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Review

Integrative Ecotoxicology of Pharmaceuticals and Nanoplastics: A PRISMA-Guided Bibliometric Review Linking Ecosystem and Environmental Health

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Abstract: Background: Ecotoxicology increasingly faces complex mixtures and multilevel responses that single-compound, single-species assays cannot capture. Aim and objectives: To synthesize recent evidence (2022–2024) on integrative ecotoxicology (combining biomarkers, omics, computational models, and bioindicators) with emphasis on pharmaceuticals and nanoplastics**,** and to outline gaps and a practical framework for research and policy. Methods: A PRISMA-guided search was conducted in Web of Science, Scopus, PubMed, Google Scholar, and Springer Link (2022–2024). Duplicates were removed in Mendeley; screening used Rayyan with PICO-style inclusion/exclusion. The qualitative synthesis was complemented by bibliometric mapping (VOSviewer) to visualize thematic co-occurrences. Results: Fifty-two articles met criteria. Across aquatic and terrestrial models, integrative designs consistently revealed sublethal effects (oxidative stress, AChE inhibition, dysregulated apoptosis, teratogenicity) and molecular pathway disruption identified by transcriptomics/proteomics/metabolomics. Computational approaches (Bayesian networks; multivariate models) improved risk prioritization. Case studies showed synergism (e.g., nanoplastics-diclofenac) and highlighted soil interfaces (biochar-mediated metal speciation; earthworm biomarkers). Conclusions: Integrative ecotoxicology strengthens causal inference across biological levels and supports One Health and regulatory decision-making. Priority needs include standardized multi-level designs, mixture-aware endpoints, cross-matrix comparability (wáter-sediment-soil), FAIR data pipelines, and translation to policies (e.g., effluent standards, product stewardship). A concise research framework for policy formulation is proposed that links problem formulation, mixture-aware testing, omics-based pathways, and decision analysis.

Keywords: integrative ecotoxicology; contaminants; environmental health; omics technologies

1. Introduction

In recent years, environmental pollution has reached alarming levels, turning ecosystems into primary recipients of substances with deleterious effects on the environment [1–4]. Everyday products such as pesticides, metals, microplastics, and emerging contaminants like pharmaceuticals are leaving an invisible but catastrophic footprint on water bodies and soils, with consequences for organisms that rely on these matrices for survival and for the crops grown in contaminated fields [5–7]. This issue impacts biodiversity and poses a latent risk to human health, particularly in vulnerable communities that directly depend on these water sources and on agriculture sustained by affected soils [8,9]. This article is a PRISMA-guided bibliometric review that synthesizes recent evidence and derives an applied framework for research and policy.

Ecotoxicology, as a science focused on determining how different contaminants impact organisms and ecosystems, has played a key role in uncovering the consequences of these substances. However, current challenges demand more integrative approaches. Instead of isolated questions about how to capture cumulative damage or extrapolate from laboratory conditions to real ecosystems, the field must systematically address mixture toxicity, context-dependent interactions, and cross-scale translation, moving from controlled assays to environmentally realistic scenarios that integrate organisms, communities, and ecosystem processes. These needs reflect the current state of the science and underscore our responsibility as a society to mitigate the environmental damage we cause [10,11].

The most recent studies in Ecotoxicology have highlighted that the use of advanced tools, such as biochemical, molecular, ecological, tissue, and toxicological biomarkers, along with innovative technological platforms like lung-on-a-chip, enables a more realistic exploration of the effects of emerging contaminants [11–13]. Additionally, biological models such as algae, birds, fish, crustaceans, mollusks, nematodes, and others have provided valuable insights into the sublethal effects of these substances, helping us identify environmental risks before they translate into ecological collapses [14,15].

This review aims to reflect on and analyze the importance of an integrative approach in ecotoxicological studies, exploring how to combine multidisciplinary tools and methods to address such a complex issue. Drawing on recent research, we seek to highlight advances, identify knowledge gaps, and provide a framework that can guide future efforts in protecting aquatic ecosystems and, ultimately, life on our planet.

Specifically, this review pursues three main objectives:

(1) to synthesize recent evidence (2022–2024) on integrative ecotoxicology across aquatic and terrestrial systems;
(2) to identify persistent knowledge and methodological gaps that limit cross-matrix comparability;
(3) to propose an applied framework linking mechanistic findings to environmental and regulatory decision-making.

2. Methods

A systematic and bibliometric review was conducted using the guidelines of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" [16]. Searches were conducted (January 2022–December 2024) in Web of Science, Scopus, PubMed, Google Scholar, and Springer Link using Boolean strings that combined: "ecotoxicology" AND ("integrative" OR "multi-level" OR "transdisciplinary") AND ("biomarker" OR "omics" OR "transcriptomic" OR "proteomic" OR "metabolomic" OR "computational model" OR "Bayesian" OR "AOP") AND ("pharmaceutical" OR "antibiotic" OR "NSAID" OR "fluoxetine" OR "diclofenac" OR "PPCP" OR "plastic" OR "microplastic" OR "nanoplastic" OR "PFAS" OR "pesticide" OR "heavy metal") AND ("fish" OR "zebrafish" OR "Daphnia" OR "alga" OR "earthworm" OR "crab" OR "plant" OR "human"). Inclusion: original research or reviews with multi-level or multi-tool designs; focus on environmental health relevance [17]; English language. Exclusion: single-endpoint acute assays without integration; non-environmental toxicology. Duplicates were removed in Mendeley**;** title/abstract screening and full-text decisions used Rayyan. Bibliometric co-occurrence maps were generated with VOSviewer. The PRISMA flow diagram is shown in Figure 1.

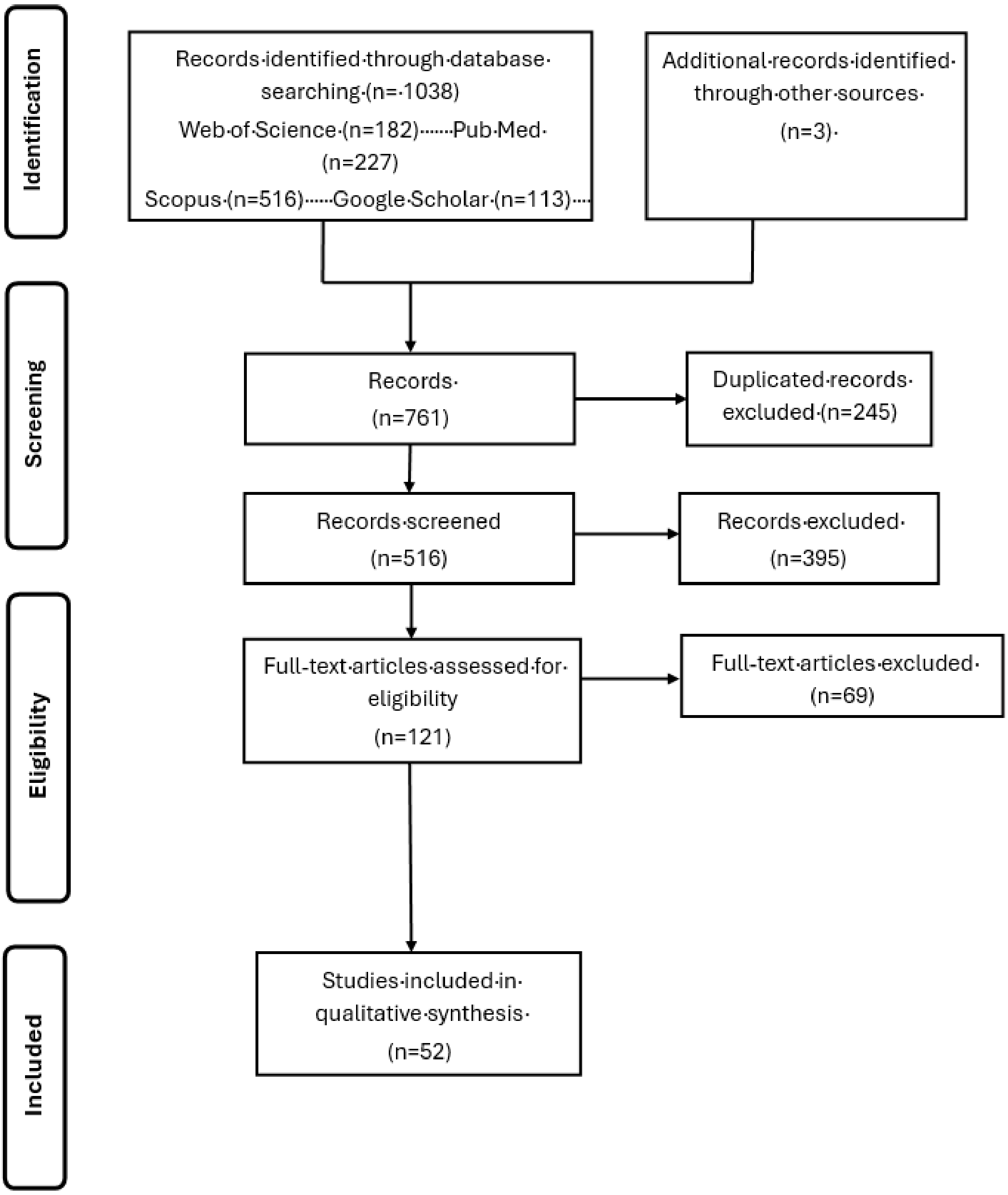

Figure 1. PRISMA flow diagram, Adapted from [16]. Copyright 2009, Moher et al.

