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Ecology-by-design: process-level toxicity assessment as the compass for a tox-minimized chemical industry

Andrey E. Kolesnikov[1], Karina D. Goncharova[1], Valentine P. Ananikov[2,*]

[1]Petrovsky National Research Center of Surgery, Moscow, 119991, Russia
[2]Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, 119991, Russia

[*]Correspondence: val@ioc.ac.ru

Abstract

Green chemistry has transformed chemical innovation by introducing quantitative metrics. However, favorable values for these metrics do not automatically translate into ecological sustainability. A chemical process comprises a dynamic mixture of reagents, catalysts, solvents, intermediates, byproducts, residual feedstocks, and waste streams, each contributing to its overall toxicological footprint. This review argues that toxicity assessment should shift from a compound-centered perspective to a process-level evaluation that considers how toxicological burden is created, transformed, displaced, concentrated, diluted, or released throughout a process life cycle. We propose an ecology-by-design framework that integrates reaction inventories, toxicological endpoints, new approach methodologies, Life Cycle Assessment, USEtox characterization, safe-and-sustainable-by-design principles, and machine-learning-enabled data infrastructures. The ultimate objective is a chemical industry in which ecological performance is optimized alongside yield, selectivity, productivity, energy use, carbon footprint, and cost.

Keywords: process toxicity, tox-Profiles, bio-Profiles, bio-Strips, cytotoxicity potentials, catalytic reactions, green chemistry, life cycle assessment, green toxicology

1. Introduction

The future chemical industry cannot be defined only by high yield, selectivity and productivity. It must also be defined by the capacity to minimize adverse biological and ecological effects of entire process chains. The classical achievements of green chemistry – atom economy, E-factor, mass intensity – remain indispensable, because they made waste and resource use visible to chemists and process engineers.[1-6] However, those metrics were not designed to answer whether a reaction mixture, side stream, catalyst residue or a solvent-rich waste phase is biologically safe. A route can be mass-efficient and still rely on substances that are acutely toxic, chronically active, bioavailable, persistent, sensitizing, endocrine-active, genotoxic or highly ecotoxic in a particular compartment.

This conceptual gap is illustrated in Figure 1. Chemistry has strong tools for mass balances, solvent ranking, hazard classification, life-cycle accounting and emerging computational toxicity prediction. At the same time, the translation of those tools into everyday reaction design remains incomplete. Catalysts

change speciation, supports leach metals, byproducts accumulate, incomplete conversions move toxic starting materials into waste, solvents dominate mass, and mixtures may behave non-additively. Thus, ecology should be treated as a design objective rather than a final label. The most useful question for a synthetic chemist is not whether one component can be called 'green', but which alternative route creates the lowest toxicological burden for the target function while satisfying performance constraints.[7-9]

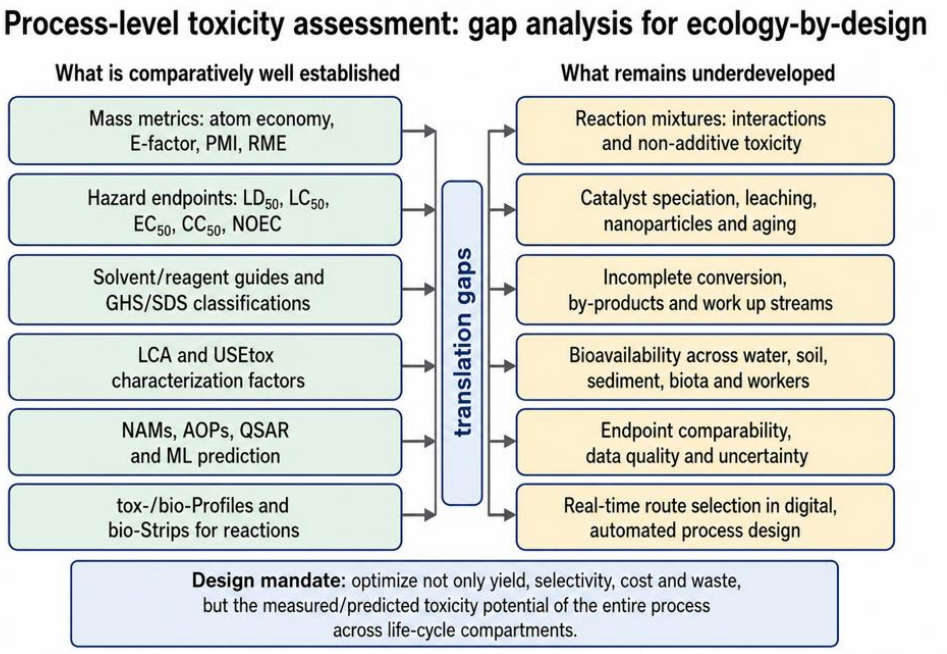

Figure 1. Gap analysis for process-level toxicity assessment. The figure separates comparatively mature tools from underdeveloped translation challenges and frames the mandate of ecology-by-design.

Process-level toxicity assessment therefore requires an inventory-based view of chemistry. Each route should be represented as a chemical system with quantities, roles and endpoints for every substance entering and leaving the process. In this view, a catalyst is not automatically safe because it is used in small amounts; a solvent is not safe because it is common; a biobased reagent is not safe because its carbon origin is renewable; and a product is not the only relevant toxicological object. The whole operation – synthesis, separation, solvent recovery, catalyst aging, residual impurities, waste treatment and accidental release – is the unit of ecological reasoning. This review develops that logic and proposes a title-level narrative: ecology by design, process-level toxicity as the compass, and a tox-minimized chemical industry as the goal.

2. Green chemistry metrics are necessary but not sufficient

The power of green chemistry metrics lies in their operational simplicity. Atom economy asks whether atoms of reactants appear in the product; E-factor and process mass intensity ask how much waste or material input is associated with product output; reaction mass efficiency, carbon efficiency and related descriptors highlight stoichiometry, yield, solvent use and recovery. More recent industrial tools, including innovation Green Aspiration Level and iGAL 2.0, combine route features and aspirational benchmarks for process improvement.[10-14] These metrics changed behavior because they are quantitative, comparable and compatible with route selection.

