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Computational Toxicology of Environmental Microplastics: In-Silico Prediction of Emerging Hepatotoxic Risks through Molecular Docking and ADMET Profiling

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Abstract

In light of the widespread presence of environmental microplastics (MPs; <5 mm) in ecosystems, humans are constantly exposed through ingestion, inhalation, and trophic transmission. The liver is a crucial target organ for microplastic-induced toxicity, as evidenced by growing biomonitoring data showing micro- and nanoplastics in human blood and hepatic tissues. The liver is especially susceptible to physicochemical interactions between microplastics, their additives, and sorbed environmental pollutants because it is the primary site of xenobiotic metabolism. Nevertheless, experimental limitations continue to restrict the ability to predict human hepatotoxic risk.

Through an emphasis on molecular docking, quantitative structure–activity relationships (QSAR), and absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling, this review critically summarizes developments in computational toxicology methods for forecasting microplastic-associated hepatotoxicity. We assess the effects of surface charge, environmental aging, polymer type, and particle size (micro- to nanoscale) on molecular reactivity and hepatic bioavailability. To clarify possible mechanisms underlying metabolic disruption, cholestasis, oxidative stress, and inflammatory liver injury, docking-based analyses focusing on important hepatic proteins—such as cytochrome P450 enzymes, bile acid transporters, nuclear receptors, and oxidative stress–inflammatory signalling regulators—are discussed. To estimate hepatotoxic endpoints, biliary clearance,

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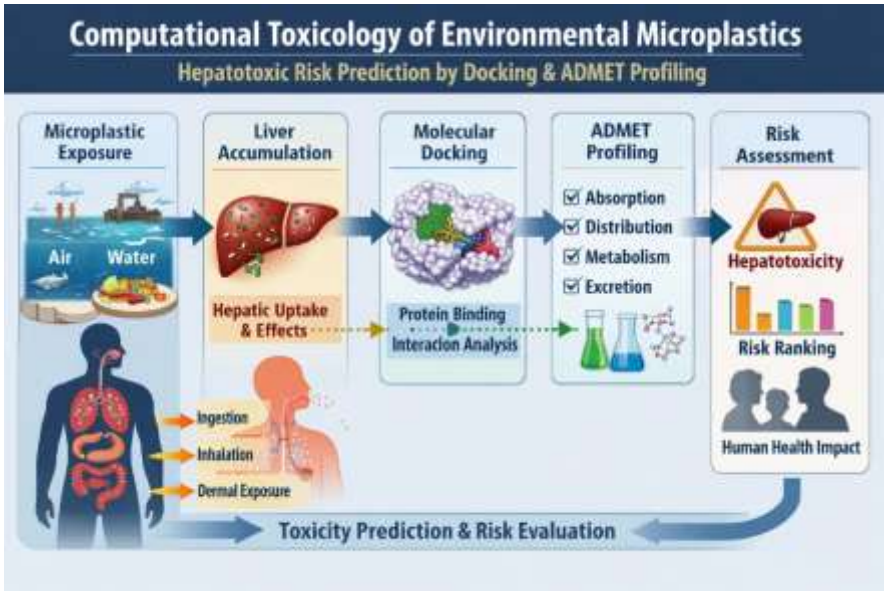
bioaccumulation, and metabolic interference, complementary ADMET predictions are evaluated.

This study illustrates the usefulness of in-silico models for mechanistic risk assessment of microplastic polymers and related compounds by combining molecular interaction data with systems toxicology and adverse outcome pathway frameworks. In order to improve predictive hepatotoxic risk assessment of environmental microplastics, important methodological constraints and future directions—such as artificial intelligence-assisted modeling and regulatory integration—are underlined.

Keywords:environmental microplastics; nanoplastics; hepatotoxicity; computational toxicology; molecular docking; ADMET profiling; cytochrome P450; adverse outcome pathways; bioaccumulation; human health risk assessment

Graphical abstract:



Key Highlights:

- Microplastics and nano plastics accumulate in the liver, posing emerging hepatotoxic risks.
- Molecular docking predicts microplastic interactions with key hepatic metabolic targets.
- ADMET profiling indicates bioaccumulation and disruption of liver metabolism pathways.
- Integrated *in-silico* models link molecular binding to hepatotoxic outcomes.
- Computational frameworks support microplastic risk ranking and regulatory assessment.

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1. Introduction

1.1 Global Burden of Microplastic Pollution

One of the most widespread and enduring environmental problems of the twenty-first century is microplastic contamination. According to Andrady (2017) and Hartmann et al. (2019), microplastics, which are generally defined as plastic particles smaller than 5 mm, can be secondary microplastics created by the fragmentation of larger plastic debris or primary microplastics purposefully produced for industrial and consumer applications. Microplastics are now widely dispersed throughout environmental compartments, including atmospheric air, freshwater and marine ecosystems, agricultural soils, and the global food chain, due to their small size, resistance to degradation, and variety of physicochemical properties (Allen et al., 2022; Li et al., 2023).

Humans are constantly exposed to microplastics through a variety of mechanisms, according to mounting research. While inhaling airborne microplastics, especially in indoor and urban settings, has drawn more attention recently, ingestion of contaminated food and drinking water remains the primary exposure route (Wright & Kelly, 2017; Zhang et al., 2020). Although its quantitative impact is still very modest, dermal exposure can also happen through contact with polluted water, synthetic fabrics, and personal care items (Prata et al., 2020). When taken as a whole, these exposure pathways raise questions about how microplastic particles are internalized and distributed throughout the human body.

Microplastics have been found in human biological samples thanks to developments in analytical and spectroscopic methods, which offer concrete proof of internal exposure. Microplastics may be able to go across biological boundaries and remain inside internal organs, as evidenced by their detection in human blood, lung tissue, placenta, and meconium (Leslie et al., 2022; Ragusa et al., 2021; Jenner et al., 2022). The liver's potential sensitivity as a crucial toxicity target is further highlighted by recent findings showing the existence of microplastics in hepatic tissues. The liver is a major site for microplastic buildup and biotransformation because of its anatomical location and function in first-pass metabolism, which exposes it directly to absorbed xenobiotics through the portal circulation (Trefts et al., 2017; Yong et al., 2020).

1.2 Hepatotoxicity as an Emerging Concern

The liver is the primary site for immunological control, lipid homeostasis, bile acid production, detoxification, and xenobiotic metabolism. In addition to membrane transporters

that control chemical uptake and efflux, hepatocytes express a broad range of phase I and phase II metabolic enzymes, including as cytochrome P450 isoforms, uridine diphosphate-glucuronosyltransferases, and glutathione-S-transferases (Gu & Manautou, 2012). Although these processes are necessary for detoxification, they also make hepatic tissue extremely vulnerable to damage from toxicants.

Microplastics can build up in the liver after oral or inhalation exposure, which can have detrimental biochemical and histological effects, according to an increasing number of experimental investigations. After being exposed to microplastics, rats and aquatic species have shown signs of oxidative stress, mitochondrial dysfunction, inflammatory reactions, dysregulation of lipid metabolism, and apoptosis in in vivo investigations (Lu et al., 2018; Deng et al., 2021; Yang et al., 2023). In vitro investigations further suggest that nanoscale microplastics exhibit enhanced cellular uptake, promoting endoplasmic reticulum stress, altered gene expression, and impaired hepatocellular function (Wu et al., 2019; Luo et al., 2022).

Microplastics have the potential to be hepatotoxic due to their ability to function as vectors for plastic additives, heavy metals, endocrine disrupting chemicals, and persistent organic pollutants that are adsorbed onto their surfaces, in addition to their particle-specific effects (Rochman et al., 2013; Campanale et al., 2020). Translating animal and cell-based discoveries into predicted risk assessments for human health is still difficult, despite this expanding body of experimental information. Predictive and mechanism-based assessment frameworks are necessary because a thorough assessment of hepatotoxic risk is hampered by species-specific differences, limited exposure realism, ethical constraints, and the vast heterogeneity of microplastic characteristics (Vethaak & Legler, 2021).

1.3 Role of Computational Toxicology

Computational toxicology has become an important tool for assessing the possible health risks associated with emerging contaminants, such as microplastics. Unlike traditional in vivo methods, in-silico methods are ethical, economical, and scalable, and can evaluate many compounds, materials, and biological targets at once (Raies & Bajic, 2016). These benefits are especially important for microplastic research, where variability in polymer composition, particle size, surface chemistry, and environmental aging causes difficulties for experimental standardization.

The use of computer models into frameworks for chemical safety evaluation is becoming more and more supported by regulatory bodies. As part of integrated approaches to testing

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and assessment, the European Union's REACH program and the Organization for Economic Co-operation and Development (OECD) recommend the use of molecular docking, ADMET prediction, and quantitative structure–activity relationship (QSAR) models (OECD, 2018; ECHA, 2023). These techniques lessen the need for animal testing while facilitating the mechanistic interpretation of toxicity pathways.

