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Review

A Brief Insight into the Toxicity Conundrum: Modeling, Measuring, Monitoring and Evaluating Ecotoxicity for Water Quality towards Environmental Sustainability

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Abstract: In view of the continuous increment of industrial residues, the risk associated with chemical toxicity in the environment has piqued the interest of researchers in pursuit of an alternative methodology for mitigating the apparent toxicity of chemicals. Over the past decade, the applicability of toxicity models and the evaluation of the apparent toxicity of chemicals have been examined for achieving sustainability of the environment and improving water quality. The prediction of toxicant effects with reasonable accuracy in organisms of water bodies and other environmental compartments lies in the application of a chemical toxicity model with further risk assessment analysis. This review summarizes well-known and recent advances of modeling techniques to evaluate and monitor toxicity in the environment. Chemical toxicity models such as the individual-based concentration addition (CA), independent action (IA) and whole-mixture-based concentration addition-independent action (CAIA) are considered, as well as their environmental applications, specific case studies, and further research needs towards sustainability. The gap that needs to be overcome in toxicity studies for the environmental sustainability is noted based on the aspects of environmental chemistry and ecotoxicology, sufficient laboratory equipment, data availability and resources for relevant social parameters needed for investigation.

Keywords: environmental sustainability; sustainable water quality; ecotoxicity; toxicity modeling; risk assessment

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1. Introduction

Comprehending the toxicity of chemicals to organisms is fundamental for a correct environmental risk assessment. Over the past decade, researchers have sought to ensure that hazardous chemicals can be replaced with safer alternatives by evaluating the toxicity of chemicals during the environmental safety assessments and sustainability [1]. Since there is a vast variety of chemicals contaminating the environment, their varied mechanisms of toxicity, relationship and exposure levels in different species are complex to identify [2,3]. Given that the anthropogenic pollution has increased significantly after the industrial revolution by producing chemical accumulation in the form of whole mixtures in the environment [4] such as chemicals and organic chemicals severely affecting all environmental compartments (air, soil, and water) with different apparent toxicity effects [5,6], changes in water species are constantly increasing due to the availability of pollutants and biomarkers responses [7].

Living organisms are constantly exposed to whole mixtures of contaminants, occasionally causing apparent toxicity at a No Observable Effect Concentration (NOEC) [8–11].

In this context, ecotoxicity models complement risk assessments for developing more precise analyses of chemical toxicity to organisms and the environment. The toxicological effects of individual chemicals differ by their physical and chemical characteristics and by their transformation in the environment, where fresh water, soil, and air systems face the problem of increased contamination [3]. Unfortunately, ecotoxicity models for risk assessment are not fully considered for standard toxicity protocols and regulatory risk assessment [2]. Half of the anthropogenic chemicals produced annually have harmful effects given their long-term chemical transformations [3,12]. Varied types of chemicals found in the environment are hazardous, such as the organic chemicals (polycyclic aromatic hydrocarbons, pesticides, biocides, surfactants) [13] and the halogenated chemicals (perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS) and per-fluorononanoic acid (PFNA)) [14]. Some of them have also been detected in fish and seafood in Europe and in Asian countries ([15]), as well as in beef in Canadian and U.S. diets [14]. Furthermore, heavy metals, including cadmium (Cd), zinc (Zn), copper (Cu), mercury (Hg), lead (Pb), and nickel (Ni) have high toxic impacts on different species in the ecosystems [4,16]. Other organic chemicals such as polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and various organochlorine pesticides act as synthetic chemicals perturbing the endocrine function of different species.

However, for bulk materials, the particle size, surface activity, shape, and active functional groups at nanoscale underlie a unique mechanism of interaction with biological systems [17]. For nanoproducts, the toxicity presented is aggravated given the complexity of biological entities and their response to chemical mixtures [18,19]. Primary assessments have been performed through in vivo studies, presenting some limitations such as cost, time consumption, and analysis constraints depending on size (nanoparticles and particles) and shape of the materials considered [15].

Quantitative structure–property relationship (QSPR) models have been presented as a cost-effective methodology for toxicity evaluation, which has evolved in recent years with the application of artificial neural networks (ANNs) [5,20,21]. Consequently, the quantitative structure–activity relationship (QSAR) model, which is one of the most used QSPRs, has been used in several studies [5,22–25]. Ghanem et al. [22] developed a highly predictive linear QSAR model based on the multiple linear regression (MLR) method and a non-linear QSAR model based on the multilayer perceptron (MLP) method of neural networks (NN) to predict the toxicity of a large database of assays with *Vibrio fischeri*. Likewise, but more experimentally, Giesen and Van Gestel [23] carried out a study developing QSARs for (chlorinated) anilines to test compound series for a lipophilicity range. He et al. [24] studied the QSAR models for the prediction of estrogen receptor (ER) binding affinity of chemicals in fish species, screening potential ER disruptors. Therefore, the QSAR models have evolved from mathematical correlation of the chemical properties from their structures and their behavior effects [23,24,26–28]. In this way, QSARs help to ensure that the atom counts are in the range of quantum chemicals [29,30].

Recent research focuses on the implementation of the concentration addition (CA) and independent action (IA) models [21,31–39]. These methodologies evaluate the chemical mixture in terms of the mode of action (MoA) of the individual chemicals. The CA model assumes a similar MoA for chemicals, whereas the IA model works for chemicals with different MoA to calculate the combined effect of chemical mixtures [40]. Furthermore, the combined effects of chemical mixtures have been tackled in previous research [41,42]. Qin et al. [42] developed an integrated model called concentration addition independent action (CAIA) model, based on MLR, to predict the additive toxicity of noninteractive mixtures regardless of their MoA. From this, there are generally two ways to approximate the toxicity of a mixture: (a) based on whole mixture toxicity or (b) based on individual chemical toxicity. Table 1 shows the literature review of toxicity models in different areas of study such as human health and environmental risk assessment. The latest research

refers to the subareas of wastewater treatment, soil, and acute toxicity in the environmental compartments and health.

Despite the many advantages of toxicity modeling techniques for chemical mixtures, their application in eco-toxicological studies is seriously lacking. To define in detail the importance of research in toxicity modeling techniques, an analysis has been conducted about scientific publications of three environmental compartments (water, soil, and air) that are highly affected and that affect water quality and sustainability. These selected environmental compartments are specifically related to chemical mixtures, nanomaterials, an acute and chronic toxicity models (Figure 1a–c) which correspond to the studies published in ScienceDirect during the last decade (2013–2022). These areas of study are pillars to several environmental guided studies carried out in the last decade. The area of water toxicity modeling contains approximately 9500 publications that were made until the year 2022 (Figure 1a), from which more than 500 publications were reviewed in the development of this study. From these publications, years 2013 and 2014 presented the lowest number of publications on nanomaterials in chemical mixtures in all the subareas that are shown in Figure 1a. More specific sub-areas, such as acute and chronic water toxicity modeling for nanomaterials in chemical mixtures, show that there has been an increased concern over the last two years on this topic.

For soil toxicity modeling studies, an amount of approximately 5600 publications has been reported in the subarea of toxicity modeling of chemical mixtures (Figure 1b). Research on nanomaterials in chemical mixtures for soil studies has been little in recent years, especially on specific analysis of acute and chronic toxicity effects of chemical mixtures. In the area of air toxicity modeling of chemical mixtures, the number of publications was approximately 15,900 in total, with a clear peak in 2019 surpassing 1500 publications (Figure 1c). For this area, the scarcest research published has been seen in the studies of acute and chronic effects of nanomaterials in chemical mixtures, where in the year of 2013 there were only 500 publications released. Figure 2 presents a flow chart of the whole mixture and component-based model approaches, and the data required for the analysis with some of the most widely used risk assessment methods for each approach. Depending on data availability, the development of a whole-mixture model is facilitated, while the individual chemical toxicity modeling may be alternatively derived from other topmost toxic chemicals found in datasets.