Their limitation is equally important. A kilogram of a low-hazard salt, a gram of a potent electrophile, a milligram of a leached metal species and a trace genotoxic impurity cannot be ranked by mass alone. Process metrics also struggle with biological specificity: the same chemical may be harmless in one assay and active in another, while the same process may be relevant to workers, algae, fish, terrestrial plants, microbial communities, sediment organisms or human cell types. Systems-based green chemistry has therefore argued that 'greener' molecular design must connect hazard, exposure, performance and life-cycle consequences rather than optimizing one indicator in isolation.[15-17]

A more mature interpretation is that mass metrics should become the skeleton of process-level toxicity assessment. They identify which substances and routes carry the largest quantities; toxicological endpoints identify how biologically active those substances are; exposure models identify where the substances may go; and life cycle analysis connects process decisions to upstream and downstream burdens. The integration is not a replacement of 'green' metrics, but their extension from waste minimization to ecological effect minimization.

3. Toxicity is a context-dependent property

The most common mistake in chemical sustainability discussions is to treat toxicity as a fixed attribute of a molecule, element or class. Toxicity depends on the endpoint being measured, the dose, the exposure time, the administration route, the biological model, the physicochemical form and the environment. Acute LD_{50}, cytotoxic CC_{50}, aquatic EC_{50}, no observed effect concentration, irritation, sensitization, genotoxicity, developmental toxicity, endocrine activity and chronic endpoints are not interchangeable. Even when the same numerical endpoint is used, assay protocol, cell line, species, solvent and exposure duration can alter the apparent ranking.[7, 18, 19]

This context-dependence is especially obvious for metals. A metal does not enter biology as an abstract element; it appears as a salt, complex, oxide, nanoparticle, dissolved ion, adsorbed species or transient catalytic intermediate. Oxidation state, ligands, counterions, solubility, particle size, surface chemistry and biotransformation govern bioavailability. Recent reviews on metals make a critical point for catalysis: the familiar contrast between toxic heavy metals and 'benign' light metals can be misleading. Nickel and copper salts may be more toxic than some palladium, platinum, rhodium or gold compounds under specific conditions, while individual platinum compounds can differ greatly by oxidation state and ligand environment.[18, 20]

The biological object is equally decisive. Rhodium chloride provides a striking case: $RhCl_3$ caused extraordinarily rapid lethal effects in terrestrial plants at early growth stages, while it was relatively low-toxic in human fibroblasts compared with several other metal salts. This divergence does not mean that one assay is wrong; it means that ecological assessment cannot be inferred from a single model system. A chemical process can be acceptable from the perspective of one cell line and problematic for plants, aquatic organisms or soil communities, especially when release routes make those organisms the first exposed receptors.[21]

Figure 2 emphasizes a broader design implication: toxicology should not enter chemistry only as compliance after development. Green Toxicology seeks to place hazard knowledge at the beginning of innovation, so that safer reagents, materials and processes can be selected before scale-up.[22, 23] Process-level toxicity assessment is the reaction-chemistry implementation of this principle. It does not claim to predict all ecological outcomes from a single number; rather, it makes the biological burden of a route visible early enough to redesign the route.

Figure 2. Principles of Green Toxicology. Early hazard thinking, mechanism-based testing and safer substitution are essential for moving toxicology upstream in chemical design. Reproduced from[23] under the Creative Commons Attribution 4.0 International (CC-BY 4.0) license.

4. From tox-Profiles to bio-Strips: making whole reactions visible

4.1. tox-Profiles: the first process-level grammar

The tox-Profile concept was proposed to correct a common asymmetry in 'green' synthesis: chemists often discuss the toxicity of a product, a starting material or a catalyst, but not the full set of reaction participants. The central idea is straightforward. For each component of a reaction, combine the amount used or formed with an appropriate toxicity index; display the relative contributions; and calculate a tox-Factor that compares the toxicity-weighted burden of substances entering and leaving the reaction. A tox-Factor below one indicates a decrease in the selected overall toxicity index during the reaction, above one indicates an increase, and near one indicates an approximately neutral transformation within the assumptions of the endpoint.[7]

This apparently simple approach has several important consequences. It exposes when a reaction to a less toxic product uses large quantities of more toxic components. It shows when an auxiliary dominates the process despite not appearing in the product. It reveals that byproducts must be considered even when they are familiar salts. It also separates a claim of non-toxicity from evidence: natural origin, biomass derivation or conventional use cannot substitute for measured biological activity.[7, 24]

4.2. bio-Profiles, bio-Factors and cytotoxicity potentials

The next step was to move from available LD_{50} values, which are incomplete and often non-comparable, to internally consistent cytotoxicity data measured under one protocol. bio-Profiles use half-maximal cytotoxic concentration (CC_{50}) values for all reaction participants to visualize their contributions to the 'overall' cytotoxicity of a process, while bio-Factors express the relative change in cytotoxicity-weighted burden through the reaction. In the first demonstration, the approach was applied to widely used

catalytic reactions such as Suzuki cross-coupling, oxidative C-C coupling, Friedel-Crafts and Heck transformations. A key lesson was chemically practical: the largest contributor was not always the catalyst. Aryl halides, solvents, electrophiles or byproducts could dominate the profile, depending on the route and cell line.[8]

Cytotoxicity potentials refined the approach by addressing a limitation of ratios. A bio-Factor can show whether the final mixture is less or more cytotoxic than the initial mixture, but two processes with very different absolute burdens may have similar ratios. Cytotoxicity potentials therefore quantify the initial burden, final burden and final burden excluding the target product, enabling comparison of routes to the same molecule. In the case studies of 36 routes to 1,1'-biphenyl and 72 routes to 4-methoxy-1,1'-biphenyl, cytotoxicity potentials and bio-Strips allowed direct comparison across catalyst, solvent, base and substrate choices, and showed the need to account for incomplete conversion and cell-line dependence.[9]