Molecular docking makes it possible to examine how important hepatic molecular targets, such as metabolic enzymes, bile acid transporters, and proteins linked to oxidative stress, interact with chemicals linked to microplastic or representative polymer fragments (Kar et al., 2021). While ADMET profiling offers information on absorption, hepatic distribution, metabolic stability, bioaccumulation potential, and adverse outcome likelihood, QSAR modeling facilitates toxicity prediction based on physicochemical characteristics (Pires et al., 2015). When combined, these computational methods provide a strong foundation for understanding the molecular and systemic pathways behind microplastic-induced hepatotoxicity.

In order to support predictive human risk assessment, inform regulatory decision-making, and direct future experimental and modeling strategies in the field of microplastic toxicology, this review integrates molecular docking, QSAR analysis, and ADMET profiling to systematically assess the emerging hepatotoxic risks of environmental microplastics.

Table 1. Sources, Classification, Human Exposure Pathways, and Hepatic Relevance of Environmental Microplastics

Classification Basis	**Category**	**Major Sources**	**Dominant Human Exposure Route**	**Hepatic Relevance**	**Key References**
Origin	Primary microplastics	Cosmetics, industrial abrasives, drug delivery carriers	Ingestion, dermal	Direct gastrointestinal absorption → first-pass liver exposure	Cole et al., 2011; Wright & Kelly, 2017
Origin	Secondary microplastics	Degraded packaging,	Ingestion, inhalation	Chronic low-dose hepatic	Geyer et al., 2017;

		textiles, tire wear		accumulation	Zhang et al., 2020
Polymer type	Polystyrene (PS)	Food containers, lab plastics	Ingestion	High bioavailability; induces oxidative stress and lipid dysregulation	Deng et al., 2017; Lu et al., 2018
Polymer type	Polyethylene (PE), Polypropylene (PP)	Packaging films, bottles	Ingestion	Persistent accumulation; additive leaching	Wright et al., 2013; Hou et al., 2021
Polymer type	PVC	Pipes, cables, medical devices	Ingestion	Plasticizer-associated hepatotoxicity	Lithner et al., 2011; Hahladakis et al., 2018
Size class	Microplastics (1 µm–5 mm)	Fragmented plastic debris	Ingestion	Limited cellular uptake but chronic exposure	EFSA, 2016; Smith et al., 2018
Size class	Nanoplastics (<1 µm)	Advanced degradation products	Ingestion, inhalation	High hepatocyte internalization and mitochondrial damage	Lehner et al., 2019; Yong et al., 2020

***Table** 1 summarizes the classification, sources, and major human exposure pathways of environmental microplastics, emphasizing their relevance to hepatic toxicity. Microplastics are categorized by origin, polymer type, and size to illustrate how diverse environmental sources contribute to human exposure through ingestion, inhalation, and dermal contact. The table highlights the liver as a primary target organ due to gastrointestinal absorption and first-pass metabolism, providing a foundational framework for liver-focused microplastic risk assessment.*

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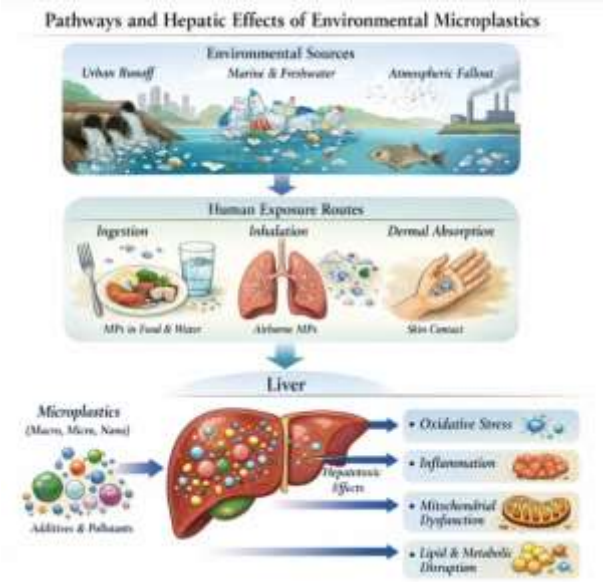

Figure 1. *Environmental sources, human exposure pathways, and key physicochemical factors governing microplastic-induced hepatotoxicity. The figure highlights ingestion and inhalation as major exposure routes, first-pass hepatic accumulation, and the role of particle size, surface modification, aging, and adsorbed contaminants in enhancing liver toxicity.*

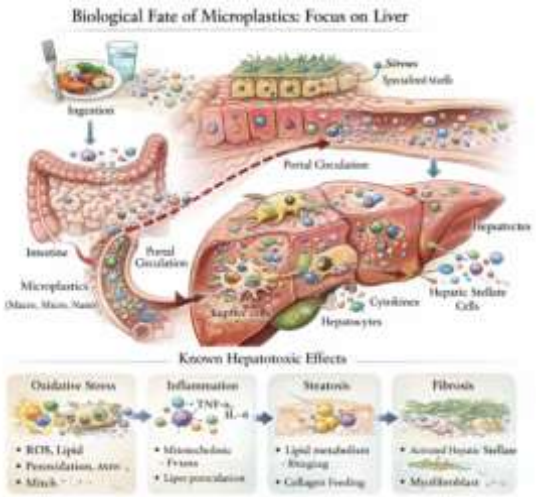

Figure 2. *Uptake and hepatic fate of microplastics: intestinal absorption via M cells and paracellular pathways, transport through portal circulation, and interactions with hepatocytes, Kupffer cells, stellate cells, and endothelial cells, leading to oxidative stress, inflammation, lipid disruption, steatosis, and fibrosis.*

2. Environmental Microplastics as Hepatotoxicants

2.1 Classification and Sources

Environmental microplastics are frequently categorized according to their origin, particle size, and polymer composition, all of which have a significant impact on their toxicological potential and environmental behaviour. Microplastics are classified as main or secondary based on where they originate. While secondary microplastics result from the fragmentation and degradation of larger plastic debris through mechanical abrasion, UV radiation, and chemical weathering processes, primary microplastics are purposefully produced microscopic particles used in industrial abrasives, cosmetics, personal care products, and biomedical applications (Andrady, 2017; Hartmann et al., 2019).

According to composition, the most common synthetic polymers found in environmental microplastics are polystyrene (PS), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC), polyethylene terephthalate (PET), and polyamide (PA). These polymers have varying environmental durability and biological interactions due to their significant differences in density, crystallinity, surface chemistry, and additive content (Lithner et al., 2011; Campanale et al., 2020). While PE and PP predominate in environmental samples because to their high worldwide production volumes and resilience to degradation, PS microplastics are among the most investigated because of their widespread usage and simplicity of laboratory synthesis (Geyer et al., 2017).

Plastic waste is further divided into three categories based on size: macroplastics (>5 mm), microplastics (1 µm–5 mm), and nanoplastics (<1 µm). Smaller particles show improved bioavailability, cellular internalization, and surface reactivity, making this size continuum toxicologically significant (Gigault et al., 2018). Because they may interact directly with subcellular structures and penetrate biological barriers, nanoplastics in particular raise concerns about their disproportionate contribution to liver toxicity as compared to bigger particles (Yong et al., 2020).

2.2 Physicochemical Properties Influencing Hepatic Toxicity

Environmental microplastics' physicochemical characteristics, which control biodistribution, cellular absorption, and molecular interactions, significantly influence their hepatotoxic potential. Two of the most important factors that determine toxicity are particle size and surface area. Because of their larger surface-area-to-volume ratio, smaller microplastics and nanoplastics can interact more readily with intracellular components and biological

membranes. According to experimental research, compared to their microscale counterparts, nanoscale polystyrene particles cause higher oxidative stress and inflammatory reactions and accumulate more easily in hepatic tissue (Lu et al., 2018; Deng et al., 2021).

Biological interactions are further modulated by surface charge and functionalization. Hepatic absorption and bioaccumulation are encouraged by positively charged or functionalized microplastics' increased affinity for negatively charged cell membranes and serum proteins (Fröhlich et al., 2018). Functional groups like carbonyl and hydroxyl moieties that are added during production or environmental aging can change the development of protein corona, affect immunological recognition, and regulate hepatocellular responses (Luo et al., 2022).

Microplastic surfaces are greatly altered by environmental aging and weathering processes, including as UV radiation, mechanical abrasion, and biofilm development. The reactivity and toxicological potential of weathered microplastics are enhanced by their increased surface roughness, oxidative functional groups, and changed hydrophobicity (Gewert et al., 2015; Sun et al., 2020). By modifying particle aggregation behavior and promoting microbial and chemical movement, biofilm-coated microplastics, often known as the "plastisphere," may further affect liver toxicity (Zettler et al., 2013).

Microplastics include intrinsic qualities as well as chemical additions such colors, stabilizers, flame retardants, and plasticizers, many of which are known to have endocrine-disrupting or hepatotoxic effects. Furthermore, because of their hydrophobic surfaces and high sorption capacity, microplastics easily absorb environmental pollutants such as pesticides, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) (Rochman et al., 2013; Hüffer & Hofmann, 2016). Together, these characteristics make microplastics complex, multi-stressor entities that can cause liver damage via both chemical-driven and particle-mediated pathways.