3. Integrative Approach in Ecotoxicology

3.1. Concept of an Integrative Approach in Ecotoxicology and Its Importance

The integrative approach in ecotoxicology involves combining efforts, tools, and disciplines to analyze and evaluate the effects of contaminants in a more comprehensive manner. This approach considers effects ranging from molecular and cellular levels to population, community, and ecosystem impacts, acknowledging the complex interactions between contaminants, bioindicator organisms, and the environment. Its significance lies in the fact that, unlike traditional ecotoxicological evaluation methods, it does not focus on studying a single contaminant or species at a time. Instead, it holistically addresses multifaceted environmental issues, such as interactions among emerging contaminants and the cumulative effects they may generate [10,17].

In addition to analyzing the damage caused by contaminants, the integrative approach focuses on understanding the mechanisms through which such damage occurs and, even more importantly, on how to prevent or mitigate their impact. For instance, it has been shown that the combined exposure to nanoplastics and pharmaceuticals can exacerbate oxidative stress and cause cellular damage in aquatic organisms. Understanding these interactions at various biological levels is essential for developing more efficient and sustainable solutions [12–14,18].

3.2. Traditional Approach Versus Integrative Approach in Ecotoxicology

Traditional methods in ecotoxicology tend to simplify environmental problems, as they usually analyze a single contaminant at a time, within a specific biological model, under controlled conditions [19–22]. While these studies are useful, they do not reflect the complexity of real ecosystems, where multiple contaminants interact unpredictably in a dynamic environment. For example, while classical studies measure the acute toxicity of a single compound, the integrative approach examines more subtle effects, such as sublethal and chronic impacts, as well as the interactions between different contaminants [5,9].

A clear example is that of PFAS (per- and polyfluoroalkyl substances), persistent compounds that accumulate in the environment. Traditional approaches often underestimate their impacts because they fail to consider how these substances interact with each other or behave within the food chain. In contrast, the integrative approach enables the analysis of these contaminants at the molecular level and across entire populations, providing a clearer and more comprehensive picture [8,10]

Building on these contrasts, Table 1 situates the shift not at the level of individual endpoints but in the logic of inquiry itself. It shows how study design moves from single-compound tests to mixture-aware problem formulation; how evidence is assembled coherently across biological organization (from molecular processes to population and ecosystem responses); and how inference transitions from descriptive patterns to AOP/omics-anchored causality that can be propagated into risk synthesis and policy decisions.

Table 1. Comparative Framework of Traditional versus Integrative Ecotoxicology Across Analytical Dimensions.

	Traditional	**Integrative**
Problem scope	Single-compound, controlled context	Mixtures & contexts
Endpoints	Mortality/acute endpoints	Sublethal, mechanistic, and population-linked
Scale	Single biological level	Molecular to Ecosystem integration
Inference	Descriptive associations	AOP & omics-informed causal pathways
Decision utility	Lab-focused, limited policy use	Policy-relevant risk synthesis (e.g., Bayesian prioritization).

Legend: Matrix outlining contrasts in problem scope, endpoints, scale of biological organization, inferential basis (AOP/omics), and decision utility for risk synthesis.

3.3. Benefits of Integrating Interdisciplinarity and Transdisciplinarity in Ecotoxicology

The main advantage of the integrative approach in Ecotoxicology is that it fosters collaboration across diverse disciplines and sectors. On one hand, interdisciplinarity, which brings together areas such as chemistry, biology, toxicology, and environmental sciences, plays a crucial role. For example, advanced technologies like biomimetic systems, such as lung-on-a-chip, have helped elucidate how nanoplastics affect human respiratory health, showcasing how biomedical engineering and ecotoxicology can work together to address complex problems [11].

Similarly, transdisciplinarity, which involves working beyond academic boundaries and collaborating with industries and governments, ensures that research does not remain confined to laboratories but translates into practical solutions. Studies such as Silva et al. (2024) [23], which used mangrove crabs to evaluate metal contamination, and Shin et al. (2023) [13], which developed innovative methods to study tire wear particles, demonstrate how such collaboration can lead to research that is more useful and representative of real-world problems.

Ultimately, the integrative approach not only enhances our ability to identify the impacts of contaminants but also strengthens the development of more effective strategies to protect ecosystems and ensure greater sustainability.

4. Key Tools and Methodologies in an Integrative Approach to Ecotoxicology

In this section, we critically analyze the main methodological and conceptual limitations that currently hinder the practical implementation of integrative ecotoxicology.

An integrative approach to ecotoxicology emphasizes the use of tools and methodologies that facilitate studying the effects of contaminants across different levels of biological organization, from molecular to ecosystem levels. This perspective seeks to understand the complexity of impacted ecosystems in a more holistic manner. Below, the most important tools supporting this approach are explored.

4.1. Experimental Methods across Multiple Levels

One of the greatest strengths of the integrative approach is its ability to assess the effects of contaminants from the simplest levels—such as molecular and cellular changes—to broader impacts on populations and ecosystems. For example, at the molecular and cellular levels, biomarkers like oxidative stress (LPX, SOD, CAT) and gene expression related to apoptosis (*bax*, *casp3*, *p53*) allow the identification of subtle but significant effects in organisms. The study by Herrera-Vázquez et al. (2024) [12], beyond reporting isolated endpoints, implemented a truly integrative design: (i) physicochemical characterization of particles (size distribution and morphology) to ensure exposure equivalence; (ii) histopathology at the organ level (gills, intestine, liver) to locate tissue damage; (iii) biochemical panel of oxidative stress (SOD, CAT, LPX) to quantify redox imbalance; and (iv) transcripts of the apoptosis pathway (bax, casp9) to anchor cell death signaling. The effects were evaluated in matched exposure scenarios to isolate material-specific risks, revealing a consistent pattern in which chitosan caused attenuated histological damage and less redox/apoptotic activation compared to polystyrene. Importantly, the authors interpreted the convergence between endpoints—lesion scores aligned with increases in LPX and upregulation of proapoptotic genes—as consistency across levels, reinforcing the causal inference. This triangulation naturally corresponds to an AOP chain (particle exposure → oxidative stress → apoptotic signaling → tissue injury), illustrating how multilevel readings support mechanism-based risk differentiation between particles of biological and petrochemical origin. Similarly, Felisbino et al. (2023) [5] documented teratogenic and oxidative stress effects of the herbicide dicamba on zebrafish embryos.

The study, conducted by Kandaswamy 2024, adopted a mixed toxicology design with crossed concentration gradients of PS-NPs and diclofenac, allowing estimation of main effects and the interaction term (two-way ANOVA/GLM). Prior to bioassays, PS-NPs were physicochemically characterized (size distribution/ζ potential/dispersion stability) to ensure exposure fidelity and separate particle-specific artifacts from solvent-specific artifacts. For oxidative stress biomarkers (e.g., SOD, CAT, GPx/TBARS, or LPX), inflammatory readouts, and target organ histopathology, the authors observed patterns inconsistent with simple additivity: co-exposures produced responses greater than the sum of the effects of a single agent, with the interaction coefficient significantly >0 at intermediate dose combinations. This was dose-dependent rather than purely nominal: responses scaled with the intensity of the administered mixture, and concordance was demonstrated between biochemical changes and injury score (e.g., gills/liver). To interrogate the mechanism, the article linked the PS-NP-enhanced redox imbalance to the known mitochondrial/COX stress of diclofenac, proposing a sequence consistent with AOP: NP-mediated membrane perturbation/ROS → amplified inflammatory signaling → tissue injury. Methodologically, the factorial design allowed for formal tests of synergy (vs. additivity benchmark), increased statistical power for the detection of interactions, and supported risk ranking taking the mixture into account. Conceptually, it demonstrates how engineered particles can potentiate pharmaceutical toxicity, an ecologically plausible scenario in receiving waters where PPCPs and nano/microplastics coexist, and exemplifies integrative practice by aligning biochemical, histological, and interaction modeling evidence to strengthen causal inference [14]. Finally, at population and ecosystem levels, research by Walther et al. (2022) [9] and Silva et al. (2024) [23] used biomonitors like fish and crabs to study metal bioaccumulation and its impact on ecosystems.

