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BIOAVAILABLE PLASTIC: FROM COGNITIVE DECLINE IN THE OLD TO HORMONAL DISRUPTION IN THE YOUNG.

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Dedication: To Casey and Calley Means, fearless science and health advocates, for their inspiring work in redefining wellness and empowering individuals to take charge of their metabolic destinies.

Micro-/nanoplastics represent a ubiquitous environmental contaminant with potential adverse effects across all living organisms. Ongoing research consistently reveals new and expands upon existing concerns regarding plastic exposure. Notably, emerging evidence suggests a link between plastic exposure and premature cognitive decline in older adults, potentially contributing to the onset or exacerbation of neurodegenerative diseases associated with dementia. Furthermore, endocrine-disrupting chemicals derived from plastics have been implicated in hormonal imbalances, potentially resulting in the masculinization of female development and the feminization of male development. If unmitigated, these impacts could precipitate a substantial and unforeseen environmental health crisis. This Perspective employs a chemistry-based approach to elucidate plastic-related health issues and introduces the concept of bioavailable plastic, i.e. plastic particles smaller than 2.5 μm capable of biological barrier penetration. We highlight lipophilicity as the key physicochemical property responsible for the uptake of these particles within organisms particularly their accumulation in adipose tissues, including the brain. Furthermore, we propose a solvation-assisted

desorption mechanism whereby oligomeric molecules released from plastics in fatty tissues generate mono- and dicarboxylic acids that mimic endogenous fatty acids. These exogenous fatty acids can integrate into phospholipid and glycolipid biosynthesis becoming components of cell membranes and myelin sheaths. These considerations should stimulate research aimed at neurological health protection in an increasingly plastic-laden environment, though the broader implications of this integration are of significant concern. Mechanistic understanding of the link between bioavailable plastic exposure and central nervous system disorders is crucial for informing transformative policy changes and preventive measures to safeguard future generations' health. To empower readers with actionable strategies for reducing plastic exposure, we offer several recommendations. Notably, limiting the consumption of fatty animal products, especially pork fat (salo) is advised. While salo is a culturally significant food, it appears to be a major reservoir for plastic particles, particularly those smaller than 200 nm, i.e. bioavailable plastic. These nanoparticles, due to their ability to traverse biological barriers in humans, pose a considerable risk. This Perspective seeks to underscore the critical need for comprehensive research into the long-term health effects of microplastics highlighting their pervasive presence and potential hidden dangers.

Key words: Bioavailable Plastic, Micro-/Nanoplastics, Environmental Contaminants, Environmental Health Crisis Systemic Pollution, Particle Size Distribution, Biological Barrier Penetration, Cognitive Decline, Neurotoxicity, Plastic Additives, Bisphenols, Phthalates, Hormonal Disruption, Endocrine System, Lipophilicity, Lipid-Mediated Transport, Adipose Tissue Accumulation, Salo (Ukrainian Cured Fat), Solvation-Assisted Desorption, Endogenous/Exogenous Fatty Acids.

INTRODUCTION. The widespread adoption of synthetic polymers, including plastics and fibers, since the 1950's has fundamentally altered material consumption patterns [1–3]. While offering demonstrable advantages in terms of cost and functional longevity, the rapid escalation of plastic production – from 1.5 million metric tons in 1950 to 413.8 million metric tons in 2023 with projected increases to 590 million metric tons by 2050 – presents a critical environmental challenge [4]. The societal perception of plastics as synonymous with hygiene and sterility has obscured the potential for deleterious effects on ecosystems and human health. Emerging evidence suggests that the accumulation of plastic debris, particularly micro- and nanoplastics, may contribute to significant ecological disruption and biological toxicity, potentially impacting the viability of diverse life forms [5–10].

Since approximately 2020, the scientific discourse has increasingly focused on the pervasive dispersion of microplastics throughout the Earth's systems, mirroring historical observations of microbial ubiquity. Microplastic particles have been quantified across a range of environmental compartments, from the cryosphere (polar regions) [11–14] and lithosphere (deep-sea trenches, mountain peaks) [15, 16] to the atmosphere (cloud formations)