2.3 Microplastics as Chemical Vectors

In addition to their inherent toxicity, microplastics act as chemical carriers, bringing co-contaminants into biological systems via the "Trojan horse" effect. This process explains how microplastics might increase toxicological consequences by absorbing, concentrating, and then releasing dangerous chemicals after internalization (Rochman et al., 2013; Vethaak & Leslie, 2016).

Numerous endocrine-disrupting substances and hepatotoxins, including as bisphenols, phthalates, PAHs, organochlorine insecticides, and metal ions, have been demonstrated to co-

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transport with microplastics. Desorption of these substances inside hepatic tissues after internalization might worsen oxidative stress, interfere with the function of metabolic enzymes, and compromise bile acid homeostasis (Campanale et al., 2020; Yang et al., 2023). Given the liver's crucial involvement in xenobiotic metabolism and detoxification, this vector-mediated toxicity is especially pertinent to the organ.

The chemical vector function of microplastics adds significant computational complexity to toxicity prediction. By ignoring combination effects and synergistic interactions of chemicals linked with plastic, traditional single-compound models may underestimate risk. By modeling competitive binding, cumulative metabolic load, and changed toxicokinetic behavior, in-silico mixture toxicology—which combines molecular docking, QSAR, and ADMET profiling—offers a viable paradigm for separating these interactions (Kar et al., 2021; Pires et al., 2015). Therefore, accurate hepatotoxic risk prediction and regulatory assessment of environmental microplastic exposure depend on the inclusion of microplastic–contaminant complexes in computer models.

Table 2. Physicochemical Properties of Microplastics Influencing Hepatic Toxicity

Property	**Description**	**Effect on Hepatic Uptake**	**Toxicological Outcome**	**Key References**
Particle size	Micro vs nano scale	Smaller particles show enhanced cellular internalization	Oxidative stress, apoptosis	Lu et al., 2018; Hu & Palić, 2020
Surface area	Increases with decreasing size	Enhanced protein corona formation	Inflammation, immune activation	Monopoli et al., 2012; Walkey et al., 2014
Surface charge	Positive / neutral / negative	Positively charged MPs interact strongly with cell membranes	Increased hepatocyte damage	Fröhlich et al., 2016
Crystallinity	Amorphous vs crystalline	Alters persistence and degradation	Chronic hepatic toxicity	Lambert et al., 2017
Aging/weathering	UV exposure, oxidation,	Increased surface roughness and	Enhanced toxicity	Liu et al., 2019; Wang

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	biofilm formation	reactivity	potential	et al., 2020
Chemical additives	Plasticizers, stabilizers, flame retardants	Leaching in hepatic microenvironment	Endocrine and metabolic disruption	Hahladakis et al., 2018
Adsorbed pollutants	PAHs, heavy metals, pesticides	Co-delivery to liver tissue	Synergistic hepatotoxicity	Rochman et al., 2013; Guo et al., 2020

Table 2 outlines the physicochemical properties of microplastics that govern hepatic uptake and toxicological outcomes. Key attributes, including particle size, surface area, surface charge, crystallinity, aging processes, and associated additives or pollutants, are linked to enhanced cellular internalization, oxidative stress, inflammation, and metabolic disruption. This table establishes mechanistic relationships essential for structure–toxicity analysis and in-silico modeling.

Table 3. Microplastics as Chemical Vectors: Implications for Hepatotoxicity and In-Silico Toxicology

Vector Mechanism	**Associated Chemicals**	**Hepatic Effect**	**Computational Toxicology Relevance**	**Key References**
Trojan horse effect	PAHs, PCBs	Enhanced oxidative stress and inflammation	Docking with CYP450 enzymes	Rochman et al., 2013; Seidensticker et al., 2017
Co-transport	Phthalates, bisphenols	Enzyme inhibition, lipid dysregulation	QSAR toxicity modeling	Hermabessiere et al., 2017
Desorption in liver	Cd, Pb, Hg	Mitochondrial dysfunction, ROS generation	ADMET bioaccumulation prediction	Brennecke et al., 2016
Mixture toxicity	Multiple contaminants	Synergistic hepatotoxicity	In-silico mixture toxicology	Kortenkamp et al., 2009; Backhaus &

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				Faust, 2012

Table 3 presents microplastics as chemical vectors and their implications for hepatotoxicity and computational toxicology. The table highlights vector-mediated mechanisms such as the Trojan horse effect, co-transport, and contaminant desorption, which contribute to synergistic hepatic toxicity. It further underscores the relevance of these processes to in-silico approaches, including molecular docking, QSAR, ADMET profiling, and mixture toxicity assessment.

3. Biological Fate of Microplastics: Focus on Liver

3.1 Absorption, Distribution, and Hepatic Accumulation

Once consumed, microplastics and nanoplastics can pass past the intestinal barrier through paracellular pathways and specialized M cells in Peyer's patches, especially if the particles are submicron or nanoscale (Stock et al., 2021). Translocation into the systemic circulation can be further facilitated by disruption of intestinal barrier integrity and increased permeability, which allows these particles to enter the portal vein and be transported straight to the liver by first pass transport (Wang et al., 2024).

Prolonged oral exposure to environmentally relevant polyethylene terephthalate (PET) microplastics causes hepatic enlargement, steatosis, and early fibrotic changes in experimental mice, indicating accumulation and progressive liver injury mediated by gut liver axis dysregulation. Kupffer cells, the native liver macrophages, come into contact with microplastics in the hepatic sinusoids. They vigorously phagocytose foreign particles, but this defensive uptake also causes local inflammation and cytokine release (Yong et al., 2020). Particle size, surface charge, and other physicochemical characteristics affect how well nanoplastics accumulate in the liver; smaller nanoplastics are more easily absorbed and held in the liver parenchyma.

3.2 Cellular Interactions in Hepatic Tissue

Microplastics interact with various hepatic cell types, resulting in a complex injury profile:

- **Hepatocytes:** These parenchymal cells are essential to xenobiotic metabolism and are especially susceptible to oxidative stress and metabolic disorders brought on by microplastics. According to in vivo research, persistent exposure to microplastics causes higher reactive oxygen species (ROS), mitochondrial dysfunction, and serum liver enzymes (ALT, AST, and ALP) that directly harm hepatocytes.

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- **Kupffer cells:** Kupffer cells, which are innate immune cells that line the hepatic sinusoids, take in microplastics and nanoplastics and release pro-inflammatory cytokines like TNF α and IL 6, which intensify local inflammation.
- **Hepatic stellate cells:** One important stage in fibrogenesis is the activation of hepatic stellate cells. In experimental settings, prolonged exposure to microplastics has been associated with extracellular matrix deposition and stellate cell activation, which promotes fibrosis, especially in high fat environments.
- **Sinusoidal endothelial cells:** Smaller nanoplastics can also be internalized by the endothelial cells that line the hepatic sinusoids, which might impair the function of the endothelial barrier and fuel inflammatory reactions and microvascular dysfunction.

These connections highlight how several cell types coordinate microplastic-induced hepatotoxicity, with innate immune activation, metabolic stress, and structural remodelling all contributing to liver damage.

3.3 Known Experimental Evidence of Hepatotoxicity

A growing body of experimental research delineates multiple mechanisms by which microplastics induce hepatic toxicity:

1. ***Oxidative Stress:*** Rats exposed chronically to polyethylene microplastics (1–15 μm) exhibit severe oxidative stress, as seen by elevated malondialdehyde (MDA) and reduced total antioxidant capacity, as well as increased expression of apoptotic markers such caspase 3 in liver tissue. Oxidative processes and liver injury are further linked by the discovery that mitochondrial ROS production is responsible for hepatocyte damage and macrophage necroptosis caused by nanoplastics.
2. ***Inflammation:*** It is widely known that Kupffer cell activation and cytokine release cause pro-inflammatory reactions. Hepatic oxidative stress and inflammatory indicators are markedly increased by co-exposure to microplastics and environmental pollutants like triclosan compared to single exposures, indicating synergistic inflammatory pathways mediated through the gut liver axis.
3. ***Lipid Metabolism Disruption:*** Hepatic glucose and lipid homeostasis is upset by microplastic exposure, which promotes lipid production while blocking catabolic pathways, causing phenotypes similar to nonalcoholic fatty liver disease (NAFLD). Microplastics disrupt PP2A/AMPK/HNF4A signaling in diabetic mice, which increases gluconeogenesis and fatty liver growth while also activating fibrotic pathways.

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4. ***Fibrosis and Steatosis Indicators:*** Exposure to polystyrene nanoplastics by intravenous or inhalation increases collagen deposition and worsens steatohepatitis, indicating that liver fibrosis may develop in the context of metabolic stresses. These histological alterations, which are associated with increasing liver damage, include chronic inflammatory infiltrates and increased expression of fibrotic markers (such as α SMA, TGF β, and collagen I).

The liver is a crucial target organ in environmental microplastic toxicity, as these studies collectively demonstrate that microplastics and nanoplastics can cause a range of hepatotoxic reactions, from oxidative stress and inflammation to disrupted lipid metabolism and fibrogenesis. Microplastics are classified as emergent hepatotoxicants due to the consistency of these findings across animal models and mechanistic assessments. This emphasizes the significance of integrating such information into computational toxicology frameworks to improve risk assessment.

