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A conceptual framework and proposed adverse outcome pathway for micro- and nanoplastics accumulation and neurovascular toxicity in the human retina

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Abstract

Micro- and nanoplastics (MNPs) have recently been detected in human retinal tissue, raising concerns about their potential role in neurovascular injury. This paper proposes a conceptual framework and provisional adverse outcome pathway (AOP) to explain how polymer-specific accumulation may contribute to retinal degeneration. Existing empirical findings on retinal plastic burdens were integrated with toxicokinetic principles to construct a polymer-specific model of uptake, retention, and clearance. Mechanistic insights from oxidative stress, inflammation, and barrier dysfunction were synthesized into a stepwise AOP linking molecular initiating events to adverse outcomes. This framework predicts differential retinal retention based on polymer polarity and density: nonpolar, low-density plastics (e.g., polyethylene) tend to clear, whereas polar, dense polymers (e.g., polymethyl methacrylate) accumulate with age. The proposed AOP outlines a cascade from plastic-cell interactions to oxidative stress, inflammation, blood-retinal barrier breakdown, and ultimately neurovascular degeneration. A feedback loop is hypothesized, whereby barrier disruption facilitates further plastic entry. This conceptual model reframes retinal microplastics as active disruptors of homeostasis rather than inert debris. It highlights the retina's potential as a biosensor for systemic plastic exposure, identifies PMMA as a priority polymer for risk assessment, and suggests therapeutic targets in oxidative stress and barrier protection. Validation through tracer studies, transgenic models, and biomarker development is recommended.

Key words: microplastics; retina; conceptual framework; neurovascular toxicity; toxicokinetics; adverse outcome pathway.

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Introduction

Micro- and nanoplastics (MNPs) are pervasive environmental contaminants whose infiltration of human tissues is now unequivocally established. A growing body of evidence documents their presence in critical biological compartments, including lung tissue,[1] placental tissue,[2] liver,[3] blood,[4] and breast milk.[5] This widespread biodistribution raises urgent, unresolved questions regarding the chronic pathophysiological consequences of MNP exposure across organ systems.

The recent first detection of MNPs in post-mortem human retinal tissue marks a critical expansion of this contamination landscape, confirming that the eye is not exempt.[6] This seminal discovery identified multiple polymer types -including polystyrene (PS), polyethylene (PE), polypropylene (PP), poly(methyl methacrylate) (PMMA), and polyvinyl chloride (PVC)- in all donor samples analyzed. Critically, it revealed suggestive polymer-specific patterns, such as a positive correlation between PMMA burden and donor age (Table 1). These findings position the human retina as a novel and critical interface between the anthroposphere (source of plastic pollution) and the biosphere (human neurovascular tissue), demanding mechanistic understanding within a total environment context. This discovery in solid retinal tissue is complemented by the detection of MNPs in human aqueous and vitreous humor,[7-8] underscoring the eye's systemic vulnerability.

The retina is a uniquely vulnerable and functionally indispensable target. As an immune-privileged site with high metabolic demand and exquisite neurovascular organization, its homeostasis depends on intact blood-retinal barriers and efficient clearance mechanisms -systems that may be highly susceptible to disruption by persistent particulate contaminants.[9] Furthermore, the retina's optical transparency and advanced imaging accessibility make it a potentially ideal *sentinel tissue* for monitoring systemic MNP exposure and investigating particle-tissue interactions.

Despite this empirical breakthrough, a significant mechanistic gap remains. While prior *in vivo* and *in vitro* studies demonstrate that MNPs can induce oxidative stress, inflammation, and cellular dysfunction in various systems,[10-13] and emerging ocular research shows polystyrene toxicity in animal models,[14] *no unified, predictive framework* links the environmental fate of MNPs -dictated by polymer physicochemistry- to a sequence of measurable biological key events culminating in human retinal injury. The fundamental mechanisms governing how different polymer types access, distribute within, persist in, and ultimately disrupt human retinal tissue remain undefined.

Therefore, with the initial hypothesis of retinal MNP existence now confirmed (a prediction presaged by a Bayesian model earlier

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Table 1. Key empirical findings from human retinal tissue and their mechanistic implications. These data collectively support the assumption that micro- and nanoplastics (MNPs) not only reach retinal tissue but display polymer-dependent behaviors consistent with biophysical selectivity. Polystyrene (PS), polyethylene (PE), polypropylene (PP), poly(methyl methacrylate) (PMMA), and polyvinyl chloride (PVC). Data derived from Zhang *et al*.[6] (supporting information).

Observation	Supporting data source	Mechanistic implication
Five polymer types detected (PS, PE, PP, PMMA, PVC)	Table S2, S3	Distinct physicochemical traits drive different tissue interactions
Particle size 20–50 µm; mostly fragmented or fibrous	Main study	Fibrous microplastics may lodge in capillaries; fragments diffuse through blood retinal barrier
Age correlation: PE −0.536, PMMA +0.555 ($p \leq 0.01$)	Table S3	PE transient (clearable), PMMA persistent (bio-accumulative)
Universal detection (12/12 samples positive)	Main study	Blood retinal barrier permeability or systemic exposure sufficient for retinal penetration
Calibration $R^2 \geq 0.99$; recoveries ≈ 100%	Table S1	Analytical robustness ensures biological interpretability

the same year),[15] the scientific imperative shifts from detection to predictive mechanism. This paper addresses this critical gap by proposing the first integrative conceptual framework and testable hypothesis for retinal MNP toxicity. We synthesize quantitative signals from Zhang *et al*.'s seminal dataset with established principles of retinal physiology,[6] polymer physics, and Adverse Outcome Pathway (AOP) methodology to construct a dual-component framework designed to guide future research. This framework aims to: i) formalize a polymer-specific toxicokinetic hypothesis to explain retinal accumulation dynamics, and ii) outline a provisional AOP that details the plausible sequential key events leading from accumulation to neurovascular dysfunction. However, the output is not a validated model but a foundational, mechanistically explicit, and deliberately testable research blueprint. Its purpose is to structure future hypothesis-driven experimentation, enable targeted risk assessment, and ultimately inform preventive strategies in the emerging field of environmental ophthalmology.

