposure-altered genes/proteins/metabolites relate to adverse outcomes. Benchmark dose (BMD) modeling on omics endpoints links molecular perturbation to risk levels. This convergent multi-omics strategy identifies biomarkers and early warning signatures of toxicity across multiple health domains, i.e. cardiorespiratory, metabolic, neurological, immunological, sleep-related, and mental health.

- **In Vitro New Approach Methods**: Complementing human data, ENVESOME uses advanced human cell models to dissect mechanisms under controlled exposures. These include:
    - *Liver toxicity*: 2D cultures of HepaRG cells and primary human hepatocytes (PHH) are exposed to suspect chemicals to monitor nuclear receptor activation (LXRα, PXR, etc.), triglyceride accumulation, and viability. We also employ a 3D organotypic EpiLiver™ model to examine long-term exposures (up to 20 days), measuring endpoints such as mitochondrial function, oxidative

stress, and lipid metabolism. Multi-omics analyses (including tRNA sequencing and DNA methylation profiling) in these liver models reveal epigenetic and transcriptional changes associated with the development of steatosis and fibrosis. Outcomes measured include lipid content, cytokine release, fibrosis markers, and single-cell transcriptomics to assign cell-type-specific pathways.

- *Neurotoxicity*: Human iPSC-derived oligodendrocytes, neurons, astrocytes and microglia are cultured to assess developmental and degenerative endpoints. We measure cell viability, expression of neural markers and hormone receptors. A specialized blood–brain barrier (BBB) Transwell model (endothelial cells + astrocytes) tests chemical permeation, barrier integrity (TEER), and effects on neurovascular functions.
- *Immunotoxicity*: THP-1 monocyte-derived macrophages and primary human immune cells (neutrophils, T/B lymphocytes) are used. ELIspot assays and cytokine panels detect immunosuppression or hyperactivation caused by exposures. T-cell proliferation assays and analyses of RACK1/steroid receptor pathways elucidate mechanisms of altered immune response.
- *Cardiotoxicity*: An hERG channel screening flags potential electrophysiological hazards. Human iPSC-derived cardiac spheroids/organoids (cardiomyocytes + support cells) assess effects on beating rate, contractility and tissue integrity.
- *Pulmonary toxicity*: Airway epithelial models (A549 cells in 2D monolayers and 3D air–liquid cultures) examine inflammatory signaling and epithelial barrier disruption after pollutant exposure. We monitor cytokine release, tight junction integrity, and extracellular vesicle content/signaling to immune cells.

These NAMs generate molecular endpoints and dose–response data that feed back into the AOP framework and help anchor omics findings to specific toxicity pathways.

- **Computational Systems Toxicology**: ENVESOME advances a multi-route PBBK model building on prior EU initiatives [25, 26]. The model includes compartments for inhalation, dermal and oral uptake, and subdivided organs (e.g. separate brain regions: cortex, hippocampus, CSF). Metabolism, transporter activity and receptor-binding are parameterized to capture mixture interactions (additive or antagonistic). Bayesian inference ties the generic PBBK model to biomonitoring data [27]: simulated blood/urine levels are matched to measured concentrations to back-calculate probable exposures. Conversely, quantitative in vitro–in vivo extrapolation (QIVIVE) algorithms adjust nominal in vitro concentrations to realistic tissue exposure levels by accounting for protein binding, lipid partitioning, and specific assay conditions [23].

Analytical pipelines then process all omics data: standardized workflows annotate, filter and statistically analyze each omics layer. Toxicogenomics databases provide context for gene–environment interactions [28]. Machine learning techniques (e.g., partial least squares discriminant analysis (PLS-DA) and multi-view autoencoders) are employed to identify latent factors and predictive patterns across

omics datasets. Benchmark dose (BMD) modeling is applied to molecular endpoints to quantify the degree of perturbation at various exposure levels. Systems biology-based AOP models are constructed by linking omics changes, internal dose estimates, and observed endpoints; tools like Biological Expression Language (BEL) graphs are used to visualize these cause–effect chains. The result is an integrated **adverse outcome network (AON)** that connects exposure drivers through key molecular events to clinical phenotypes. This platform enables causal hypotheses and selection of early diagnostic biomarkers (meta-analyses fuse markers into predictive signatures), strengthening mechanistic insight for risk assessment and regulatory decisions.

- **Data Science and AI**: All data are managed under FAIR principles (Findable, Accessible, Interoperable, Reusable). Metadata and selected datasets will be deposited in public repositories (e.g., Zenodo), and a consortium-wide Data Management Plan ensures standardization and compliance with these principles. Semantic ontologies (LinkML, BioPAX) unify diverse data types (chemical, omic, sensor, literature) under common vocabularies. A dynamic knowledge graph connects these datasets, enabling complex queries. Advanced natural language processing (NLP) techniques are employed, using hybrid deep-learning models (large language models such as LLaMA, Mistral, or BioGPT) combined with rule-based methods to extract insights from scientific and regulatory texts. Reinforcement learning with human feedback (RLHF) is used to align the NLP outputs with expert knowledge. This integrated NLP toolkit greatly accelerates literature mining on chemical hazards and risk assessment methods. Together, these approaches produce a searchable, AI-driven knowledge base. A user-friendly chatbot interfaces with this knowledge graph, accepting natural language queries from policymakers and practitioners to quickly retrieve evidence-based guidance.
- **Statistical Analysis (Exposure–Health Associations)**: Rigorous epidemiological models are applied to combined exposure and biomarker data. After quality checks and grouping of compatible data, confounder selection uses both theoretical (causal directed acyclic graphs) and data-driven (subset searches) methods. Bayesian analyses and sensitivity tests quantify uncertainty. Multivariate methods (e.g. principal components, network analysis) reduce dimensionality and highlight correlated exposure–biomarker clusters. Exposome-wide association scans (EWAS) integrate environmental factors, internal dose estimates, and altered pathway signals to clarify how stressors jointly influence disease risk [29]. Survey-weighted logistic and multilevel regressions (adjusted for covariates) estimate associations with health outcomes or intermediate markers. Interpretations apply Bradford-Hill criteria and counterfactual reasoning for causal inference. Cross-validation with in vitro results reinforces mechanistic plausibility. This approach yields robust exposure–effect functions and highlights susceptible subgroups, thereby informing targeted prevention strategies.