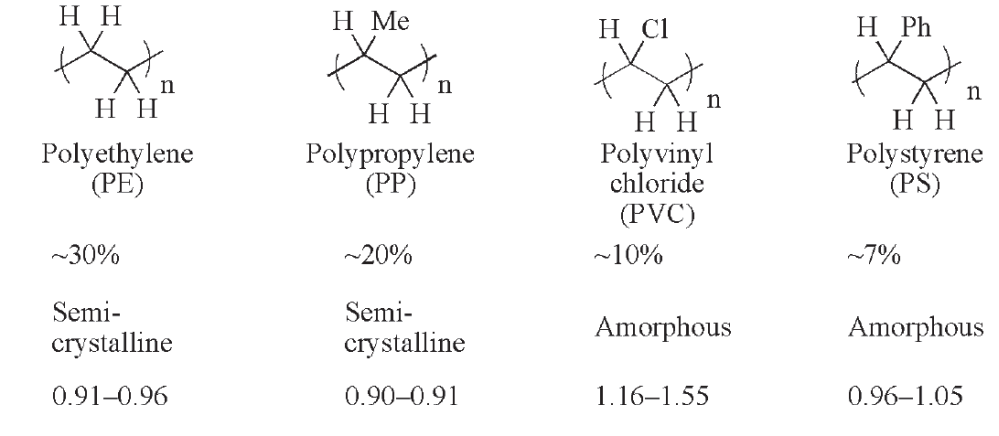
[17] and hydrosphere (oceanic sediments) [18–21]. Furthermore, evidence of bioaccumulation in diverse organisms, including human populations, highlights systemic exposure via respiratory [22], digestive [23], and cutaneous (dermal absorption) routes [24].

Recent studies have revealed an alarming amount of data depicting the pervasive presence of microplastics and their significant impact on the environment and human health [25–29]. However, the actual situation is likely far worse due to limitations in current analytical and capture methods [30]. For example, research indicates that the amount of microplastics in the environment is vastly underestimated. Specifically, data show that when nets with a 100 μm mesh are used, the microplastic particle numbers are 2.5 times and 10 times greater than nets with 333 and 500 μm meshes, respectively, are used,. Moreover, it is estimated that microplastic particle numbers might possibly exceed 3,700 particles/mm^3 when nets with a 1 μm mesh size are employed [31]. Furthemore, thousands of additives are utilized to enhance the durability, flexibility, color, flame retardancy, and/or strength of plastics. These additives, predominantly aromatic organic compounds, often are only bound to superficial regulation by authorities. As plastics degrade, these chemicals are released into the environment and permeate various forms of life [32–34]. Unfortunately, a similar scenario is observed with the regulation of numerous chemical additives in the food industry. Given the prolonged lifespan of various plastics, anywhere from 20–1,000 years, it seems that we are merely at the nascent stages of the microplastic pandemic [35].

Despite the surge in research activity in the field of microplastics, the novelty of the subject matter has resulted in a lack of systematic approaches leaving critical areas of impact unaddressed. While the scientific community is actively exploring the pervasive presence and consequences of microplastics, certain key aspects remain overlooked due to the nascent stage of the research. As a result, there is an urgent need for a more comprehensive and organized framework to ensure that all relevant environmental and health implications are thoroughly investigated and understood. In this Perspective we address the ongoing debate and lack of consensus regarding the size classification of microplastics and the end-products of their degradation [36]. Importantly, we introduce the concept of *bioavailable plastic*, emphasizing their impact on living organisms, including humans. This approach prioritizes understanding the interactions between microplastics and biological systems, highlighting the significance of their effects on health and the environment. In our view, the ability of microplastics to penetrate biological barriers is of paramount concern. Additionally, we delve into the often underdiscussed and occasionally misrepresented issue of the physicochemical properties of microplastics and their end-products. Understanding these properties will enable us to map the preferential distribution and accumulation of microplastics within the body and guide future research efforts. Considering the limited effectiveness of governmental regulation on microplastics, we provide practical recommendations throughout this discussion. Our aim is to empower readers to take proactive steps in managing their exposure to microplastics, fostering a sense of personal agency and responsibility in addressing this pressing issue.

Plastic degradation and end-products.

The major types of plastics (Fig. 1) – polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC), polystyrene (PS), polyurethane (PUR), and polyethylene terephthalate (PET) – account for more than 80% of the plastic market [37]. These materials are widely used in various applications, including packaging, construction materials, automobiles, and consumer goods, making them the dominant types of plastics in the markets. PUR and PET can undergo hydrolysis under specific environmental conditions (either slightly basic or slightly acidic) and therefore they are not typically considered the primary culprits in discussions on the "plastic apocalypse" [38, 39]. Nonetheless, both PUR and PET still contribute to plastic pollution and environmental issues making it essential to consider their impact and seek sustainable alternatives whenever possible. In sharp contrast, PE, PP, PVC, and PS are chemically inert and can persist in environmental conditions for a very long time. The decomposition of this group of plastics, which contribute approximately 70% of worldwide pollution, is a highly complex and multifaceted process [40].



