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Lipophilic Chemical Accumulation, A Systems Level Driver of Chronic Disease. An Integrated Multi-Omics and Toxicokinetic Framework.

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ABSTRACT

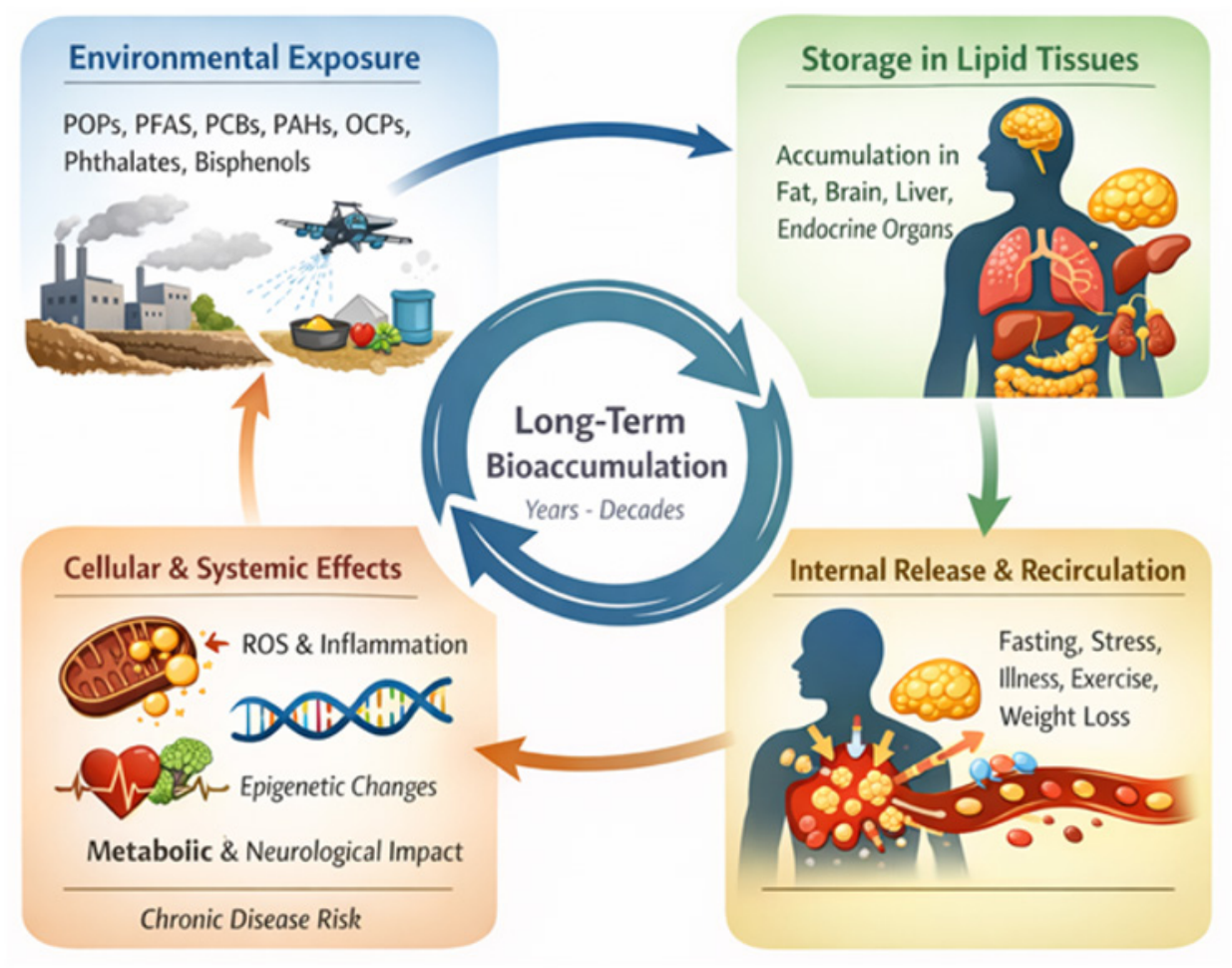
Background: Lipophilic environmental contaminants - including persistent organic pollutants (POPs), exert a long-term biological influence that cannot be explained by acute toxicity alone. Their extreme hydrophobicity drives high-affinity sequestration within lipid-rich tissues, such as adipose depots, myelin sheaths, and endocrine glands, creating "internal reservoirs" with biological half-lives measured in decades. These reservoirs fuel continuous, low-grade endogenous exposure and sequential absorption of hydrophilic species, persisting regardless of ongoing environmental contact.

Scope of Review: This review article integrates toxicokinetic modeling with modern multi-omics evidence to update Zeliger's model of lipophilicity-driven chronic disease. How these diverse compounds activate a conserved set of biological injury pathways, regardless of their specific chemical structure. Specifically, we analyze the convergence of nuclear receptor disruption, mitochondrial dysfunction (amplified ROS production), calcium dysregulation, neuroimmune activation, and persistent epigenetic remodeling is examined.

Major Conclusions: Lipophilic pollutants function as a unified category of systemic toxicants that reorganize cellular and metabolic systems. The identified mechanistic signatures provide a systems-level explanation for the epidemiological links between pollutant burdens and metabolic syndrome, cardiovascular morbidity, neurodegeneration, and cross-generational epigenetic effects. These findings validate the use of "total oxidative stress" as a predictor for non-communicable disease onset and support a paradigm shift toward mixture-based regulation and exposomic biomarkers for early detection.