Table 4. Experimental Evidence of Microplastic-Induced Hepatotoxicity

Experimental Model	Microplastic Type	Exposure Route & Dose	Key Hepatic Endpoints	Mechanistic Insights	Key References
Mouse	Polystyrene (PS), 50 nm–5 µm	Oral, 10 mg/kg/day, 28 days	↑ALT, ↑AST, ↑ROS, lipid accumulation	Oxidative stress, hepatocyte apoptosis, lipid metabolism disruption	Lu et al., 2018; Luo et al., 2022
Rat	Polyethylene (PE), 1–15 µm	Oral, 100 mg/kg/day, 90 days	↑MDA, ↓SOD, inflammatory cytokines	Oxidative stress, Kupffer cell activation, inflammation	Deng et al., 2021; Wu et al., 2019
Zebrafish	Polystyrene, 5 µm	Waterborne, 1 mg/L, 21 days	↑ROS, ↑TNF-α, liver histopathology	ROS-mediated hepatocyte	Yong et al., 2020

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				injury, inflammatory response	
Mouse	Polystyrene, 70 nm	Oral + High-fat diet, 8 weeks	↑Liver triglycerides, ↑α-SMA, collagen deposition	Hepatic stellate cell activation, fibrosis, steatosis	Yang et al., 2023; Jiang et al., 2022
Rat	Polyvinyl chloride (PVC) microplastics	Oral, 50 mg/kg/day, 60 days	↑ALT, lipid droplets, inflammatory markers	Lipid metabolism disruption, inflammation	Hahladakis et al., 2018; Li et al., 2023
Mouse	Polystyrene nanoplastics	Intravenous, 5 mg/kg, single dose	↑ROS, Kupffer cell phagocytosis, cytokine release	Nanoplastic-induced immune activation, oxidative stress	Stock et al., 2021; Deng et al., 2021

Table 4 summarizes experimental studies investigating microplastic-induced hepatotoxicity across various animal models. The table includes microplastic type, exposure route and dose, primary hepatic endpoints, and mechanistic insights, highlighting oxidative stress, inflammatory activation, lipid metabolism disruption, and fibrosis as common pathways. This synthesis provides a clear framework for understanding liver-specific toxic responses and supports subsequent in-silico mechanistic modelling.

4. Computational Toxicology Approaches for Microplastic Risk Prediction

4.1 Overview of In-Silico Toxicology Paradigms

Quantitative, mechanism-driven risk assessment is required due to the increasing environmental prevalence of microplastics and associated chemical adsorbates. Prior to experimental testing, hepatotoxic results may be predicted thanks to computational toxicology's multi-scale modeling framework, which includes whole-organ predictions and molecular interactions (Raies & Bajic, 2016; Carrió & Montes, 2025).

Molecular Docking and Molecular Dynamics Simulation

High-resolution predictions of the interactions between important hepatic proteins and microplastic-sorbed compounds (PAHs, phthalates, and heavy metals) are made possible by molecular docking. Docking techniques compute conformational changes, binding free energies (ΔG), and interaction fingerprints that can be linked to receptor activation or enzyme inhibition. For instance, molecular docking of PAHs adsorbed on polystyrene (PS) nanoparticles reveals ΔG values for human CYP3A4 ranging from −7 to −10 kcal/mol, indicating high-affinity interactions that may change the metabolism of xenobiotics (Gadaleta et al., 2019). In addition to docking, molecular dynamics (MD) simulations assess the dynamic stability, solvation effects, and structural flexibility of protein-ligand complexes on timescales ranging from nanoseconds to microseconds.

Solvent-accessible surface area (SASA) estimates reveal the accessibility of hydrophobic pockets to microplastic-bound toxins, whereas root mean square deviation (RMSD) and fluctuation (RMSF) analysis highlight important residues interacting with sorbed compounds (Šoša, 2025).Advanced docking techniques capture the heterogeneity in enzyme-substrate interactions for various compounds involved with microplastics by integrating ensemble docking across several conformations and protein isoforms. These methods are especially useful for multi-target predictions, which connect xenobiotics bound to microplastics to many liver endpoints such oxidative stress and disturbance of lipid metabolism.

QSAR and Read-Across Approaches

Particle size, zeta potential, surface area, hydrophobicity (logP), and chemical composition are examples of physicochemical descriptors that are quantitatively related to biological endpoints such as hepatocyte viability, production of reactive oxygen species (ROS), and induction of pro-inflammatory cytokines. To address non-linear interactions between descriptors and toxicity, recent ML-enhanced QSAR models include random forest, gradient boosting, and neural network techniques (Yuan et al., 2024; Yang et al., 2018).

- Feature importance analysis consistently identifies particle size (<1 μm), surface charge (> +15 mV or < −15 mV), and adsorbed hydrophobic contaminants as dominant drivers of predicted hepatotoxicity.
- Model performance metrics typically include R^2train > 0.98, R^2test > 0.92, and mean absolute error (MAE) < 0.15, indicating robust predictive accuracy.
- Read-across methods use structural similarity metrics (Tanimoto coefficients) to infer toxicity of data-poor polymers, providing mechanistically interpretable predictions for regulatory assessment (OECD, 2023; Šoša, 2025).

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Physiologically Based Pharmacokinetic (PBPK/PBTK) Modeling

PBPK models simulate organ-level biodistribution of microplastics and associated chemicals using compartmentalized physiology:

- Gastrointestinal absorption modeled via Fick's diffusion equations across enterocyte membranes and M-cell-mediated translocation for particles <150 nm.
- Hepatic distribution modeled as a combination of perfusion-limited and permeability-limited kinetics, including Kupffer cell uptake and sinusoidal endothelial transcytosis.
- Particle-specific parameters: hydrodynamic diameter, aggregation state, surface functionalization, and protein corona formation are integrated to modify tissue partition coefficients (Kp) and clearance rates (Chou & Lin, 2023).

PBPK simulations allow estimation of internal microplastic doses, peak hepatic concentrations (Cmax), area under the curve (AUC), and exposure duration, which are crucial for linking external environmental exposure to potential hepatotoxicity.

Machine Learning and Artificial Intelligence

Machine learning (ML) frameworks integrate multi-dimensional datasets:

- Input features: particle size, shape, polymer type, surface chemistry, adsorbed contaminants, zeta potential, hydrophobicity, and experimental endpoint data (hepatocyte ROS, inflammatory markers).
- Algorithms: Random Forest, Gradient Boosting (XGBoost), Support Vector Machines, Artificial Neural Networks, and Graph Neural Networks.
- Outputs: predicted hepatotoxicity probability, classification into low, moderate, high risk, and identification of mechanistic drivers via SHAP (SHapley Additive exPlanations) values.

Deep learning models also enable multi-endpoint predictions, integrating molecular docking scores, QSAR descriptors, and PBPK-derived organ concentrations into a single predictive framework, allowing holistic, mechanism-driven hazard ranking (Wang et al., 2025; Kleandrova et al., 2023).

4.2 Advantages of In-Silico Approaches for Microplastic Assessment

High-Throughput Screening: Computational methods can screen thousands of microplastic-chemical combinations within hours, which would require years of in vitro or in vivo experimentation.

Mechanistic Insights: Docking and PBPK integration allow molecular-level prediction of

enzyme inhibition, receptor binding, oxidative stress induction, lipid metabolism dysregulation, and immune activation in the liver.

Reduction of Animal Testing: By generating reliable predictive data, computational toxicology supports 3R principles (Replacement, Reduction, Refinement) in animal research (Carrió & Montes, 2025).

Early Hazard Identification: Models allow identification of high-risk microplastic types and exposure scenarios prior to human or environmental exposure, enabling proactive mitigation strategies.

***Regulatory Relevance*:** Validated computational approaches, following OECD guidelines, support Next-Generation Risk Assessment (NGRA) and can inform regulatory decision-making for environmental microplastic contamination (Raies & Bajic, 2016; OECD, 2023).

Integrating molecular docking, QSAR/read-across, PBPK/PBTK modeling, and ML/AI provides a multi-scale, mechanistic, and data-driven framework for predicting hepatotoxicity of microplastics. This integrated approach allows:

- High-resolution prediction of molecular interactions with hepatic targets.
- Quantification of internal liver exposure using physiologically realistic models.
- Multi-endpoint hazard ranking using AI-driven predictive frameworks.
- Ethical and regulatory-aligned hazard assessment.