4.3. bio-Strips, online tools and high-throughput route landscapes

bio-Strips compress bio-Profiles into a form that is suitable for comparing many routes. The length of a segment reflects its normalized toxicity contribution and the color reflects the toxicity endpoint, allowing a researcher to see both how much a component contributes and how intrinsically active it is. The Build-a-Bio-Strip platform translates this idea into a user-facing workflow: assign roles to all reaction substances, provide masses, molar masses and CC_{50} or LD_{50} values, and generate bio-Strips, bio-Factors and cytotoxicity potentials for route comparison.[25]

Recent developments push the idea toward route landscapes. In cross-coupling chemistry, hundreds of routes can be enumerated from combinations of electrophiles, nucleophiles, catalysts, bases and solvents, then screened for cytotoxicity determinants. The recent study analyzed 864 individual reactions and 2592 bio-Strips to identify major determinants of environmental safety in catalytic fine-chemical synthesis, while further work extended the field to mixture-level toxicity assessment and tox-Scapes for visual selection of safer routes.[26-28] These developments are important not because they solve toxicology, but because they make toxicity-aware route selection chemically practical at the scale of reaction discovery.

5. Catalysis as a proving ground for process-level toxicity

5.1. The catalyst is a process actor, not a single substance

Catalysis is often described as the foundation of green chemistry because it reduces stoichiometric waste and enables milder, more selective transformations. Yet catalytic systems are dynamic. A homogeneous metal complex can decompose, exchange ligands, form colloids or produce nanoparticles. A heterogeneous catalyst can leach soluble species, then redeposit them; a support can adsorb or release species; and an aged catalyst can differ from the fresh material. Therefore, catalyst toxicity cannot be inferred from the name of the metal or the nominal catalyst loading. It requires attention to speciation, solubility, leaching, particle morphology and the biological form that actually reaches model organisms or workers.[18, 20]

The comparative Suzuki-Miyaura study of heterogeneous and homogeneous catalysts illustrates why the process perspective matters. Supported catalysts had lower cytotoxicity than soluble palladium complexes as materials, but the preparation route and neglected biological effects of catalyst precursors or supports still mattered. Moreover, common byproducts could contribute more to the ‘overall’ toxicity of the reaction system than the catalyst itself. In other words, a catalyst substitution that looks attractive

from a separation standpoint is not a sufficient toxicity analysis unless the whole reaction inventory is evaluated.[29]

5.2. Metal choice: beyond precious-versus-abundant stereotypes

The considered metal-toxicity studies are particularly valuable because they challenge a popular sustainability narrative: replacing precious metals with abundant first-row metals is automatically 'greener'. Abundance and cost are crucial, but they do not define biological safety. Nickel, copper and iron have essential roles in biology, but essential metals can be toxic in excess, and nickel compounds are of high concern in several toxicological contexts. Palladium, platinum, rhodium and gold compounds may be less toxic than expected in some assays but problematic in others, especially when environmental exposure is changing through catalytic converter emissions, industrial use and nanoparticle release.[20, 21]

The practical conclusion is not to rehabilitate precious metals or condemn first-row metals. It is to reject metal identity as a proxy for process safety. A catalyst claim should specify the species present before, during and after the reaction; the fraction leached into product and waste; the endpoints used; the route of potential exposure; and the uncertainty of the toxicity data. For pharmaceutical processes, this connects naturally with elemental impurity control, but ecology requires a broader lens because waste streams and environmental compartments can be the dominant receptors.

5.3. Mixtures, byproducts and incomplete conversion

Catalytic reactions are rarely single-compound exposures. They are mixtures of substrates, products, salts, bases, ligands, solvents, residual catalyst and sometimes unidentified side products. Classical mixture toxicology distinguishes concentration addition, independent action and interaction models, but reaction mixtures can be especially difficult because chemical transformations continue during work-up, disposal or environmental release. Recent integrated toxicity assessment of complex catalytic mixtures is therefore a critical frontier: a whole reaction mixture may have an effect that cannot be reconstructed from the most visible component alone.[27, 30]

Incomplete conversion is a practical example. From a synthetic perspective, residual starting material reduces yield and complicates purification. From a toxicity perspective, residual starting material can dominate the profile if it is much more active than the product or byproducts. bio-Strips at 25, 50, 75 and 100% conversion show how the same nominal route changes its toxicity potential as conversion progresses. This moves toxicity optimization into the same space as kinetics and process control: the safest process may require not only a better reagent set, but also a conversion window, quench strategy, separation method and waste-treatment protocol that minimize toxic residuals.[9]

6. Solvents, auxiliaries and the hidden mass of toxicity

Solvents often dominate the mass of fine-chemical processes, and therefore solvent selection has become one of the most mature areas of green chemistry. Industrial solvent guides and comprehensive reviews rank solvents by safety, health, environmental and process criteria; the CHEM21 guide and GSK guide are prominent examples.[31-34] However, a process-level toxicity view adds two cautions. First, solvent labels are context-dependent: an acceptable solvent in a closed system may be problematic in open handling, high-temperature operation or poorly controlled recovery. Second, toxicity can be displaced rather than removed if a solvent substitution increases energy demand, requires more auxiliary materials or generates harder-to-treat waste.