4.2. Advanced Techniques such as Omics

Omics technologies (genomics, transcriptomics, proteomics, and metabolomics) are revolutionizing Ecotoxicology by providing a comprehensive view of the deleterious effects of contaminants on bioindicator organisms. In a study by Beale (2024) working with free-ranging turtles along an environmental exposure gradient, target/analyte-based PFAS tissue loadings were combined with untargeted metabolomics and proteomics. They then used multivariate modeling (PCA/PLS) to relate internal doses to molecular phenotypes. Rigorous quality control (batch correction, feature filtering, and replicate alignment) preceded modeling to reduce technical variance. Loadings and variable importance metrics highlighted coordinated changes in lipid and energy metabolism, amino acid turnover, and redox homeostasis, while pathway enrichment mapped these features to nodes consistent with reproductive physiology (e.g., steroidogenesis, vitellogenic lipid handling). Critically, the authors assessed covariates (sex/age/body condition) to minimize confounding and demonstrated that PFAS profiles, rather than demographic structure, determined separation in chemometric space. Model stability was assessed using cross-validation/permutation testing, and selected features were biologically validated using concordant proteomic changes (e.g., transporters, enzymes in β-oxidation, and antioxidant defense), yielding an omics-phenotypic inference linking PFAS burden to impaired reproductive fitness. Conceptually, the study exemplifies an integrative process (internal dosimetry → multi-omics signals → pathway-level inference → fitness-relevant endpoints) that is reproducible and policy-relevant in wildlife health assessments [19]. Similarly, Yang et al. (2023) took advantage of a microphysiological alveolar model that maintains an air-liquid interface (ALI) and the interaction between the endothelium and epithelium, thus preserving barrier function and realistic deposition, while allowing control of the dose per surface area (mass/surface area and number of particles). Prior to exposure, nanoplastics were physicochemically characterized (size distribution, morphology, ζ-potential, dispersibility) and stability was verified under ALI conditions to minimize artefacts from agglomeration. The platform enabled aerosolized delivery and time-resolved sampling on both epithelial and endothelial sides, with barrier integrity tracked (e.g., permeability/TEER surrogates) to couple functional changes with molecular signals. Downstream, transcriptomic and proteomic profiling revealed concordant enrichment of inflammatory and oxidative-stress programs—consistent with activation of canonical stress sensors and downstream cytokine networks—while pathway analysis connected these signatures to cell-injury processes and paracrine signaling across the vascular interface. The authors strengthened attribution by using vehicle and inert-particle controls, aligning omics signals with phenotypic readouts (ROS surrogates, stress-response markers) and verifying that responses scaled with delivered dose rather than nominal concentration. Conceptually, the study exemplifies an AOP-aligned workflow in an engineered human-relevant system: exposure at ALI → redox imbalance/inflammatory signaling → barrier perturbation → tissue-level dysfunction. This integration of dosimetry-aware exposure, multi-omic readouts, and functional barrier metrics illustrates how organ-on-chip methodologies can resolve nanoplastic hazards with translational relevance beyond submerged monocultures [11]. These techniques are essential for identifying toxicity mechanisms and establishing specific biomarkers for more accurate risk assessment.

4.3. Computational Models and Big Data Tools

Computational models and big data analysis now play a critical role in the integrative approach to Ecotoxicology. These tools allow the elucidation of ecological impacts and the extrapolation of experimental results to broader, more complex scenarios. For example, Kuang et al. (2023) developed a probabilistic model based on Bayesian networks to assess the risks of exposure to volatile organic compounds (VOCs) and metals in children living near e-waste recycling sites [8]. This model not only identified priority contaminants but also estimated human health risks.

Moreover, multivariate data analysis facilitates the identification of complex response patterns to contaminants. Beale et al. (2024) used principal component analysis (PCA) and multivariate regressions to correlate turtle metabolic profiles with different PFAS exposure levels, demonstrating how these techniques improve our understanding of ecological impacts [19].

4.4. Environmental Monitoring and the Use of Biochemical and Physiological Indicators

Environmental monitoring using biochemical and physiological indicators is another key tool in the integrative approach. This allows for the detection of contaminants and the assessment of their impacts in real time. Studies like those by [9,24] have combined physicochemical analyses and biomarkers to identify contaminants in air and water, highlighting the importance of comprehensive monitoring in urban and industrial ecosystems.

In aquatic environments, biomarkers such as acetylcholinesterase (AChE) activity and histological alterations have been used to study exposure to pesticides and heavy metals. For instance, Elizalde-Velázquez et al. (2024) identified oxidative damage and dysfunction in key organs of zebrafish exposed to quaternary surfactants, emphasizing the sensitivity of these indicators as essential tools for environmental monitoring [18].

4.5. Terrestrial and Soil Interfaces in Integrative Ecotoxicology: Implications for One Health

Extending the integrative logic beyond aquatic systems, terrestrial interfaces illustrate how bringing together chemistry, materials characterization, and biology yields evidence that can inform remediation and product stewardship. In biochar–metal contexts, speciation and bioaccessibility analyses paired with bacterial toxicity and early plant performance indicate that feedstock-dependent sorbent properties govern copper partitioning and tangible hazard reduction, linking material design to ecological function [25]. Multi-environment testing of bio-based mulch films translates leachate chemistry into matrix-specific risks across soil, freshwater, and marine compartments, with divergent impacts on earthworm reproduction and microalgal growth that would be missed in single-medium assays [26]. At the waste–soil boundary, earthworm biomarker indices integrating oxidative stress, cytotoxicity, and behavior detect sublethal effects of complex mixtures beyond what routine chemistry captures, enabling biological prioritization for landfill management [27]. Photocatalytic treatment of a neonicotinoid further demonstrates that transformation products can retain chronic toxicity in *Eisenia andrei*, underscoring the need to evaluate degradates alongside parent compounds [28]. Finally, phytoremediation engineering in *Brassica napus* shows that organic acids can shift lead bioavailability, reinforce antioxidant defenses, and improve growth while elevating transfer metrics relevant to field deployment [29]. Collectively, these soil-centric studies exemplify the review's framework by coupling mixture- and matrix-aware problem formulation with multi-level endpoints and chemistry–biology integration, advancing an evidence base aligned with One Health by connecting terrestrial exposure pathways to food safety and ecosystem services [25–29].

5. Examples of Integrative Ecotoxicological Studies

In this section, we summarize the most relevant advances reported in recent literature (2022–2024), emphasizing cross-matrix studies and multilevel biological endpoints.

Table 2 provides a consolidated summary of recent integrative ecotoxicology studies published between 2022 and 2024. It compiles nearly twenty-four studies, each outlining the research aim, the bioindicator organism or system used, the pollutants examined, the methods and biomarkers applied, the key findings, and the level(s) of biological organization addressed. The studies are organized by ecosystem or context—grouped into Aquatic, Terrestrial/Soil, and Human categories—and each entry is annotated with the class of contaminants involved (such as pharmaceuticals, plastics, heavy metals, pesticides, etc.). This structured layout highlights the breadth of environments and pollutants covered and improves readability by allowing direct comparisons within each cluster. In essence, Table 2 presents a comprehensive overview of how integrative approaches have been applied across different contexts: from aquatic organisms and ecosystems, through soil and terrestrial studies, to investigations that link environmental pollution with human health. By summarizing the methodologies and outcomes side-by-side, the table serves as a quick reference that underscores the multi-disciplinary tools and endpoints utilized in these studies, as well as their relevance to the integrative ecotoxicology framework.

The data compiled in Table 2 reveal important patterns and gaps in the current state of integrative ecotoxicology research. A prominent observation is the imbalance in focus across ecosystems: the majority of studies documented are in aquatic environments (e.g., fish, algae, aquatic invertebrates), whereas comparatively fewer studies address terrestrial (soil) ecosystems or direct human health contexts. This skew suggests that integrative ecotoxicological approaches have been more extensively applied in aquatic systems, highlighting a relative gap in soil ecotoxicology and human-focused studies. The inclusion of a handful of terrestrial and human-related studies in the table (such as those examining biodegradable plastic impacts on soil biota, heavy metal transfer to humans via food chains, or pollution-related oxidative stress in human populations) helps broaden the perspective beyond aquatic examples. However, the smaller number of such studies indicates that these areas are still emerging, and further research is needed to fully bridge environmental contamination with terrestrial ecosystem and public health outcomes. Identifying this gap is important, as it points to opportunities for future integrative studies in soil environments and at the environment-human interface (for instance, linking pollution to food safety and human risk in a more comprehensive way).