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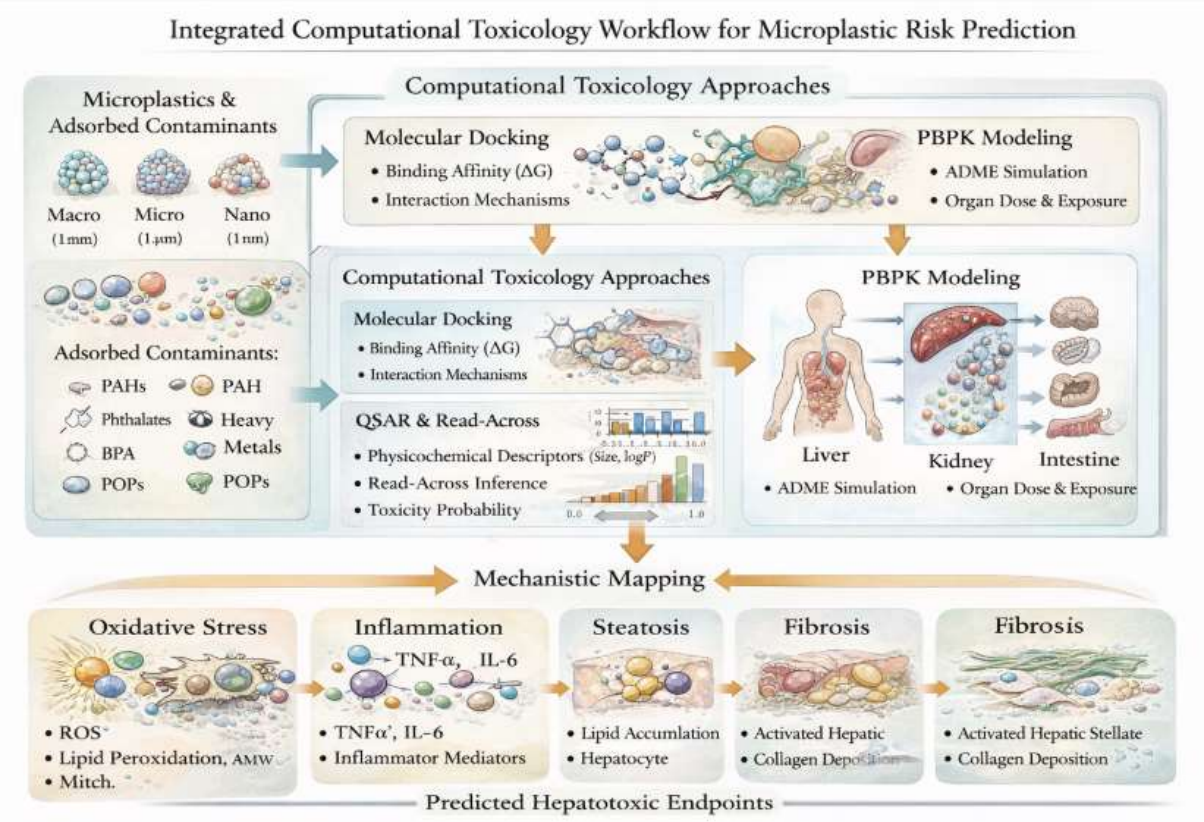

Figure 3 *illustrates the integrated computational toxicology workflow for predicting microplastic-induced hepatotoxicity. It shows the progression from environmental microplastic exposure and adsorbed contaminants, through molecular docking, QSAR/ML prediction, and PBPK modeling, to mechanistic mapping and predicted liver toxicity endpoints such as oxidative stress, inflammation, steatosis, and fibrosis.*

5. Molecular Docking for Predicting Microplastic–Protein Interactions

5.1 Rationale for Docking Microplastic-Derived Ligands

Due of their high surface area and heterogeneous surface chemistries, which promote the formation of reactive sites and "protein like" interactions, microplastics and nanoplastics in the environment are not biologically inert; under physiological conditions, they fragment and release a variety of monomers, oligomers, additives, and degradation products (Allen et al., 2022; Li et al., 2023). Many of these molecules are known or suspected to interfere with important biological processes. For instance, polar functional groups that resemble endogenous substrates are introduced by surface oxidation and biofilm development during environmental weathering, increasing affinity for biomolecular targets (Gewert et al., 2015). Before undergoing arduous experimental verification, researchers can develop mechanistic hypotheses about microplastic-induced hepatotoxicity by using molecular docking to

investigate how these compounds and nanoplastic surface analogues may bind to important hepatic proteins and disrupt their functions (Šoša, 2025).

Since compounds linked to microplastics do not cleanly fall into conventional toxicant categories, docking is especially useful for studying non-classical toxicants. Docking studies may rank possible interactions between ligands produced from microplastics and a variety of liver proteins by computationally predicting binding conformations and binding energies (ΔG). This approach is being used in an increasing number of environmental toxicology investigations to identify molecular mechanisms behind reported phenotypic effects, such as oxidative stress and metabolic disturbance in liver cells (Gadaleta et al., 2019).

5.2 Selection of Hepatotoxic Molecular Targets

5.2.1 Drug-Metabolizing Enzymes

Drug metabolizing enzymes are ideal targets for molecular docking in microplastic toxicity due to the liver's crucial involvement in xenobiotic metabolism. The metabolic destiny of both endogenous and exogenous substances is frequently determined by the phase I oxidation processes catalyzed by cytochrome P450 (CYP) enzymes, namely CYP1A2, CYP2E1, and CYP3A4. When these enzymes are disrupted by chemicals linked to microplastics, metabolic activation or inhibition may result, generating reactive metabolites that exacerbate oxidative stress and hepatocellular damage (Raies & Bajic, 2016). For example, CYP3A4's large active site allows it to interact with a wide range of hydrophobic ligands; docking studies reveal that hydrophobic additives frequently found on microplastic surfaces can exhibit ΔG values similar to known CYP3A4 substrates, suggesting potential competitive inhibition (Toxicity evaluation of microplastics..., 2022).

By adding polar groups to metabolites and aiding excretion, phase II conjugation enzymes such UDP glucuronosyltransferases (UGTs), glutathione S transferases (GSTs), and sulfotransferases (SULTs) also play crucial roles in detoxification. Molecular docking to these enzymes can show how the electronic and steric characteristics of ligands formed from microplastics affect accessibility to catalytic sites, which may result in a build-up of hazardous intermediates and a reduction in detoxifying ability (Šoša, 2025).

5.2.2 Transporters and Nuclear Receptors

Hepatic and systemic homeostasis depend on nuclear receptors and transport proteins. Hepatic transporters that facilitate the absorption and efflux of bile acids and xenobiotics include P glycoprotein (P gp), organic anion transporting polypeptides (OATP), and bile salt

export pump (BSEP). Cholestasis, the intracellular buildup of toxins, and subsequent inflammation can all be caused by impairment of these transporters (Carrió & Montes, 2025). Nuclear receptors that control the expression of transporters and enzymes involved in drug metabolism include farnesoid X receptor (FXR), aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR), and pregnane X receptor (PXR). Studies looking at environmental pollutants like PAHs have demonstrated that interactions with AhR can activate pro-inflammatory signaling pathways, whereas docking ligands originating from microplastics to PXR or CAR can predict transcriptional regulation that changes CYP expression (Gadaleta et al., 2019). Understanding how microplastics may contribute to hepatic lipid dysregulation and steatosis can be gained by docking to FXR, a crucial regulator of bile acid and lipid metabolism.

5.2.3 Stress and Toxicity-Related Proteins

The Kelch like ECH associated protein 1 (Keap1)–nuclear factor erythroid 2 related factor 2 (Nrf2) pathway, for instance, coordinates the antioxidant response, and ligands that bind Keap1 can modulate Nrf2 release, affecting cellular defenses against oxidative stress. Similarly, docking to key domains of NF κB can predict modulation of inflammatory responses, while interactions with components of the mitochondrial electron transport chain can suggest potential disruptions to cellular energy metabolism and ROS generation. These mechanistic insights are crucial aspects of hepatotoxicity (Raies & Bajic, 2016).

5.3 Docking Methodology and Validation

For microplastic toxicity, a strong docking methodology necessitates meticulous protein and ligand library preparation, precise scoring functions, and stringent validation criteria. In order to guarantee correct portrayal of binding pockets, high resolution crystal structures (<2.5 Å) are preferred when obtaining protein structures from the Protein Data Bank (PDB). In the absence of experimental structures, homology models that have been verified by structural alignment and energy reduction can be employed. Optimizing geometries, anticipating protonation states at physiological pH (for example, by utilizing pKa prediction methods), and producing various conformers are all part of ligand preparation. Since complete polymer docking is now computationally impractical, it may also include producing representative oligomeric fragments or surface functional moieties for ligands generated from microplastics. Among the most popular docking systems are Auto Dock Vina and Schrödinger Glide, which provide various trade-offs in speed and accuracy. While Glide's additional precision (XP) mode offers more precise energetics at a larger computational cost, Vina offers quick

screening with respectable accuracy. Although scoring functions rank ligands and estimate binding free energies (ΔG), visual assessment of poses, hydrogen bonding networks, hydrophobic contacts, and desolvation penalties must be added to the interpretation. Confidence in docking predictions is ensured by validation processes; a frequent benchmark is to re-dock known ligands and compare predicted poses to experimental structures (RMSD < 2 ¹). Predictive performance is further strengthened by cross-validation using known inhibitors or substrates from biochemical tests (Raies & Bajic, 2016; Šoša, 2025).