To clarify, this paper it does not present primary empirical data or a fully validated model. Instead, we propose a foundational, mechanistically explicit, and deliberately testable research blueprint. Its primary purpose is to structure future hypothesis-driven experimentation, enable targeted risk assessment, and inform preventive strategies in environmental ophthalmology.

A proposed biophysical and mechanistic framework for retinal MNP toxicity

This section outlines the core components of a proposed conceptual framework designed to explore the journey and potential impact of MNPs in the human retina. It integrates a polymer-specific kinetic hypothesis with a provisional Adverse Outcome Pathway (AOP), forming a testable scaffold for future research.

Proposed entry routes: pathways to the retina

We hypothesize that MNPs access the retina through multiple physiological and iatrogenic pathways, which can be categorized as systemic or direct (Figure 1). Understanding these routes is critical for parameterizing the uptake term (U_i) in the kinetic hypothesis.

The primary systemic route involves vascular transport. Circulating particles may traverse the outer blood-retinal barrier (oBRB) at the retinal pigment epithelium (RPE) via endocytic or paracellular mechanisms, particularly under conditions of aging, inflammation, or oxidative stress.[16] Similarly, the inner BRB (iBRB), formed by retinal capillary endothelial tight junctions, may exhibit transient permeability, allowing smaller MNPs to infiltrate inner retinal layers.[17-18] A third systemic pathway could involve retrograde axonal transport along the optic nerve or perivascular channels, a mechanism analogous to documented nanoparticle trafficking from the cerebrospinal fluid into retinal tissue.[19] Collectively, these vascular and neural routes may lead to a diffuse or perivascular distribution of particles.

Beyond systemic exposure, several *direct entry routes* may bypass traditional barriers. Intraocular surgery (e.g., cataract extraction, vitrectomy) and penetrating ocular trauma could inadvertently introduce environmental or material-derived polymers from surgical instruments, intraocular lenses, or irrigation systems directly into the vitreous or subretinal space. Such events likely generate localized, high-concentration deposits.

Intravitreal injections represent another direct pathway. While performed under sterile conditions, particulate contaminants from glass vials, syringe lubricants, or polymeric carriers could be introduced into the vitreous cavity. The ultimate localization of these particles -whether settling on the macula or lodging inferiorly- would be governed by their size, density, and buoyancy.

Finally, transocular surface absorption may provide a chronic,

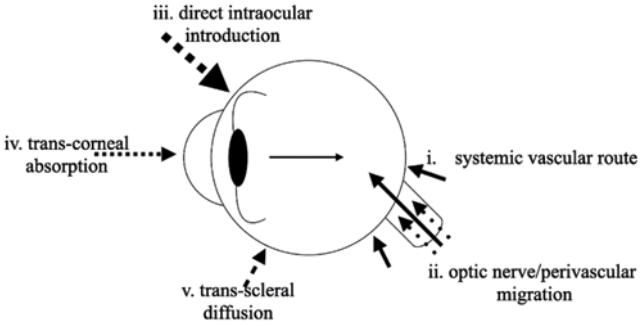


Figure 1. Anatomical pathways of retinal microplastic entry. Schematic cross-section of the eye illustrating i) systemic vascular routes through the choroidal and retinal circulations, ii) optic-nerve/perivascular migration, iii) direct intraocular introduction *via* surgery or intravitreal injection, iv) transcorneal absorption from topical formulations, and iv) transscleral diffusion following subtenon or periocular exposure. Arrows of varying thickness represent relative flux magnitude and temporal pattern (continuous, vascular; dashed, episodic).

Table 2. Physicochemical properties of microplastics detected in human retinal tissue and inferred retention behavior. Summary of the principal physicochemical characteristics of microplastics identified in human retinal samples and their inferred biophysical behavior within retinal tissue. Density and polarity govern buoyancy and molecular affinity for lipophilic or proteinaceous matrices, while observed age correlations reflect the interplay between cumulative exposure and clearance efficiency. Polymers with higher polarity and density -particularly poly(methyl methacrylate) (PMMA)- demonstrate stronger adhesion and age-associated accumulation, whereas low-density, nonpolar polymers such as polyethylene (PE) exhibit transient presence and efficient clearance.