	Polyethylene (PE)	Polypropylene (PP)	Polyvinyl chloride (PVC)	Polystyrene (PS)
Demand distribution	~30%	~20%	~10%	~7%
Morphology	Semi-crystalline	Semi-crystalline	Amorphous	Amorphous
Density [g/cm^3]	0.91–0.96	0.90–0.91	1.16–1.55	0.96–1.05

	Polyurethane (PUR)	Polyethylene terephthalate (PET)
Demand distribution	~8%	~8%
Morphology	Amorphous	Semi-crystalline
Density [g/cm^3]	0.01–1.25	1.38–1.40

Fig. 1 Structure and properties of the major types of plastics collectively accounting for more than 80% of the global plastic market.

One of the most common degradation processes is mechanical degradation. This pathway involves the physical breakdown of plastic materials into smaller fragments through abrasion, cutting, or other physical forces [41–43]. Another general process is oxidative degradation, which occurs when plastics are exposed to oxygen, often accelerated by heat [44, 45] or UV radiation [46 47]. Other degradation routes include photodegradation, where exposure to UV radiation from sunlight causes the breakdown of plastic polymers [48]; hydrolytic degradation, which involves the chemical breakdown of polyester or polyamide plastics in the presence of water or moisture [49]; and biodegradation by microorganisms such as bacteria and fungi, which break down certain types of plastics through enzymatic processes, converting them into simpler compounds [50]. Thermal degradation can also be considered as a separate category since excessive temperatures alone can cause the breakdown of plastic polymers through pyrolysis [51].

These classifications reflect either the initial step of the degradation process (e.g., mechanical) or its chemical nature (e.g., oxidation). However, from a chemical standpoint, the processes are similar, involving the generation of free radicals followed by a cascade of stabilization reactions. Even mechanical degradation, such as tearing and ripping, involves homolytic cleavage of C–C bonds in the polymer chains, leading to the formation of free radicals. From this perspective, there is no significant difference between mechanical, UV light, or thermal degradation routes.

Although a fundamental distinction can be made between abiotic and biotic degradation, this classification is not particularly useful however from a biotoxicity standpoint as biotic degradation only plays a relatively minor role in the overall degradation of plastics, accounting for less than 1% of plastic degradation. A more meaningful distinction is between processes that affect the bulk of plastic particles and those that primarily impact the surface. Mechanical processes like tensile, compressive, and shear stresses, creep, fatigue, impact, and delamination affect the entire or a significantly large part of the plastic body [52]. In contrast, other mechanical processes such as abrasion and erosion, as well as the previously mentioned pathways, occur primarily on the first layer of molecules exposed on the surface [53]. From a statistical perspective, one can expect that at the onset of the decomposition process, bulk-related degradation processes constitute the major means for degradation, but as decomposition progresses, surface-related processes are likely to take over as the primary process [54]. Furthermore, as the particles become smaller, the rate of degradation is expected to increase. However, these considerations only hold true if the degradation occurs under constant conditions conducive to surface processes. For example, PVC can undergo dehydrochlorination, i.e. the elimination of HCl, and typically occurs when PVC is exposed to heat, basic conditions, or UV radiation leading to the release of HCl and formation of double bonds in the polymer chain [55]. When exposed to UV light, these double bonds can be easily oxidized, resulting in rapid degradation. However, in reality, due to its relatively high density, PVC often settles at the bottom of aquatic environments or becomes otherwise shielded from UV light and oxygen, allowing it to remain intact for millennia. Understanding these various routes of plastic degradation helps in developing strategies to manage

plastic waste and mitigate its environmental impact [56].

It should be noted that the degradation of plastics via the various environmental processes discussed above occur only very slowly, decreasing the size of the plastic particles by 10^3 μm/year depending on the plastic type [57] and the environmental conditions [58] yielding particles that vary in size [59] and shape [60]. A recent study showed that oxidation occurs at up to 600 μm depth from the surface layer of plastic [61]. Thus, the surface of plastics in the environment contains oxidized, less hydrophobic moieties in varying amounts, which facilitates the adsorption of environmental compounds [61–63]. Consequently, a plethora of different compounds can be produced from plastic waste with highly diverse structures and thus constitutes one of the major challenges in the characterization of plastics' impact on health. While the end-products of plastic degradation are a complex mixture of oxidized hydrocarbons, among them as significant components are the corresponding carboxylic acids and α,ω-dicarboxylic acids which are capable of mimicking endogenous fatty acids.