Keywords: Lipophilic Toxicants; Persistent Organic Pollutants; Pfas; Endocrine Disruption; Mitochondrial Dysfunction; Toxicokinetics; Chronic Disease

Abbreviations: AhR: Aryl Hydrocarbon Receptor; ATP: Adenosine Triphosphate; CNS: Central Nervous System; DOHaD: Developmental Origins of Health and Disease; ETC: Electron Transport Chain, GR: Glucocorticoid Receptor; IL-1β: Interleukin 1β; IL-6: Interleukin 6; IL-18: Interleukin-18; Kow: Octanol Water Partition Coefficient; MMP: Matrix Metalloproteinase; NAFLD: Non-Alcoholic Fatty Liver Disease; Nash: Non-Alcoholic Steatohepatitis; NCD: Non-Communicative Disease; NF-kB: Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B Cells; NLRP3: NOD-Like Receptor Family Pyrin Domain-Coating 3; PAHs: Polynuclear Aromatic Hydrocarbons; PBPK: Physiologically Based Pharmacokinetic; PCBs: Polychlorinated Biphenyls; PFAS: Per- and Polyfluoroalkyl Substances; OCPs: Organo Chlorine Pollutants; OS: Oxidative Stress; PPARy: Peroxisome Proliferator-Activated Receptor Gamma; PXR: Pregnane X Receptor; CAR: Constitutive Androstane Receptor; ROS: Reactive Oxygen Species; TCDD: 2,3,7,8-Tétrachlorodibenzo-P-Dioxine, TNF-α: Tumor Necrosis Factor Alpha.



Graphical Figure: Toxicokinetic Cycle of Lipophilic Pollutants.

Introduction

Lipophilic environmental chemicals represent a large and heterogeneous class of pollutants that include persistent organic pollutants (POPs), per- and polyfluoroalkyl substances (PFAS), polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polycyclic aromatic hydrocarbons (PAHs), phthalates, and bisphenols. Many of these compounds are widely distributed in air, food, water, and consumer products, resulting in continuous low-level human exposure across the lifespan [1-4]. Unlike hydrophilic xenobiotics that are rapidly eliminated, lipophilic compounds possess high lipid solubility and strong partitioning into biological membranes and lipid-rich tissues. This physicochemical property drives their progressive accumulation in adipose tissue, neural membranes, endocrine organs, and hepatic lipid pools, generating long-term internal reservoirs with biological half-lives that may extend for years or even decades [5,6]. The toxicological implications of this persistence are increasingly recognized. Stored lipophilic pollutants can be re-mobilized into circulation during physiological lipid turnover processes such as fasting, illness, pregnancy, lactation, or rapid weight loss [7,8]. These mobilization events generate endogenous pulses of exposure that may occur long after the original environmental contact. As a result, internal exposure may persist even in populations where environmental levels of pollutants are declining [6].

This toxicokinetic behavior challenges traditional toxicological paradigms that primarily relate disease risk to external exposure levels. A second emerging concept concerns the interactions between lipophilic toxicants and complex chemical mixtures. Zeliger originally proposed that lipophilic compounds accumulated in biological membranes could facilitate the cellular penetration of additional hydrophilic toxicants that would otherwise be poorly absorbed [9,10]. Effectively, hydrophilic chemicals, that alone cannot penetrate cellular lipophilic membranes but are soluble in lipophilic species, dissolve into lipophiles and are thus carried across cell membranes [11-13]. This carrier or facilitator effect could enhance toxicity

by enabling the co-transport of multiple compounds across lipid barriers and thereby generating synergistic biological responses. Experimental evidence suggests that lipophilic pollutants may indeed modify membrane properties and cellular permeability, thereby influencing the uptake and biological activity of co-exposed xenobiotics [14,15]. Beyond these toxicokinetic properties, a growing body of mechanistic research suggests that many lipophilic pollutants converge on a limited number of cellular injury pathways despite their chemical diversity. Experimental studies consistently report disruption of nuclear receptor signaling, mitochondrial dysfunction, oxidative stress, neuroimmune activation, inflammasome signaling, and epigenetic remodeling following exposure to diverse classes of lipophilic contaminants [4,5,16].

Epidemiological studies further support these mechanistic observations. Population-based investigations have repeatedly demonstrated associations between circulating burdens of persistent pollutants and increased risk of diabetes, obesity, atherosclerosis, hypertension, cognitive impairment, and neurodevelopmental disorders [1,17,18]. These associations persist after adjustment for traditional lifestyle risk factors, suggesting that environmental toxicants may act as independent contributors to chronic disease development. Despite these advances, a comprehensive framework integrating toxicokinetic persistence with modern mechanistic and multi-omics evidence remains lacking. Most studies focus either on individual pollutants or on isolated biological pathways, making it difficult to understand how chemically diverse lipophilic toxicants may influence disease processes. The objective of this review is therefore to integrate toxicokinetic modeling, mechanistic toxicology, multi-omics evidence, and epidemiological findings in order to update and expand Zeliger's hypothesis of lipophilicity-driven chronic disease. Specifically, we propose a systems toxicology framework in which the persistent accumulation of lipophilic pollutants generates sustained biological perturbations across metabolic, cardiovascular, neurological, immune, and epigenetic systems.