Polymer	Density (g/cm³)	Polarity	Observed trend with age	Inferred retinal retention behavior
Polyethylene (PE)	0.915- 0.965	Nonpolar	↓↓↓↓↓	Rapid diffusion and clearance; minimal long-term retention
Polypropylene (PP)	0.895- 0.92	Nonpolar	—	Moderate mobility with transient presence; near steady-state clearance
Polystyrene (PS)	1.04- 1.10	Nonpolar	↓↓	Surface adsorption possible; partial retention at lipid–protein interfaces
Poly(methyl methacrylate) (PMMA)	1.17- 1.20	Polar +	↑↑↑↑↑	Strong adhesion and protein binding; progressive accumulation with age
Polyvinyl chloride (PVC)	1.16- 1.45	Polar+++	↓↓↓	Dense and polar; may become trapped in tissue matrices but undergo partial degradation or fragmentation over time

low-level entry mechanism. Topical exposure could permit nanoscale plastics to penetrate a compromised corneal epithelium, after which they might diffuse posteriorly through aqueous outflow pathways to reach the posterior segment.[8,20] Similarly, transscleral absorption following periocular injections may allow particles to diffuse through the porous scleral matrix into the choroid.[21] This route is particularly plausible for small, lipophilic polymers.

A critical consideration: the reported size of detected particles (20-50 µm) appears to conflict with the steric constraints of an intact BRB. We propose this may be reconciled through size-resolved pathways. Systemic vascular routes are likely dominated by the trafficking of true nanoplastics (<1 µm) and small microplastics, which could traverse compromised tight junctions or be shuttled via endocytosis. In contrast, the larger, fibrous particles (20-50 µm) detected in post-mortem tissue are unlikely to have recently crossed an intact BRB. Their presence is more plausibly explained by direct iatrogenic introduction or, speculatively, by retrograde axonal transport where size constraints differ. The long-term accumulation of larger particles may itself contribute to chronic barrier disruption, facilitating the subsequent ingress of smaller, systemically derived particles. This hypothesis clarifies that the full spectrum of MNP sizes may access the retina, but through distinct and size-dependent mechanisms that require empirical validation.

Hypothesized retention and distribution: a matter of physicochemistry

We propose that once MNPs enter the ocular environment, their retention and distribution within retinal tissue are governed by a critical interplay between polymer physicochemical properties and retinal microanatomy. The retina's dense, lipid- and protein-rich architecture creates a heterogeneous environment where particle fate may be determined by density, polarity, and surface characteristics,[22] which rapidly recruit biomolecules to form a dynamic protein corona that further modulates polymer-specific interactions.

Empirical human data reveal clear polymer-specific retention trends that form the cornerstone of our kinetic hypothesis.[6] Low-density, nonpolar polymers like PE exhibit lower tissue persistence, consistent with high diffusivity and weak intermolecular interactions.[23] In contrast, higher-density, polar polymers like PMMA display strong adhesion to lipid-protein interfaces and electrostatic affinity, suggesting prolonged retention.[12] This is evidenced by a positive correlation between PMMA burden and donor age -interpreted here as consistent with progressive accumulation- whereas PE shows an inverse correlation with age, consistent with effective clearance (Table 2, Figure 2).

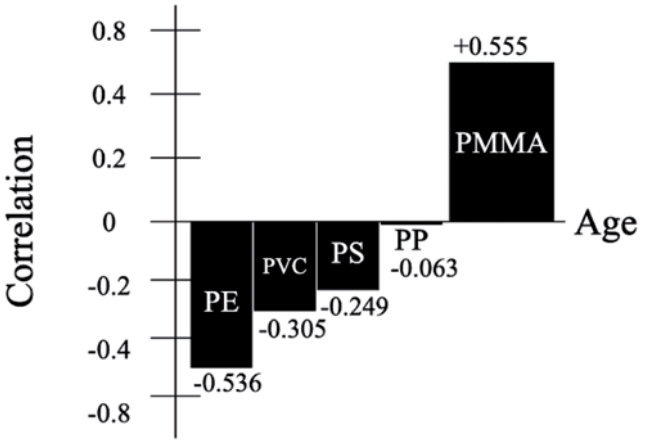


Figure 2. Dynamic balance model of retinal microplastic retention. Steady-state retinal concentration (M*) emerges from the interplay between uptake and clearance. Uptake encompasses multiple route-specific inputs -vascular, surgical/traumatic, intravitreal, corneal, and scleral- while clearance is polymer- and site-dependent, governed by the coefficient *k*. Accumulation occurs when uptake exceeds clearance. The accompanying bar graph illustrates age-dependent trajectories of five polymers: polyethylene (PE), polyvinyl chloride (PVC), polystyrene (PS), and polypropylene (PP) show declining concentrations with age, while poly(methyl methacrylate) (PMMA) increases, reflecting differential retention dynamics. Low-density, nonpolar polymers (e.g., PE) exhibit efficient clearance, whereas higher-density or polar polymers (e.g., PMMA) demonstrate stronger adhesion and persistent accumulation. Data derived from Zhang *et al*.[6] (supporting information).

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Particle morphology is further hypothesized to dictate localization. Fibrous particles >20 µm could physically lodge within the lumina of retinal capillaries, potentially causing microvascular stasis. Conversely, fragmented or spherical particles <10 µm may penetrate deeper neural layers, becoming entrapped in the inner nuclear or ganglion cell layers. These smaller particles are also more susceptible to internalization by Müller glia and microglia, potentially initiating localized oxidative and inflammatory responses.[24]

Thus, we posit that MNPs are not passive contaminants but dynamic particulates whose distribution is subject to precise biophysical partitioning based on size, shape, and chemical composition. Quantifying these retention rules is essential for testing the pathophysiological impact of specific polymer types and for parameterizing the clearance term in the kinetic hypothesis.

A formal structure for a dynamic balance model

Given the nascent stage of quantitative data on retinal MNP kinetics, we here establish the formal structure of a polymer-specific kinetic hypothesis. This structure is designed to be populated with future experimental data and provides a testable, quantitative scaffold for investigating the environmental fate of MNPs in retinal tissue.