Another key insight from Table 2 is the diversity of contaminants and methodologies covered, alongside some notable limitations. The studies encompass a range of pollutant classes—including pharmaceuticals and personal care products (PPCPs), microplastics/bioplastics, heavy metals, pesticides (traditional and bio-based), and complex mixtures—demonstrating that integrative approaches are being applied to various contemporary pollution issues. Many of the aquatic studies, for example, focus on emerging contaminants like pharmaceuticals and nanomaterials, while others examine metals and persistent organic pollutants in sediments. Terrestrial studies tend to explore contaminants such as agrochemicals or waste by-products (e.g., landfill leachate, soil amendments), often with an eye toward remediation or environmental health. This breadth is a strength, but it also underscores that certain contaminant groups (beyond those listed) may still be underrepresented. Importantly, the methodologies used across these studies are multi-faceted, combining traditional toxicity assays with biochemical, molecular, and even computational techniques. Common to many entries is the use of biochemical biomarkers (e.g., antioxidant enzymes, oxidative stress indicators) alongside chemical analyses of pollutant levels. Several studies integrate higher-tier approaches: for instance, some incorporate omics technologies (proteomics, metabolomics), advanced imaging or modeling (e.g., molecular docking simulations), and formal risk assessment metrics. The inclusion of these innovative tools illustrates how integrative ecotoxicology strives to connect molecular-level effects with organismal and ecosystem-level outcomes. It's noteworthy, however, that while a few studies employ comprehensive omics and multi-level analyses, many others rely on more conventional biomarker and toxicity test combinations. This suggests that truly holistic, multi-scale approaches are still limited to select cases, and there is room for wider adoption of advanced integrative techniques in future studies.

Table 2. Integrative ecotoxicology studies (2022–2024) grouped by ecosystem and contaminant class, highlighting the applied biomarkers, analytical methods, and multi-level integrative approaches used in each case.

Ecosystem/ Bioindicator	Organism/Model	Contaminant Class	Contaminant(s)	Methods/Biomarkers (Integrative)	Key Findings	Level of Evaluation	Relevance to Integrative Approach	Reference
A. AQUATIC								
Aquatic (marine microalgae)	Marine diatoms (*Phaeodactylum tricornutum*)	Pharmaceuticals /PPCPs	Propranolol, fluoxetine, ibuprofen; Cu (nanoparticle & dissolved); surfactant (SDS); biocides	Fatty acid profiling (GC–MS); integrated biomarker index (LipidTOX)	Contaminants significantly alter fatty acid profiles; LipidTOX efficiently indicates ecotoxicological effects	Molecular, Biochemical	Introduces a fatty-acid-based biomarker index for assessing marine contamination; informs ecosystem management decisions	[30]
Aquatic (freshwater fish)	Adult zebrafish (*Danio rerio*)	Pharmaceuticals /PPCPs	Fluoxetine (antidepressant)	Behavioral assays (novel tank test); oxidative stress biomarkers (SOD, CAT, GPx, LPx, etc.); AChE activity; LC–MS/MS analysis	Fluoxetine alters exploratory behavior, induces oxidative stress, and reduces brain AChE activity, linking behavioral changes to oxidative damage and neurotoxicity	Biochemical, Neurotoxic & Behavioral	Demonstrates sublethal behavioral and biochemical effects of an emerging contaminant, highlighting potential food-web impacts on aquatic ecosystem health	[20]
Aquatic (freshwater fish)	Adult zebrafish (*Danio rerio*)	Pharmaceuticals /PPCPs	Mixed hospital effluent (Pharmaceuticals: ranitidine, ketorolac, dexamethasone, etc.; trace metals; pathogenic bacteria)	Antioxidant biomarkers (SOD, CAT, LPx, PCC, HPC); gene expression (RT-qPCR of antioxidant & apoptotic genes); meta-taxonomic (microbial) analysis	Treated effluent induces oxidative stress and alters gene expression (e.g., *sod, cat, cyp1a1, bax, casp9*), triggering apoptosis in gill, intestine, liver; resistant pathogenic bacteria detected	Molecular, Biochemical & Genetic	Combines biochemical and molecular biomarkers with microbiome analysis to evaluate complex real-world effluent toxicity risks	[4]
Aquatic (river biota)	Algae, fish, invertebrates (Musi River ecosystem)	Pharmaceuticals /PPCPs	Multiple PPCPs (antibiotics: ciprofloxacin, norfloxacin; antifungal: fluconazole; caffeine; carbamazepine; naproxen)	Solid-phase extraction; LC–MS/MS quantification; ecological risk assessment (risk quotients, PNEC)	Ciprofloxacin and fluconazole pose high ecotoxicological risk to algae and long-term threat to fish/invertebrates; PPCPs also drive antimicrobial resistance in microbes	Ecological, Toxicological	Highlights the dual threat of PPCPs and antibiotic resistance; integrates chemical data and bioassays for comprehensive risk assessment, informing urban water management strategies	[31]
Aquatic (riverine system)	Water, sediments, fish (*Sardinella longiceps*, *Centropristis striata*)	Plastics	Phthalate esters (DBP, DEHP, DiBP, DCHP)	GC–MS analysis (water/sediment); bioaccumulation factors in fish; ecological and human risk indices (HQ, THQ)	Phthalates are prevalent in water and sediment; DBP and DEHP yield HQ > 1 for aquatic organisms, indicating significant risk; minimal risk to humans via water or fish consumption	Ecological	Integrates chemical monitoring with bioaccumulation and risk assessment, underlining the need for routine monitoring and management of plasticizers in aquatic systems	[1]
Aquatic (freshwater invertebrates)	Water flea (*Daphnia magna*); marine bacterium (*Vibrio fischeri*); benthic macroinvertebrate community	Metals	Pb, Cu, Cd, Cr, Zn (urban river pollution)	Acute and chronic toxicity tests (*Daphnia* 48 h, 21 d); Microtox® bioluminescence assay; macroinvertebrate biodiversity index (BMWP); metal quantification (FAAS)	No acute toxicity observed, but chronic exposure caused reproductive impairment in *D. magna* (urban sites); benthic macroinvertebrate diversity declined in highly anthropized areas	Ecological	Uses multi-species bioindicators and physicochemical analyses to assess chronic contamination impacts, showcasing an interdisciplinary approach for ecological risk evaluation in freshwater habitats	[32]

Table 2. *Cont.*

Ecosystem/ Bioindicator	Organism/Model	Contaminant Class	Contaminant(s)	Methods/Biomarkers (Integrative)	Key Findings	Level of Evaluation	Relevance to Integrative Approach	Reference
Aquatic (freshwater & sediment organisms)	Amphipods (*Hyalella azteca*), midge larvae (*Chironomus riparius*), water flea (*D. magna*), rainbow trout (*Oncorhynchus mykiss*)	Metals	Cd, Zn, Pb, Hg, Ni, Cu, As (watershed runoff)	Integrated monitoring: metal analysis (ICP–MS); sediment toxicity tests (standardized bioassays)	Cd and Zn identified as key toxicants in water, Cd and As in sediments; Zn in sediment eluates drives toxicity; sediment resuspension serves as a secondary contamination source	Chemical, Ecological & Toxicological	Combines chemical analytics with multi-species toxicity data and modeling to pinpoint contamination sources and assess ecological risks in a complex watershed	[33]
Aquatic (sediment quality)	Reservoir sediments (fish breeding area)	Metals	Hg, Cd, Pb, As, Cu, Ni, Zn, Cr, Mn, Fe (potentially toxic elements)	ICP–MS multi-element analysis; sediment contamination indices (mHQ, EF, Igeo, CF, etc.); ecological and human health risk assessment	Cr, Ni, Cu, As levels exceed TEL/PEL sediment guidelines; however, probabilistic risk assessment indicates low-to-moderate actual ecological and human health risk	Ecological	Employs geochemical indices and health risk models to evaluate sediment contamination from natural and anthropogenic sources, demonstrating a holistic approach to ecosystem and public health risk appraisal	[34]
Aquatic (benthic invertebrates)	Clam (*Anomalocardia flexuosa*), harpacticoid copepod (*Nitokra* sp.), amphipod (*Tiburonella viscana*), brine shrimp (*Artemia salina*)	Pesticides	Chlorothalonil (fungicide)	Biochemical biomarkers (LPx, GPx, GST, GSH, DNA damage in tissues); acute (48–96 h) and chronic (sediment 10-d, 28-d) toxicity tests	Chlorothalonil caused oxidative stress and DNA damage in benthic organisms, reduced copepod fecundity, and increased mortality, affecting biological organization from biochemical to population levels	Biochemical, Individual & Population	Uses a multilevel approach (from molecular biomarkers to reproduction and survival) to evaluate sediment pesticide risks, emphasizing effects on non-target coastal species in a realistic exposure scenario	[35]
Aquatic (freshwater fish)	Adult zebrafish (*Danio rerio*)	Pesticides	Spinosad (bioinsecticide)	96 h acute and 28 d chronic exposure; oxidative stress biomarkers (SOD, CAT, GST, TBARS); neurotoxicity marker (AChE); energy reserve assays (glycogen, lipids, protein)	Sublethal spinosad exposure induces oxidative stress, disrupts energy metabolism, and causes neurotoxic effects in fish	Biochemical, Cellular	Leverages multiple biomarkers to detect sublethal impacts of a "green" pesticide on a non-target species, providing essential data for ecological impact assessment and biopesticide regulation	[7]
Aquatic (freshwater ecosystem)	Water, sediment, fish (Anyim River, Nigeria)	Pesticides	Glyphosate-based herbicides (residues of glyphosate and byproducts)	Chemical analysis of herbicide residues in water/sediment/fish (HPLC or GC methods); ecological risk assessment (hazard quotients)	Glyphosate residues detected in water, sediments, and fish; risk quotients > 1 indicate potential harm to aquatic organisms, though current levels pose low risk via fish consumption	Ecological	Integrates multi-compartment contaminant monitoring with ecological risk modeling, highlighting herbicide pollution as an emerging concern for tropical freshwater ecosystems and the need for mitigative measures	[36]