Methods

This systems toxicology framework integrates evidence from toxicokinetic, mechanistic toxicology, multi-omics, developmental neurotoxicology, lipidomic and epidemiology. Because lipophilic chemicals produce persistent and multi-organ effects, a multi-layered analytical approach was required to map mechanistic convergence across biological domains. Mechanistic evidence was identified through comprehensive searches of PubMed, Scopus, Web of Science and Embase using terms related to endocrine disruption, mitochondrial dysfunction, oxidative stress, neuroimmune signaling, inflammasome activation and epigenetic remodeling. Studies were included when they demonstrated biologically plausible mechanisms, at both human-relevant doses and when toxicokinetic parameters support tissue distribution consistent with lipophilic persistence. Emphasis was placed on reproducibility across species, tissue types and pollutant classes. Toxicokinetic insights were drawn from physiologically-based pharmacokinetic (PBPK) models, human biomonitoring studies (including NHANES and HBM4EU), depuration and lactational transfer studies and pollutant-specific half-life analyses. Key parameters included Kow, lipid partitioning coefficients, adipose-serum release dynamics and re-mobilization kinetics during lipid turnover [19-21].

These data provided constraints for interpreting mechanistic pathways, Mechanistic toxicology was evaluated across endocrine receptor biology, mitochondrial function, lipid metabolism, immune signaling and neuronal physiology. Nuclear receptive studies using ligand-binding assays, reporter-gene activation, ChlP-seq and transcriptional profiling were integrated with mitochondrial assays measuring electron transport chain activity, membrane potential, ATP synthesis and mitochondrial ROS generation [19,21-25]. Neurodevelopmental pathways were assessed through neuronal differentiation and oligodendrocyte maturation models, synaptic physiology, electrophysiology and microglial activation assays [26]. Immune and oxidative mechanisms were examined through cytokine profiling, NF-κB pathway analysis, NLRP3 inflammasome activation and ROS assays [22,23]. Also, metabolomics, the large-scale study of metabolites within organisms, tissues and cells, might be considered a fundamental tool for elucidating the associations between environmental pollutants and health, as well as the etiology of certain diseases [27,28]. Epigenomic evidence was drawn from DNA methylation studies, histone modification analyses, chromatin accessibility (ATAC-seq) and small RNA datasets with emphasis on long-term or transgenerational alterations induced by POPs, PFAS and related pollutants [29].

Epidemiological studies were evaluated for coherence with mechanistic findings, with special attention given to prenatal exposures, longitudinal cohorts and chronic disease incidence. Mechanisms were incorporated into the final model only when supported by toxicokinetic feasibility, mechanistic reproducibility and multi-ohmic or epidemiologic validation. The results describe how lipophilic pollutant persistence, mixture synergy and mechanistic convergence collectively drive chronic disease across organ systems.

Results

The integrated evaluation of toxicokinetic, mechanistic and multi-omic evidence demonstrates that lipophilic environmental pollutants act through a set of convergent biological pathways that collectively disrupt metabolic, cardiovascular, neurological, immune and epigenetic systems. Despite the structural diversity among POPs, PFAS, PCBs, OCPs, PAHs, phthalates and bisphenols, their high lipophilicity drives similar patterns of tissue accumulation and mechanistic injury [30]. All of these species chronically elevate OS as free radicals formed in them are stabilized by substitution on the

radical carbon, resonance and having the radical α- to a π-bond with which it can overlap [31]. These shared patterns reflect a unifying systems-level architecture in which persistent internal reservoirs of pollutants continually perturb cellular regulation and physiological homeostasis. A central finding is the profound disruption of metabolic and endocrine systems. Nuclear receptor interference has emerged as a dominant mechanism, with pollutants consistently impairing PPARγ, RXR, Erα/β, CAR, PXR and AhR signaling networks, as shown in Table 1. [9,19,22,26,32,33]. These receptors regulate core metabolic functions – including lipid uptake, adipocyte differentiation, glucose homeostasis, bile acid metabolism and xenobiotic processing. Their perturbation produces the metabolic inflexibility characteristic of pollutant-associated insulin resistance, dyslipidemia and hepatic steatosis [9,17,19].

Table 1: Description of the pollutant classes, their primary target and the key mechanisms that underlies health outcomes.

Pollutant Class	Primary Target	Key Mechanisms & Health Outcomes	Refs
PFAS	Adipose tissue, Liver, CNS, Vascular system	Linked to Metabolic Syndrome, Type 2 Diabetes, and NAFLD/NASH. Strongly associated with hypertension, coronary artery disease, and stroke. Connected to neurodevelopmental disorders (ASD, ADHD).	[9,17,19], [22,26,30,34-37]
PCBs	Adipose tissue, Myelin sheaths, CNS	Associated with impaired cognitive function, reduced executive functioning, and neurodevelopmental disorders. Disrupts neuronal differentiation and synaptogenesis. Linked to hypertension.	[23,26,30,36-38]
OCPs (Pesticides)	Adipose tissue, CNS	Readily integrate into cell membranes and neural lipid structures. Linked to neurodevelopmental impairments and cognitive deficits.	[26,30,36,37]
PAHs	Vascular tissue, Adipose tissue	Mechanistically linked to atherogenesis, oxidized LDL formation, and plaque instability. Contributes to cardiovascular events and vascular inflammation.	[19,39]
Phthalates & Bisphenols	Endocrine organs, CNS	Act as endocrine disruptors altering estrogen receptor-dependent metabolic pathways. Associated with ADHD, cognitive impairment, and behavioral dysfunction.	[22,30] [26,36,37]