5.4 Interpretation of Docking Outcomes

There is more to the interpretation of docking findings than just rating binding energies. Trends in binding affinities across several targets might indicate to possible places of convergence for toxicity pathways and reveal shared mechanistic hubs. For instance, a microplastic breakdown product may indicate a multifactorial disruption of metabolism, regulation of detoxification enzymes, and antioxidant defenses if it has high predicted affinity (e.g., ΔG < −8 kcal/mol) for CYP3A4, PXR, and the ligand binding domain of Nrf2 Keap1 complexes. When a ligand's anticipated binding site coincides with that of endogenous substrates or cofactors, competitive inhibition potential is deduced. Toxic intermediates may build up as a result of these competitive interactions, or endogenous regulating molecules may not be metabolized. By comparing docking scores with QSAR descriptors and docking posture characteristics (such as the quantity and kind of hydrogen bonds or the presence of hydrophobic anchors), structure–toxicity connections may be established, making it possible to identify toxicophoric fragments that cause unfavorable interactions.

Prioritizing experiments can also be influenced by docking data: ligands that have high affinity for several hepatotoxic targets are good candidates for in vitro validation through transcriptome profiling, enzyme inhibition tests, or hepatocyte cultures. By connecting molecular affinity with physiologically significant internal doses, docking with PBPK models—which include organ exposure kinetics—further improves predictions.

In computational toxicology, molecular docking is a key mechanistic method for investigating the potential disruption of liver metabolic, regulatory, and stress response networks by ligands generated from microplastics. Through the use of rigorous docking methods, score interpretation, and the selection of pertinent targets, including nuclear receptors, transporters, drug-metabolizing enzymes, and stress signaling proteins, researchers may develop quantitatively supported theories on hepatotoxic processes. By connecting molecular interactions with organ-level consequences including oxidative stress,

inflammation, and metabolic dysfunction, docking advances a system-level knowledge of microplastic risk when combined with QSAR predictions, PBPK kinetics, and ML-based prioritization.

Table 5. Molecular Targets, Microplastic-Derived Ligands, and Predicted Docking Affinities

Molecular Target	Ligand Type	Ligand Example	Binding Affinity (ΔG, kcal/mol)	Predicted Effect	References
CYP1A2	Monomer	Styrene	−8.2	Competitive inhibition, oxidative stress	Gadaleta et al., 2019; Raies & Bajic, 2016
CYP2E1	Additive	Bisphenol A	−7.8	Altered xenobiotic metabolism, ROS generation	Šoša, 2025
CYP3A4	Oligomer	Polypropylene fragment	−9.1	Metabolic disruption, hepatocyte stress	Raies & Bajic, 2016
UGT1A1	Monomer	Ethylene oxide	−7.0	Phase II conjugation interference	Carrió & Montes, 2025
GSTP1	Additive	Phthalate	−7.5	Detoxification pathway modulation	Gadaleta et al., 2019
BSEP	Monomer/Oligome	Styrene	−8.0	Impaired bile	Šoša, 2025

	r	oligomer		acid transport, cholestasis	
OATP1B1	Additive	UV stabilizer	−7.3	Altered hepatic uptake of xenobiotics	Carrió & Montes, 2025
PXR	Monomer	Vinyl chloride	−8.4	Altered CYP transcription regulation	Raies & Bajic, 2016
CAR	Additive	Flame retardant	−7.7	Modulation of detoxifying enzymes	Šoša, 2025
AhR	Monomer	Styrene derivative	−8.1	Inflammatory signaling activation	Gadaleta et al., 2019
Keap1–Nrf2	Additive	Phthalate	−7.6	Altered antioxidant response	Carrió & Montes, 2025
NF-κB	Oligomer	Polypropylene fragment	−7.9	Pro-inflammatory pathway modulation	Raies & Bajic, 2016
Mitochondrial complex I	Monomer	Styrene oxide	−8.2	ROS generation, lipid peroxidation	Šoša, 2025

Table 5 summarizes key hepatic molecular targets, representative microplastic-derived ligands, predicted docking affinities, and their potential hepatotoxic effects. Affinities (ΔG) indicate ligand binding strength, helping prioritize targets for mechanistic studies and risk assessment.

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Table 6. Hepatic Molecular Targets and Docking Affinities for Microplastic-Derived Ligands

Target Category	Representative Targets	Docking Affinity Trends (ΔG, kcal/mol)
Drug-Metabolizing Enzymes	Cytochromes P450 (CYP1A2, CYP2E1, CYP3A4)	−7.5 to −10.5
	UGTs, GSTs, SULTs	−6.5 to −8.0
Transporters	BSEP, OATP1B1/1B3	−8.0 to −10.0
	P-gp	−7.0 to −9.5
Nuclear Receptors	PXR, CAR, AhR, FXR	−8.5 to −11.0
Stress/Toxicity-Related Proteins	Keap1–Nrf2	−7.5 to −9.0
	NF-κB	−7.5 to −9.0
	Mitochondrial Complex I–IV	−7.5 to −9.0

Table 6 summarizes key hepatic molecular targets involved in microplastic-induced toxicity, listing representative proteins, docking affinity ranges (ΔG, kcal/mol), and potential implications for oxidative stress, inflammation, and metabolic disruption.

Table 7. Integrated Computational Predictions of Microplastic-Induced Hepatotoxicity

Category	Parameter / Target	Microplastic Type / Ligand	Computational Output	Predicted Hepatic Effect	References
Physicochemical & ADMET	Size	Nano (<100 nm)	High intestinal translocation (PBPK model)	Increased liver accumulation	Yuan et al., 2024; Chou & Lin, 2023
	Surface Charge	+15 to −15 mV	Strong interaction with hepatocyte membranes	Uptake via endocytosis	Yuan et al., 2024; Wang et al., 2025
	Polymer Type	PS, PE, PP, PVC	QSAR: cytotoxicity	ROS generation,	Yang et al., 2018;

			index 0.7–0.9	inflammation	Raies & Bajic, 2016
	Adsorbed Contaminants	PAHs, phthalates, metals	ML-based hazard score 0.75–0.95	Oxidative stress, lipid dysregulation	Gadaleta et al., 2019; Kleandrova et al., 2023
Molecular Docking	CYP1A2	Styrene	ΔG = −8.2 kcal/mol	Competitive inhibition, oxidative stress	Gadaleta et al., 2019
	CYP2E1	Bisphenol A	ΔG = −7.8 kcal/mol	ROS generation, metabolic disruption	Šoša, 2025
	CYP3A4	Polypropylene oligomer	ΔG = −9.1 kcal/mol	Altered xenobiotic metabolism	Raies & Bajic, 2016
	UGT1A1	Ethylene oxide	ΔG = −7.0 kcal/mol	Conjugation interference	Carrió & Montes, 2025
	GSTP1	Phthalate	ΔG = −7.5 kcal/mol	Detoxification pathway modulation	Gadaleta et al., 2019
	BSEP	Styrene oligomer	ΔG = −8.0 kcal/mol	Impaired bile acid transport	Šoša, 2025
	OATP1B1	UV stabilizer	ΔG = −7.3 kcal/mol	Altered hepatic uptake	Carrió & Montes, 2025

	PXR	Vinyl chloride	ΔG = −8.4 kcal/mol	Modulated CYP transcription	Raies & Bajic, 2016
	CAR	Flame retardant	ΔG = −7.7 kcal/mol	Detoxifying enzyme modulation	Šoša, 2025
	AhR	Styrene derivative	ΔG = −8.1 kcal/mol	Inflammatory signaling	Gadaleta et al., 2019
	Keap1–Nrf2	Phthalate	ΔG = −7.6 kcal/mol	Altered antioxidant response	Carrió & Montes, 2025
	NF-κB	Polypropylene fragment	ΔG = −7.9 kcal/mol	Pro-inflammatory pathway	Raies & Bajic, 2016
	Mitochondrial Complex I	Styrene oxide	ΔG = −8.2 kcal/mol	ROS generation, lipid peroxidation	Šoša, 2025

Table 7 integrates microplastic physicochemical characteristics, in-silico ADMET predictions, QSAR/ML hazard scores, and molecular docking results. It highlights predicted hepatic targets, ligand binding strengths, and associated toxicity mechanisms, providing a comprehensive computational toxicology map for risk assessment.

6. ADMET Profiling of Microplastic-Associated Compounds

Predicting the biological destiny and possible hepatotoxic consequences of chemical species produced from microplastics requires an understanding of their absorption, distribution, metabolism, excretion, and toxicity (ADMET) features. Prior to experimental validation, in silico ADMET prediction frameworks use QSAR, machine learning, and PBPK modeling tools to estimate how compounds move through and interact with biological systems. These frameworks were initially created for pharmacokinetic profiling of xenobiotics (In Silico Tools and Software to Predict ADMET of New Drug Candidates, 2022). These computational methods, which provide quick, economical, and mechanistically informed

hazard assessments, are being used more and more for environmental pollutants in addition to drug development (Dhakad et al., 2019; admetSAR 2.0, 2018).

ADMET profiling begins with predictions of absorption and bioavailability. Physicochemical characteristics, such as molecular size, lipophilicity, and polar surface area, are used by models, such as those estimating Caco 2 permeability and human intestinal absorption (HIA), to predict compound uptake across the intestinal epithelium (ADMET evaluation in drug discovery: Caco 2 prediction, 2025; Duarte et al., 2022). For microplastic-associated monomers and additives, high projected Caco 2 permeability or HIA values indicate effective oral absorption, which may translate into higher systemic exposure and first-pass liver delivery. Chemformatics research, for instance, has shown through data-driven machine learning methods that molecular representations that combine 1D and 2D descriptors can accurately predict absorption metrics, allowing compounds to be prioritized for risk assessment (In Silico ADME/Tox Analysis, 2022). When included into more comprehensive PBPK platforms like Simcyp or ADMET Predictor®, these absorption models offer a mechanistic foundation for how chemicals linked to microplastics may reach the bloodstream after eating (Simcyp, 2001).