Table 2. *Cont.*

Ecosystem/ Bioindicator	Organism/Model	Contaminant Class	Contaminant(s)	Methods/Biomarkers (Integrative)	Key Findings	Level of Evaluation	Relevance to Integrative Approach	Reference
Aquatic (estuarine ecosystem)	Sediments; fish (estuarine species)	Pesticides	Organochlorine pesticides (OCPs; e.g., DDTs, HCHs, cyclodienes)	Chemical analysis of OCPs in sediment and fish (GC–ECD); environmental distribution assessment; human health risk evaluation (fish consumption risk indices)	OCPs persist in estuary sediments and bioaccumulate in fish; several compounds exceed ecological safety thresholds, and risk assessment indicates potential health risks for consumers of local fish	Ecological, Human	Couples environmental monitoring of legacy pesticides with human health risk assessment, illustrating an integrative framework to address contamination in coastal ecosystems and inform regulatory policies	[37]
Aquatic (sentinel predators)	Top predator fish (protected World Heritage Site)	Others (mixed pollutants)	Multiple water contaminants (pollution gradient in reserve)	Biomarker assays in fish (e.g., antioxidative enzymes, histopathology); water quality and contaminant measurements; multivariate environmental analysis	Detectable biomarker responses (oxidative stress, tissue alterations) in fish correspond to areas of higher pollution, reflecting sublethal impacts of mixed contaminants on biota in the reserve	Biochemical, Ecological	Demonstrates the use of wild fish biomarkers to monitor ecosystem health in a protected area, linking subtle molecular effects to broader water quality issues and supporting One Health-oriented conservation strategies	[38]
Aquatic (marine bioactive compound)	Marine mussels (*Mytilus galloprovincialis*); marine bacteria; diatoms (*Navicula* sp.); brine shrimp (*Artemia salina*); barnacle (*Amphibalanus amphitrite*); zebrafish (*Danio rerio*)	Others (biocide/natural product)	Nocuolin A (cyanobacterial oxadiazine compound)	Enzymatic assays (AChE, tyrosinase inhibition in vitro); proteomics (LC–MS/MS); in vitro toxicity tests; in silico modeling (QSAR; antifouling fate models)	Nocuolin A effectively inhibits mussel larvae and diatom biofouling (low EC_{50} values) but is highly toxic to non-target species (zebrafish LC_{50} = 0.058 μM), indicating significant environmental risk	Molecular, Cellular & Ecological	Utilizes advanced omics and modeling tools to evaluate a natural antifoulant, underscoring its promising efficacy and highlighting its toxicity trade-offs, crucial for sustainable marine antifouling solutions	[39]
				B. TERRESTRIAL–SOIL				
Terrestrial (agro-ecosystem)	Soil, freshwater & marine bioassays: plants (*Sorghum saccharatum, Lepidium sativum, Sinapis alba*); earthworms (*Eisenia andrei*); water flea (*D. magna*); diatom (*Phaeodactylum tricornutum*); polychaete worm (*Arenicola marina*)	Plastics	Biodegradable plastic mulch (PLA–PBAT polymer film & leachates)	Multi-environment bioassays: seed germination and plant growth; earthworm reproduction; Daphnia and Artemia toxicity (leachate); marine algae growth inhibition; oxidative stress enzyme assays	PLA/PBAT mulch leachates impaired earthworm reproduction and *D. magna* survival, inhibited marine algal growth, and slightly enhanced marine worm enzymatic activity; overall hazard profile varies by environmental compartment	Biochemical, Cellular, Ecological	Employs a cross-matrix integrative assessment of a bio-based plastic, demonstrating how coordinated bioassays across soil, freshwater, and marine systems can evaluate the safety and sustainability of novel materials	[26]

Table 2. *Cont.*

Ecosystem/ Bioindicator	Organism/Model	Contaminant Class	Contaminant(s)	Methods/Biomarkers (Integrative)	Key Findings	Level of Evaluation	Relevance to Integrative Approach	Reference
Terrestrial (soil remediation)	Contaminated soil; bacteria (*Arthrobacter globiformis*); plant seedlings (various species)	Metals	Cu, Cr, As (CCA wood-treatment chemicals in soil)	Amendment trials with 14 biochar types; bioaccessible metal analysis (soil extractions); bacterial growth inhibition test; plant seedling growth assay; material characterization of biochars	Biochar amendments reduced Cu bioavailability and soil toxicity by up to 55% for soil bacteria and improved plant growth by ~73%; efficacy varied with biochar feedstock (rapeseed straw biochar most effective)	Cellular, Ecosystem	Integrates materials science, microbiology, and plant bioassays to link biochar properties with remediation performance, informing design of effective soil amendment strategies for metal-polluted soils	[25]
Terrestrial (phytoremediation)	Canola (*Brassica napus* L.)	Metals	Lead (Pb)	Hydroponic exposure with organic acids (malic, tartaric); oxidative stress biomarkers (MDA, H_2O_2, electrolyte leakage); antioxidant enzymes (SOD, CAT, APX, POD); spectroscopic analysis (FTIR); electron microscopy (SEM/TEM); bioaccumulation metrics (BAF, TF)	Organic acids enhanced plant growth, photosynthesis, and nutrient uptake under Pb stress; significantly lowered oxidative damage (MDA, H_2O_2) and increased Pb phytoextraction (BAF, TF > 1) in canola roots and shoots	Biochemical, Physiological & Molecular	Combines biochemical stress markers, ultrastructural analysis, and uptake metrics to demonstrate how amendments mitigate heavy-metal toxicity, providing a framework for improving phytoremediation in agriculture	[29]
Terrestrial (soil invertebrate)	Earthworm (*Eisenia andrei*)	Pesticides	Acetamiprid (neonicotinoid)—photocatalytic degradation mixture	Exposure to TiO_2/UV-degraded acetamiprid: 72 h acute and 45 d chronic tests; antioxidant biomarkers (CAT, GST, GSH); coelomocyte cytotoxicity assays (cell viability, density)	Acetamiprid degradates caused significant chronic toxicity in earthworms, with elevated CAT/GST activities (oxidative stress) and subtle cytotoxic effects, indicating persistent soil toxicity despite parent compound breakdown	Biochemical, Cellular & Ecological	Uses advanced degradation techniques and ecotoxicological biomarkers to reveal "hidden" risks of pesticide transformation products in soil, highlighting the importance of assessing breakdown products in integrative ecotoxicology	[28]
Terrestrial (wild fauna sentinel)	White stork (*Ciconia ciconia*) chicks (field study in Poland)	Pesticides (and PCBs)	Organochlorine pesticides and PCBs (in eggs/food web)	Field contaminant analysis (pesticide and PCB levels in blood/food); blood chemistry and antioxidant biomarkers (e.g., ALT, AST, GSH-Px, SOD); oxidative stress markers	Elevated organochlorine pesticide and PCB exposure is associated with altered blood parameters and increased oxidative stress in stork chicks from polluted areas, indicating contaminant-induced physiological stress	Biochemical, Individual	Links environmental pollutant burdens to biochemical stress responses in wild birds, demonstrating the utility of top predators as bioindicators and the ecological relevance of biomarker-based field evaluations	[40]
Terrestrial (waste pollution)	Earthworm (*Eisenia andrei*)	Others (complex mixture)	Landfill leachate (mixed contaminants: metals, high COD, BOD, chlorides)	Chronic 45 d earthworm assay; biomarker response index (integrating antioxidant enzymes SOD, CAT, GST, GSH, metallothionein; oxidative damage markers MDA, PTC; coelomocyte viability; behavioral changes)	Prolonged leachate exposure provoked moderate oxidative stress and cytotoxic effects in earthworms; a composite biomarker index sensitively detected sublethal mixture effects not evident from chemistry alone	Biochemical, Cellular & Ecological	Demonstrates an integrative biomarker approach for complex waste exposure, where biological responses in a soil indicator species reveal ecological risks that complement traditional chemical analysis	[27]