2.2 Urban Living Labs and case studies

ENVESOME implements its methodology through **10 Urban Living Labs (ULLs)** across Europe (Athens, Thessaloniki, Ljubljana, Barcelona, Madrid, Porto, Vienna, Berlin, Łódź, Aarhus). Best practices from URBANOME and other EU initiatives were reviewed to design each ULL as a co-creation platform. Each

ULL brings together city authorities, researchers, businesses and community actors (quadruple helix) using participatory protocols that ensure data protection and inclusivity. Context-specific co-creation guidelines address roles, governance, and sustainability of interventions.

A co-design process (Task 12.1) engages stakeholders in defining interventions and metrics. For urban contexts, focus areas include sustainable mobility, green/blue infrastructure, building energy (heating/lighting), teleworking and urban planning – measures expected to simultaneously improve air quality, reduce noise, and enhance wellbeing. In parallel, ULLs in peri-urban/waste regions collaborate with health and waste experts to identify contamination sources; planned actions include optimized waste disposal programs and targeted public education. Workshops with policymakers and citizens validate intervention plans and success criteria, producing qualitative narratives and quantitative key-performance indicators (e.g. pollutant levels, EEB biomarkers).

2.2.1 Case studies

Two pilot case studies apply this framework through the ENVESOME prospective cohorts (intervention studies), presented in Table 2.

- **Urban Environmental Study**: This cohort involves ~ 10,000 city residents (ages 2–80, > 1 year residence) across the ULLs. All participants complete detailed lifestyle and socioeconomic questionnaires. Based on initial risk screening, a sub-cohort of approximately 2,460 ‘high-risk’ individuals (about 246 from each ULL, assuming 10 lab sites) is selected for the intervention phase. Baseline medical exams and biospecimens (blood/urine) are collected, along with personal exposure monitoring (wearables for air, noise, light; stationary sensors) and environmental sampling (ambient air, indoor dust, pollen). Participants are then randomized to intervention (e.g., home retrofits, traffic restrictions) or control. After implementing ULL-specific measures, follow-up assessments repeat all data collection. Wearable apps and sensors continuously capture behavior (location, activity, sleep). Measured biomarkers include indicators of inflammation, oxidative stress, cardiometabolic health, neural activity and sleep function, enabling holistic evaluation of intervention impacts.
- **Hazardous Waste Study**: A community cohort of ~ 500 residents (ages 2–80) living near municipal or industrial waste sites (0.5–12 km distance) participates. Initial surveys and biosampling quantify exposure to heavy metals (As, Cd, Hg, Mn, Pb), plasticizers (e.g., bisphenols and phthalates), and persistent organic pollutants (PCBs, dioxins/furans, and PFAS) from soil, dust, and drinking water. Dietary and proximity data serve as additional exposure indices. Participants are split into control and intervention groups. Follow-up sampling measures the same contaminants along with neurocognitive evaluations: age-appropriate neurological scales (neurodevelopmental, cognitive, motor tests) and neurodegeneration biomarkers. Metabolic and immune biomarkers are tracked to gauge chronic disease risk. Multi-omics analysis of samples links exposure profiles to molecular pathways. Pre- and post-intervention comparisons guide precision prevention strategies specific to each site.

Table 2
ENVESOME prospective cohorts (intervention studies)

Feature	Urban Well (Urban Case Study)	eCO Waste ENVESOME (Waste Case Study)
Geographic Scope	10 Cities (Athens, Thessaloniki, Ljubljana, Barcelona, Madrid, Porto, Vienna, Berlin, Lodz, Aarhus)	4 Locations (Athens, Madrid, Porto, Lodz) near waste sites
Primary Stressors	UFP, BC, Noise, Light, Aeroallergens	Metals (As, Cd, Hg, Pb), Dioxins, PFAS, Plasticizers
Sample Size	Phase I: 10,000 (Screening) Phase II: ~2,460 (Intervention)	~ 500 Individuals (Aged 2–80)
Key Health Outcomes	Cardiorespiratory, Metabolic, Mental Health, Sleep	Neurotoxicity, Immunotoxicity, Metabolic Syndrome
Biomarkers	IgE/IgG (Allergy), IL-6/TNFα (Inflammation), 8-OHdG (Oxidative Stress), BDNF (Neuro)	Heavy metals (Urine/Blood), Serum Lipids, Cytokines
Interventions	Green routing, Active mobility, Indoor air filtration, Urban greening	Dietary antioxidants, Hygiene protocols, Exposure avoidance education

2.2.2 Intervention implementation and evaluation

The co-created interventions are implemented within local governance. The intervention effects are continuously monitored: co-monitoring approaches use environmental sensors and health surveillance to track progress relative to urban plans/regulations. Data collection combines existing health records, targeted questionnaires and interviews to capture social equity impacts. Post-intervention workshops engage communities to discuss outcomes and refine actions. Novel or modified urban plans (e.g. new bike lanes, waste processing changes) are documented as interventions. This participatory evaluation ensures interventions address real needs and fosters long-term adoption beyond the project.