The core hypothesis can be expressed as a mass-balance differential equation:

$$\frac{dM(t)}{dt} = \Sigma_i U_i(t) - C(M,t) \quad \text{(Eq. 1)}$$

Here, $M(t)$ represents the hypothesized retinal MNP load (concentration or mass) over time t. The total uptake rate, $\Sigma_i U_i(t)$, is the sum of contributions from the pathways previously detailed:

$$\sum_i U_i(t) = U_{vascular(t)} + U_{surgical(t)} + U_{intravitreal(t)} + U_{corneal(t)} + U_{scleral(t)}$$

The clearance rate, $C(M,t)$, is proposed to be polymer- and site-dependent. As an initial, testable assumption, we hypothesize it follows a first-order kinetic process:

$$C(M,t) = k(t) \bullet M(t) \quad \text{(Eq. 2)}$$

Here, $k(t)$ is an effective, time-dependent clearance rate constant (unit: time $^{-1}$). This first-order assumption is a pragmatic starting point for modeling the removal of foreign bodies, where the clearance rate is proportional to the burden. The coefficient $k(t)$ is hypothesized to integrate the phagocytic activity of Müller glia and microglia, the enzymatic degradation capacity of RPE cells, and the efficiency of perivascular clearance pathways. It is predicted to be high for diffusible, nonadherent polymers (e.g., PE) and low for strongly adhesive, nonbiodegradable polymers (e.g., PMMA), as inferred from the empirical age correlations. Furthermore, $k(t)$ is postulated to decrease with age due to declining metabolic and phagocytic efficiency, potentially amplifying retention in older retinas.

Substituting (2) into (1) yields the governing equation for the proposed hypothesis:

$$\frac{dM(t)}{dt} = \Sigma_i U_i(t) - k(t) \bullet M(t) \quad \text{(Eq. 3)}$$

This formal structure makes the critical knowledge gaps explicit and directly guides future research. For instance:

- A primary goal is to experimentally determine the polymer-specific clearance rate constant k.
- It is essential to quantify how k changes with age and retinal health status.
- Research must focus on measuring the relative magnitudes of the uptake terms U_i to identify the most significant exposure routes.

Therefore, this model does not aim to simulate retinal MNP load with current data, but to provide the necessary mechanistic scaffold and mathematical structure to design the targeted experiments that will enable predictive simulations and risk assessment.

Proposed AOP for MNP-induced neurovascular injury

Building upon the kinetic fate model, we propose that the retained MNP burden $M(t)$ could initiate a sequence of biological perturbations. Here, we formalize this sequence as a provisional Adverse Outcome Pathway (AOP) (Figure 3), outlining the plausible causal chain from molecular initiation to tissue-level injury, in accordance with Organization for Economic Co-operation and Development (OECD) framework principles as a starting point for development.

- **Molecular Initiating event (MIE):** The physical interaction of retained MNPs with retinal cellular structures. This encompasses: i) mechanical obstruction of capillaries (>5 µm particles) potentially causing ischemia and endothelial shear stress; and ii) biophysical interaction of nanoplastics with cell membranes (e.g., of Müller glia, microglia, RPE), potentially inducing membrane distortion or receptor activation.
- **Key events (KEs):** A hypothesized cascade of measurable cellular and tissue responses.
  - **KE1: oxidative stress and mitochondrial dysfunction.** Weathered or oxidized MNPs may generate reactive oxygen species (ROS), suppress antioxidant defenses (Nrf2/HO-1), and disrupt mitochondrial function.[25-27]
  - **KE2: inflammatory activation.** MNP internalization or surface interaction activates Müller glia, microglia, and RPE cells, leading to NLRP3 inflammasome activation and the release of pro-inflammatory cytokines (TNF-α, IL-1β, VEGF).[11,13]
  - **KE3: blood-retinal barrier (BRB) dysfunction.** The combined oxidative and inflammatory insult, along with direct pericyte loss,[28] disrupts endothelial tight junctions, increasing vascular permeability—a critical step hypothesized to enable further MNP influx.
- **Adverse outcome (AO): retinal neurovascular degeneration.** The culmination of sustained BRB breakdown, chronic inflammation, and metabolic stress may lead to photoreceptor apoptosis, neuronal loss, and dysfunctional vasculature, potentially manifesting as diminished electroretinographic responses and visual decline.[10-11]

This proposed AOP framework establishes a *hypothesized self-reinforcing positive feedback loop*: accumulation ($M(t)$) → MIE/KEs → BRB Breakdown → enhanced Uptake (U_i) → further accumulation. Critically, the nonbiodegradable nature of MNPs could make this stressor persistent, driving the cycle indefinitely and distinguishing it from transient metabolic insults. The proposed causal linkages between these events, along with an assessment of current empirical support and the critical data gaps required for formal validation, are summarized in Table 3.

In summary, this integrated framework -combining a polymer-specific kinetic hypothesis with a provisional AOP- provides a coherent, testable blueprint for future research. It transforms MNPs from inert debris into hypothesized active neurovascular disruptors with a predictable mechanistic signature, guiding efforts from quantifying fate parameters k and U_i to validating the proposed key events *in vitro* and *in vivo*.