Ionic liquids and biobased solvents sharpen this point. Ionic liquids have negligible vapor pressure and tunable structures, but their biological activity can be significant and strongly dependent on cation,

anion, alkyl chain, functionalization and organism being treated. Amino-acid-derived or biomass-derived motifs do not guarantee safety. Recent mechanistic reviews and high-quality cytotoxicity datasets for ionic liquids (see Figure 3) make it possible to move beyond generic labels and toward structure-aware, endpoint-specific selection.[24, 35-39]

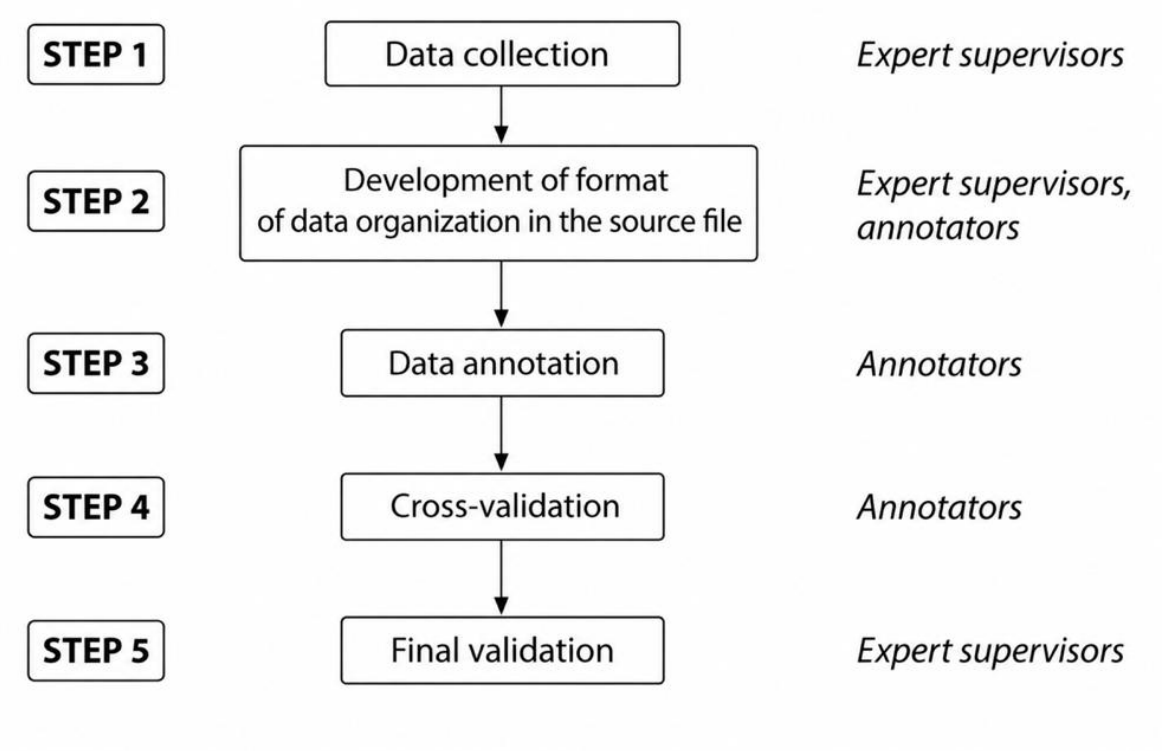

Figure 3. Dataset-building and validation workflow for cytotoxicity data on ionic liquids. Data quality, duplicate handling and consistency checks are prerequisites for reliable process-level toxicity modeling. Reproduced from[36] under the Creative Commons Attribution 4.0 International (CC-BY 4.0) license.

The lesson for process design is that solvents and auxiliaries should be evaluated as part of the route rather than as background. In many bio-Profile analyses, solvents such as *N*-methyl-2-pyrrolidone (NMP) can contribute substantially to route burden, and bases or counterion-derived byproducts can shift rankings even when the same target molecule is obtained. A toxicity-minimized solvent strategy should therefore combine intrinsic hazard, amount, volatility, exposure, recovery efficiency, persistence, degradation products, waste treatment and compatibility with safer work-up. The goal is not simply to choose a 'green' solvent from a list, but to select a solvent system that minimizes the toxicity potential of the entire process.

7. From flask to environment: Life Cycle Toxicity and USEtox

Reaction-level bio-Strips and tox-Profiles are fast, chemically interpretable tools, but they are not substitutes for Life Cycle Assessment (LCA). They describe the toxicity potential of process inventories under chosen endpoints; LCA asks how emissions, resource extraction, energy use, upstream synthesis, transportation, product use and end-of-life contribute to impacts. Connecting these levels is essential because a toxicity-minimized reaction step can be outweighed by toxic upstream feedstock production or downstream disposal, while a higher-burden reaction step may be justified if it eliminates a more

damaging life-cycle stage, and because emerging pollutants and future chemical releases must be anticipated rather than treated retrospectively.[40-44]

USEtox provides a consensus framework for translating chemical emissions into human toxicity and freshwater ecotoxicity characterization factors. Its logic separates fate, exposure and effect: where the chemical goes, which receptors encounter it and what effect level is expected. Recent global recommendations have updated ecotoxicity and human toxicity characterization, emphasizing better effect-data selection, near-field and far-field exposure (see Figure 4).[45-48]