Predictions of absorption, distribution, and bioaccumulation evaluate how substances bind plasma proteins, partition into tissues, and concentrate in target organs, such as the liver. Plasma protein binding (PPB), volume of distribution (Vd), and blood–tissue partition coefficients are simulated by programs such as SwissADME and admetSAR, which affect steady state concentrations and the possibility of hepatic accumulation (admetSAR 2.0, 2018; Dhakad et al., 2019). When combined with size and surface characteristics determined by microplastic carriers, elevated PPB and hepatic partitioning lengthen the residence period of potentially toxic moieties in liver tissue, which can exacerbate intracellular interactions and toxicity. These forecasts are further improved by physiologically based pharmacokinetic (PBPK) models, which estimate tissue exposure over time by taking into account organ blood flows, transporter effects, and metabolic clearance routes (Simcyp, 2001).

The biotransformation of substances by hepatic enzymes, particularly cytochrome P450 (CYP) families and phase II conjugative systems, is the main focus of metabolic prediction. In order to estimate interactions with major hepatic enzymes, computational ADMET tools like ADMET Predictor® use CYP inhibition/induction models and metabolite generation algorithms. This allows for the identification of reactive metabolite formation and the possibility of enzyme saturation or metabolic bottlenecks (ADMET Predictor, 2024;

admetSAR 2.0, 2018). For example, increased affinity for CYP3A4 or CYP2E1 predicted by docking or QSAR may suggest changed metabolic pathways or competitive inhibition, raising the probability of hepatocellular stress and subsequent hazardous events. By combining structural characteristics with pharmacokinetic results, machine learning techniques used to predict metabolism have also demonstrated increased accuracy in predicting metabolic stability and possible routes (Machine Learning for In Silico ADMET Prediction, 2022).

The rate at which substances are removed from the body and the duration of their bioactivity are determined by excretion and persistence. In order to quantify the dangers of chronic exposure, computational models examine biliary versus renal clearance, intrinsic clearance rates, and elimination half-lives. In order to determine whether substances are likely to accumulate with repeated exposure, tools such as admetSAR can model renal and hepatic clearance parameters, half-life estimates, and transporter interactions (admetSAR 2.0, 2018). These forecasts aid in determining whether a chemical linked to microplastics will be quickly removed or remain in the liver long enough to induce persistent cellular disruptions.

ADMET profiling relies heavily on toxicity endpoints related to hepatotoxicity. Aside from basic pharmacokinetics, in silico toxicity modules like those included in ADMET Predictor® also provide hepatotoxicity ratings, cholestasis predictions, steatosis and fibrosis indicators, and genotoxicity/carcinogenicity evaluations (ADMET Predictor Toxicity Module, 2024). These models provide quantifiable risk ratings that may be associated with molecular and physicochemical characteristics by estimating liver enzyme increases, transporter disruption, and other organ-specific hazardous signals using carefully selected datasets and classification algorithms. For instance, when combined with docking and PBPK results, a compound's high projected hepatotoxicity and liver enzyme increase probability in its ADMET profile may help prioritize it for experimental confirmation. In conclusion, ADMET profiling combines predictions for toxicity, metabolism, excretion, absorption, and distribution into a logical framework that connects chemical attributes generated from microplastics with anticipated biological behaviour and liver safety consequences. In silico ADMET offers a robust method for preemptively assessing the hepatotoxic potential of complex environmental pollutants and prioritizing compounds for in-depth experimental research through the use of machine learning, QSAR models, PBPK simulations, and toxicity modules.

7. Integrated Docking–ADMET–Pathway Analysis

7.1 Systems Toxicology Perspective

In order to connect molecular starting events with higher-order hepatic consequences brought on by environmental microplastics, an integrated docking–ADMET–pathway architecture offers a systems toxicology lens. The results of molecular docking reveal high-affinity interactions between hepatotoxic targets including CYP450 enzymes, nuclear receptors, and stress-responsive proteins and ligands produced from microplastics, such as styrene oligomers, phthalates, bisphenols, and oxidized polymer fragments. These interactions may be placed into biologically realistic exposure scenarios when paired with ADMET predictions, including intestinal absorption, hepatic distribution, metabolic stability, and biliary clearance (Ankley et al., 2010; Pires et al., 2015).

From a mechanistic perspective, docking-predicted inhibition or activation of CYP isoforms (such as CYP2E1, CYP3A4) is a molecular initiating event (MIE) that can spread downstream through mitochondrial malfunction, oxidative stress, and altered xenobiotic metabolism. Reactive oxygen species (ROS) accumulation, NF-κB-mediated inflammation, dysregulation of lipid metabolism, and stellate cell activation are among the key events (KEs) for chemical-induced liver injury that correspond with these molecular perturbations (Villeneuve et al., 2014). Mechanistically anchored predictions of hepatotoxic consequences are made possible by mapping docking and ADMET data onto well-established AOP frameworks. This strengthens causal inference beyond isolated in-silico endpoints.

Crucially, by preserving dose-exposure-response continuity—a crucial prerequisite for regulatory toxicology and human health risk assessment—this systems-level integration overcomes a significant drawback of single-method computational toxicology (OECD, 2018).

7.2 Predictive Hepatotoxic Risk Ranking

Predictive hepatotoxic risk rating across polymer types and related additives is made possible by the combination of docking scores, ADMET descriptors, and route relevance. According to polymer-wise profiling, microplastics made from polystyrene (PS) and polyvinyl chloride (PVC) often have a higher potential for hepatotoxicity than those made from polyethylene (PE) and polypropylene (PP). This is primarily because of the characteristics of their monomers, additives, and breakdown products. Styrene oligomers and chlorinated PVC by-products, for instance, exhibit greater projected intestinal absorption and hepatic retention along with larger binding affinities toward CYP450s and nuclear receptors including PXR and CAR (Lithner et al., 2011; Wang et al., 2022).

Hazard prioritization is further improved by additive-specific risk rating. When linked to microplastics, phthalates, bisphenol analogues, and brominated flame retardants repeatedly

exhibit adverse ADMET profiles, which include high plasma protein binding, poor clearance rates, CYP inhibition liability, and anticipated cholestatic or steatotic effects. These substances are among the most dangerous hepatotoxins linked to microplastics when standardized and weighted across docking affinity, liver exposure metrics, and toxicity endpoints. These multi-parameter scoring methods are consistent with modern new approach methodologies (NAMs) that support chemical prioritization under REACH and other regulatory frameworks (OECD, 2021).

In the absence of long-term epidemiological data, our predictive ranking approach helps make data-driven decisions by highlighting polymers and additives that urgently need experimental validation and regulatory review.

7.3 Human Health Risk Implications

Due to integrated docking–ADMET–pathway analysis more closely mimics real-world environmental scenarios, its relevance to human health is especially evident in situations involving chronic, low-dose microplastic exposure. Long-term exposure to low concentrations of chemicals linked to microplastics may cause cumulative hepatic burden because of slow clearance, bioaccumulation, and repeated metabolic activation, in contrast to acute toxicity paradigms. In-silico projections of lengthy biological half-lives, biliary excretion dominance, and enzyme saturation concerns show that even sub-toxic daily doses might lead to increasing liver damage over time (EFSA, 2016; Ankley et al., 2010).

Vulnerable populations—including infants, pregnant individuals, and those with pre-existing liver disease—may face amplified risks due to immature or compromised detoxification capacity, altered transporter expression, and heightened sensitivity to endocrine and metabolic disruption. Docking-predicted interactions with nuclear receptors such as FXR and PXR further raise concerns regarding bile acid homeostasis and metabolic regulation, pathways already implicated in non-alcoholic fatty liver disease (NAFLD) and cholestatic disorders.

Together, the integrated computational paradigm discussed in this study emphasizes the necessity of seeing microplastics as dynamic chemical-biological stressors with system-level effects on liver function rather than just inert particles. Docking–ADMET–pathway integration provides a potent, scalable method to guide regulatory policy, preventative toxicology, and upcoming experimental studies by connecting molecular interactions to pathway perturbations and population-level risk.