Discussion

This work proposes an integrative conceptual framework designed to bridge the gap between the recent detection of MNPs in the human retina and the unresolved question of their potential pathophysiological impact. By synthesizing *a polymer-specific toxicokinetic hypothesis* with a *provisional AOP*, we provide a structured, testable scaffold to explore how retinal MNP accumulation may progress from environmental exposure to neurovascular injury. This synthesis directly addresses the critical shift in scientific inquiry, now necessitated by empirical discovery, from *detection* to *predictive mechanism*.

The framework as a unifying, testable hypothesis

The central novelty of this framework lies in its deliberate integration of two foundational paradigms in environmental health sciences. First, the *kinetic hypothesis* $\frac{dM(t)}{dt} = \Sigma_i U_i(t) - k(t) \bullet M(t)$ formalizes the proposition that retinal MNP burden is a dynamic equilibrium, with the polymer-specific clearance rate k as the critical determinant of long-term accumulation. This structure directly translates the problem of *environmental fate* into a quantitative, falsifiable hypothesis. Second, the proposed AOP outlines a plausible biological sequence linking retained burden $M(t)$ to the adverse outcome of neurovascular degeneration. By adopting the OECD AOP structure (MIE → KEs → AO), we move beyond descriptive association to propose a *chain of causality* that is experimentally testable. The combination establishes a multidimensional research blueprint capable of generating both *quantitative predictions* (*via* the kinetic model's parameters) and *qualitative, mechanistic hypotheses* (*via* the AOP's key event relationships).

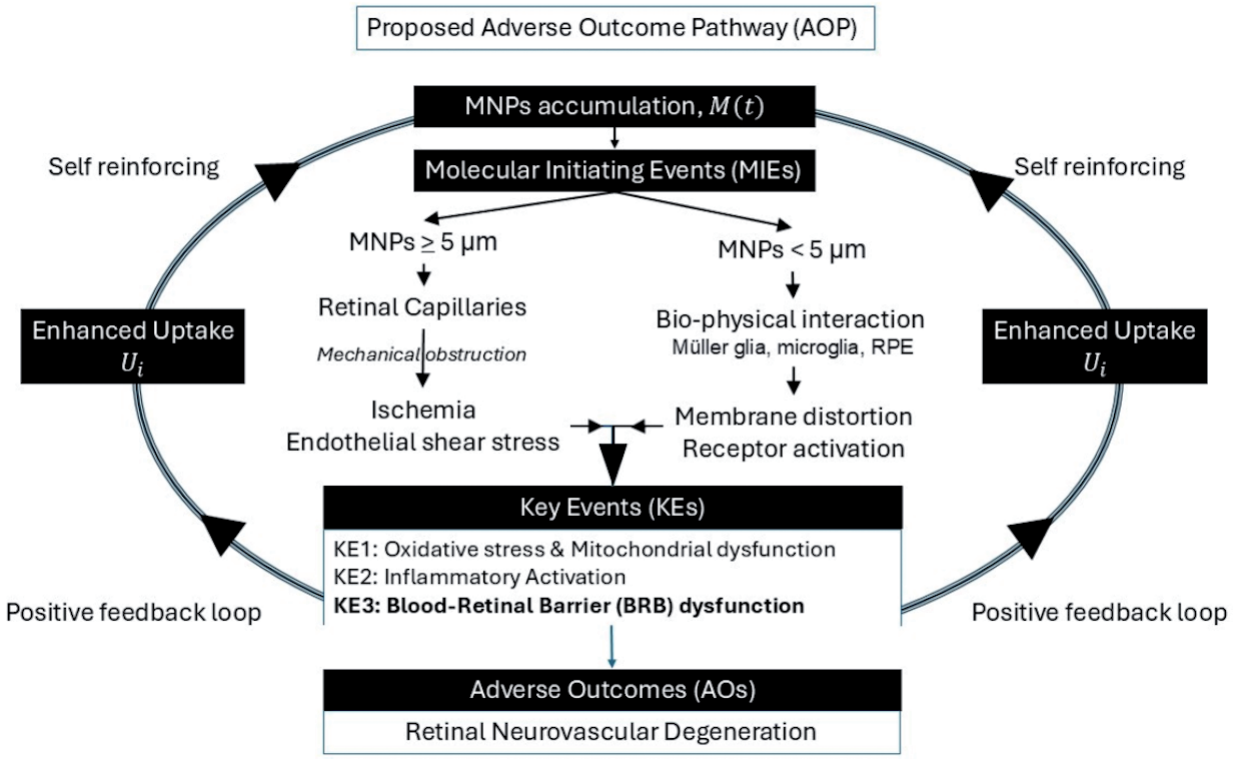


Figure 3. Schematic representation of the proposed adverse outcome pathway (AOP) linking retinal micro- and nanoplastics (MNPs) accumulation to neurovascular degeneration. The pathway begins with the molecular initiating event (MIE): physical interaction of retained MNPs with retinal structures, including i) mechanical microvascular obstruction by >5 µm particles and ii) biophysical membrane interaction of nanoplastics with Müller glia, microglia, and retinal pigment epithelium (RPE). This initiates a sequence of key events (KEs): KE1, oxidative stress and mitochondrial dysfunction, driven by ROS generation and impaired antioxidant responses; KE2, inflammatory activation, characterized by glial activation, NLRP3 inflammasome signaling, and release of TNF-α, IL-1β, and VEGF; and KE3, blood-retinal barrier (BRB) dysfunction, resulting from tight-junction disruption and pericyte loss. Progression of these KEs leads to the adverse outcome (AO) of retinal neurovascular degeneration, including photoreceptor apoptosis, neuronal loss, vascular instability, and functional decline. The figure emphasizes the self-reinforcing positive feedback loop in which BRB breakdown enhances MNP uptake (↑U_i), thereby increasing the retained burden M(t) and perpetuating the injury cycle. This AOP integrates the polymer-specific kinetic fate model with mechanistic toxicology to provide a testable framework for understanding MNP-induced retinal pathology.