2.3 Limit value derivation

ENVESOME is designed to establish **updated exposure limit values** based on mechanistic evidence. Using in vitro dose-response experiments (from WP7) and multi-omics data (WP5), we perform a pathway-based adverse-response analysis. Key molecular and cellular endpoints are identified via metabolomics, proteomics and transcriptomics across doses and time points. Statistical modeling (DRomics framework) computes Benchmark Dose (BMD) for each pathway perturbation. These BMDs are integrated into quantitative AOP models to define points-of-departure for each hazard category (cardiorespiratory, metabolic, neurotoxic, immunotoxic, etc.). A **biological impact factor** is derived summarizing effect severity. Next, human in vivo kinetics (PBBK) and biomonitoring back-calculation yield protective exposure margins accounting for uncertainty and variability. Resulting reference points translate to environmental concentration limits via the exposure reconstruction model (Task 6.1), aligning with OECD guidance.

For **noise and light**, cohort analyses identify exposure levels associated with early-effect biomarkers or clinical outcomes. Data from the Urban case study (pre/post intervention) inform safe thresholds of sound and illuminance, especially for sensitive groups (e.g. children, night-shift workers). Together, these path-based and population-derived thresholds produce science-driven guidelines surpassing traditional single-exposure standards.

2.4 Decision support and prevention tools

ENVESOME delivers a suite of user-oriented tools for environmental health management (summarized in Table 3):

- **Healthy Cities Toolkit**: Collating evidence from WP9 on health impacts, the toolkit guides urban planners and public health officials in designing interventions. It includes scenario examples and socio-economic considerations (gender, culture) with cost–benefit insights.
- **Mobile Coaching App**: A smartphone app educates citizens on environmental health and healthy lifestyles. It allows users to track personal exposures (via phone sensors and self-report), set health goals (diet, exercise, sleep) and receive tailored advice. Interactive modules provide practical guidance and simulations of “what-if” lifestyle changes on personal risk. The app is designed for accessibility (with special support for vulnerable groups) and includes digital coaching (personalized feedback and progress monitoring).
- **Policy Chatbot**: An AI-driven chatbot assists city administrators and health agencies by answering policy questions in natural language. It synthesizes ENVESOME data and literature to provide evidence-based insights on intervention outcomes and health implications of various actions. The development follows user-centered design, iteratively refined with urban stakeholders.
- **Decision Support System (DSS)**: A modular, open-source DSS platform (for planners and policymakers) integrates city data and models in a WebGIS environment. Components include (a) a guidebook for estimating policy effects in each city context; (b) a geospatial database of collected exposure and health metrics; (c) computational modules for urban air-quality, noise, light, and waste modeling; (d) real-time digital services (e.g. mobility and mental-health indicators from AI analyses). Stakeholders can simulate interventions (e.g. traffic changes, greening) and visualize spatial outcomes (pollution maps, risk hotspots) in real time. The DSS quantifies uncertainty at each step and is customizable to local conditions (regulations, demographics). Stakeholder feedback (via workshops, Delphi) shapes features to ensure practical relevance.
- **Risk Stratification Module**: Central to the project's clinical application is the concept of Multi-Tiered Risk Stratification. The project develops a fuzzy-logic-based AI engine that integrates genetic susceptibility, environmental exposure history, lifestyle factors, and biomarker data to classify individuals into risk categories. This allows for "precise prevention", moving away from one-size-fits-all advice to tailored interventions. For example, a high-risk individual identified by the system might receive specific alerts about air quality days that would not trigger warnings for the general population.

Table 3
Technical toolkit and innovation outputs

Tool	Target User	Functionality
Decision Support System (DSS)	Policymakers / Regulators	Simulation of policy scenarios, Cost-benefit analysis of interventions, GIS-based risk mapping
Healthy Cities Toolkit	Urban Planners / Managers	Best practice guidelines for infrastructure design, Health impact assessment metrics
Coaching Mobile App	Citizens	Personal exposure tracking (via sensors), Behavioral nudging, Gamified health goals
ENVE-Chatbot	Health Practitioners / Citizens	AI-driven Q&A on environmental risks, Access to project Knowledge Graph
Risk Stratification Engine	Clinicians / Public Health	Fuzzy-logic categorization of patients into risk tiers based on exposome and biological data
Updated Limit Values	EU Regulatory Bodies	Proposed thresholds for UFP, Light, and Noise based on mechanistic toxicity thresholds (POD)

3 DISCUSSION

ENVESOME embodies a transformative framework that shifts traditional approaches in environmental health research toward a richer, more integrated vision. Instead of focusing on single pollutants or simplistic associations, it merges detailed external and internal exposure assessment, multi-omics profiling, computational toxicology, and co-creative policy design into a coherent exposome-driven program [30]. In doing so, it unifies mechanistic toxicological evidence [31], Adverse Outcome Pathways (AOPs) [32], and real-life socio-behavioral data [8] in order to understand how multiple stressors interact and ultimately shape human health across the lifespan [33].

A foundational aspect of the project lies in reimagining toxicology under real-world conditions [34]. Conventional toxicological methods often rely on single-chemical tests or endpoint-centric analyses, which may overlook how individuals concurrently encounter chemical, physical, and biological stressors [35]. ENVESOME expands the scope by simultaneously measuring a spectrum of environmental and lifestyle factors, socio-economic determinants, and omics-based biomarkers [36]. Through advanced biomonitoring, multi-tiered in vitro experimentation, and computational modeling, it deciphers how stressors converge to produce biologically significant outcomes that range from subtle pathway disruptions to clinically relevant diseases. By anchoring these processes to physiologically based biokinetic (PBBK) models [37], ENVESOME ensures that in vitro exposure levels meaningfully reflect real human experiences, thus offering an evidence base that more accurately mirrors life-course exposures and vulnerability patterns.