Chronic liver diseases, including metabolic dysfunction-associated steatosic liver disease (MASLD) and hepatocellular carcinoma (HCC), are on the rise, potentially due to daily exposure to complex mixtures of chemical compounds forming part of the exposome [34]. Experimental studies demonstrate that pollutant-induced suppression of PPARγ and RXR disrupt. As shown in Figure 1, toxicokinetic and mechanistic findings are synthesized into a systems-level model, showing how lipophilic toxicants exert persistent effects across organs. Enduring depot storage and re-mobilization feed mitochondrial ROS, endocrine disruption, neuroimmune activation, chronic inflammation, and epigenomic change. These interconnected pathways underpin the observed epidemiological links to metabolic, cardiovascular, neurological, immune, and transgenerational diseases associated with lipophilic persistence [1-12]. Adipose tissue plays a dual role as both a pollutant reservoir and an active endocrine organ. Lipophilic pollutants accumulate in adipocytes at concentrations exceeding those found in blood or lean tissues [17,35]. This accumulation triggers chronic local accumulation: M1 polarization, NF-κB activation and elevated secretion of TNF-α, IL-6 and Ilβ have been observed in pollutant-exposed adipose tissue [9,19,36,37]. Lipidomic analyses reveal that pollutant exposure increases ceremide and phospholipid levels, biochemicals signatures closely linked to insulin resistance and lipotoxicity [9,19].

As shown in Figure 1, pollutants shift adipose tissue from a metabolic buffer to an inflammatory driver, amplifying systemic metabolic dysfunction. Toxicokinetic models demonstrate that pollutant burdens in adipose tissue also propagate metabolic disease through episodic re-mobilization of stored toxicants during periods of lipid turnover. Fasting, illness, pregnancy, lactation and rapid weight loss all promote the release of POP and PFAS into circulation, creating transient spikes in internal exposure that may exceed levels at the time of original uptake [17,19]. These internal exposure cycles explain why metabolic diseases remain strongly associated with POP and PFAS levels even in populations with declining environmental exposures. Cardiovascular and vascular tissues exhibit a similarly coherent mechanistic profile. Endothelial cells exposed to lipophilic pollutants show OS-driven dysfunction, reduced nitric oxide availability, impaired vasodilation and increased expression of adhesion molecules associated with vascular inflammation [17,35,38]. Mitochondrial dysfunction plays a central role as pollution exposure impairs electron transport chain activity, increases mitochondrial ROS generation and disrupts mitochondrial membrane potential [17,35,38]. These deficits compromise endothelial metabolism and induce vascular stiffness, laying the groundwork for hypertension and atherosclerosis.