This review discusses the scientific concepts behind the ecotoxicological modeling methodologies, the evolution in different environmental areas of study (water, soil, and air) of toxicity models in chemical mixtures that include and exclude nanomaterials, and case studies on these environmental compartments. The latest approaches for the prediction of mixture toxicity are addressed, evaluating the outputs of the models to obtain a current understanding of the effects of chemical mixtures in the environment.

Table 1. Summary of studies of chemical mixture toxicity modeling and evaluation.

Research Area	Methodology	Toxic Compounds	Chemical Concentration	Reference
Wastewater treatment	Adenosine triphosphate (ATP) analysis to study the response of cells to their environment.	(a) Mercury chloride (b) Arsenite (c) Chromium	(a) 0, 2, 5, 7.5, 10, 12.5, 15 mg/L (b) 134.3 mg/L (c) 164.02 mg/L	[43]
	Combined respirometric–titrimetric method for characterization of activated sludge and wastewater.	Creoline	25 mg/L	[44]
	QSARs models for estimated bio-toxicity of chemicals.	(a) Benzene (b) Toluene (c) Ethylbenzene (d) Xylene (e) Styrene (f) Chlorobenzene (g) Nitrobenzene (h) Phenol (i) O-cresol (j) M-cresol (k) P-cresol (l) P-aminophenol (m) M-dihydroxybenzene (n) 2,4-dichlorophenol (o) Aniline (p) O-toluidine (q) M-toluidine (r) P-toluidine (s) O-nitroaniline (t) M-nitroaniline P-nitroaniline (u) O-phenylenediamine (v) M-phenylenediame (w) P-phenylenediame (x) 2,4-diamninotoluene(2,4-DT) (y) 2,4-dinitroaniline(2,4-DA)	Mid-term toxicity: 211–23,000 mg/L Short-term toxicity: 2–4996 mg/L	[45]

Table 1. *Cont.*

Research Area	Methodology	Toxic Compounds	Chemical Concentration	Reference
	Simulation-aided TIE in a wastewater treatment plant simulation model.	(a) Copper (II) chloride (b) Zinc (c) Aluminum chloride	(a) 0.13 mg/L (b) 0.17 mg/L (c) 0.52 mg/L	[46]
	Numerical approach as a geochemical speciation, metal–organic binding, and toxicological model.	(a) Sulfate (b) Chloride	(a) 0.096–278.4 mg/L (b) 0.32–279.72 mg/L	[47]
	Chinese standard GB/T 23486 method carried out on phytotoxicity tests conducted with plant species Brassica rapa chinensis (Chinese cabbage) and Lactuca sativa (Lettuce). Control standard of pollutants in sludge for agricultural (GB 4284-2018, China) from municipal wastewater treatment plant.	(a) As (b) Cd (c) Cr (d) Cu (e) Pb (f) Zn	Liquid-phase contents of As, Cd, Pb and Zn were 0.0514, 0.0088, 0.0053 and 0.2350 mg/L, respectively.	[48]
	Electrochemical advanced oxidation process (EAOP) focused on the wastewater treatment for metal ions removal (EDTA-Ni complex) containing ethylenediaminetetraacetic acid (EDTA). Nickel ion concentration was measured by atomic absorption spectroscopy (AAS, PinAAcle 900 T, Perkin Elmer), standard method.	EDTA-Ni complex	10 mg/L	[49]
Soil	Biotic ligand model for prediction of acute copper toxicity.	Copper	NR	[50]
	Free ion approach for derivation of critical limits for copper and other metals.	Copper	NR	[51]
	Toxicity tests in lead salt-spiked soils applied to potentially different exposure routes of plants, invertebrates, and microbial processes.	Lead	NR	[52]
	Diffusive gradients in thin film (DGT) method for correlation between the metal of the shoots and metal concentrations.	(a) Lead (b) Zinc (c) Cadmium (d) Copper (e) Nickel	Varied in different soil types.	[53]

Table 1. *Cont.*

Research Area	Methodology	Toxic Compounds	Chemical Concentration	Reference
Acute toxicology	LC-MS technology in metabolomics and the chromatographic method.	(a) Aristolochic acid (b) Ricin (c) Triptolide (d) Aconitine, mesaconitine, and hypaconitine (e) Yuanhuapine	NR	[54]
	NR	NR	2.5–50 mg/kg	[55]
	FED approach for non-toxicologist.	NR	NR	[56]
	Nemerow index andUSEPA model methodology.	(a) Lead (b) Arsenic (c) Cadmium (d) Mercury (e) Chromium	NR	[57]
	NR	(a) Monoethylene glycol (b) Diethylene glycol (c) Triethylene glycol (d) Tetraethylene glycol (e) Pentaethylene glycol (f) Hexaethylene glycol	NR	[58]

NR: No reference.

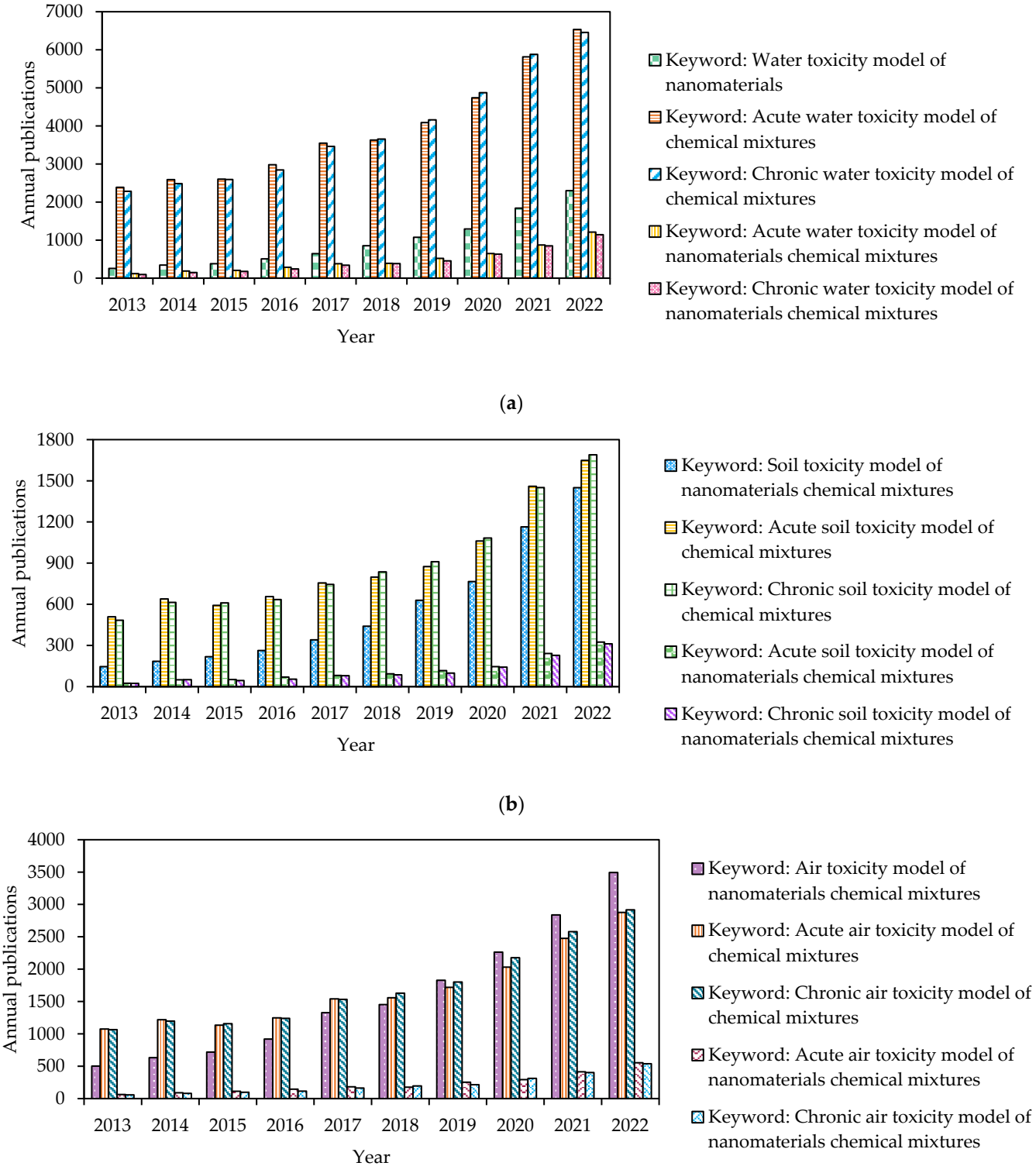

Figure 1. Annual publishing activity of the last decade in which toxicity modeling methodologies were addressed for chemical mixtures in (**a**) water toxicity modeling studies; (**b**) soil toxicity modeling studies; and (**c**) air toxicity modeling studies. Data were extracted from ScienceDirect on 31 March 2023.