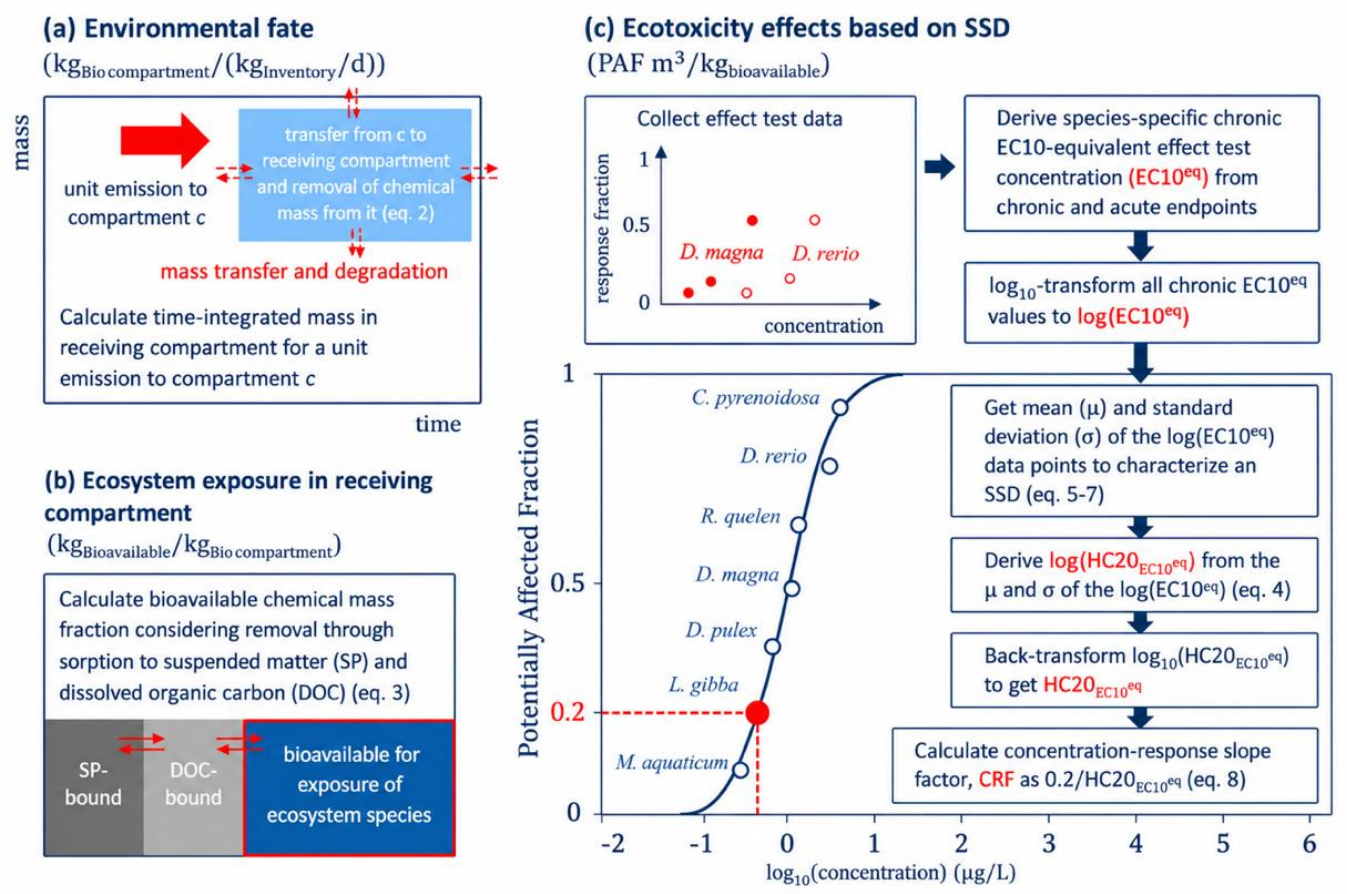

Figure 4. Ecotoxicity characterization framework connecting fate, exposure and effect in life-cycle impact assessment. Reproduced from[47] under the Creative Commons Attribution 4.0 International (CC-BY 4.0) license.

For process chemists, the value of USEtox is not merely regulatory. It teaches that toxicity ranking is incomplete without fate and exposure. A compound with high activity but negligible release may represent a lower ecological burden than a less active compound emitted in large quantities to water. Conversely, a dilute but persistent and bioavailable emission can be significant. The next generation of reaction toxicity tools should therefore export inventories in forms compatible with LCA and USEtox, including chemical identity, quantity, emission compartment, recovery, and destruction efficiency. Recent work on prospective and scale-up LCA for chemical processes provides practical methods for estimating inventories when full industrial data are not yet available (see Figure 5).[49-53]