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Critically, the framework posits a *self-reinforcing feedback loop*, wherein a Key Event -BRB breakdown- hypothetically enhances the uptake rate U_i, driving further accumulation and injury escalation. This loop uniquely captures the potential for a persistent, nonbiodegradable stressor like MNPs to create a progressive, self-amplifying pathology distinct from transient metabolic insults.

Validation and implications of the kinetic hypothesis

A central, testable prediction of the kinetic hypothesis is that retinal MNP retention is governed by polymer physicochemical signatures. The empirical observation that low-density, nonpolar PE

Table 3. Proposed key event relationships (KERs) for retinal MNP toxicity: empirical support and critical data gaps. This table outlines the proposed causal linkages within the adverse outcome pathway (AOP) for retinal MNP toxicity. **KERs** describe how one measurable biological event is hypothesized to lead to another. The **empirical support** column lists existing evidence that makes the link plausible, while the **critical data gaps** column explicitly states the experiments required to establish *essentiality* (proof that one event is necessary for the next) and *quantitative understanding* (defining dose-response and temporal relationships).

Key event relationship (KER)	Description of proposed causal link	Empirical support (current evidence)	Essentiality and quantitative understanding (critical data gaps)
MIE → KE1 (Physical interaction → oxidative stress)	Mechanical distortion of cellular structures (capillaries, membranes) and/or surface-chemical reactivity of weathered MNPs disrupts electron transport, induces mitochondrial dysfunction, and generates reactive oxygen species (ROS)	• PS-NPs induce ROS and mitochondrial depolarization in RPE cells (Li *et al*., 2024). • Oxidized PE generates greater retinal oxidative stress *vs*. pristine PE (Yang *et al*., 2024). • MNP surface oxidation states correlate with oxidative potential (Kadac-Czapska *et al*., 2024).	**Essentiality:** Does inhibition of specific oxidant pathways (e.g., NOX, mitochondrial ROS) block downstream KEs? **Quantitative:** What is the dose- and polymer-dependent relationship between MNP burden and ROS biomarkers *in vivo*?
KE1 → KE2 (Oxidative stress → inflammatory activation)	ROS act as signaling molecules activating redox-sensitive transcription factors (NF-κB), priming the NLRP3 inflammasome, and triggering pro-inflammatory cytokine release (TNF-α, IL-1β, VEGF) from glial and endothelial cells.	• PS-NP-induced ROS precedes NLRP3 activation in RPE cells (Li *et al*., 2024). • Antioxidants mitigate MNP-induced cytokine release in other cell types (Kadac-Czapska *et al*., 2024). • Oxidative stress is a known upstream driver of retinal inflammation (Zhao *et al*., 2024).	**Essentiality:** Are KE2 markers absent in models with genetically or pharmacologically ablated KE1? **Quantitative:** What is the temporal delay and proportionality between ROS bursts and cytokine elevation in retinal tissue?
KE2 → KE3 (Inflammatory activation → BRB dysfunction)	Pro-inflammatory cytokines (e.g., VEGF, TNF-α) downregulate tight junction proteins (ZO-1, occludin), induce pericyte apoptosis, and increase retinal endothelial cell permeability.	• PS microplastics directly impair human retinal endothelial/pericyte viability and increase permeability *in vitro* (Yun, 2025). • PS-NP exposure leads to *in vivo* BRB leakage concurrent with cytokine elevation (Zheng *et al*., 2025). • VEGF is a canonical mediator of BRB breakdown in retinopathies.	**Essentiality:** Does neutralization of specific cytokines (e.g., anti-VEGF) prevent BRB dysfunction despite ongoing inflammation? **Quantitative:** What is the quantitative relationship between intraocular cytokine levels and permeability metrics (e.g., vitreous fluorophotometry)?
KE3 → AO (BRB dysfunction → neurovascular degeneration)	Chronic barrier failure leads to increased infiltration of plasma components, further inflammatory cells, and possibly more MNPs, creating a toxic milieu that drives neuronal apoptosis (photoreceptors, ganglion cells) and vascular rarefaction.	• Chronic PS-NP exposure in mice reduces ERG responses and exacerbates photoreceptor degeneration (He *et al*., 2024). • PS-NPs disrupt neurogenesis in human retinal organoids (Gao *et al*., 2025). • BRB breakdown is a hallmark of progressive retinal degenerations (AMD, diabetic retinopathy).	**Essentiality:** Can barrier-stabilizing agents (e.g., anti-permeability factors) prevent neuronal loss despite elevated *M(t)*? **Quantitative:** What are the exposure duration and burden thresholds required to transition from subclinical barrier leak to irreversible functional loss?
KE3 → ↑Uptake (feedback loop) (BRB dysfunction → enhanced MNP accumulation)	Increased vascular and outer BRB permeability facilitates greater systemic MNP influx, directly increasing the uptake term U_i in the kinetic model and amplifying the retained burden *M(t)*.	• The hypothesis is mechanistically plausible given the size-resolved entry routes proposed. • Analogous "barrier leak → oxin influx" cycles are described tin neurotoxicology (e.g., in blood-brain barrier disorders).	**Essentiality: This is the major untested prediction of the framework.** Does experimentally induced BRB breakdown accelerate retinal MNPs accumulation in a controlled exposure model? **Quantitative:** Can the magnitude of increased U_i be quantified as a function of permeability metrics?