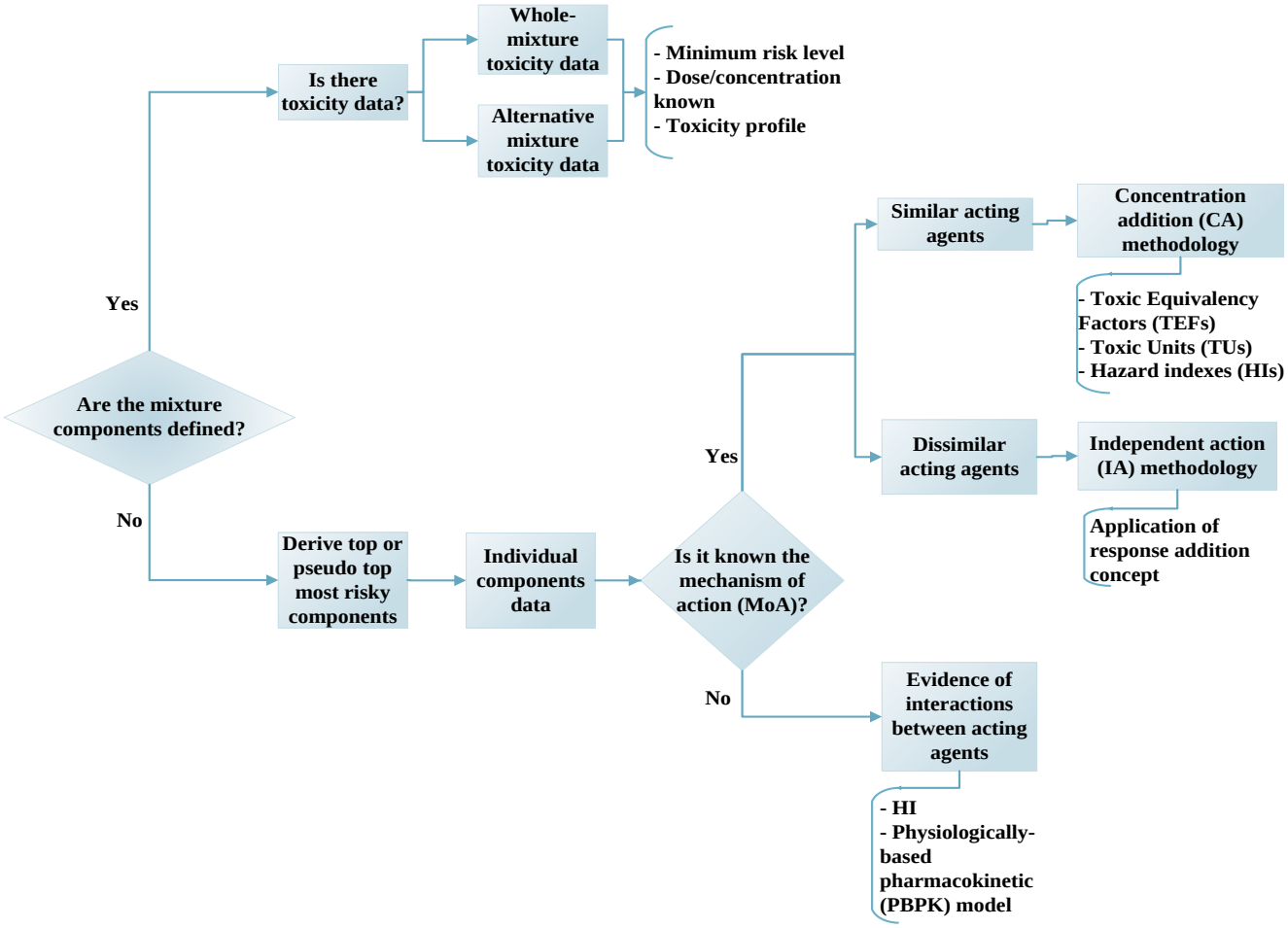

Figure 2. Flow chart of toxicity data availability for chemical mixture assessment on toxicological modeling studies. Adapted from [59].

2. Evaluation of Ecotoxicity Modeling Methodologies

For the assessment of the joint toxicity of a mixture, especially for the potential synergistic effect of environmental mixtures, different model approaches are presented, such as the CA, IA, and CAIA models [31,42,60,61].

2.1. Individual Chemical Modeling

Individual chemical modeling methods are widely utilized for the chemical mixture toxicity evaluation. Table 2 presents the literature review of the component-based modeling of chemical mixtures. In this summary, varied relevant studies based on the two approaches of CA and IA models are described. These two approaches are the most used for toxicity modeling; therefore, the studies evaluated were selected considering the areas of human health and environmental risk assessment. The toxic chemicals studied, methodology, and major results obtained for different conditions are presented.

Table 2. Literature review of individual components toxicity models in different studies (CA and IA).

Toxicity Model	Methodology	Toxic Compounds	Compound Concentration	Reference
Concentration addition (CA)	Approach to incorporate interactions among chemical constituents.	(a) Malathion (b) Parathion (c) Piperonyl butoxide	(a) 0.0107 µM (b) 0.0113 µM (c) 6.34 µM	[62]
	Two-step prediction (TSP) method.	(a) p-Octylphenol (b) Butyl benzyl phthalate (c) Di-iso-butyl phthalate (d) Isofenphos (e) Di-n-butyl phthalate (f) Pendimethaline (g) 2,4,6-Trichlorophenol (h) 2-Chlorophenol (i) Diazinon (j) Fenobucarb	NR	[63]
	CA model based on an index from the concentration–response curves (CRCs).	(a) Zinc (b) Flusilazole (c) Cadmium (d) TCCA (e) SDBS	NR	[64]
	Dose–response dynamic models.	Nitrofurazone	NR	[65]
	NR	(a) Chlorpyrifos (CPF) (b) Clothianidin (CLO) (c) Acetochlor (ACE) (d) Fenobucarb (FEN)	NR	[66]
	Generalized concentration addition (GCA) model.	(a) Copper (b) Zinc	NR	[67]

Table 2. *Cont.*

Toxicity Model	Methodology	Toxic Compounds	Compound Concentration	Reference
Independent action (IA)	NR	(a) Carbamazepine (b) Diclofenac (c) Fluoxetine (d) Gemfibrozil (e) Naproxen (f) Doxycycline (g) Monensin (h) Sulfamethizole (i) Sulfamethoxazole (j) Tetracycline	NR	[68]
	Biotic ligand-based TK-TD model for aquatic systems.	(a) Copper (b) Zinc	NR	[61]
	Microtox® test to investigate the toxicity effects of chemical compounds and mixtures.	NR	NR	[69]
	Bioavailability model (MMBM) to predict chronic toxicity.	(a) Nickel (b) Zinc (c) Lead	NR	[70]

NR: No reference.