Within this framework, AOPs occupy a central role by tracing the sequence of key molecular events that bridge initial exposure to ultimate disease phenotypes. Rather than simply identifying which toxins correlate with adverse effects, ENVESOME explores how these toxins act, at what molecular targets, and

with which synergistic or antagonistic interactions [38]. Sublethal or early-response endpoints (e.g., epigenetic shifts, changes in nuclear receptor activity, alterations in metabolic flux) become part of the chain of evidence, building a transparent progression from exposure to clinical pathology. The focus on multi-omics data, such as transcriptomics, proteomics, metabolomics, and epigenomics, further enriches this approach [4, 39]. By gathering comprehensive molecular signatures in individuals or in vitro cells exposed to realistic chemical mixtures, ENVESOME pinpoints the sensitive events that underlie the emergence of diseases such as cardiovascular problems, metabolic disorders, immunotoxicity, neurodegenerative conditions, or mental health disturbances. These identified events, when mapped onto AOPs, produce a refined structure for interpreting data and strengthen inferences about causality.

Unlike many previous efforts, ENVESOME ties its toxicological inquiries to the broader concept of the exposome. In essence, the exposome frames each individual's total exposure, both external (for instance, air pollution, noise, or dietary contaminants) and internal (e.g., epigenetic or metabolic changes), as a dynamic entity that evolves over time. The innovation here arises from using advanced sensors, wearable devices, and agent-based models to capture the external environment people encounter daily. That information is then correlated with biological readouts from biomonitoring and omics-based studies. This dual viewpoint clarifies the extent to which various pollutants or stressors enter and affect the body, indicating which pathways or physiological systems bear the brunt of exposure. ENVESOME overlays these phenomena with quantitative in vitro-to-in vivo extrapolation (QIVIVE) strategies and Bayesian methods to ensure dose estimations align with actual conditions.

A key goal is to ensure that these mechanistic insights do not remain locked in scientific literature. Instead, the project translates them into practical applications, namely updated limit values, decision support systems (DSS), and user-friendly digital platforms. Limit values grounded in AOP logic differ from traditional standards, which often rely on generic thresholds or incomplete epidemiological data. By uncovering how chemicals modify specific pathways at particular dose ranges and evaluating the relative importance of these pathways in driving adverse health outcomes, ENVESOME delivers more nuanced, and arguably more protective, limits. These updated thresholds reflect the mechanistic realities of how pollutants transform biology. Given the thorough quantitative approach (including Benchmark Dose analysis and integration of human biomonitoring data), this method stands to yield recommendations with robust biological underpinnings and a higher degree of confidence.

Parallel to limit value derivation is the translation of findings into real-world tools for policy makers, health practitioners, and citizens. ENVESOME gives structure to knowledge transfer through a multi-tiered system that includes a Decision Support System (DSS), specialized mobile applications, and chatbots. The DSS weaves together environmental, clinical, and socio-economic information into a single analytical engine, enabling stakeholders to model the outcomes of different interventions. By simulating changes in traffic flows, industrial emissions, or urban design, local authorities can observe how those shifts might reduce harmful exposures or lower the burden of disease, based on mechanistic data about disrupted pathways. This evidence-based approach supports cost-effective measures, transparency, and the possibility of collaborative governance. Because data on mechanistic alterations from AOPs are

folded into the DSS, the system clarifies exactly which biomarkers or pathways stand to benefit the most, thereby clarifying and streamlining decision-making.

Another cornerstone is the focus on risk-based stratification, derived from fuzzy logic architectures that incorporate not only exposure data but also personal vulnerabilities, genetic predisposition, and socio-behavioral variables. This approach recognizes that the health effects of pollutants are not uniform across all populations. Individuals living in marginalized neighborhoods or those with compromised immune systems or higher baseline stress levels may face far worse outcomes for identical pollutant concentrations. By layering these complexities into a stratification engine, ENVESOME accounts for real-world disparities in exposure and resilience. This information is relayed into a user-centric mobile coaching app that provides personalized recommendations, drawing on real-time data from sensors or user-reported behaviors, and also flags higher-risk individuals who might benefit from medical interventions, education, or environmental policy changes.

Throughout the project, co-creative processes in Urban Living Labs (ULLs) ensure a tangible interface between data-driven evidence and local communities. These labs allow city administrators, businesses, and residents to collaboratively interpret the science, including AOP data, in light of their own lived contexts. For example, if an industrial region exhibits consistent markers of early liver damage in local populations, and omics evidence indicates that certain chemical clusters are the culprits, the community might prioritize interventions (such as advanced waste management methods or green infrastructure) tailored to these mechanistic findings. By testing policies in a localized ULL environment and observing the subsequent changes in measured biomarkers or health outcomes, knowledge refines quickly into implementable steps. The participatory nature of this process broadens acceptance and sustainability, because stakeholders who co-create solutions are more likely to champion them over the long term.

Another dimension of the project is the way it integrates socio-demographic drivers of exposure into a mechanistic toxicology framework. Historically, risk assessments have rarely incorporated deep social science perspectives. ENVESOME addresses this gap by modeling how low social capital, limited education, or subpar housing might lead to higher ambient pollution exposures or decreased resilience. By systematically collecting data on these factors and including them in the agent-based models that feed into the DSS, ENVESOME clarifies what interventions might simultaneously reduce pollution exposures and combat social inequalities. The synergy of the exposome with AOP-based mechanistic data broadens environmental justice discussions, shining light on how disproportionate risks can be alleviated through targeted measures [40]. The project thus merges the scientific rigor of molecular biology with the pragmatism of policy science, highlighting how sociopolitical contexts modify the toxicological impacts of pollutants. By illuminating these social modifiers of risk, ENVESOME provides evidence to inform environmental justice interventions that reduce disproportionate pollutant burdens in vulnerable communities.