MIE, molecular initiating event; KE, key event; AO, adverse outcome; BRB, blood-retinal barrier.

shows an inverse correlation with donor age, while polar, dense PMMA accumulates positively with age, provides compelling preliminary support.[6] This pattern is consistent with a high hypothesized clearance rate k for PE and a low k for PMMA. Independent laboratory evidence strengthens this proposition: oxidized PE exhibits increased tissue affinity and oxidative toxicity,[26] and polar polymers demonstrate strong adhesion to biological interfaces.[12] Thus, the human data generate the hypothesis of differential clearance, which is both explained by fundamental polymer physics and corroborated by controlled studies. These correlations not only validate the conceptual logic of the kinetic hypothesis but also provide the first human-derived constraints for prioritizing polymers in experimental studies. The definitive validation of this hypothesis requires future kinetic studies using isotopically labeled polymers *in vivo* to directly measure the parameter k.

Plausibility and cross-model support for the proposed AOP

As summarized in Table 3, the biological plausibility of each proposed Key Event Relationship (KER) is supported by convergent evidence from diverse models. However, the table also highlights that the *essentiality* of these relationships and the quantitative, temporal dynamics of the cascade remain unproven, defining the primary experimental agenda arising from this framework. These essentiality gaps are precisely what define this as a proposed, rather than a validated, AOP.

- **KE1 (oxidative stress):** polystyrene nanoplastics (PS-NPs) downregulate retinal antioxidant defenses.[27] Oxidized PE induces greater retinal oxidative damage than pristine PE.[26]
- **KE2 (inflammatory activation):** PS-NPs trigger NLRP3 inflammasome activation and cytokine release in RPE cells.[13]
- **KE3 (BRB Dysfunction):** PS microplastics directly impair human retinal endothelial cell and pericyte viability, increasing vascular permeability *in vitro*.[28] *In vivo*, PS-NP exposure leads to BRB leakage.[27]
- **AO (neurovascular degeneration):** chronic PS-NP exposure in mice results in photoreceptor gene dysregulation, reduced electroretinographic responses,[11] and disrupted neurogenesis in human retinal organoids.[10]

This reproducibility across cell, animal, and organoid models reinforces the biological plausibility of the proposed pathway. Notably, the KE sequence mirrors canonical pathways seen in diabetic retinopathy and age-related macular degeneration, suggesting MNP-driven stress may intersect with established neurovascular disease mechanisms.

Clinical, regulatory, and methodological implications

This mechanistic framework repositions the retina as a potential sensitive biosensor for systemic plastic pollution and iatrogenic exposure, carrying several immediate implications:

1. **Sentinel tissue potential:** The retina's optical accessibility could allow for the noninvasive monitoring of systemic MNP exposure or its early vascular effects *via* advanced imaging (e.g., hyperspectral imaging, optical coherence tomography),[15,29] positioning retinal imaging as a potentially scalable surveillance tool for environmental toxicology.
2. **Iatrogenic source control:** The identification of direct entry routes (surgery, injections) underscores the need for stringent particulate testing in ophthalmic medical devices, pharmaceuticals, and irrigation solutions. The kinetic hypothesis suggests that reducing iatrogenic U_i inputs may have disproportionately large benefits when k is low, especially for persistent polymers like PMMA.
3. **Polymer-specific risk assessment:** The framework provides a template for a dual-axis evaluation: *physicochemical persistence* (low k) and *KE potency*. Polymers with low k that also drive potent oxidative/inflammatory KEs (e.g., PMMA) should be prioritized for study and regulation, offering a more nuanced basis for regulatory triage than hazard characterization alone.
4. **Therapeutic targets:** The defined KEs (e.g., oxidative stress, specific cytokine pathways) identify potential intervention points to mitigate MNP toxicity, even during ongoing exposure. Interventions that bolster barrier integrity may be particularly impactful in interrupting the proposed positive feedback loop.

Ethical considerations for future clinical validation

The translation of this conceptual framework into clinical practice requires careful consideration of ethical principles governing human subject research. We propose a phased approach that balances scientific rigor with participant protection, adhering to the Declaration of Helsinki and relevant regulatory guidelines.

Phase 1: observational studies in existing clinical populations

The most ethically straightforward approach involves leveraging existing clinical populations undergoing routine ophthalmic procedures. *Post-mortem* retinal tissue analysis, building upon the methodology of Zhang *et al*., could be expanded to include donor eyes from individuals with known exposure histories (e.g., occupational plastic workers, residents of heavily polluted regions).

This approach requires: i) informed consent: obtaining consent for research use of ocular tissue during lifetime or from next-of-kin for post-mortem donation, with clear disclosure of study aims and potential findings, ii) anonymization: ensuring donor confidentiality through coded identifiers and secure data storage, and iii) equitable selection: avoiding disproportionate enrollment of vulnerable populations who may have limited access to healthcare or understanding of research participation.

Phase 2: noninvasive retinal imaging in living participants

The retina's optical accessibility enables noninvasive monitoring that poses minimal risk to participants. Advanced imaging modalities -including OCT, OCT angiography, and hyperspectral imaging- could be employed to detect early signs of BRB dysfunction or vascular abnormalities in cohorts with documented high MNP exposure.