Bioavailable plastic.

The complex nature of plastic pollution stems from its variable physicochemical properties as well as the size and shape of the particles. Addressing this problem requires multidisciplinary knowledge and expertise from researchers to develop standardized approaches for studying it. One of the key factors that determines the detrimental effect of plastics on human health is particle size.

The field of micro- and nanoplastics research, reflecting its nascent stage, is characterized by a lack of standardization in methodologies, data collection, and terminology. This variability extends to particle size classification with microplastic upper limits ranging from 5 to 500 μm and lower limits inconsistently defined from no lower bound to thresholds of 0.1, 1, 20, or 63 μm. The most commonly used microplastic size range is approximately 1 to 5,000 μm [62, 64–70]. While nanoplastic classification also varies, discrepancies are less pronounced, likely due to the field's relative immaturity. Typically, nanoplastics are defined as particles up to 1 μm, with either no lower limit or a range of 1 to 1,000 nm [71, 72]. However, this definition is problematic as the lower bounds would then include molecules like hexane (~1 nm) and long-chain fatty acids (~3.39 nm), which are clearly within the molecular, rather than particulate, size range.

Although precise particle size classification remains a relevant issue, we contend that, from a human health perspective, the critical characteristic is a particle's capacity for systemic intrusion into an organism. In this respect, it is important to note the already established marker PM2.5 [73–75] which refers to fine particulate matter with a diameter of 2.5 μm or smaller. These tiny particles are a major component of air pollution and can be composed of various substances, including dust, dirt, soot, smoke, and plastics. Due to their small size, PM2.5 particles can penetrate deep into the respiratory system, reaching the lungs and even entering the bloodstream. Exposure to PM2.5 has been linked to a range of adverse health effects, including respiratory and cardiovascular diseases as well as premature death [76]. The sources of PM2.5 pollution can be either natural, such as wildfires and dust storms, or anthropogenic, such as vehicle emissions, industrial process-

es, construction activities, and plastic pollution [77]. Therefore, we propose defining bioavailable plastic as plastic particles ≤ 2.5 μm which are capable of systemic translocation following ingestion, inhalation, or dermal absorption. Particles of this size can traverse critical biological barriers, including the gut [78], skin [79], blood–retinal [80], ovarian [81], placental [82], blood–testis [83], blood–cerebrospinal fluid [84, 85], and blood–brain (BBB) barriers [84–86]. Of particular concern are particles < 200 nm which exhibit enhanced permeability across the BBB, potentially leading to significant neurological impacts. Bioavailable plastic thus pose a range of potential health problems due to its capacity to penetrate biological barriers and access internal tissues [87]. Anticipated health issues stem from its physicochemical properties, potential for bioaccumulation, and interactions with cellular processes. Anticipated health problems include inflammatory responses as bioavailable plastic can trigger inflammation in various tissues due to its foreign nature. Chronic inflammation may lead to tissue damage and contribute to the development of chronic diseases. Additionally, these particles can induce oxidative stress leading to the production of reactive oxygen species that can damage cellular components including DNA, lipids, and proteins.

Bioavailable plastic can also disrupt cellular processes by interfering with signaling pathways, enzyme activity, and other essential functions, potentially resulting in cellular dysfunction and various diseases. The presence of bioavailable plastic in an organism can modulate the immune system potentially causing immunosuppression or autoimmune responses, increasing susceptibility to infections, or contributing to autoimmune diseases.

Endocrine disruption is another concern as certain chemicals incorporated into plastic, such as phthalates and bisphenols, are known endocrine disruptors. Bioavailable plastic can act as carriers for these chemicals, enhancing their delivery to internal organs and disrupting hormonal balance.

Neurological impacts are potentially significant as particles smaller than 200 nm can cross the BBB leading to neuroinflammation, neuronal damage, and cognitive dysfunction. Cardiovascular effects are also possible, as particles entering the bloodstream can induce vascular inflammation and other cardiovascular problems.

Reproductive toxicity is a concern because bioavailable plastic can accumulate in reproductive organs, potentially affecting fertility and reproductive development. Disruption of hormonal balance also contributes to reproductive toxicity. Additionally, barriers that protect genetic information, such as the testicular and ovarian barriers, can be compromised by bioavailable plastic which can penetrate and potentially harm genetic material within reproductive cells.