Table 2. *Cont.*

Ecosystem/ Bioindicator	Organism/Model	Contaminant Class	Contaminant(s)	Methods/Biomarkers (Integrative)	Key Findings	Level of Evaluation	Relevance to Integrative Approach	Reference
C. HUMAN								
Human (food-chain exposure)	Edible insects (*Cirina forda*, *Imbrasia obscura*); agricultural soils; crop plants	Metals	As, Cd, Cr, Cu, Fe, Ni, Pb, Zn (mining area contamination)	AAS/ICP–OES metal analysis (soil, plant, insect); transfer factor (TF) calculations; estimated daily intake (EDI); health risk indices (THQ, HI)	Edible insects bioaccumulate heavy metals with levels up to 9× above FAO/WHO limits; transfer factors >1 for several metals, and risk indices indicate significant human health risks for local consumers	Ecological, Human	Employs an integrative soil-plant-insect-human assessment to trace contaminant biomagnification, linking environmental pollution from mining to food safety and public health risk management	[2]
Human (community health)	Residents (142 humans near reservoir)	Others (mixed pollutants)	Heavy metals in drinking water (Fe, Al, Cr, Pb, Cd) and air pollutants (SO_2, NO_2, O_3, CO, PM_{10})	Biomarkers of oxidative stress (lipid peroxidation levels); clinical enzymes (ALT, AST, ALP, LDH); chemical analysis of water metals; personal exposure assessment (air quality)	Elevated metal (Fe, Al) in drinking water and local air pollution are associated with increased lipid peroxidation and altered liver enzymes (↑ALP, LDH) in residents, linking environmental pollution to oxidative stress and potential health effects	Human & Biochemical	Integrates environmental monitoring with human biomarker responses and statistical analysis to connect ecosystem pollution with community health, exemplifying a One Health approach to pollution impact assessment	[41]
Human (urban pollution exposure)	Children (e-waste recycling community)	Others (mixed pollutants)	Volatile organic compounds (VOCs); metals/metalloids (from e-waste)	Exposure monitoring post-intervention (air VOC sampling; blood/urine metal levels); comparative risk analysis; identification of priority pollutants	Despite recent e-waste control measures, children exhibit significant residual exposure to certain VOCs and metals; identified priority pollutants (e.g., lead, benzene) remain above safe levels, indicating ongoing health risk and need for further mitigation	Human & Biochemical	Bridges environmental management and public health by using exposure biomarkers in children to evaluate the effectiveness of pollution control, highlighting gaps and guiding targeted interventions in a vulnerable population	[8]
Human (seafood safety)	Wild mud crab (*Scylla olivacea*)—consumer perspective	Metals	Ni, Cu, Zn, Pb, Cr, Cd, As (coastal sediment pollution)	Multi-omics (proteomics 2D-PAGE; NMR-based metabolomics); metal analysis (ICP–MS); molecular docking of toxins to proteins; human health risk assessment (EDI, THQ)	Heavy metal exposure disrupts crab gill/liver proteome and metabolome, impairing osmoregulation and energy pathways; molecular docking revealed arsenical binding to key proteins, and risk assessment indicates potential health concerns for humans consuming contaminated crabs	Molecular, Metabolic, Ecological & Human	Integrates molecular biomarkers (omics) in a wildlife indicator with human risk models, demonstrating a transdisciplinary approach that links subcellular toxic mechanisms to ecosystem health and food safety implications	[42]

Abbreviations: 2D—two-dimensional (gel electrophoresis in proteomic analysis); A. marina—Arenicola marina; A. persimilis—Artemia persimilis; AAS—atomic absorption spectroscopy; AChE—acetylcholinesterase; ALP—alkaline phosphatase (enzyme); ALT—alanine aminotransferase (enzyme); APX—ascorbate peroxidase (antioxidant enzyme); AST—aspartate aminotransferase (enzyme); AutoDock—AutoDock (molecular docking software); BAF—bioaccumulation factor (ratio of contaminant in organism vs. environment); BMWP—Biological Monitoring Working Party (aquatic macroinvertebrate index); BOD—biochemical oxygen demand; CAT—catalase (antioxidant enzyme); CCA—chromated copper arsenate (Cu–Cr–As wood preservative); CF—contamination factor (pollution index); CO—carbon monoxide (air pollutant); COD—chemical oxygen demand; D. magna—Daphnia magna; D. rerio—Danio rerio; DBP—dibutyl phthalate (phthalate ester); DCHP—dicyclohexyl phthalate (phthalate ester); DEHP—di(2-ethylhexyl) phthalate (phthalate ester); DiBP—diisobutyl phthalate (phthalate ester); DNA—deoxyribonucleic acid; EC50—median effective concentration (causing 50% effect); EDI—estimated daily intake (human exposure); EF—enrichment factor (contamination index); EL—electrolyte leakage (cell-membrane damage indicator); FAAS—flame atomic absorption spectroscopy; FAO—Food and Agriculture Organization (United Nations); FTIR—Fourier transform infrared spectroscopy; GC-MS—gas chromatography–mass spectrometry; GLY—glycogen (energy reserve); GPX—glutathione peroxidase (antioxidant enzyme); GSH—

glutathione (reduced form, antioxidant); GST—glutathione S-transferase (detoxification enzyme); H_2O_2—hydrogen peroxide; HI—hazard index (sum of hazard quotients); HPC—hydroperoxide content (total peroxides, oxidative stress biomarker); HPX—lipid hydroperoxides (oxidative stress biomarker); HQ—hazard quotient; ICP-MS—inductively coupled plasma mass spectrometry; ICP-OES—inductively coupled plasma optical emission spectrometry; LC50—median lethal concentration (causing 50% mortality); LC-MS—liquid chromatography–mass spectrometry; LC-MS/MS—liquid chromatography–tandem mass spectrometry; LDH—lactate dehydrogenase (enzyme); LIP—lipids (total lipid content); LPX—lipid peroxidation (oxidative damage indicator, e.g., MDA level); MAMPEC—Marine Antifoulant Model to Predict Environmental Concentrations; MDA—malondialdehyde (lipid peroxidation marker); M-ERM-Q—meSan Effects Range-Median quotient (sediment contamination index); MT—metallothionein (metal-binding protein); NMR—nuclear magnetic resonance; NO_2—nitrogen dioxide (air pollutant); O_3—ozone (air pollutant); PBAT—poly(butylene adipate-co-terephthalate) biopolymer; PCC—protein carbonyl content (protein oxidation marker); PEL—Probable Effect Level (sediment quality guideline); PLA—polylactic acid (biopolymer); PM_{10}—particulate matter $\leq$ 10 µm (air pollutant particles); PNEC—predicted no-effect concentration; POD—peroxidase (enzyme activity, e.g., guaiacol peroxidase); POX—protein oxidation (general oxidative damage to proteins); PPCP—pharmaceutical and personal care product; PROT—proteins (total protein content); PTC—protein thiol content (free thiol groups, oxidative stress marker); PTE—potentially toxic elements (trace metals/metalloids); QSAR—quantitative structure–activity relationship; RQ—risk quotient; RT-qPCR—reverse transcription quantitative polymerase chain reaction; S. olivacea—Scylla olivacea (mud crab); SDS—sodium dodecyl sulfate (anionic surfactant); SDS-PAGE—sodium dodecyl sulfate polyacrylamide gel electrophoresis; SEM—scanning electron microscopy; SO_2—sulfur dioxide (air pollutant); SOD—superoxide dismutase (antioxidant enzyme); TBARS—thiobarbituric acid reactive substances (lipid peroxidation assay); TEL—Threshold Effect Level (sediment quality guideline); TEM—transmission electron microscopy; TF—translocation factor (plant metal uptake ratio, shoot/root); THQ—target hazard quotient (human health risk); TiO_2—titanium dioxide; UV—ultraviolet (radiation); WHO—World Health Organization; XRF—X-ray fluorescence spectroscopy.