Ethical considerations include: i) minimal risk justification: noninvasive imaging carries negligible physical risk, satisfying the ethical requirement for minimal-risk research, ii) incidental findings: establishing protocols for managing incidental ocular or systemic

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findings, including referral pathways and participant notification, iii) data privacy: implementing robust data protection measures, particularly given the potential for retinal images to serve as unique biometric identifiers, and iv) community engagement: involving affected communities in study design and dissemination to ensure cultural sensitivity and relevance.

Phase 3: invasive biomarker studies

More invasive procedures -such as aqueous or vitreous humor sampling during clinically indicated surgeries (e.g., cataract extraction, vitrectomy)- could provide direct evidence of intraocular MNP burden.

These studies must address: i) therapeutic misconception: ensuring participants understand that research procedures are distinct from clinical care and may not provide direct benefit, ii) risk-benefit analysis: justifying additional procedures only when clinically indicated, avoiding unnecessary interventions solely for research purposes, and iii) vulnerable populations: implementing additional safeguards for pediatric, cognitively impaired, or economically disadvantaged participants.

Phase 4: interventional studies

Future interventional trials -such as testing barrier-protective therapies in MNP-exposed populations- would require: i) demonstrated safety: preclinical evidence of therapeutic safety and preliminary efficacy before human trials, ii) validated endpoints: establishing reliable biomarkers (e.g., retinal permeability metrics, inflammatory cytokines) as primary outcomes, iii) equipoise: ensuring genuine uncertainty about intervention benefits, preventing premature adoption of unproven therapies, and iv) long-term follow-up: committing to extended monitoring for delayed adverse effects, given the chronic nature of MNP exposure.

Additional ethical considerations

Additional ethical considerations for research involve prioritizing environmental justice by recognizing that MNP exposure disproportionately affects marginalized communities, thereby ensuring equitable benefit-sharing and avoiding the reinforcement of health disparities. Researchers must also address global equity by sharing research capacity and benefits across high-, middle-, and low-income countries where plastic pollution burdens vary substantially. Furthermore, transparency should be maintained through pre-registering study protocols, publishing negative findings, and making data openly available to facilitate replication and meta-analysis. Finally, robust regulatory oversight requires engaging institutional review boards and national regulatory bodies early in the study design phase to guarantee compliance with evolving ethical standards in environmental health research.

This phased approach ensures that clinical validation proceeds ethically, with appropriate safeguards at each stage of translation from concept to practice.

Limitations, future directions, and concluding synthesis

As a conceptual framework synthesizing secondary evidence, this proposal has inherent limitations. First, the kinetic parameters (U_i, k) are hypothetical and require direct quantification. Second, the human tissue data are correlative and lack individual exposure histories. Third, the proposed AOP requires formal empirical validation of the essentiality, concordance, and quantitative relationships between its key events (Table 3). Fourth, the predicted feedback amplification—where barrier dysfunction accelerates accumulation—remains theoretically compelling but unproven *in vivo*. These limitations define the primary experimental agenda arising from this framework.

Therefore, this framework's primary utility is to chart a course for targeted validation. The most pressing future directions are:

- **Quantify fate parameters:** determine polymer-specific k values using tracer studies in animal models and measure U_i from various exposure routes to enable the first data-driven simulations of lifetime retinal burden.
- **Validate the AOP:** use transgenic models and targeted inhibitors to establish the essentiality of proposed KEs in mediating MNP-induced retinal injury. Time-course studies are needed to confirm the predicted ordering of the KE cascade.
- **Develop biomarkers:** identify noninvasive biomarkers (imaging, serum) corresponding to the KEs (e.g., vascular permeability, inflammatory cytokines) for human epidemiological studies and to validate the coupling between $M(t)$ and early vascular dysfunction.
- **Integrated computational modeling:** populate the kinetic structure with experimental data to create predictive simulations of lifetime retinal burden under different exposure scenarios, guiding exposure standards and regulatory thresholds.

Conclusions

In conclusion, this work establishes an integrated, mechanistic framework that delineates a *testable hypothesis* for the pathway of MNPs from environmental exposure to potential retinal neurovascular injury. It posits that retinal MNP burden is governed by a dynamic kinetic equilibrium, formalized by a polymer-specific mass-balance equation where the clearance rate k is a critical parameter predicted by physicochemical properties. This fate hypothesis explains empirical observations of differential, age-dependent polymer accumulation and provides a quantitative scaffold for predicting long-term retinal load.

Critically, the retained burden $M(t)$ is linked to pathophysiology *via* a proposed AOP, outlining a causal sequence from molecular initiating events through key cellular events to the adverse outcome of neurovascular degeneration. The hypothesized self-reinforcing feedback loop -where barrier breakdown facilitates further accumulation- captures the unique, escalating threat posed by persistent, non-biodegradable particulates.

By integrating a predictive environmental chemistry hypothesis with a formal toxicological pathway, this framework reframes MNPs from inert contaminants to hypothesized active disruptors of retinal homeostasis. It establishes the retina as a sensitive, optically accessible biosensor for systemic plastic pollution and yields testable predictions at every level - from uptake and clearance to KE activation and clinical outcomes. This synthesis provides a foundational, risk-assessment-ready *research blueprint* for the emerging field of environmental ophthalmology. The immediate imperative is the experimental validation of the framework's parameters and key event relationships, which will enable the development of targeted preventive strategies and evidence-based guidelines to mitigate this pervasive, newly recognized threat to human vision.

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