Validation of the ENVESOME approach occurs at multiple levels. The same biological endpoints or omics signatures identified in in vitro experiments with realistic exposures are examined in population

cohorts, bridging clinical epidemiological data with fundamental mechanistic insights. This multi-level validation approach is crucial for moving from correlation toward causation. If the same disruption in, for example, a mitochondrial pathway is seen both in cells treated with real-world pollutant doses and in a cohort sample of individuals living near an industrial zone [23, 41], the argument for causality is greatly strengthened. Additionally, sampling is repeated post-intervention to verify improvements in biomarkers or other health indicators, confirming that recommended policies are having the biological effect predicted by mechanistic analyses. These multiple lines of evidence, epidemiological, biochemical, socio-economic, produce a robust, cross-validated body of knowledge that can shift the policy conversation from uncertainty to well-founded action.

Such a holistic perspective supplies significant advances over prior state-of-the-art research. Where earlier exposomic projects might have focused predominantly on broad environmental variables or partial sets of biomarkers, ENVESOME systematically accounts for the entire exposure-to-effect continuum: from a pollutant's presence in a given microenvironment, to modeling how it accumulates in human tissues, to revealing which genes, proteins, or metabolic pathways it alters, and finally to validating that chain of events in both living labs and in vitro. This approach is not only academically compelling but also has a direct and immediate benefit for public health. Updated limit values, co-developed with local authorities, can align with mechanistic thresholds rather than broad estimates, leading to more equitable outcomes for at-risk communities. Meanwhile, dynamic tools like the risk stratification engine can identify whether specific interventions, be they less polluting waste management, improved public transport, or health education campaigns, provide meaningful, measurable benefits.

The flexible and modular nature of ENVESOME's methodology makes it adaptable for future expansions or global replication. Omics-based analyses, agent-based models, and multi-compartment toxicology frameworks can be tailored to specific local conditions in any region or city with a high pollution load or unique environmental challenges. The project's emphasis on interdisciplinary collaboration offers a template for bridging the gap between natural sciences, clinical medicine, social sciences, and public policy. That synergy is increasingly vital as global urbanization intensifies, bringing complex mixtures of pollutants and heightened health inequalities.

From a theoretical standpoint, the melding of AOPs with exposomic data highlights how mechanistic events translate into multi-faceted disease phenotypes [42, 43]. Each stressor or mixture of stressors potentially alters different nodes in a shared network of pathways. For instance, persistent organic pollutants and ultrafine particles might converge on inflammatory and mitochondrial pathways, intensifying the risk for metabolic disorders or neurodegenerative conditions. Meanwhile, socio-economic strains can magnify these harms by affecting stress hormone levels or limiting individuals' capacities to mitigate exposure. ENVESOME's computational pipeline [7], which deploys network and correlation analyses, unravels these convergences, indicating common or synergistic routes. The outcome is a more holistic mechanistic approach that can systematically investigate not only what is

happening but precisely how and why, an essential step to push environmental health beyond correlative evidence.

The implementation of ENVESOME's strategies is projected to yield significant dividends. By facilitating the early detection of environmental risks via biomarkers, the project enables interventions before irreversible pathology occurs. This shift from reactive treatment to proactive prevention is expected to reduce the incidence of NCDs, thereby lowering healthcare costs and improving Quality Adjusted Life Years (QALYs) across the EU. The definition of new, biologically grounded limit values for pollutants like UFP and light at night will drive regulatory updates, ensuring that standards protect the most vulnerable.

Furthermore, ENVESOME places a strong emphasis on capacity-building and knowledge transfer. A targeted training program for stakeholders (from local authorities to health professionals) is being implemented to ensure that the projecttools and findings are understood and adopted in practice. This co-creative learning process among policymakers and community leaders will help sustain ENVESOME’s impact beyond the project’s duration.

Finally, ENVESOME’s dynamic contribution lies in its ongoing creation of new knowledge even after official project timelines. The open data resources, interoperability with other EU projects, and harmonized protocols for sample collection and analysis provide a foundation for continuous improvement and expansion. Researchers in other regions, or even future projects, can draw on these data sets for meta-analyses, re-validate them with new modeling technologies, or adapt them to newly discovered pollutants. In parallel, local governments and civil organizations can continue using the integrated software tools, sustaining the participatory processes first set in motion in Urban Living Labs.

4 Conclusion

ENVESOME represents a landmark effort to decode the complexity of the environment-health nexus. By creating a seamless workflow that connects satellite data to molecular pathways, and scientific discovery to policy implementation, it offers a blueprint for the future of public health. It moves beyond the simplistic "one pollutant, one disease" model to embrace the reality of the exposome, providing the tools necessary to build healthier, more resilient cities for the future. By situating itself at the crossroads of exposomic research, computational toxicology, and participatory policy making, ENVESOME is poised to advance the state of environmental health science significantly. First, the project capacity to combine sensor technologies, big data analytics, agent-based modelling, and novel in vitro test systems ensures that previously uncharted or poorly characterized exposures (e.g., ultrafine particles, emerging contaminants) are properly accounted for. Second, the systematic incorporation of multi-omics layers and quantitative Adverse Outcome Pathway (qAOP) frameworks will refine the identification of causal pathways, enabling a deeper mechanistic understanding of environment-driven diseases. This depth of analysis holds the promise of discovering new biomarker panels for early disease detection. Such depth of analysis holds the promise of discovering new biomarker panels for early disease detection. Third, the deliberate focus on social drivers of exposure, particularly through agent-based modelling of socio-

demographic inequalities, highlights opportunities to reduce health disparities through evidence-based strategies. ENVESOME does not merely identify risk factors; it co-creates targeted interventions with local governments, businesses, and communities, thereby promoting sustainable and inclusive solutions. The integration of these interventions into a dynamic DSS, coupled with an AI-powered chatbot and a risk stratification engine, offers stakeholders, from citizens to policymakers, a suite of actionable tools for informed decision-making.