Critically, while Table 2 is informative in cataloging recent studies, a purely descriptive summary is not sufficient on its own—it must be leveraged to draw deeper conclusions. A critical examination of the compiled studies indicates that researchers have made significant progress in developing indices and combined methods to assess ecotoxicological effects (for example, creating integrated biomarker indices or multi-species test batteries for risk assessment). These efforts support the notion that an integrative approach can yield a more nuanced understanding of pollutant impacts than single-method studies. For instance, several aquatic studies in the table demonstrate how combining chemical analytics with biological endpoints can identify sublethal effects that would be missed by chemistry data alone, or how multi-organism experiments reveal ecosystem-level consequences of contaminants. In the terrestrial context, studies show the value of cross-matrix designs (soil, water, biota) and the effectiveness of interventions like biochar or phytoremediation in reducing toxicity. Despite these advances, the table also hints at certain shortcomings and research gaps that call for a more critical discussion. One such shortcoming is the limited scope of temporal and geographical coverage—most studies are short-term assessments and many are laboratory or controlled field experiments, with relatively few long-term or large-scale field studies. This raises questions about the long-term applicability of the findings and whether the observed effects translate to real-world scenarios over time. Additionally, since the table covers only literature from 2022–2024, it provides a snapshot of the very recent state of the field; this recency focus, while highlighting current trends, means that earlier foundational work (prior to 2022) is not represented, which could be addressed by contextualizing these findings within the broader historical framework of integrative ecotoxicology in the narrative.

From the table, it becomes evident that integrative ecotoxicology is a burgeoning field marked by interdisciplinary strategies, yet it is still evolving in its critical depth. Many of the compiled studies provide proof-of-concept demonstrations of integrating multiple tools (e.g., combining biomarker assays with chemical measurements and computational models) and emphasize the advantages of such integration, like improved sensitivity or more comprehensive risk evaluation. At the same time, there is a need for the review to explicitly draw out common themes and challenges that emerge from these studies. For example, one theme is the challenge of data integration itself: how to meaningfully combine diverse data streams (molecular, toxicological, ecological) to inform environmental management decisions. Several studies in the table hint at this by developing indices or composite measures, but comparing those approaches could uncover which strategies are most effective in different contexts. Another theme is the identification of knowledge gaps: as noted, underexplored areas such as soil ecotoxicology or long-term ecosystem responses represent gaps that the current literature has not fully addressed.

To complement the table described earlier, a term map was generated using the VOSviewer software, illustrating a network of co-occurrences in publications related to ecotoxicology (Figure 2). In this visualization, the nodes represent key concepts, while the connections between them depict the relationships or frequencies of their co-occurrence within the analyzed studies. The size of each node indicates the term's relevance or frequency, and the colors correspond to a temporal range from 2022 to 2024, as shown on the time scale bar at the bottom.

Prominent terms identified in the map include "ecotoxicology," "oxidative stress," "heavy metals," "environmental health," and "bioaccumulation." These are interconnected with related concepts such as "zebrafish," "apoptosis," "antifouling," and "health risk assessment." This network highlights major research areas, including the effects of emerging contaminants, environmental and human health risks, and the application of bioindicator organisms like *Daphnia magna* and zebrafish.

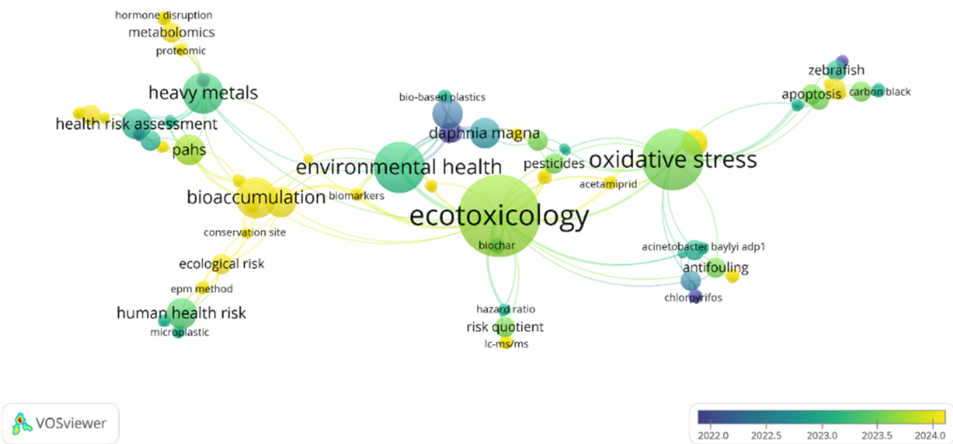

Figure 2. Co-occurrence network of key terms in integrative ecotoxicology (2022–2024) generated with VOSviewer; node size reflects term frequency and color encodes average publication year.

5.1. Recent Notable Studies

Recent studies in Ecotoxicology have combined multiple tools and levels of analysis to tackle complex problems. For instance, Herrera-Vázquez et al. (2024) compared the effects of polystyrene microplastics and chitosan biopolymer films on zebrafish (*Danio rerio*), demonstrating how biopolymers could serve as a less harmful alternative for aquatic ecosystems [12]. This study integrated molecular, biochemical, and histological analyses to evaluate the health effects on organisms.

In another study, Beale et al. (2024) investigated the impact of PFAS compounds on freshwater turtles (*Emydura macquarii macquarii*), using metabolomic and proteomic analyses to identify metabolic changes linked to reproductive health [19]. This research highlighted how persistent compounds can have significant cumulative effects on wildlife species.

5.2. Cases of Emerging Contaminants: Pharmaceuticals and Nanoplastics

Emerging contaminants, including nanoplastics and pharmaceuticals, pose growing concerns due to their persistence, continuous release into the environment, and toxicity. Kandaswamy et al. (2024) explored the synergistic effects of polystyrene nanoplastics and diclofenac on adult zebrafish, demonstrating that the combination of these contaminants exacerbated oxidative stress, inflammation, and cellular damage. This study underscored the importance of assessing contaminant interactions to understand their real impacts on ecosystems [14].

Yang et al. (2023) developed an innovative lung-on-a-chip model to study how nanoplastics affect human respiratory tissue [11]. This model, which simulates the conditions of the alveolar-capillary barrier, revealed that nanoplastics induce oxidative stress and inflammatory damage, highlighting potential risks to both human and environmental health.

5.3. Aquatic Bioindicators in Integrative Ecotoxicology Research

Aquatic bioindicator organisms, such as fish, crabs, and algae, have been widely used in integrative studies due to their ability to represent different trophic levels [32, 36-38]. *Danio rerio* (zebrafish) is one of the most popular models because of its sensitivity to contaminants and ease of studying molecular and physiological responses. For example, Felisbino et al. (2023) documented the teratogenic effects of the herbicide dicamba on zebrafish embryos, emphasizing its utility in assessing risks during early developmental stages [5].

Another notable model is the mangrove crab (*Ucides cordatus*), used by Silva et al. (2024) to assess metal contamination in coastal ecosystems. This study demonstrated how these organisms can serve as effective bioindicators for monitoring the health of tropical ecosystems [23].

5.4. Relationship between Ecotoxicology and Global Health Strategies (One Health)

Ecotoxicology plays a key role in the One Health approach by evaluating the impact of contaminants on ecosystems, as well as on human and animal health. Kuang et al. (2023) studied the effects of volatile organic compounds (VOCs) and metals on children exposed to electronic waste recycling, revealing significant health risks such as oxidative damage and metabolic alterations. This study emphasized the need to integrate human and environmental health into mitigation strategies [8].

Similarly, Walther et al. (2022) investigated mercury bioaccumulation in fish (*Lota lota*) in Alaska and its impact on human communities that rely on these resources for food. The findings demonstrated how contaminant exposure can directly affect food security and public health, underscoring the importance of linking ecotoxicology with global health [9].

6. Challenges and Limitations of the Integrative Approach in Ecotoxicology

In this section, we identify explicit knowledge gaps that persist despite recent progress, providing a foundation for future experimental and regulatory efforts.

Although the integrative approach in ecotoxicology has achieved significant advancements, its implementation faces critical technical, economic, and logistical challenges, along with barriers related to knowledge gaps and data interpretation. Below, these key challenges are analyzed.