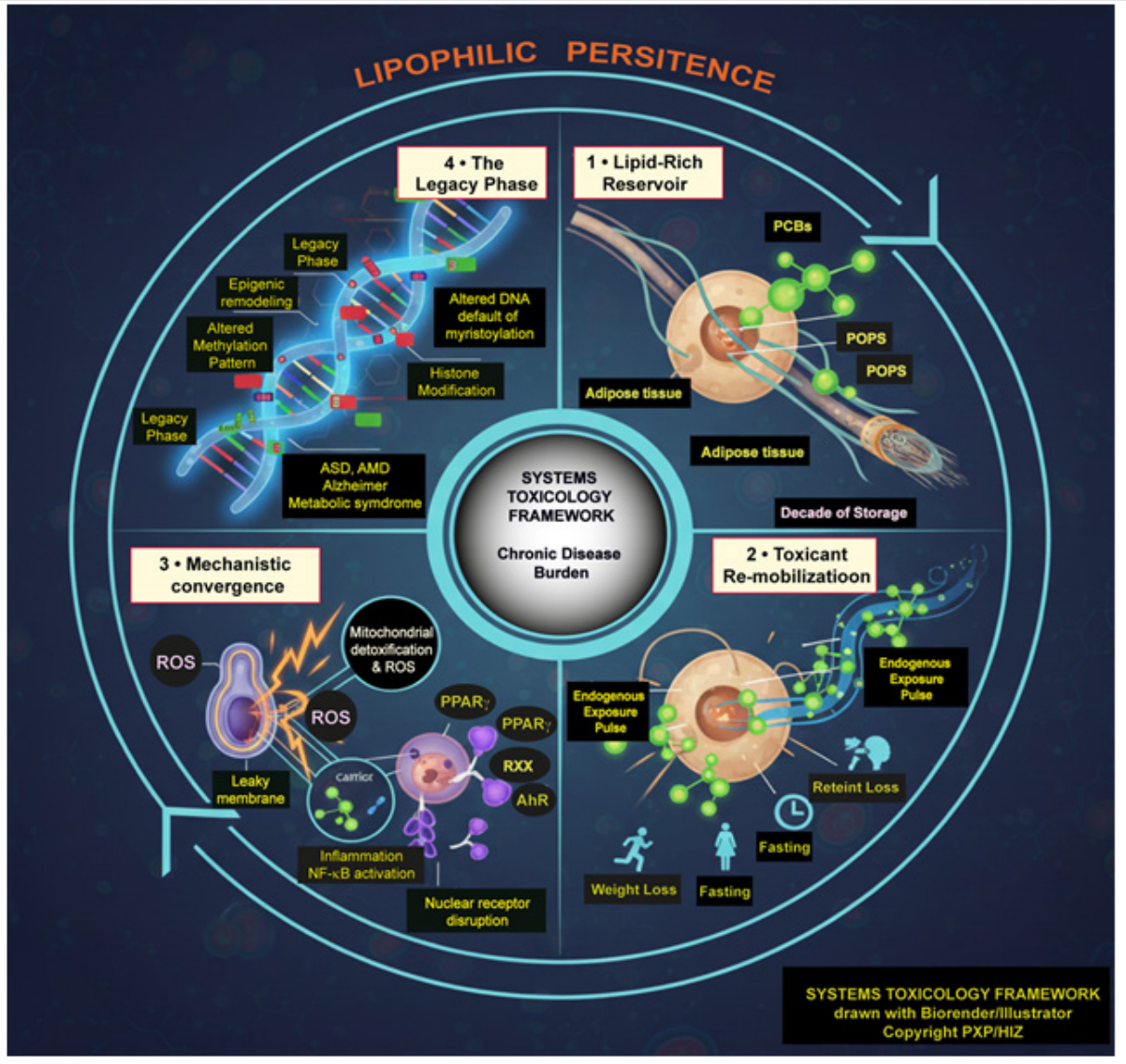


Figure 1: Integrated Systems Toxicology Mechanistic Model.

The vascular injury observed experimentally aligns with the strong epidemiological associations between circulating POP and PFAS burdens and increased risk for hypertension, carotid-media thickness, coronary artery disease and ischemic stroke [17,38]. Oxidized LDL and foam cell formation are consistently elevated in pollutant exposure models, linking POPs and PAHs mechanistically to atherogenesis. Pollutant induced matrix metalloproteinase activation further contributes to plaque instability providing a rationale for increases in cardiovascular events in exposed populations [17,38] The central nervous system (CNS) presents even greater vulnerability due to its high lipid content, extended cellular lifespans and limited regenerative capacity. Human and animal studies have repeatedly shown that prenatal and early-life exposure to PCBs, PFAS, OCPs, phthalates and bisphenols is associated with impaired cognitive function, reduced executive functioning, behavioral dysfunction and neurodevelopmental disorders such as ASD and ADHD [26,31,39]. These findings are consistent with mechanistic evidence demonstrating that lipophilic pollutants disrupt neuronal differentiation, synaptogenesis, and oligodendrocyte maturation. Calcium imaging studies reveal pollutant-induced dysregulation of Ca^{2+} signaling and increased excitotoxicity, while electrophysiological recordings document reduced synaptic strength and altered neurotransmission [30].

Neuroimmune interactions have emerged as powerful unifying pathways linking pollutant exposure to both neurodevelopmental and neurodegenerative outcomes. Pollutant-exposed microglia consistently exhibit a primed inflammatory state characterized by exaggerated cytokine responses, increased ROS production and impaired synaptic pruning [26,30,39]. This priming lowers the threshold for neural injury throughout life, aligning with epidemiological evidence linking cumulative burdens to accelerated cognitive decline and risk of Alzheimer's and Parkinson's disease [26,33]. Experimental models show pollutant-induced tau phosphorylation, amyloidogenic processing and α-synuclein aggregation, suggesting a direct molecular link between pollutant exposure and hallmark features of neurodegenerative pathology. Across immune issues, lipophilic pollutants activate a persistent inflammatory state that bridges multiple chronic diseases. NF-κB signaling is reliably elevated in pollutant-exposed immune cells, accompanied by increased secretion of TNF-α, IL-6 and IL-1β [22,23]. The NLRP3 inflammasome is repeatedly activated pollutant-induced mitochondrial ROS, oxidized lipids and mitochondrial DNA leakage, leading to caspase-1 activation and release of IL-1β, and IL-18 [22,23]. These innate immune disturbances reproduce clinical inflammatory states linked to metabolic syndrome, cardiovascular disease, and autoimmune disorders. Perhaps the most groundbreaking mechanistic insight is the pervasive epigenomic remodeling induced by lipophilic pollutant exposure.

Genome-wide methylation studies in both humans and experimental models demonstrate global hypomethylation. Promotor-specific hypermethylation in metabolic and inflammatory genes, as well as altered methylation patterns in neurodevelopmental pathways [29]. Histone modifications and chromatin accessibility further indicate pollutant-induced reprogramming of transcriptional landscapes, often persisting long after external exposure ends. In prenatal and early-life contexts, these epigenetic alterations shape developmental trajectories, aligning with developmental origins of health and disease principle (DOHaD) that is an approach to medical research factors which can lead to the development of human diseases during early life development.