Overall, ENVESOME goes beyond traditional pollutant-centric research by offering a holistic approach that merges mechanistic toxicology, social determinants, advanced modelling, and co-creative governance. This design fosters the translation of scientific findings into tangible interventions and updated regulatory guidelines, ultimately paving the way for healthier living environments and more effective public health policies across Europe. By fully embracing the exposome paradigm, ENVESOME not only advances our scientific understanding of how complex exposures influence health, but also delivers robust, scalable, and equitable strategies to mitigate those risks. This represents a compelling step toward a future in which environmental determinants of health can be more effectively controlled and prevented, aligning with modern precision-prevention strategies.

Abbreviations

AOPs
Adverse Outcome Pathways
BE
Biomonitoring Equivalent
BED
Biologically Effective Dose
EFSA
European Food Safety Authority
ERCs
Environmental Release Categories
FAO
Food and Agriculture Organization of the United Nations
INTEGRA
Integrated External and Internal Exposure Modelling Platform
NOAEL
No Observed Adverse Effect Level
PBTK
Physiologically Based ToxicoKinetic
PK
PharmacoKinetic
QSAR
Quantitative structure-activity relationship

RfC
Reference Concentration
RfD
Reference Dose
t-TDI
temporary Tolerable Daily Intake
WHO
World Health Organization

Declarations

Author Contribution

D.A.S. conceived and coordinated the ENVESOME project and supervised the overall scientific framework. D.A.S. and S.P.K. designed the exposome methodology and systems toxicology integration. V.B.S., D.D., V.K., P.M.-S., and B.N.C. contributed to regulatory toxicology, risk assessment, and new approach methodologies. S.D., D.K., A.M., and G.S. developed the artificial intelligence, data science, and decision-support system components. E.F., I.F., K.G., A.K., M.K., A.G., T.M., and S.P.K. contributed to exposure assessment, agent-based modelling, and computational toxicology. J.G., M.H., D.Ko., D.M., J.S.T., and E.H. contributed to the human biomonitoring strategy and analytical methodology. A.J. and K.P. contributed to cohort design and epidemiological analysis. A.Je., J.P.T., and J.M. contributed to environmental health assessment and urban living lab implementation. W.N., C.N., and K.V. contributed to multi-omics methodology and biomarker development. L.L. and T.M. contributed to atmospheric monitoring and environmental measurements. N.M. contributed to stakeholder engagement and implementation planning. S.P., N.P., and S.P.K. drafted sections of the manuscript. D.A.S. and S.P.K. wrote the main manuscript text. All authors critically revised the manuscript for important intellectual content and approved the final version.

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AVAILABILITY OF DATA AND MATERIALS

The dataset(s) supporting the conclusions of this article is(are) included within the article (and its additional file(s)).

References

1. Sarigiannis D. Combined or multiple exposure to health stressors in indoor built environments. Multiple environmental exposures and risks. World Health Organisation: Geneva: WHO Regional Office for Europe, Editor.; 2014.
2. Wild CP. Complementing the genome with an exposome: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidem Biomar. 2005;14(8):1847–50.
3. Wild CP. The exposome: from concept to utility. Int J Epidemiol. 2012;41(1):24–32.
4. Babu M, Snyder M. Multi-Omics Profiling for Health. Mol Cell Proteom. 2023;22(6):100561.
5. Ballard JL, Wang Z, Li W, Shen L, Long Q. *Deep learning-based approaches for multi-omics data integration and analysis.* BioData Mining, 2024. 17(1): p. 38.
6. Loh M, Sarigiannis D, Gotti A, Karakitsios S, Pronk A, Kuijpers E, Annesi-Maesano I, Baiz N, Madureira J. Oliveira Fernandes, *How sensors might help define the external exposome*. Int J Environ Res Public Health. 2017;14(4):434.
7. Sarigiannis DA, Gotti A, Handakas E, Karakitsios SP. *Informatics and data analytics to support exposome-based discovery: part 2-computational exposure biology*, in *Applying Big Data Analytics in Bioinformatics and Medicine*, M.D. Lytras and P. Papadopoulou, Editors. 2018, IGI Global. pp. 145–187.
8. Sarigiannis DA, Karakitsios SP, Handakas E, Papadaki K, Chapizanis D, Gotti A. *Informatics and data analytics to support exposome-based discovery: Part 1-assessment of external and internal exposure*, in *Applying Big Data Analytics in Bioinformatics and Medicine*. 2018, IGI Global. pp. 115–144.
9. Hernandez AF, Buha A, Constantin C, Wallace DR, Sarigiannis D, Neagu M, Antonijevic B, Hayes AW, Wilks MF, Tsatsakis A. Critical Assess Integr Sep lines Evid risk Assess Chem mixtures Archives Toxicol. 2019;93(10):2741–57.
10. Gavriilidis GI, Vasileiou V, Orfanou A, Ishaque N, Psomopoulos F. A mini-review on perturbation modelling across single-cell omic modalities. Comput Struct Biotechnol J. 2024;23:1886–96.
11. Manrai AK, Cui Y, Bushel PR, Hall M, Karakitsios S, Mattingly CJ, Ritchie M, Schmitt C, Sarigiannis DA, Thomas DC, Wishart D, Balshaw DM, Patel CJ. Informatics and data analytics to support exposome-based discovery for public health. Annu Rev Public Health. 2017;38:279–94.
12. Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, Mount DR, Nichols JW, Russom CL, Schmieder PK, Serrrano JA, Tietge JE, Villeneuve DL. Adverse outcome pathways: A conceptual framework to support ecotoxicology research and risk assessment. Environ Toxicol Chem. 2010;29(3):730–41.
13. Hartung T, Kleinstreuer N. Challenges and opportunities for validation of AI-based new approach methods. ALTEX - Altern Anim experimentation. 2025;42(1):3–21.
14. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. Public Health Rep. 2014;129(Suppl 2):19–31.