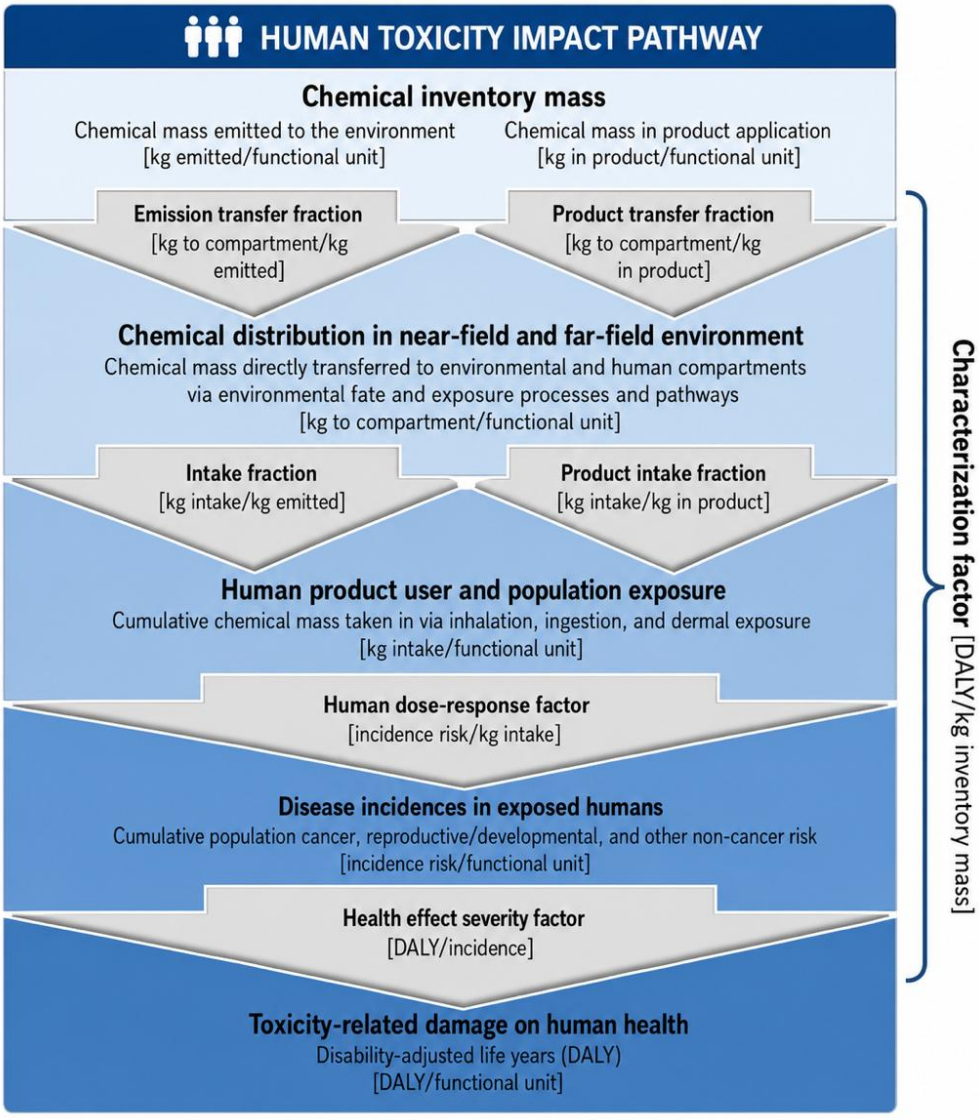

Figure 5. Human toxicity impact pathway in USEtox, linking emissions or product chemicals to exposure, dose, response and damage. Reproduced from[48] under the Creative Commons Attribution 4.0 International (CC-BY 4.0) license.

8. New approach methodologies, adverse outcome pathways and uncertainty-aware prediction

A central bottleneck in process-level toxicity assessment is data scarcity. Most reaction components, intermediates and byproducts lack comparable toxicity data across relevant organisms and endpoints. New approach methodologies can help by combining *in vitro* assays, high-content screening, omics, organotypic systems, and computational toxicology. The vision of toxicity testing in the 21st century moved the field toward mechanistic, pathway-based assessment rather than slow, animal-intensive testing for every chemical and endpoint.[54-57]

Adverse outcome pathways provide a language to connect molecular initiating events to cellular responses, organ effects, organism-level outcomes and population-level consequences. For chemical process assessment, adverse outcome pathways (AOP) can help distinguish non-specific baseline cytotoxicity from specific modes of action such as electrophilic reactivity, mitochondrial toxicity,

oxidative stress, endocrine signaling or DNA damage. ToxCast and Tox21 demonstrate the value and limitations of high-throughput biological profiling: they reveal activity landscapes for thousands of chemicals, but interpretation requires assay quality, exposure relevance and uncertainty analysis.[58-61]

Computational prediction is equally necessary and equally constrained. QSAR, read-across and machine learning can triage large route spaces before experimental testing, but models are domain-limited and endpoint-specific. The absence of predicted toxicity is not proof of safety, especially for organometallic species, unstable intermediates, salts, polymers, nanoparticles and mixtures. Practical tools must therefore report uncertainty, applicability domain and data provenance. Recent work on new approach methodologies (NAM) uncertainty and computational toxicology emphasizes that uncertainty should be quantified and used for decision-making rather than hidden behind single-point predictions.[62-68]

The most realistic near-term workflow is tiered. Early route ideation uses predicted endpoints, read-across and conservative hazard flags; route narrowing uses experimental cytotoxicity or ecotoxicity panels for all major components; scale-up uses targeted assays for likely receptors and release compartments; and final process validation uses mixture testing, LCA and monitoring. This tiered strategy is not as neat as a single ‘green’ score, but it matches the complexity of ecological safety.

9. Data infrastructures and digital tools for toxicity-aware synthesis

The transition from case studies to routine practice requires data infrastructure. Each reaction toxicity analysis needs standardized roles, masses, molar quantities, endpoints, assay conditions, cell lines or species, exposure times, solubility limits, uncertainty and provenance. Without these metadata, toxicity values become incomparable. This problem is already visible in LD_{50}-based compilations and supplier safety data sheets, where routes of administration, species, purity, formulation and protocol details may be incomplete or inconsistent.[8, 9]

Build-a-Bio-Strip is an important practical step because it gives chemists a structured template for reaction toxicity analysis. It requires explicit assignment of roles such as starting material, catalyst, reagent, solvent, product and byproduct; uses masses and molar masses; accepts measured CC_{50} or LD_{50} values; and can generate visual and numerical outputs that can be compared across routes.[25] Such tools should eventually integrate with electronic laboratory notebooks, reaction optimization platforms, inventory systems, supplier databases, LCA software and regulatory data repositories.

Future data systems should also learn from ionic-liquid cytotoxicity databases and other curated toxicology resources. The scientific value of these datasets is not only the number of entries, but the filtering, duplicate handling, assay annotation and chemical representation that make modeling possible.[36, 37] For process chemistry, analogous datasets are needed for reaction components, common byproducts, salts, metal complexes, ligand families, solvent systems, quench products and waste mixtures. The data gap is not peripheral; it is the central infrastructure challenge for tox-minimized industry.

10. Safe and sustainable by design: embedding ecology into industrial decisions

Safe and sustainable by design (SSbD) provides a policy and innovation framework in which safety and sustainability are considered from early development through iterative redesign (see Figure 6). The European Commission and JRC guidance connect hazard, exposure, risk and sustainability assessment in a tiered approach, making it highly relevant to chemicals, materials and processes.[69-71] Process-level toxicity assessment can be viewed as the reaction-engineering layer of SSbD: it converts the framework into choices among catalysts, solvents, reagents, bases, operations and separations.