These factors include the role of prenatal and perinatal exposure to environmental factors, such as undernutrition, stress, environmental chemical [26]. Together, these results show that lipophilic pollutants form a unified mechanistic class whose toxicokinetic persistence and mechanistic convergence explain their broad epidemiological associations with chronic disease. The resulting framework significantly strengthens Zeliger's hypothesis regarding lipophilicity-driven systemic toxicity [40] These results also strengthen Zeliger's more recent findings that as total oxidative stress increases, the likelihood of initial or additional NCD onset increases accordingly and that a measure of total oxidative stress may be used to predict the likelihood of NCD onset [20,41].

Discussion

The integrated results presented here reveal a coherent and biologically robust mechanism through which lipophilic environmental pollutants contribute to the global burden of chronic disease. Despite structural diversity among PFAS, POPs, PCBs, OCPs, PAHs, phthalates and bisphenols, their toxicokinetic persistence and lipid affinity drive accumulation in adipose tissue, neuronal membranes, endocrine organs and hepatic lipid pools, creating a prolonged internal exposure state independent of ongoing environmental contact [19,42,43]. This persistence forms the basis for a systemic and multi-organ pattern of biological disruption. Zeliger's foundational hypothesis – that lipophilic chemicals act as carriers facilitating toxicity of multiple compounds – accurately anticipated the modern systems toxicology perspective [20]. Yet, current evidence indicates that lipophilic pollutants act not just as carriers, but as biological integrators, coordinating mechanistic disruptions across metabolic, cardiovascular, neurological, immune and epigenetic domains [44-46]. This evolution in understanding is driven by advancements in exposomics, toxicogenomics, lipidomics and developmental neurobiology that collectively illuminate the breath of pathways altered by lipophilic toxicity. A key unifying mechanism is nuclear receptor disruption. Pollutants interfere with PPARy, RXR, Erα/β, CAR, PXR and AhR signaling pathways, impairing metabolic regulation, lipid homeostasis, bile acid metabolism and endocrine disruption [20,47-49].

These receptor interactions produce a metabolic signaling bottleneck that aligns closely with the phenotype of metabolic syndrome, insulin resistance and NAFLD/NASH circulating POP levels [20,47,48]. The coherence of mechanistic and epidemiological evidence strengthens the causal inference that lipophilic pollutants contribute directly to metabolic disease. One of the most consistent mechanistic signatures observed across diverse lipophilic pollutants is mitochondrial dysfunction accompanied by increased production of reactive oxygen species (ROS). Because mitochondrial membranes are highly enriched in phospholipids and possess large electrochemical gradients, they represent particularly sensitive targets for lipophilic xenobiotics [50]. As shown in Figure 2, many lipophilic pollutants readily partition into mitochondrial membranes, where they can interfere with the function of electron transport chain complexes and disrupt oxidative phosphorylation ([35]). Experimental studies have demonstrated that several classes of lipophilic pollutants - including PCBs, dioxins, organochlorine pesticides, and PFAS - can inhibit components of the electron transport chain, particularly complexes I and III [16,50]. This inhibition results in impaired electron transfer and leakage of electrons to molecular oxygen, leading to the formation of superoxide and other reactive oxygen species. In addition, membrane incorporation of lipophilic toxicants can alter mitochondrial membrane fluidity and permeability, promoting depolarization of the mitochondrial membrane potential and further impairing ATP synthesis [50].