2.1.1. Similar Mode of Action Approach

The CA model or dose addition model was introduced by Loewe and Muischneck in 1926 [71]. This model is based on the dilution principle of chemicals and it is designed for substances with similar MoA, which has been evaluated in several studies [72–76]. Generally, non-interacting chemicals varying in potency could not be defined as a dilution of another chemical. The dose/concentration addition takes place with chemicals in a mixture acting with the same mechanism, but differing only in their potencies [75,77]. Table 2 shows the studies of CA application in the environmental area for a better description of the conditions and chemicals studied individually.

The effect prediction of mixture concentrations by concentration addition was originally calculated according to the Loewe equation [78] as presented in Equation (1):

$$EC_{X_{MIX}} = \left(\sum_{i}^{n} \frac{p_i}{ECx_i} \right)^{-1}, \quad (1)$$

where ECx_{MIX} is the effect concentration of the mixture provoking a certain (%) effect, ECx_i is the concentration of the chemical component i that causes a certain effect (x%) when applied individually, and p_i is the molar concentration of each chemical.

Dose additivity is assumed to predict the mixture toxicity over the entire dose range, including the dose/concentration of the individual with No Observed Adverse Effect Level/Concentration (NOAEL/C) of the mixture chemicals [34,79,80]. It was noted that this approach relied on the identified grouping of "similar" chemicals. Although guidance on chemical grouping has been issued by different organizations, such as the European Chemicals Agency (ECHA), Organization for Economic Cooperation and Development (OECD), and the European Food Safety Authority (EFSA), currently there is no agreement on the scientifically best approach. Thus, the grouping of chemicals often relies on expert judgment on a case-by-case basis [75].

As reviewed by Kortenkamp et al. [81], there is evidence that dose/concentration addition could produce reliable estimation of the combined effects for the chemical components that share either a strictly identical molecular MoA or baseline toxicants. Altenburger et al. [82] studied 137 binary mixtures of different pesticides and surfactants for which the CA model provided a better overall prediction in the observed toxicity data compared to the IA model. A similar result was obtained by Faust et al. [78], who concluded that the toxicity of 66% of the 38 binary pesticide mixtures was predictable by the CA. However, the test mixtures were composed of herbicides and fungicides, which differs from the previous studies analyzed.

The CA model is appropriate for risk assessment of chemical mixtures with simple similar action [83]. The addition of doses implies that the toxicity can be estimated if the summed dose is higher than the threshold of the mixture toxicity, even when the dose level of each individual chemical is below its own effect threshold. In a 4-week toxicity study conducted by Jonker et al. [84], rats were exposed to a combination of four different but similarly acting nephrotoxicants (tetrachloroethylene, trichloroethylene, hexachloro-1:3-butadiene, and 1,1,2-trichloro-3,3,3-trifluoropropene). Kidney effects of the mixture showed no renal toxicity for the individual chemicals. The study supported the assumption of dose additivity for mixtures of systemic toxicants acting similarly under a concurrent condition and repeated exposure at dose levels below the toxicity thresholds of the individual constituents. In addition, the combined exposure at one quarter of no-observed nephrotoxic-effect level did not show toxicity, which portrayed the absence of synergistic interaction at this level. Furthermore, a dose-additive approach was adopted by Wolansky et al. [85] suggesting that a sub-threshold dose of individual pyrethroids produced measurable neurotoxicity in rats when combined in a mixture. Finally, for the 11 tested pyrethroids with a common target site, the deltamethrin and bioresmethrin chemicals did not lead to effect additive outcomes.

Regarding human health, different studies on dose additivity present the effects of carcinogenicity through exposure to chemical mixtures [86,87]. Walker et al. [88] conducted

a study on organochlorine pollutants and polychlorinated dioxins in which the concept of dose additivity applying toxic equivalency factors (TEFs) was used to adjust the dose, specifying the tumor as the endpoint. For the case of the gingival Squamous Cell Carcinoma (SCC), the chemical mixture showed more than 45% of the predicted response presenting an antagonistic effect. This signified that the response to exposure was less than it would have been expected if the known effect chemicals were added together. Moreover, exposure to estrogen-like activity in previous research has defined that they have the same MoA, referring to the dose additivity of chemical mixtures [89,90]. The dose additivity of individual chemicals was found to act through the same receptor (ERα or ERβ) to produce inhibitory or stimulatory effects [89,90]. The studies finally supported the theory of dose additivity for mixtures with chemicals presenting similar MoA given their repeated exposure at dose levels.

Tichý et al. [91] observed deviations from concentration additivity for a mixture of benzene and ethanol in a short-term assay with Tubifex. The observed EC50 only deviated by a factor of 1.5 from the predicted EC50. Since the prediction was not calculated according to the IA for the mixture, it remained unclear whether the combined effect was better as described with this model. The effects of contaminants were typically studied in individual exposures, which were rarely presented from a single contaminant, as described in in vivo studies where individual contaminants are analyzed by their correlation alone and in combination with biological responses [92]. Thus, it is extremely important to define the interaction or non-interaction of chemicals to determine their apparent toxicity effects.

2.1.2. Dissimilar Mode of Action Approach

The IA model, also called the response addition or effects addition model, can be applied if chemicals act independently of each other, usually through different modes of action that do not influence each other. This type of action is also referred to as simple dissimilar action [77,93]. In this model, the term response addition presented the sum of probabilistic risks, and the effect of addition showed the sum of biological responses [93,94]. The toxicity of a mixture in terms of the probability of an affected individual can be expressed as Equation (2) [42].

$$p_M = 1 - (1 - p_1)(1 - p_2)(1 - p_3) \ldots (1 - p_n), \quad (2)$$

where p_M is the response to the mixture and $p_1, p_2, \ldots, p_n$ are the responses due to exposure to the individual chemicals $C_1, C_2, \ldots C_n$ when present in a specified concentration.

Equation (2) is usually also expressed in the form of Equation (3) [42,93,94],

$$E(C_{MIX}) = 1 - \prod_{i=1}^{n} (1 - E(c_i)), \quad (3)$$

where $E(C_{MIX})$ is the combined effect of the mixture concentration (C_{MIX}) and $E(c_i)$ is the effect of the individual mixture chemical component (i) applied at the concentration (c_i). Effects are expressed as fractions of a maximum possible effect ($0\% \leq E \leq 100\%$).

According to Equation (3), any chemical for which $E(c_i)$ equals zero does not contribute to the joint effect of the mixture. Consequently, mixtures of independently acting chemicals pose no health concern if the doses/concentrations of each individual chemical remain below their individual zero-effect level [93]. It is important to note that NOAELs and No Observed Adverse Effect Concentrations (NOAECs) derived from experimental studies do not always represent a zero-effect level. The NOAEL/Cs and NOECs estimated in toxicity and ecotoxicity studies, respectively, are often associated with an effect level in the range of 5 to 20% and therefore have no zero-effect level [81,95]. Thus, it cannot be assumed that in all cases $E(c_i)$ is equal to zero for exposures at NOAEL/C or NOEC, as the NOAEL/C or NOEC do not necessarily represent a value for which $E(c_i)$ is zero. Exposures equal to these levels may contribute to the mixture effect for dissimilarly acting

chemicals. Therefore, the exposures at the NOAEL/C level may contribute to mixture effects of dissimilarly acting chemicals [81].

2.1.3. Selection between the CA and IA Modeling Approaches

For evaluation of a mixture, the question of how to select the appropriate model often arises. The applied model must be chosen on the basis of formulating a quantitative idea about mixture toxicity according to expected additive effects (additivity expectation) [81]. A larger number of substances in a mixture shows a stronger combined effect leading to additive effects of the individual components in the substances [32], which is important as diverse concepts often suggest different mixture toxicities. In an attempt to deal with this decision problem, assumptions that underpin dose addition and independent action have been allied to the broad mechanism of combined toxicity.