6.1. Technical, Economic, and Logistical Barriers

The integrative approach requires the use of advanced technologies and multidisciplinary methodologies, which often entail high costs and technical complexities. For example, omics techniques such as transcriptomics and metabolomics provide detailed information on the molecular effects of contaminants but require specialized equipment, trained personnel, and computationally intensive data analysis [11,19]. This can pose a barrier to adoption in resource-limited countries.

Additionally, implementing innovative models, such as lung-on-a-chip to study the effects of nanoplastics on human tissues, while promising, involves high development and validation costs, as well as logistical challenges for integration into broader ecological studies [11]. On a practical level, logistics for collecting and handling representative environmental samples, as in studies on metal bioaccumulation in fish and crabs [9,23] can also be complex and costly.

6.2. Knowledge Gaps and Need for Standardization

Although the integrative approach considers multiple levels of biological organization and contaminants, significant knowledge gaps remain. For instance, relatively little is known about the synergistic or antagonistic interactions between emerging contaminants, such as pharmaceuticals and nanoplastics, under real environmental [12,14]. The effects of these interactions on biodiversity, ecosystems, and human health are not fully understood, limiting the ability to extrapolate experimental results.

Furthermore, the lack of international standards in experimental design and result interpretation complicates the comparison of studies. For example, while some studies evaluate contaminant effects using biochemical, microbiological biomarkers, others use histopathological analyses or omics techniques, making it difficult to effectively integrate and compare results [43–51].

Despite remarkable advances achieved through integrative ecotoxicology between 2022 and 2024, several critical gaps persist that limit the extrapolation and regulatory application of current evidence.

Gaps include:

(i) the absence of mixture-aware experimental designs that explicitly test interaction terms and use environmentally realistic exposure levels, hindering accurate assessment of combined pollutant effects;
(ii) the need for standardization of multi-level endpoints (linking omics data to traditional biomarkers, histopathology, and demographic parameters) along with harmonized reporting templates that enable cross-study comparison;
(iii) insufficient attention to cross-matrix comparability among water, sediment, and soil systems, and the lack of time-resolved fate studies to evaluate transformation and persistence of contaminants under dynamic conditions;
(iv) the limited implementation of FAIR (Findable, Accessible, Interoperable, and Reusable) data pipelines, which would facilitate meta-analyses and large-scale syntheses across ecotoxicological datasets; and
(v) the absence of translation metrics that connect mechanistic evidence to regulatory benchmarks—such as effect-based trigger values or threshold levels for decision-making.

Bridging these gaps will require a coordinated effort integrating experimental, computational, and regulatory perspectives to ensure that mechanistic and multi-scale evidence can be directly applied in environmental risk assessment and management frameworks.

6.3. Challenges in Interpreting Integrated Data

The analysis and interpretation of large volumes of data generated by the integrative approach present another significant challenge. Tools such as omics and computational models produce massive datasets that require advanced analysis techniques, such as Bayesian networks and PCA, to identify meaningful patterns [8,19]. However, the complexity of these data can lead to misinterpretations or inconsistencies if robust methodologies and adequate expertise are not applied.

For instance, in studies combining molecular, physiological, and population-level biomarkers, such as those by Silva et al. (2024) [12] and Herrera-Vázquez et al. (2024) [23], integrating these levels can yield contradictory or difficult-to-interpret results without a clear conceptual framework. This underscores the need to develop methodologies for integrated data interpretation that account for connections between biological and ecological levels [46–51].

7. Future Perspectives and Practical Applications

This section outlines future research directions and practical applications, linking the integrative ecotoxicology framework to One Health principles and environmental policy strategies.

The integrative approach in Ecotoxicology not only provides a robust conceptual framework for understanding the impacts of contaminants on ecosystems but also has the potential to significantly influence environmental policies, mitigation strategies, and ecosystem restoration efforts. Below, we discuss the technological innovations, practical applications, and future perspectives of this approach.

7.1. Technological Innovations to Enhance the Integrative Approach

The advancement of omics technologies and biomimetic tools offers new opportunities to deepen our understanding of the effects of contaminants. For instance, Yang et al. (2023) developed a lung-on-a-chip model to assess the impacts of nanoplastics on the human respiratory system [11]. This type of innovation enables not only the study of toxic effects of emerging contaminants on human tissues but also the establishment of links between environmental and human health.

Moreover, advanced multi-omics analysis techniques, such as those employed by Beale et al. (2024), allow the identification of metabolic pathways disrupted by persistent contaminants like PFAS [19]. These tools have the potential to become standard practices in ecotoxicology, providing more comprehensive data on toxicity mechanisms and facilitating the design of targeted mitigation strategies.

The use of computational models and big data is another promising area. Kuang et al. (2023) demonstrated how probabilistic models based on Bayesian networks can assess the risks associated with contaminants in vulnerable communities [8]. These tools are not only useful for analyzing large datasets but also for predicting the cumulative and synergistic effects of multiple contaminants, optimizing decision-making in environmental policy.

These technological advances directly address several of the previously identified gaps, particularly by promoting mixture-aware designs (point i), standardization of multi-level endpoints (point ii), and the establishment of FAIR-compliant data pipelines for omics and biomarker integration (point iv).

7.2. Applications in Environmental Policies and Regulations

The integrative approach directly impacts the formulation of environmental policies and regulations by providing a more comprehensive view of the risks associated with contaminants. For example, studies like that of Silva et al. (2024), which assessed metal contamination in mangrove crabs, can inform sustainable management policies for coastal ecosystems [23]. The findings from these studies are essential for establishing permissible contaminant limits in sensitive environments.

Similarly, the research by Walther et al. (2022) on mercury bioaccumulation in fish and its impact on human health can inform regulations on heavy metal emissions in polar regions [9]. The connection between scientific results and public policy highlights the need for a multidisciplinary approach that includes scientists, policymakers, and affected communities.

Translating integrative evidence into regulatory frameworks also bridges the remaining gaps by improving cross-matrix comparability (point iii) and generating quantitative translation metrics that link mechanistic responses to effect-based trigger values (point v).

7.3. Potential to Influence Mitigation and Ecosystem Restoration Strategies

The integrative approach is essential for mitigating impacts and restoring ecosystems. For example, Herrera-Vázquez et al. (2024) demonstrated that chitosan biopolymers are a less harmful alternative to traditional microplastics, which could promote their use in biodegradable products to reduce plastic pollution [12].

In terms of restoration, Felisbino et al. (2023) identified the teratogenic effects of the herbicide dicamba, providing valuable information for mitigating the impact of agrochemicals on water bodies [5]. Additionally, biomarker-based studies, such as those focused on oxidative damage and enzymatic activity, can be used to monitor the effectiveness of interventions in contaminated ecosystems (Elizalde-Velázquez et al., 2024) [18].

On a broader scale, the integrative approach can also support global initiatives like One Health by linking ecotoxicology to human and animal health. For example, findings on exposure risks to VOCs and metals in communities near e-waste recycling sites underscore the importance of integrating environmental management with public health strategies [8].

Strengthening interdisciplinary and trans-sectoral collaboration will be essential to close all identified gaps (i–v), ensuring that integrative ecotoxicology informs not only environmental regulation but also global One Health and sustainability agendas.

8. Conclusions

Integrative ecotoxicology has evolved as a cornerstone discipline for understanding the complex interactions between pollutants and biological systems across multiple scales of organization. By combining mixture-aware experimental designs, standardized multi-level endpoints, and advanced computational synthesis, this approach reveals sublethal mechanisms and ecosystem-relevant disturbances that traditional single-tier assays often fail to detect. Its capacity to integrate molecular, biochemical, histological, and ecological responses provides a more realistic and predictive understanding of contaminant impacts under environmentally relevant conditions.

Moving forward, the consolidation of this field depends on four strategic priorities: (i) the harmonization of protocols and analytical frameworks across environmental matrices to enhance comparability; (ii) the alignment of omics data with Adverse Outcome Pathways (AOPs) to improve mechanistic inference; (iii) the implementation of FAIR-compliant data infrastructures to facilitate data sharing, interoperability, and meta-analyses; and (iv) the strengthening of decision-analytic tools that connect experimental evidence to policy instruments within the One Health paradigm.

Implementing the proposed research-to-policy framework will enable the transition from descriptive toxicology to predictive, actionable ecotoxicology. This integration will accelerate the development of evidence-based mitigation strategies (such as effluent standards, safer-by-design materials, and adaptive environmental monitoring systems) thereby reinforcing the protection of ecosystems, biodiversity, and public health. Ultimately, integrative ecotoxicology provides not only a scientific pathway but also a policy bridge toward sustainable environmental governance.

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Use of AI and AI-assisted Technologies

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