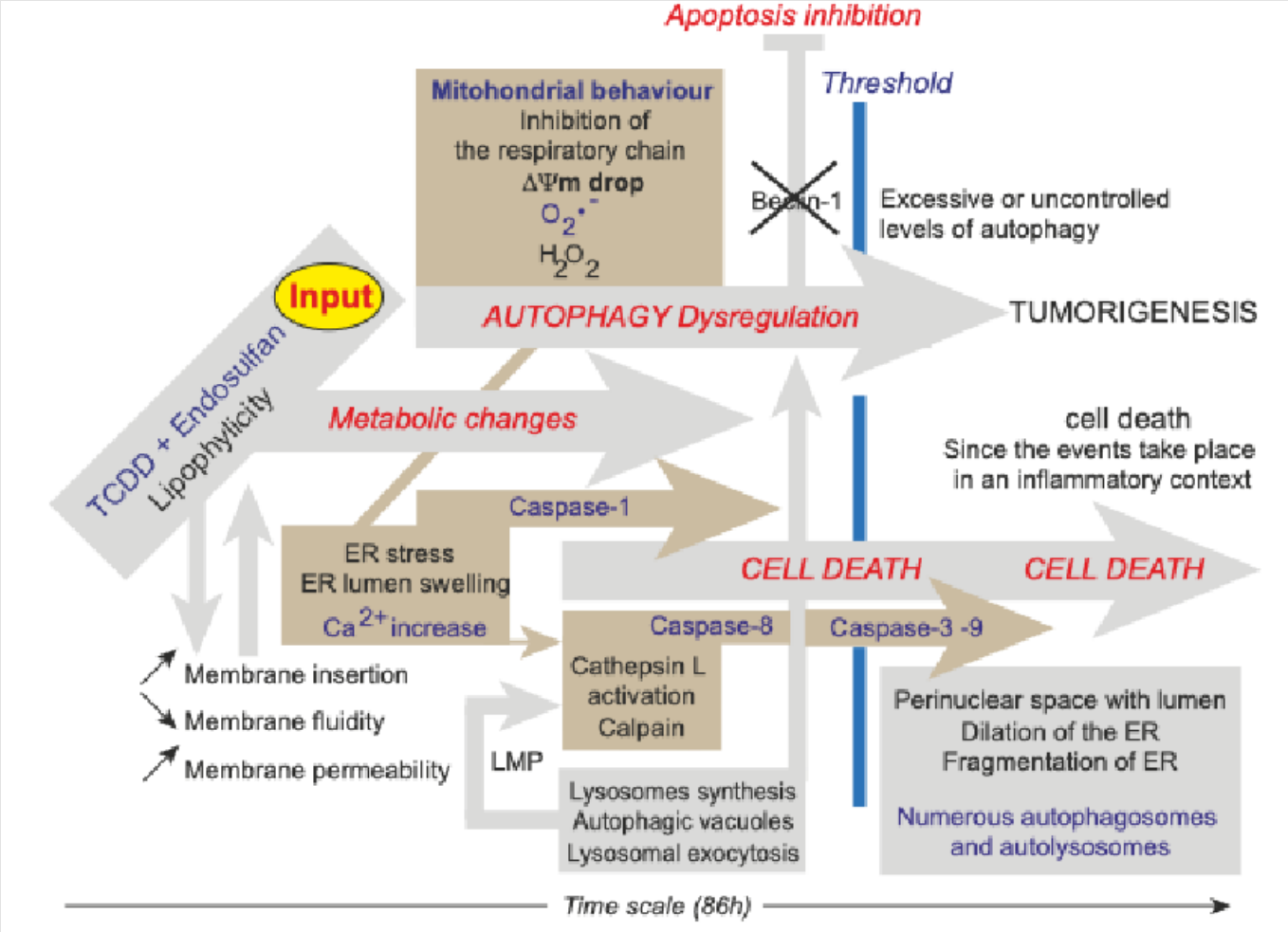


Figure 2: Schematic interpretation of the biology events associated to the low exposure with two powerful pollutants (Endosufan + TCDD "dioxin") issued and modified from [41] with permission of Zeliger H.I. and Petit P.X.

The resulting increase in mitochondrial ROS has consequences that extend far beyond oxidative damage alone. Mitochondrial ROS act as signaling molecules capable of activating multiple downstream inflammatory and stress-response pathways. In particular, ROS-mediated signaling can activate NF-κB transcriptional pathways and promote assembly of the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines such as IL-1β and IL-18 [16,51]. These signaling cascades provide a mechanistic bridge linking pollutant exposure with chronic inflammatory states observed in metabolic syndrome, cardiovascular disease, and neurodegenerative disorders [4]. Importantly, mitochondrial dysfunction may also amplify toxicity through feed-forward mechanisms. Increased ROS production can damage mitochondrial DNA, proteins, and lipids, further impairing respiratory chain function and perpetuating oxidative stress [52]. Because mitochondria play central roles in cellular metabolism, calcium signaling, apoptosis regulation, and innate immune activation, persistent mitochondrial impairment may therefore represent a key integrative mechanism through which chemically diverse lipophilic pollutants produce convergent pathological outcomes. The neurodevelopmental and neurodegenerative findings highlight a lifespan perspective on pollutant toxicity. Prenatal exposure alters neuronal differentiation, synaptic architecture, oligodendrocyte maturation and microglial function, creating neurodevelopmental trajectories associated with ASD, ADHD and cognitive impairment [33,53].

These early-life disruptions establish conditions favorable to later-life neurodegenerative processes. Experimental evidence of pollutant-induced phosphorylation, amyloidogenic processing and α-synuclein aggregation supports a mechanistic continuum linking developmental exposures to age-related neurodegeneration [39]. The immune system also plays a crucial integrating role. Chronic pollutant

exposure induces sustained activation of innate immune pathways, particularly through NF-κB signaling and the NLRP3 inflammasome [33,54]. These immune signatures produce systemic inflammation that fosters metabolic dysfunction, endothelial injury and CNS vulnerability. The mechanistic overlap between pollutant-induced inflammation and chronic disease biology helps clarify long-standing epidemiological associations across diverse conditions. Perhaps the most durable and far-reaching effect of lipophilic pollutant exposure lies in epigenomic programming DNA methylation drift, altered histone modification patterns and changes in chromatin accessibility persist long after pollutant removal, particularly when exposure occurs prenatally or early in life [26,55]. These changes encode molecular "memory" of exposure that shapes long-term health trajectories, and in some cases, extends to future generations [29,56]. This epigenic evidence strongly supports the DOHaD paradigm and suggests that lipophilic pollutants play a significant role in transgenerational disease risk.