15. Chapizanis D, Karakitsios S, Gotti A, Sarigiannis DA. Assessing personal exposure using Agent Based Modelling informed by sensors technology. Environ Res. 2021;192:110141.
16. Karakoltzidis A, Agalliadou A, Kermenidou M, Nikiforou F, Chatzimpaloglou A, Feleki E, Karakitsios S, Gotti A, Sarigiannis D. Agent-based modelling: A stochastic approach to assessing personal exposure to environmental pollutants – Insights from the URBANOME project. Sci Total Environ, 2025. 967.
17. Jin Y, Qi G, Feng M, Yu D. The path via pathway-based approaches towards safety assessment: A concise review. Toxicol Appl Pharmcol. 2022;452:116195.
18. Alamanos A, Rolston A, Papaioannou G. Development of a Decision Support System for Sustainable Environmental Management and Stakeholder Engagement. Hydrology. 2021;8(1):40.
19. Popescu SM, Mansoor S, Wani OA, Kumar SS, Sharma V, Sharma A, Arya VM, Kirkham MB, Hou D, Bolan N, Chung YS. Artificial intelligence and IoT driven technologies for environmental pollution monitoring and management. Front Environ Sci, 2024. 12.
20. Rossi A, Lenzini G. Transparency by design in data-informed research: A collection of information design patterns. Comput Law Secur Rev. 2020;37:105402.
21. Steckling N, Gotti A, Bose-O'Reilly S, Chapizanis D, Costopoulou D, De Vocht F, Garí M, Grimalt JO, Heath E, Hiscock R, Jagodic M, Karakitsios SP, Kedikoglou K, Kosjek T, Leondiadis L, Maggos T, Mazej D, Polańska K, Povey A, Rovira J, Schoierer J, Schuhmacher M, Špirić Z, Stajnko A, Stierum R, Tratnik JS, Vassiliadou I, Annesi-Maesano I, Horvat M, Sarigiannis DA. Biomarkers of exposure in environment-wide association studies – Opportunities to decode the exposome using human biomonitoring data. Environ Res. 2018;164:597–624.
22. Sarigiannis DA, Karakitsios SP. *Modeling complex exposures*, in *Chemical mixtures and combined chemical and nonchemical stressors: exposure, toxicity, analysis, and risk*, C.V. Rider and J.E. Simmons, Editors. 2018, Springer. pp. 81–125.
23. Papaioannou N, Distel E, de Oliveira E, Gabriel C, Frydas IS, Anesti O, Attignon EA, Odena A, Díaz R, Aggerbeck M, Horvat M, Barouki R, Karakitsios S, Sarigiannis DA. Multi-omics analysis reveals that co-exposure to phthalates and metals disturbs urea cycle and choline metabolism. Environ Res. 2021;192:110041.
24. Sarigiannis DA. Assessing the impact of hazardous waste on children's health: The exposome paradigm. Environ Res. 2017;158:531–41.
25. Sarigiannis DA, Karakitsios S, Dominguez-Romero E, Papadaki K, Brochot C, Kumar V, Schuhmacher M, Sy M, Mielke H, Greiner M, Mengelers M, Scheringer M. Physiology-based toxicokinetic modelling frame Eur Hum Biomonitoring Initiative Environ Res. 2019;172:216–30.
26. Sarigiannis D, Karakitsios SP, Handakas E, Gotti A. Development of a generic lifelong physiologically based biokinetic model for exposome studies. Environ Res. 2020;185:109307.
27. Sarigiannis DA, Tratnik JS, Mazej D, Kosjek T, Heath E, Horvat M, Anesti O, Karakitsios SP. Risk characterization of bisphenol-A in the Slovenian population starting from human biomonitoring data. Environ Res. 2019;170:293–300.

28. Sarigiannis DA. *Transcriptomics within the exposome paradigm*, in *Unraveling the Exposome: A Practical View*. 2019. pp. 183–214.
29. Anesti O, Papaioannou N, Gabriel C, Karakoltzidis A, Dzhedzheia V, Petridis I, Stratidakis A, Dickinson M, Horvat M, Snoj Tratnik J, Tsatsakis A, Karakitsios S, Sarigiannis DA. An exposome connectivity paradigm for the mechanistic assessment of the effects of prenatal and early life exposure to metals on neurodevelopment. Front Public Health. 2022;10:871218.
30. Sarigiannis D, Karakitsios S, Anesti O, Stem A, Valvi D, Sumner SCJ, Chatzi L, Snyder MP, Thompson DC, Vasiliou V. Advancing translational exposomics: bridging genome, exposome and personalized medicine. Hum Genomics. 2025;19(1):48.
31. Sillé F, Karakitsios S, Kleensang A, Koehler K, Maertens A, Miller GW, Prasse C, Quiros-Alcala L, Ramachandran G, Hartung T. *The exposome: a new approach for risk assessment.* 2020.
32. De Vries RBM, Angrish M, Browne P, Brozek J, Rooney AA, Wikoff DS, Whaley P, Edwards SW, Morgan RL, Druwe IL, Hoffmann S, Hartung T, Thayer K, Avey MT, Beverly BEJ, Falavigna M, Gibbons C, Goyak K, Kraft A, Nampo F, Qaseem A, Sears M, Singh JA, Willett C, Yost EY, Schünemann H, Tsaioun K. Applying evidence-based methods to the development and use of adverse outcome pathways. Altex. 2021;38(2):336–47.
33. Sarigiannis DA. The exposome: A new tool for improved health risk assessment. In: Roig B, Weiss K, Thireau V, editors. Management of emerging public health issues and risks. Editors: Elsevier; 2019. pp. 30–45.
34. Barouki R, Audouze K, Becker C, Blaha L, Coumoul X, Karakitsios S, Klanova J, Miller GW, Price EJ, Sarigiannis D. The exposome and toxicology: a win-win collaboration. Toxicol Sci. 2022;186(1):1–11.
35. Sarigiannis DA, Hansen U. Considering the cumulative risk of mixtures of chemicals - A challenge for policy makers. Environmental Health: A Global Access Science Source; 2012. 11(SUPPL.1).
36. Sarigiannis DA. *The exposome paradigm in environmental health*, in *Environmental exposures and human health challenges*, P. Papadopoulou, C. Marouli, and A. Misseyanni, Editors. 2019, IGI Global. pp. 1–29.
37. Sarigiannis DA, Hartung T, Karakitsios SP. *The exposome — A new paradigm for non-animal toxicology and integrated risk assessment*, in *Toxicological Risk Assessment and Multi-System Health Impacts from Exposure*. Elsevier; 2021. pp. 23–30. A.M. Tsatsakis, Editor.
38. Lahiani A, Yavin E, Lazarovici P. The Molecular Basis of Toxins' Interactions with Intracellular Signaling via Discrete Portals. Toxins (Basel), 2017. 9(3).
39. Dugourd A, Kuppe C, Sciacovelli M, Gjerga E, Gabor A, Emdal KB, Vieira V, Bekker-Jensen DB, Kranz J, Bindels EMJ, Costa ASH, Sousa A, Beltrao P, Rocha M, Olsen JV, Frezza C, Kramann R. Saez-Rodriguez, *Causal integration of multi-omics data with prior knowledge to generate mechanistic hypotheses*. Mol Syst Biol. 2021;17(1):e9730.
40. Sarigiannis D. Environmental and health inequities. Fresenius Environ Bull. 2019;28(2):516–7.
41. Sarigiannis DA, Papaioannou N, Handakas E, Anesti O, Polanska K, Hanke W, Salifoglou A, Gabriel C, Karakitsios S. Neurodevelopmental exposome: The effect of in utero co-exposure to heavy metals