Dose addition is applicable to mixtures composed of chemicals that act through a similar or common MoA [33]. Although the original study by Loewe and Muischnek [71] contained little information that rooted dose addition in mechanistic considerations, the idea of a similar action was derived from the dilution principle concept that formed the basis of the principle. Conversely, the IA is widely held to be appropriate for mixtures of agents with diverse or "dissimilar" modes of action. Although rarely explicitly stated, this presumably stems from the principles of this concept. By activating differing effector chains, each chemical in a mixture provokes effects independent of other agents. This feature would also appear to lend itself to the statistical concept of independent events [72,93]. Early work on these three main models of mixture effects was developed after [71], in the 1930s.

The CA and IA may be regarded as special cases that provide a reference framework, defining the severity range of possible additivity expectations [72,81]. Mixtures of heterogeneous pollutants that include not only strictly dissimilarly acting chemicals, but also multi-site inhibitors and non-specifically acting chemicals may be expected to exert intermediate toxicity within the window of mixture toxicity whose severity range is defined by CA and IA [72].

2.2. Whole-Mixture Based Modeling

Whole-mixture models, or so-called top-down models, utilize toxicity data in the form of biological responses to the entire mixture or a fraction of the mixture in hydrocarbon mixtures [61,96–100]. This modeling technique consists of testing the whole-mixture in bioassays (in the laboratory and in situ) applying a similar principle to that used in a single chemical toxicity test [61,98,101]. However, the limitation of this model relies on the little information about the nature of chemicals grouped in the mixture. On the contrary, the main experimentally based technique for calculating chemical toxicity is the Toxicity Identification Evaluation (TIE) approach. This approach includes chemical fractionation of a sample providing further insight into the chemicals that are responsible for a large part of the toxicity of the mixture. The advantage of this type of toxicological technique used for risk assessment is that by considering the whole mixture, any interactions between the chemicals that may have been missed in a component-based approach are considered [81,102–104]. A disadvantage of TIE is the specific assessment information resulting from each mixture, which cannot be extrapolated to other mixtures or situations. TIE is only applicable to mixtures that are very stable in the environment, as it does not account for any change in composition that is typical of whole mixtures [59].

Figure 3a shows a framework of the whole-mixture approach to assess the risk from toxicity of a chemical mixture, starting with the required data to develop the model to the final estimation of hazard and risk analysis by chemical mixtures. For toxicity modeling of chemical mixtures, a specific dataset must be defined for each whole-mixture- and individual-based toxicity model (Figure 3b). For each dataset of chemical mixtures in a study, the requirements should represent the environmental transformation, potency of toxicity, reference dose/concentration, dose addition or response addition which depend on the similarity of the mixtures. These parameters and methods are analyzed for an exposure

assessment of the mixture based on measurements of the hazard of toxicity of chemical mixtures. Table 3 presents a summary of the most cited studies on the latest whole-mixture-based models (also called integrated models). In these studies, the chemical mixtures are treated as a single entity, not individually, and an efficiency compared to regular models (CA and IA) is estimated. These studies highlight a concern for the improvement of the methodology to provide more accurate results about the toxicity effects of mixtures, which will lead to a correct risk assessment of the environment.

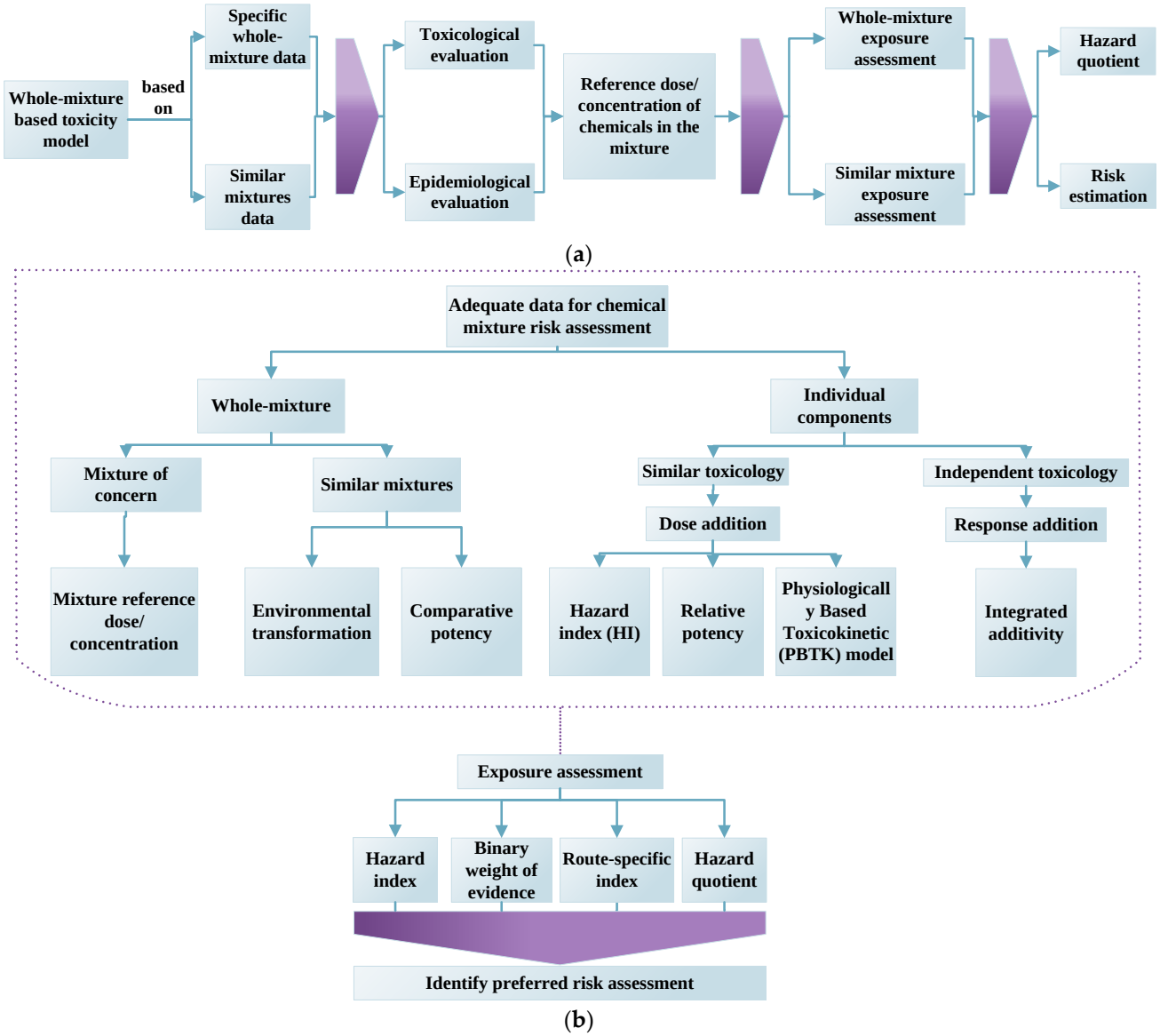

Figure 3. Individual- and whole-mixture -based toxicity models for exposure assessment. (**a**) Whole-mixture model approach for the estimation of toxicity risk in mixture toxicity. Adapted from [105]. (**b**) Quality of chemical mixture data for toxicity exposure assessment. Adapted from [105].

Table 3. Literature review of whole-mixture-based toxicity models.

Topic	Methodology	Major Highlights	Reference
The interaction model for assessing the toxicity of chemical mixtures	Integrated model (IAI).	Toxicokinetic interactions could be incorporated into mixture assessments by qualitative weight of evidence or a quantitative approach.	[62]
Toxicity by chemical mixtures from WWTP effluents	Two-step prediction (TSP) method.	The combined toxicity could be predicted appropriately by the TSP model for chemicals with similar modes of action by the CA model in the first stage and for chemicals with dissimilar modes of action by the IA model in the second stage.	[63]
Mixture effects using different additivity models	Integrated fuzzy concentration addition-independent action (IFCA-IA) model.	TEF overestimated the mixture response but had the advantage of easy interpretability and use.	[106]
Estrogenic potentials of mixtures and environmental samples containing partial agonists	Generalized concentration addition (GCA) model.	The heuristic assumption of the GCA approach that the cumulative effect of all components in a particular mixture is subject to a particular toxic interaction rule (TIR) regardless of the number of components.	[68]

NR: No reference.