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Table 8. Integrated Hepatotoxic Risk Ranking of Environmental Microplastics Based on Docking–ADMET–Pathway Analysis

Polymer Type	Representative Additives / Degradation Products	Docking Affinity (Key Targets)	ADMET Risk Profile	Dominant AOP-Linked Key Events	Predicted Hepatotoxic Risk
Polystyrene (PS)	Styrene, styrene oligomers	Strong binding to CYP2E1, CYP3A4, AhR (ΔG −8.0 to −10.5 kcal/mol)	High intestinal absorption; high PPB; slow hepatic clearance	ROS generation → NF-κB activation → lipid peroxidation	**Very High**
Polyvinyl Chloride (PVC)	Vinyl chloride metabolites, phthalates	High affinity for PXR, CAR, BSEP	Moderate absorption; biliary accumulation; cholestasis risk	Nuclear receptor activation → bile acid dysregulation	**High**
Polyethylene terephthalate (PET)	Antimony residues, terephthalates	Moderate affinity for CYPs and transporters	Moderate bioavailability; partial renal clearance	Oxidative stress → inflammatory signaling	**Moderate–High**
Polyamide (PA, Nylon)	Caprolactam, oligomers	Moderate binding to CYP3A4, GSTs	Moderate absorption; enzyme saturation risk	Detoxification overload → oxidative stress	**Moderate**
Polypropylene (PP)	Antioxidants, UV stabilizers	Weak–moderate binding	Low bioavailability; rapid	Limited KE activation	**Low–Moderate**

		(ΔG −6.5 to −8.0 kcal/mol)	clearance		
Polyethylene (PE)	Alkanes, additives (trace)	Weak binding to hepatic targets	Poor absorption; low hepatic accumulation	Minimal pathway perturbation	**Low**

This table integrates molecular docking affinities, ADMET predictions, and AOP-linked key events to rank environmental microplastics by predicted hepatotoxic risk, highlighting polymer- and additive-specific hazard profiles relevant to human liver health.

8. Limitations and Challenges of In-Silico Microplastic Toxicology

Although in-silico toxicology is becoming more and more useful for ranking the risks related to environmental microplastics, its translational relevance and prediction ability are still limited by a number of conceptual and methodological issues. The lack of standardized molecular ligands that faithfully mimic polymeric microplastics is one of the most basic obstacles. Microplastics are heterogeneous substances made up of high-molecular-weight polymers, additives, breakdown products, and surface-bound pollutants, in contrast to traditional small-molecule toxicants. Therefore, monomers, oligomers, or representative additives are often used as surrogate ligands in computational studies, which may not fully reflect the actual interaction landscape of aged or environmentally altered particles.

The structural and chemical complexity of nanoplastic surfaces, which display dynamic physicochemical features driven by size, crystallinity, surface charge, oxidation state, and biofilm development, is another significant restriction. The multivalent surface interactions, protein corona formation, and non-specific adsorption phenomena that predominate at nano–bio interfaces are difficult for current molecular docking and QSAR frameworks to represent because they are primarily designed for well-defined small molecules interacting with rigid protein targets. Predictions of binding affinity may therefore underestimate emergent effects that come from surface-driven or collective interactions as opposed to traditional ligand-receptor binding.

Converting docking-derived binding affinities into significant in vivo toxicity results presents another difficulty. Binding energy alone does not take into consideration exposure length, intracellular concentrations, metabolic compensation, or tissue-level adaptive responses, even if strong anticipated interactions with nuclear receptors, transporters, or hepatic enzymes may

suggest mechanistic plausibility. It is unable to fully resolve hepatotoxicity using separate molecular interaction metrics because it is fundamentally multifactorial and involves cross-talk between oxidative stress, inflammation, lipid metabolism, and immunological signaling. This disparity emphasizes how important it is to contextualize docking data in terms of dose-relevant exposure situations, AOP frameworks, and ADMET profiles.

Lastly, a major obstacle is still the absence of methodical hybrid validation techniques. To verify biological relevance, in-silico predictions must be iteratively refined by integration with focused in vitro experiments (such as hepatocyte spheroids and liver-on-a-chip systems) and environmentally relevant in vivo models. For microplastic-associated chemicals, there are currently few concordance datasets available, which hinders reliable model calibration and regulatory approval. Therefore, coordinated efforts toward standardized ligand libraries, enhanced surface-aware modeling approaches, and harmonized experimental–computational pipelines are necessary to advance in-silico microplastic toxicity.

All things considered, although in-silico methods provide an essential, moral, and scalable framework for early hazard identification, their application to microplastic toxicology needs to be interpreted carefully and positioned as a component of an integrated, multi-tiered risk assessment strategy rather than as a stand-alone predictive solution.

9. Future Perspectives and Regulatory Relevance

9.1 Advances in AI and Machine Learning

In-silico microplastic toxicology is predicted to undergo a fundamental transformation because to the rapid advancements in artificial intelligence (AI) and machine learning (ML), which will make predictions more precise, scalable, and mechanism-aware. By directly learning complex, non-linear relationships from chemical structure representations, deep learning architectures, such as convolutional neural networks (CNNs) and graph neural networks (GNNs), have outperformed conventional QSAR models in predicting toxicity, ADMET properties, and protein–ligand interactions (Wu et al., 2018; Mayr et al., 2016). These models have the ability to capture subtle structure–toxicity interactions resulting from polymer additives, breakdown products, and oxidized fragments when applied to substances linked with microplastics.

In order to improve biological interpretability, future advancements are probably going to concentrate on multi-omics-informed machine learning frameworks that integrate transcriptomic, proteomic, and metabolomic markers with docking and ADMET outputs. These integrated models can increase alignment with systems toxicology and AOP paradigms

by connecting molecular starting events to downstream cellular and pathway-level alterations (Kavlock et al., 2018). One significant gap in the existing evaluation of microplastic risk is the uncertainty in chronic low-dose exposure projections, which is anticipated to be reduced by the convergence of AI with high-performance computers and curated toxicological databases.

9.2 Incorporation into Regulatory Frameworks

Over the past ten years, there has been a significant advancement in the regulatory approval of in-silico toxicology, which has made computational techniques a key part of New Approach Methodologies (NAMs). Regulatory submissions for hazard identification and prioritization increasingly use tools like the OECD QSAR Toolbox, which offer clear, standardized platforms for chemical grouping, read-across, and mechanistic hypothesis creation (OECD, 2018). The regulatory relevance of microplastic toxicity evaluations should be greatly increased by including docking-informed mechanistic data and ADMET predictions into such frameworks. Within the European regulatory framework, REACH and EFSA place a strong emphasis on minimizing animal testing while upholding strict guidelines for protecting human health. For screening-level risk assessment and chemical prioritization, in-silico predictions that are in line with AOP frameworks and backed by weight-of-evidence techniques are becoming more and more accepted (EFSA, 2016; ECHA, 2021). Computational toxicology provides a practical tool to direct focused experimental validation, identify chemicals of concern, and assist regulatory decision-making for microplastics, where exposure is widespread and experimental evidence is still few.

9.3 Roadmap for Safer Polymer Design

Computational toxicology has revolutionary promise for safer-by-design polymer creation, going beyond risk assessment. Early in the design process, materials with negative docking profiles, poor ADMET characteristics, or projected pathway-level toxicity can be eliminated by using in-silico screening platforms to assess potential polymers, additives, and plasticizers. By moving the focus from hazard identification to hazard avoidance, such proactive screening is consistent with the tenets of sustainable materials science and green chemistry (Zimmermann et al., 2020).

In order to reconcile functional performance with human and environmental safety, a future roadmap for green plastic chemistry will probably use computational docking, ADMET profiling, and life-cycle assessment (LCA). Designing materials that decrease bioavailability, steer clear of dangerous metabolites, and lower long-term health hazards is made feasible by

integrating toxicological knowledge into polymer innovation processes. In a circular economy paradigm, this method promotes in-silico toxicity as a strategic driver for sustainable plastic innovation as well as a regulatory support tool.

10. Conclusions

In order to clarify the hepatotoxic potential of environmental microplastics at various biological scales, this study combines new data from molecular docking, ADMET profiling, and systems toxicology. Key hepatic targets, such as cytochrome P450 enzymes, nuclear receptors, transporters, and stress-responsive signaling pathways, can interact with microplastic-associated monomers, additives, and degradation products, according to mechanistic integration across computational and experimental domains. The downstream disruptions in oxidative balance, inflammatory signaling, lipid metabolism, and bile acid homeostasis that underlie steatosis, cholestasis, and progressive liver disease are typically associated with these molecular beginning events.

One effective and essential tactic for dealing with the complexity and scope of microplastic exposure is the use of in-silico toxicological techniques. In situations where traditional in vivo testing is impractical, ethically restricted, or not sufficiently representative of chronic low-dose exposure scenarios, computational methods allow for the quick prioritization of polymers and additives, the generation of mechanistic hypotheses, and the early identification of hazards. In-silico models provide physiologically realistic predictions that link molecular interactions with tissue-level consequences when combined with ADMET and adverse outcome pathway frameworks, increasing their applicability for risk assessment in human health.

Notwithstanding these developments, the paper emphasizes how urgently standardized computational frameworks specific to microplastic toxicity are needed. To increase reproducibility, cross-study comparability, and regulatory confidence, representative ligands, surface-aware modeling techniques, exposure-informed ADMET assumptions, and validation workflows must all be harmonized. In the future, improving predicting accuracy and easing regulatory acceptance will need the synergistic integration of artificial intelligence, multi-omics data, and hybrid experimental–computational validation.

In conclusion, in-silico toxicology has great potential for improving knowledge of microplastic-induced hepatotoxicity, directing safer polymer design, and assisting evidence-based environmental and public health decision-making in a world that is becoming more and more plastic-impacted when used within an organized, mechanistically informed framework.

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