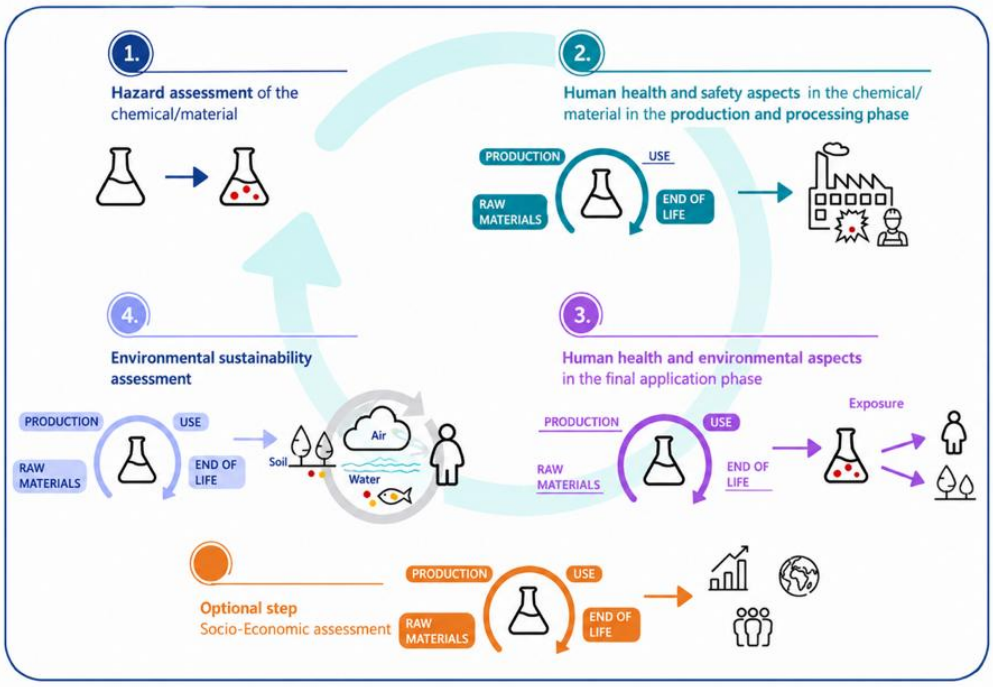

Figure 6. Safe-and-sustainable-by-design framework for chemicals and materials. Process-level toxicity profiling can operationalize the safety dimension during route invention and process development. Reproduced from[71] under the Creative Commons Attribution 4.0 International (CC-BY 4.0) license.

Industrial adoption will require three cultural shifts. First, toxicity should be reported as a route property alongside yield, selectivity, productivity, cost and carbon footprint. Second, safer substitution should be evaluated at the process level rather than by replacing one named component with another presumed benign analogue. Third, decisions should be documented with uncertainty: endpoint availability, assay relevance, exposure assumptions and fate modeling should accompany any ranking. This does not slow innovation; it prevents late-stage failure, regrettable substitution and expensive remediation.[72, 73]

Successful green chemistry examples demonstrate that performance and environmental improvement can align. Engineered biocatalysis for the synthesis of sitagliptin (a prescription oral medication used alongside diet and exercise to lower blood sugar in adults with Type 2 diabetes), continuous processing and lower-burden API manufacturing show that route redesign can reduce waste, improve selectivity and change the hazard profile of operations.[74-76] The next generation of such examples should include explicit process-level toxicity profiles, not only mass and energy metrics. Even carbon-utilization and CO_2-conversion technologies should be assessed through full life cycles and toxicity burdens, because climate benefit does not automatically imply ecological safety.[77]

11. Conclusions

The core conclusion of this review is that toxicity-minimized chemistry requires a change in the unit of analysis. Individual compounds remain important, but they are not the full ecological object. The object is the chemical process: a dynamic, mass-weighted, endpoint- and compartment-dependent system that includes everything used, formed, recycled, emitted and discarded. Table 1 summarizes how this perspective changes practical questions. Instead of asking whether a catalyst is ‘green’, one asks which catalyst-derived species are present and bioavailable. Instead of asking whether a solvent is recommended,

one asks whether the solvent system minimizes total process burden under realistic recovery and exposure. Instead of asking whether a product is less toxic, one asks whether the overall route reduces or increases toxicity potential.

Recent studies mark a coherent progression: metal-toxicity myths were challenged;[18] tox-Profiles proposed a way to visualize whole-reaction toxicity; bio-Profiles and bio-Factors introduced cytotoxicity-based reaction analysis; bio-Strips and cytotoxicity potentials enabled compact route comparison; heterogeneous and homogeneous catalyst systems were compared in a process context; and online tools made the workflow accessible. The broader literature now adds green toxicology, life-cycle toxicity characterization, NAMs, AOPs, machine learning, curated datasets and SSbD frameworks. The field is therefore ready to move from argument to implementation.

Figure 7 summarizes possible research topics for the future direction. A tox-minimized chemical industry will not rely on *post hoc* declarations of sustainability. It will use toxicity-aware inventories in electronic laboratory notebooks, supplier data streams, route dashboards, automated optimization and life-cycle models. It will treat ecological performance as a key process variable beside yield, selectivity, productivity, energy, carbon, cost and waste. It will identify toxicity drivers early, quantify uncertainty, avoid regrettable substitutions and validate priority processes in organism- and compartment-relevant systems. The scientific frontier remains demanding – mixture toxicity, chronic low-dose exposure, soil and sediment models, plant and microbiome endpoints, reactive intermediates, catalyst aging and uncertainty-aware AI are all underdeveloped. Nevertheless, the direction is clear: ecology must become a measurable design goal for chemistry, not a rhetorical adjective added after synthesis.