Bhattacharya et al. [15] presented a review by the U.S. National Research Council (NRC) which introduced an approach using in vitro assays. Recently, many methods for toxicity assessment and tests were developed for animal testing in the USA and EU [23,107]. Alves et al. [1] proposed a new approach for the chemical safety assessment of new chemicals by integrating structural alerts and QSAR models which utilized structural alerts alone to predict the biological activity of the whole mixture. QSAR models were implemented into the integrated approach to balance the transparency and interpretability of the structural alerts [23].

Integrated Model Approach

The CAIA model integrates both concepts of the CA and IA models into one algorithm. This methodology was proposed by Qin et al. [42], who utilized the MLR technique to combine results from the CA and IA models which were considered as the predictor variables (independent variables) for the model. Furthermore, the experimental concentrations obtained from the characterization of the concentration–response curves were considered as the response variable (dependent variable) to determine the predicted toxicity. The results of the CA model, IA model, and experimental concentration values were transformed into log values and consecutively linked using the MRL technique. Equation (4) showed the CAIA model adopted from Qin et al. [42]:

$$\log_{10}(EC_{mix,\exp}) = b_0 + b_1 \log_{10}(ECx_{mix,CA}) + b_2 \log_{10}(ECx_{mix,IA}), \quad (4)$$

where b_0 is the intercept, b_1 and b_2 are the regression coefficients that result from the MRL technique, $EC_{mix,\exp}$ are the experimental concentrations of the mixture provoking a certain (%) of effect, $ECx_{mix,CA}$ are the values that result from the CA model, and $ECx_{mix,IA}$ are the concentrations of the chemicals that result from the IA model.

The predicted power of the CAIA model according to Qin et al. [42] was validated using two datasets including thirteen mixtures of nine chemicals and six mixtures of six chemicals, respectively. For dataset one, 10 Uniformed Designs with Fixed Concentration Ration Ray (UDCR) mixtures were used as a training set. The model was later used to predict the toxicity of the test set consisting of three Equivalent-Effect Concentration Ratio (EECR) mixtures. For dataset two, the CAIA model based on four UDCR mixtures was used to predict the remaining two EECR mixtures. The CAIA model showed a strong predictive power for mixture toxicity in the two datasets, and its prediction was better than

that of CA and IA, where the two models deviated from the concentration–response data of the mixtures.

Through these models, the overall toxicity of a mixture of a known composition can be determined prospectively. For the environmental mixtures, the ecotoxicity is usually investigated by one of the two following approaches: whole-mixture approach (using a simple in vivo or in vitro study) or by the eco-toxicological data on individual chemicals combined with the chemical–analytical concentration data [72,81].

The chemical–analytical concentration data can then feed into a mathematical model to predict the final ecotoxicity of the mixture and the exposure to living organisms, as presented by Giubilato et al. [108] for an integrated exposure assessment of the toxicity models. Whole-mixture testing was frequently applied for environmental mixtures, as it allowed for the assessment of ecotoxicity of mixtures of unknown compositions; however, the chemicals responsible for the response frequently remained unidentified [72]. Moreover, although the component-based approach was generally utilized, it required more information regarding identity, concentration, and toxicity, including MoA of the individual chemicals [34]. Figure 3b presents a framework of the component-based model approach for the prediction of chemical exposure assessment, which indicated that for chemical component and whole-mixture data availability, there are three types of toxicology: multiple, partial, and full.

3. Case Studies of Toxicity Modeling Applications

Toxicity studies could be screened into three specific areas of research (acute, soil, and water) that are constantly interacting with each other. The acute effects on living organisms (animals, plants, and humans) are investigated in all these areas, noting their relationship to the effects on soil toxicity presented through the high utilization of chemical pesticides around the world, and later polluting water through soil and various other sources such as the industry toxicity. This chain of pollution is perpetually hindering the environmental sustainability worldwide. Acute toxicity is the harmfulness that appears after the administration of a toxic chemical, and unless death occurs, there is a recovery process in the organism analysis [109]. It is highly important for risk assessment studies to recognize the acute effects since they reveal the adverse effects resulting from the exposure of living organisms to a chemical or a mixture of chemicals in the surrounding environment [110–113].

Sweeney et al. [114] analyzed the acute toxicity considering the variation in concentration over time by using carbon monoxide (CO) as the chemical, rats as the species to test, and a periodic exposure time (10 min, 20 min, 40 min, and 60 min). The results showed that in periods of 10–20 min, the pulses of a level of toxicity were identical to continuous exposures, while in a 60 min period, average concentrations and toxic loads were found. A pulse concentration with a ratio of 3:1 portrayed a higher influence on the upper profile of the lethality concentration as ten profiles of concentration variation in time were presented. Thus, the fluctuations in exposure over a short period portrayed a fundamental impact on the outcomes. Profiles 5 and 6 best fitted the range of the data. The dose–response model for a 60 min pulse showed better prediction for Profiles 5, 6, and 10.

Dose–response models were widely used to predict toxicity but were limited by the temporal dimension. In this way, the Toxicokinetic–Toxicodynamic (TK-TD) model was developed to include both the chemical concentration and temporal dimension [115], which provides information on the chemical toxicity and the capacity to simulate the temporal sides of toxicity, acting as an extrapolation tool for risk assessment of fluctuating or pulsed exposures to pollutants [115,116]. The TK-TD models can then be used for ecological risk assessment with Individual-Based Models (IBMs). Moreover, the Quantitative Structure Toxicity Relationship (QSTR) model is used for the assessment of the acute and chronic mixture toxicity of chemicals, among which sulfonamides and tetracyclines are present. Here, chronic mixture toxicity is predicted by additional docking-based descriptors, where

there is a complex relationship between the acute and chronic toxicity of the effects of pollutants [37,117,118].

3.1. Nanoparticles Toxicity Studies

Engineered nanoparticles present potential adverse effects as they are applied in the electronics, pharmaceutical, energy, and agriculture sectors, by which lead to serious concerns about human health as well as the environment [5,119–132]. It has become a contemporary issue of great magnitude due to the toxicity resulting from their production, utilization, and their unique properties. Large-scale synthesis and utilization can have a significant impact on multiple parts of the human body, such as the lungs, liver, kidneys, brain, and the immune system [133]. These impacts depend on several factors and are based on the physicochemical features of the particles, such as their size, shape, and surface properties [134]. Nanoparticles can induce oxidative stress in the body, leading to neurobehavioral alterations and changes in vital organs, including the central nervous system [135]. Essentially, the toxic effect of nanoparticles on a single cell line could be approximated via in vitro or in vivo models, where much effort has been made for understanding the colloidal forces governing the nanomaterial chemical sedimentation, aggregation, and agglomeration over time (corona evolution) [130].

To date, the understanding of nanotoxicology has been mostly developed on the laboratory scale. However, recent studies have focused on the estimation through modeling techniques of the most probable apparent toxicity of the nanoparticles to the environment. Thus, in QSPR modeling, Kovalishyn et al. [5] developed enhanced models by Associative Neural Network (ASNN), the k-Nearest Neighbor method (kNN), and the random forest (WEKA-RF) of metal oxide nanoparticles, focusing on the intrinsic properties of the nanomaterials and their eco-toxic and human health effects obtained from the Online Chemical Modeling Environment (OCHEM) database. The "exposure concentration" and "material" of the nanoparticles were shown as the most influent descriptors for the fourth dataset of the study. It was proven that documentation of the physicochemical characteristics of specific nanoparticles is crucial to correlate the observed biological effects. In addition, the OCHEM was shown to develop well for the combination of one model of experimentally measured properties and theoretical descriptors.