Conclusions

This systems toxicology framework demonstrates that lipophilic environmental chemicals represent a unified mechanistic class of chronic disease drivers whose effects stem from toxicokinetic persistence and multi-organ mechanistic convergence. Their extreme hydrophobicity insure long-term sequestration within adipose deposits, hepatic lipid pools, neuronal membranes, myelin sheaths and endocrine issues resulting in half-d internal reservoir that releases pollutants during lipid mobilization, generating recurrent endogenous exposure spikes that can exceed original intake levels [9,19]. Mechanistic evidence reveals that lipophilic pollutants consistently disrupt nuclear receptor networks – particularly PPARγ, RXR, ERα/β, CAR, PXR and non-AhR-altering metabolic regulation, adipogenesis, lipid homeostasis, glucose signaling and hormonal balance [19,26,57]. These receptor-level disturbances are reinforced by mitochondrial dysfunction, including impaired electron chain activity, reduced ATP synthesis and pathological elevation of mitochondrial ROS [17,35,47]. ROS amplification activates NF-kB signaling and NLRP3 inflammasome establishing a chronic inflammatory milieu associated with metabolic disease, endothelial dysfunction and immune dysregulation [23,58]. In the cardiovascular system, these mechanisms manifest as endothelial oxidative stress, diminished nitric oxide bioavailability, impaired vasodilation, increased vascular stiffness and accelerated atherogenesis [13,17].

These injury patterns explain epidemiological associations between POP and PFAS burdens as well as heightened risk of hypertension, coronary heart disease and stroke [23,58]. The central nervous system shows pronounced vulnerability due to its lipid richness and long-lived neuronal populations. Prenatal and early-life exposures to PCBs, PFAS, OCPs, bisphenols and phthalates are strongly associated with impaired neurodevelopment and increased risk of ASD, ADHD and cognitive deficits [26,57] Mechanisms include excitotoxic calcium dysregulation, disrupted oligodendrocyte maturation, impaired synaptogenesis and microglial priming [26,54]. These early-life alterations persist through adulthood and converge with pollutant-induced tau phosphorylation, amyloidogenic processing and α-synuclein sensitization, linking developmental exposures to neurodegenerative pathways associated with Alzheimer's and Parkinson's disease [26]. Epigenomic remodeling is perhaps the most enduring consequence of lipophilic toxicant exposure. Across human cohort studies and experimental models, pollutants induce stable changes in DNA methylation, histone modifications, chromatin accessibility and non-coding RNA networks [26,38]. These changes provide a molecular memory of exposure that aligns with the Developmental Origins of Health and Disease paradigm [9]. Transgenerational studies reveal inheritance of pollutant-associated epigenomic marks across multiple generations [26,38].

Our findings demonstrate that lipophilic pollutants function not as isolated toxicants but as biological integrators whose persistence, internal cycling and multi-organ mechanistic convergence render them central contributors to chronic disease etiology. Responses must, therefore, shift from single-chemical risk assessment to mixture-aware toxicokinetic-informed frameworks, incorporating exposomic biomarkers and systems-level models of biological disruption. Exposures to lipophilic toxicants lead to disease onsets in multiple organs and make it virtually impossible to predict which NCD will strike first or next in one exposed to these toxicants. Multi-morbidities almost always follow the onset of an initial NCD, and bidirectionality between most NCD pairs have been reported [8]. Also, genomic alterations attributed to lipophilic toxicants leave one to wonder how future human evolution will be impacted [59,60]. Finally, it has been demonstrated that highly lipophilic exosomes (30-150 nm in diameter) derived from stem cells, readily penetrate the blood brain barrier and offer a therapeutic role in reversing neurodegenerative diseases that include AD, PD and ALS [24,25]. This suggests that other lipophilic species can similarly be investigated as therapeutic agents for other NCDs. The mechanistic cascade proposed in this review can also be interpreted within the Adverse Outcome Pathway (AOP) framework, which provides a structured approach for linking molecular initiating events to adverse health outcomes through a sequence of measurable key biological events [61,62].

Within this context, the molecular initiating events [62] triggered by lipophilic toxicants include interactions with nuclear receptors such as PPARγ, RXR, AhR, CAR, and PXR, as well as direct integration of lipophilic molecules into cellular and mitochondrial membranes [5,16]. The subsequent key events include mitochondrial dysfunction, excessive production of reactive oxygen species (ROS), disruption of calcium homeostasis, and activation of inflammatory signaling pathways such as NF-κB and the NLRP3 inflammasome [16,51]. These processes are frequently accompanied by metabolic dysregulation, endothelial dysfunction, neuroimmune activation, and epigenetic remodeling. At higher levels of biological organization, these disturbances propagate into organ-level events, including

adipose tissue inflammation, impaired insulin signaling, endothelial injury, neuronal dysfunction, and chronic immune activation [4,16]. The ultimate adverse outcomes associated with these pathways include metabolic syndrome, type 2 diabetes, cardiovascular disease, neurodevelopmental disorders, neurodegenerative diseases, and immune dysregulation [3,63]. Interpreting lipophilic toxicant effects through an AOP perspective highlights how chemically distinct pollutants can produce convergent biological outcomes through shared mechanistic pathways [64,65].

Summary

Overall, the results of this integrative review suggest that lipophilic pollutants form a systems-disrupting toxicological class whose effects are rooted in persistence, toxicokinetic cycling, mixture interactions and multi-organ mechanistic convergence. Addressing these pollutants requires rethinking environmental regulation to incorporate mixture toxicity, long-term internal exposure and early-life sensitivity. The findings justify the adoption of exposomic biomarkers, systems biology models and mixture-aware risk assessments in both environmental policy and clinical practice.

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Author Contributions

P.X.P. and H.I.Z. conceived and wrote the manuscript

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Competing Interests

The authors declare that they have no competing interests.

Copyright issues

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