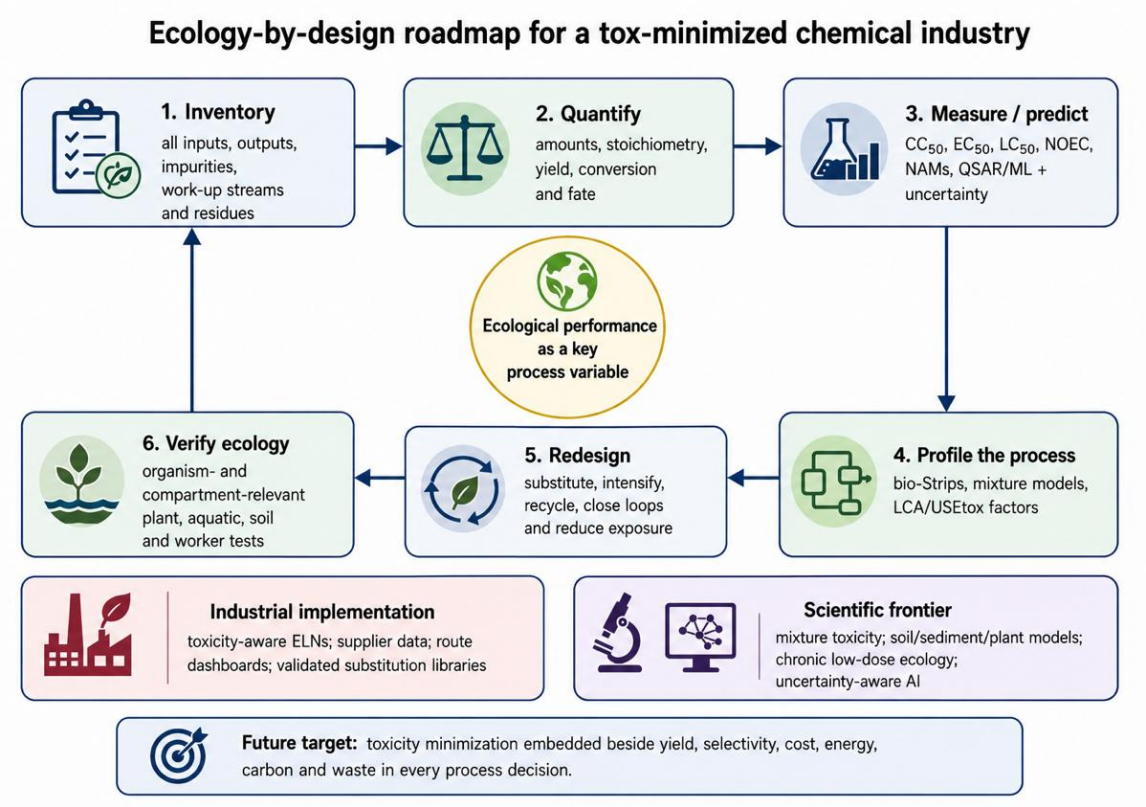

Figure 7. Ecology-by-design roadmap for a tox-minimized chemical industry.

Table 1. Summary analysis of process-level toxicity dimensions.

Process dimension	Question for process-level toxicity assessment	Current evidence/tools	Design conclusion
Catalyst and metal species	Which species are present before, during and after the reaction, and which forms are bioavailable?	Metal toxicity is controlled by oxidation state, ligands, solubility, morphology, leaching and environment; bio-Profiles reveal that catalysts are not always dominant.	Do not rank catalysts by metal identity alone; measure or model actual species, leaching and post-reaction forms.
Reagents and starting materials	Do electrophiles, nucleophiles or stoichiometric reagents dominate initial toxicity potential?	Cross-coupling case studies show that aryl halides and reactive monomers can dominate profiles more than low-loading catalysts.	Optimize reagent class, stoichiometry and conversion together with yield and selectivity.
Solvents and co-solvents	Does the largest mass component carry hidden health, ecological or recovery burdens?	Solvent guides are mature, but bio-Profile data show that solvent choice can shift route rankings.	Select solvent systems by amount, endpoint, exposure, recovery, degradation and compatibility with closed-loop operation.
Bases, salts and additives	Are familiar salts or additives harmless, or do they contribute to final waste burden?	bio-Strips and cytotoxicity potentials show byproduct salts and counterions may affect route safety.	Include bases, quench agents, counterions and auxiliary-derived byproducts in all inventories.
Products, byproducts and impurities	Does the process increase or decrease 'overall' toxicity relative to the incoming mixture?	tox-Factors and bio-Factors reveal directional change, while cytotoxicity potentials give absolute route burdens.	Report both ratio metrics and absolute potentials; exclude the target product only for route-to-route comparisons when justified.
Incomplete conversion and residuals	How does toxicity change at realistic conversions rather than idealized quantitative yield?	bio-Strips at different conversions show that residual starting material can dominate final burden.	Treat toxicity as a process-control variable and link it to conversion, quench, hold time and separation efficiency.
Mixtures and reaction cocktails	Are mixture effects additive, independent or interactive?	Recent integrated mixture toxicity work highlights limits of single-component reasoning for catalytic reaction mixtures.	Use mixture tests for priority routes and apply mixture models with uncertainty for screening.
Environmental fate and exposure	Where will emitted or residual chemicals go, and which organisms encounter them?	USEtox and LCA connect fate, exposure and effect for human toxicity and freshwater ecotoxicity.	Connect reaction inventories to compartments, emissions and life-cycle impact rather than reporting hazard alone.
Data and prediction	Are endpoint data comparable, reproducible and within model applicability domains?	NAMs, AOPs, ToxCast/Tox21, QSAR and ML expand coverage but require metadata and uncertainty.	Use tiered evidence: prediction for triage, standardized experiments for decisions and uncertainty for governance.
Industrial governance	How can toxicity minimization become routine in research, development and manufacturing?	SSbD, electronic tools and Build-a-Bio-Strip-like platforms enable early, documented and iterative decisions.	Embed toxicity dashboards in ELNs, route selection, procurement, scale-up, LCA and waste management.

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AI use declaration: During the preparation of this work, AI tools were used to perform text processing, English language, style, text corrections and translations for some parts of the text. After using this tool, the authors have reviewed and edited the content as needed. The authors take full responsibility on the content provided.