On the other hand, Brown et al. [136] studied aquatic organism toxicity (*R. subcapitata*, *D. magna*, and *L. variegatus*) in freshwater conditions. The selected nanomaterials were silver (Ag), iron oxide (Fe_2O_3), titanium dioxide (TiO_2), aluminum oxide (Al_2O_3), zinc oxide (ZnO), cobalt aluminum oxide ($CoAl_2O_4$), and cadmium selenide/zinc sulfide (CdSe/ZnS) quantum dots (QDs). A cross-species comparison analysis of the toxicity of these nanomaterials was developed to evaluate the environmental models to nanoparticle sensitivity. Although the study was presented on a laboratory scale, the results obtained provided insights on the similarity of the patterns of toxicity of some nanoparticles, particularly for ZnO, Ag, and QDs, which were recognized as the most toxic materials. It was suggested that the nanoparticles stimulate inflammatory responses in cells, which eventually leads to genotoxicity and cytotoxicity.

In addition, ZnO nanoparticle effects on *Artemia franciscana* larvae in saltwater were investigated [137]. The toxicity of varying ZnO concentrations was analyzed for 48 h and 96 h of exposure. The immobilization rate of larvae was found to be between 0% and 3.33% at different concentrations of ZnO, while the exposure time over 96 h showed an immobilization between 6.66% and 100% at different concentrations [137]. Similarly, the toxicity of Ag nanoparticles (AgNPs) to *D. magna* was evaluated under the conditions of six different boreal lakes. The environmental variables studied in water from a lake (Lake (L) 979 at the IISD-Experimental Lakes Area (IISD-ELA) in northern Ontario, Canada) were conductivity, dissolved nutrients, bacterial abundance, and algal biomass. The toxicity was determined to be highly variant among the lakes ($p < 0.001$) [138].

A study conducted in China analyzed the synergistic effects of heavy metals and engineered nanoparticles on the physiology of *Brassica napus* and their accumulation

in plant tissues [139]. An ANN approach was applied to identify physiological factors affecting the plant uptake of co-existing Cd and CeO2NPs. Three levels of Cd (0, 0.25, and 1 mg/kg of dry soil) and two concentrations of CeO2NPs (0 and 500 mg/kg of dry soil) were used. The results highlighted key physiological factors that lead to the uptake of co-occurring Cd and CeO2NPs. The findings also showed that root fresh weight and net photosynthesis rate govern Ce uptake, while root fresh weight and Fv/Fm ratio affect the Cd uptake [139]. Overall, the potential impacts of nanoparticles suggest a need for continued research into their safety and toxicity, mainly as their use continues to increase in diverse industries. Therefore, this study highlights the importance of developing strategies to minimize their negative impacts on ecosystems and human health.

3.2. Water Toxicity Modeling Studies

Water is the most basic and crucial supply for all living organisms, requiring extensive control and treatment for utilization in different areas. For better evaluation of the chemical status in bodies of water, quantification of the influence of toxicant bioavailability in the environment is needed, as well as the key toxicants disrupting biological communities [140]. In the Catalan River Basin District in Spain, biological communities were monitored using biological indices. The river receives several loads of pesticides from the areas of irrigation, agriculture, fruit and vegetable crops, and rice fields in the lower delta. The available fraction of metals in the water phase was calculated, as well as the fraction of organic contaminants [140]. Soil contamination through the utilization of pesticides containing high metal concentration adds up to the contamination of water. In [140], a mixture toxicity model was developed to analyze the effect of the whole mixture of contaminants. ANN methodology was applied to maximize the Potentially Affected Fraction (PAF) values of biota for each chemical. A poor quality of the chemical status was shown in the urban and industrial areas of Barcelona. A contaminated hot spot showed a maximum PAF of 0.350 for nonylphenol and 0.134 for chlorpyrifos. Additionally, cases of high pesticide contamination were identified in the Northeastern part of the region.

The ecological impact of pesticides was studied in Lake Vistonis (Greece) from three sampling locations. In total, 68 pesticides and transformation products were detected: 27 herbicides, 27 insecticides, 11 fungicides, and 3 pesticide/transformation products. The results for the risk quotients (RQmax) were high for the toxicity to fish and aquatic invertebrates. Herbicides were the most detected pesticides, and insecticides were defined as responsible for eco-toxicological risk for an RQ higher than 1. The chemical alphamethrin was involved in most of the environmental quality standard exceedances in this study [141]. Likewise, reflecting the acute effects of toxicity in bodies of water, the study developed by Movahedian et al. [142] on the organism *Daphnia magna* determined the acute fish toxicity from the effluents of different units in the Isfahan Wastewater Treatment Plant (IWTP) in Iran. Acute fish toxicity was required for environmental risk assessment on the exposure of aquatic species to chemicals (pesticides, biocides, and pharmaceuticals). Results of the Acute Toxicity Unit (ATU) in raw wastewater were 3.1 for the preliminary effluent, 1.9 for the primary effluent, and 1.8 for the secondary effluent.

In the same way, the characterization of binary mixtures on non-target crustaceans was presented by Rose et al. [143]. For pesticides, it was observed that the effects of binary mixtures exceeded those of each chemical in isolation. For the mixture ratios presented, a similar prediction between the IA and CA models was seen, but with a higher predicted response. The highest toxicity was shown by the chemical azamethiphos, which was reflected by 96 h LC50 values of approximately 0.5 µg/L in larval European lobster (*Homarus gammarus*), mysid shrimp (*Mysidopsis bahia*), and *D. magna* with a 24 h EC50 value of 0.167 µg/L. Thus, the combination of deltamethrin and malathion showed a small additive toxicity with D. magna. Further results of acute toxicity for bodies of water were shown for the Belgian marine environment, where bezafibrate showed no effect up to its limit of solubility while *Phaeodactylum tricornutum* seemed to be more sensitive to the

chemicals than other species. Furthermore, *P. tricornutum* was much less sensitive to the other tested b-blocker, atenolol [144].

On the other hand, water toxicity studies integrate research on the influence of heavy metals in water, and lately the introduction to Machine Learning techniques is being integrated to identify and evaluate toxicity for water and wastewater treatment. For instance, Wang et al. [145] investigated the methodologies of removal of toxicity in wastewater. The authors worked on batch experiments to evaluate the removal of the Cu ions from aqueous solutions. Their study implemented adsorption kinetics pseudo-first- and -second-order models based on Chitosan (CS) experiments. They reported that the Cu distribution was decreased from outside to inside the CS microspheres, with almost no response of Cu in the interior of the CS microspheres. After the desorption process, the CS microspheres turned back into reddish brown, indicating that the loaded Cu ions were desorbed significantly. The CS proved to be an excellent material capable of being reutilized, and quite good for the removal of heavy metals such as Cu ions from industrial wastewater.

The application of sustainable chemistry in wastewater treatment has been described as a promising methodology for the removal of heavy metals [146,147] that are discharged to bodies of water. Yang et al. [146] explored a more efficient and stable photocatalysts method to degrade antibiotic and remove heavy metal ions from wastewater. The authors implemented an organic–inorganic hybrid $PW_{12}/CN@Bi_2WO_6$ composite photocatalyst that was synthesized via PW_{12}/CN and Bi_2WO_6 by the hydrothermal method. The photocatalytic activity was assessed with the degradation of tetracycline hydrochloride (TC) and reducing hexavalent chromium (Cr (VI)). A pseudo-first-order model was developed to simulate the degradation kinetics of the catalysts for Cr^{6+} and TC. As a result, the composite $PW_{12}/CN@Bi_2WO_6$ system portrayed high photocatalytic performance, obtaining a Cr (VI) photocatalytic removal rate of 98.7% and an oxidation removal of 97.5% for TC. In Yang et al. [147], the authors used a similar methodology with $BiVO_4/FeVO_4$@rGO heterojunction photocatalyst with a 3D/2D/2D structure. TC and Cr solutions were prepared using tap water, river water, and simulated dyeing wastewater. The authors evaluated the photocatalytic performance by photo-oxidative degradation of TC and photo-reduction of Cr, showing degradation rates above 85% of both TC and Cr (VI). The studies showed excellent photocatalytic performance for wastewater treatment and removal of heavy metals.