and phthalates on child neurodevelopment. Environ Res. 2021;197:110949.

42. van den Brand AD, Meerman JJ, Veltman CHJ, Luijten M. Refinement of a workflow for human relevance assessment of adverse outcome pathways and associated new approach methodologies. Front Toxicol, 2025. Volume 7–2025.

43. Marx-Stoelting P, Rivière G, Luijten M, Aiello-Holden K, Bandow N, Baken K, Cañas A, Castano A, Denys S, Fillol C. A walk in the PARC: developing and implementing 21st century chemical risk assessment in Europe. Archives of Toxicology; 2023. pp. 1–16.

Figures

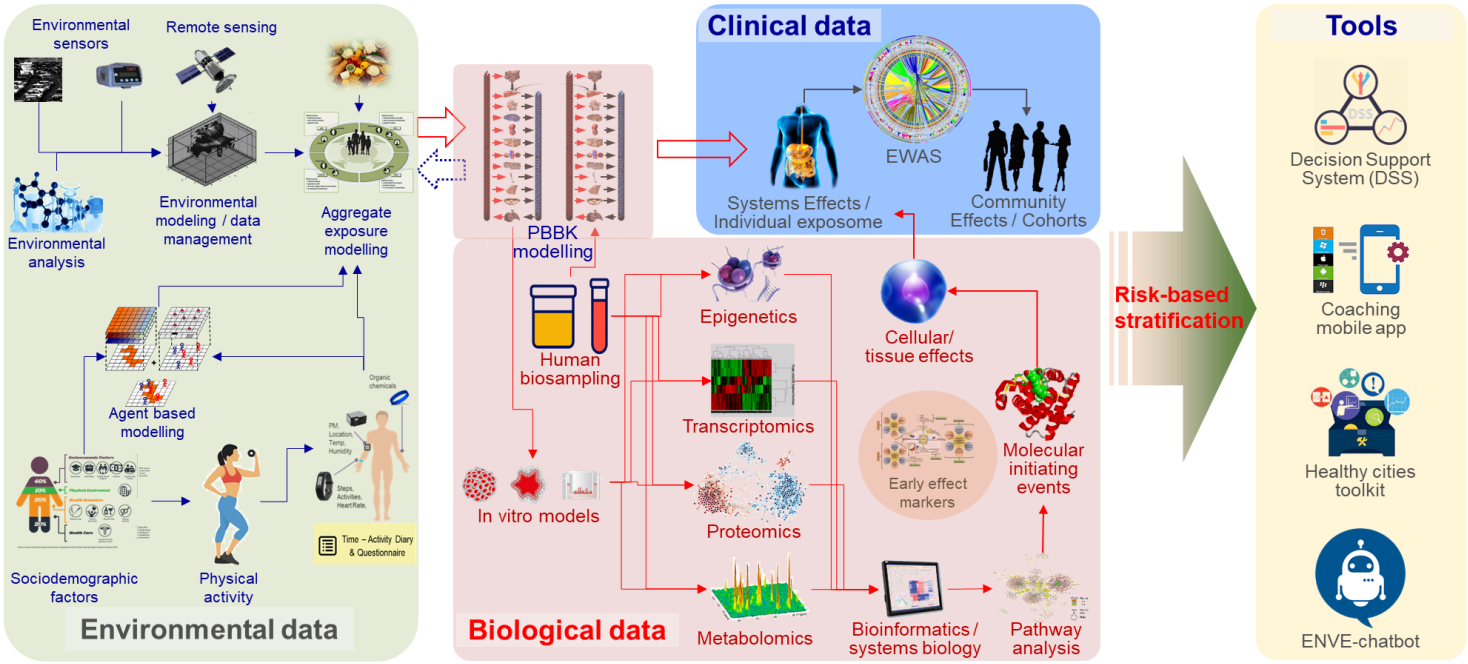


Figure 1

ENVESOME conceptual model