In real-world pollutant mixtures, the authors of [148] summarized a guide of different methodologies that they have worked on for five years of research dealing with mixtures of pollutants for water resource management. The authors cite a mobile dynamic passive sampling approach used in the case study of the Joint Danube Survey JDS3. This approach characterized chemical pollution along a large river providing chemical patterns. In another case study, mutagenic wastewaters from mixed industrial and municipal sources showed varying levels of mutagenicity in a periodicity of six weeks, with thousands of chemical signals of varying intensity. The authors also highlight that in an effect-directed analysis (EDA), an unbiased investigation is possible to study unidentified chemicals with unexplained biological effects. The EDA methodology is suitable when it is needed to work without any previous information of the types and sources of pollution. Finally, more balanced effect data aid in improving evidence for water quality assessments.

Furthermore, Machine Learning (ML) and ANN model advancements are addressed for water treatment studies by Yaseen [149]. The authors cite a work where an ANN model is developed to predict heavy metal (Cr, Cu, Pb, Ni, Zn) concentrations in the Karachi harbor area in Pakistan. They report the utilization of the Levenberg–Marquardt (LM) functions and the scale conjugate Gradient (SCG). The prediction accuracy was shown better with SCG. Similarly, hybrid artificial intelligence (AI) models are cited for the long-term prediction of As, Pb and Zn, revealing good performance for long-term predictions. Moreover, in another reported case, heavy metal concentrations were measured at Taihu lake in China. The researchers simulated the total, dissolved and particulate concentration of Ti, Cr, Mn, Ni, As, Cd, Sb, Pb, reporting good prediction results and reliable methodology for the limitations with datasets that can commonly occur.

3.3. Soil Toxicity Modeling Evaluation for Water Quality

Soil is a critical component in the life cycle that directly affects agriculture and food crops where toxic constituents define the soil quality based on the potential impact on human health [150,151]. The incidence of soil contamination of water quality is increasingly being investigated. The pesticides lost from the agricultural fields end up being transported to surface and ground waters because of several factors such as soil characteristics, weather, agriculture management and fundamentally the physicochemical properties of the pesticides [141]. Non-ferrous metals are determined as one of the most important toxicity sources in various soil types. For a study conducted on the Khuzestan plain (Iran), a systematic gridding procedure was applied to collect 54 samples using the kriging method. The stations were categorized using a pollution load index ranging from one to four. The results suggested that a control and monitoring plan is needed to protect human health across this vast region [152].

The concentration, distribution, and specification of lead (Pb), zinc (Zn), cadmium (Cd), chromium (Cr), nickel (Ni), and copper (Cu) were studied in Iran using single factor pollution and comprehensive pollution indices. By determining the physicochemical properties of the samples, statistical models were developed to identify the relationship between the source point and the contamination distribution. The results showed that the amounts of metal in non-residual fractions were higher at the locations closer to the pollution source. Unlike Cu, Cr, and Ni, the geogenic-originated metals exhibited generally followed the background values of topsoil. Metal-contaminated soils may represent significant risks to groundwater because the high metal concentration in soils can be transferred under certain conditions [153].

Likewise, the hazardous waste from the glass production industry, for instance, due to metals such as Cr, cobalt (Co), iron (Fe), manganese (Mn), Pb and uranium (U), becomes harmful with toxic effects to the biota. Metal-contaminated soils in southern Sweden were studied to determine the biological effect of such metals through the methods of the *C. elegans* nematode model (gene expression), fatty acid staining and lifespan assays. Total element concentrations for As, Cd, and Pb were concluded to be higher than the standards of the Swedish Environment Protection Agency in some samples. Subsequently, there is a strong influence on the biological availability of the metals, and those that are extracted by 18.2 MΩ water and ion displacement (neutral and acidic pH) in aerobic and sedimental soil. Although no significant mortality was reported in *C. elegans* upon exposure, the reduction in lifespan was evident as an effect of metals on the environment (long-term exposure). Furthermore, less than 10% of the total metal concentration in the soil was encountered in the water-soluble leachates [154].

On the other hand, a full cubic model with 90 predictors was conducted to obtain an Optimal and Reduced Cubic Model (ORCM) with 12 targeted toxic metals. The backward elimination procedure accompanied by an MLR model was used to determine significant relationships in 15 steps. All predictors contributed to ORCM showing a *p*-value of 0.07 at a degree of freedom of 36. An interaction occurred when a pair of elements produced no similar trend in the response at different levels of another element. By investigation, a dis-ordinal interaction effect occurs on deposits for Au-As-Mn, Au-Ag-As, and Au-Hg-Mn when the third element varies across the background. In contrast, ordinal effects were observed for Au-Ag-Hg and Au-As-Hg [155].

4. Limitations and Future Research Studies

The literature on online databases was searched to carry out a scoping literature review considering mostly research papers and only those published in the English language. Other sources such as newspaper articles, magazine articles, reports and dissertations were not considered. Although huge efforts have been made by the authors to search all the crux studies on this topic, it is possible that some studies may have been missed.

Overall, although toxicity analysis on mixtures as an entity (whole-mixture) seems to be complete, a reliable combined model is still far from being achieved. First, there is

inconsistency in model terminology in the literature [42]. Standardizing the terminology is urgently needed to avoid confusion. Second, an accurate connection between the CA and IA models for an integrated methodology is lacking. The different approaches referenced poorly portray a common base for application in the same chemical mixture. A better methodological approach should be developed to reflect the combined action of chemicals in one media, which further affects water quality. Furthermore, it is difficult to determine the accurate concentration level of mixture toxicants and their exact area of affectation given the lack of environmental measurements and monitoring [27,29]. Therefore, an extended database of toxic chemicals should be created to define better toxicity mechanisms of mixtures. This would help to build a bridge to better understand and evaluate toxicity to achieve environmental sustainability.

In short, the difficulties observed in an integrated model remain for the correct implementation for some environmental compartments. The following work should be considered in the future:

- Conservative risk of chemical mixtures and greater accuracy could be achieved with the implementation of up-to-date monitoring techniques such as sensor integration in endangered regions worldwide.
- To assist with predictive approach implementation, mechanistic data must be included in the assessment given that the modeling design needs to be based on real data to be validated. In addition, given the lack of understanding of the nanomaterial in chemical mixtures, the effects of the corona and colloid characteristics of chemicals need to be deeply accounted for future studies.
- The interactions between multiple stressors, their alternative usage, and the stress they present to the ecosystem-expanding populations should be equally integrated into the combined model analysis to cover global problems such as the increasing number of industries and climate change.
- Ecotoxicity of chemical mixtures in environmental compartments could be better applied to endangered species with appropriate biomonitoring of living organisms, which would additionally benefit national economies.

5. Conclusions

The different characteristics of the application of the toxicological models are important to consider for specific conditions and areas of study. Throughout the years, ecotoxicology studies have been developed to evaluate responses to a single or occasional binary stressor under laboratory conditions. However, they are limited by the basic understanding of the stressors in laboratory tests. Laboratory assays cannot accurately represent the interaction of multiple contaminants in exposure in space and time, and only provide an overview of the contaminant's influence on biotic interactions. Hence, the greatest challenge is to understand how organisms commute to adequately respond to a complex array of natural and anthropogenic stressors. Through the application of biodiversity profiles, an unattainable view of its components can be obtained, which would be helpful for the examination of anthropogenic activities affecting the different environmental systems and their deeper interactions influencing water quality.

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