Lastly, the persistence of bioavailable plastic in the body can lead to bioaccumulation and chronic toxicity, with long-term exposure potentially resulting in the gradual development of chronic diseases.

Physicochemical properties of plastics, lipophilicity.

Characterizing the physicochemical properties of plastics presents a complex and multifaceted challenge. This complexity arises from the significant dependence of these properties on monomer chemical structure, polymerization methods, and the sample's size and age.

The following properties are commonly considered: chemical structure, density, strength, flexibility, heat resistance, and transparency. When plastic is reduced to nanoscale dimensions, its properties can undergo significant changes due to quantum and surface effects, both of which become increasingly prominent at such scales [88]. These nanoscale transformations can affect all of the aforementioned physicochemical properties of plastics [89]. However, one property remains constant: the fundamental chemical structure dictated by the parent monomer. For the primary contributors to plastic pollution – PE, PP, PVC, and PS – both the monomers and their polymeric forms retain a key characteristic shared by all aliphatic compounds: hydrophobicity or lipophilicity. The lipophilicity of aliphatic plastics, a property rooted in their chemical structure, is a pivotal yet often overlooked characteristic in the literature. From a chemistry standpoint, this intrinsic feature is arguably the most critical aspect that defines plastics, transcending particle size and shape. Lipophilicity, or the tendency of these plastics to interact with and dissolve in nonpolar, lipid-like environments, is not merely a mundane trait – it provides both explanatory and predictive power to understand and anticipate the behavior of plastics across a wide range of contexts.

For instance, hydrophobic deep eutectic solvents (HDESs, Fig. 2) have been demonstrated to be effective agents for the liquid–liquid extraction of PS particles ranging from 100 to 1,000 nm in size, from both freshwater and brine. HDES systems formulated with 1:2 or 1:1 molar ratios of tetrabutylammonium bromide and decanoic acid, or tetraoctylammonium bromide and decanoic acid, have achieved remarkable efficiency with nearly complete (98.4%) removal of nanoplastics in a single extraction step [90].

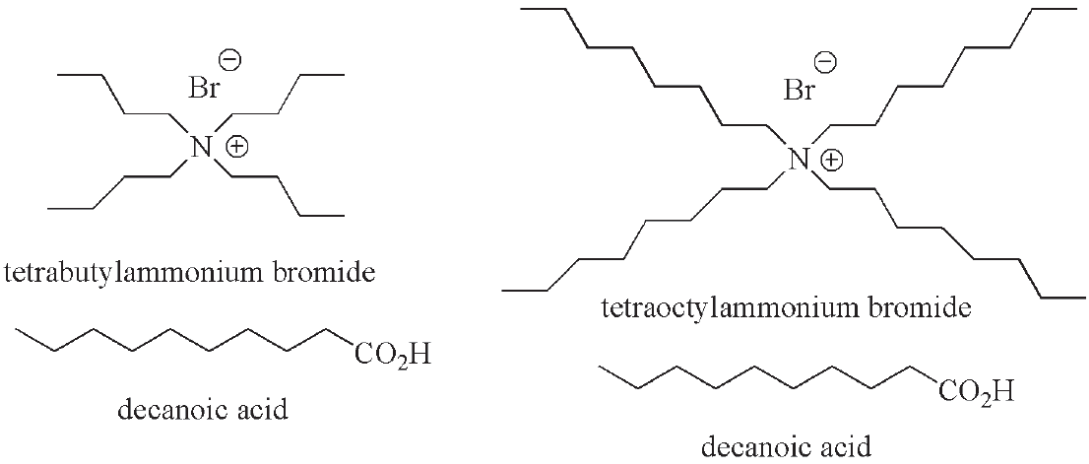


Fig. 2. Structures of HDES systems used for the extraction of PS nanoparticles.

The study underscores that aliphatic plastics possess strong lipophilic properties, a fundamental trait rooted in their chemical structure. This property enables their preferential interaction with nonpolar, lipid-like environments over polar ones like water. The efficient extraction of

PS particles from water by HDESs highlights the practical implications of this lipophilicity, which explains the bioaccumulation of plastics in lipid-rich tissues like adipose tissue in humans and animals. Such an understanding advances theoretical insights into the behavior of plastics and paves the way for strategies to mitigate their environmental and health impacts.

The lipophilicity of aliphatic plastics also influences their behavior as carriers of pollutants, affecting their interactions with organic matter, membranes, and lipids. This explains their persistence and degradation patterns in aquatic and terrestrial ecosystems where their hydrophobic nature favors affinities with lipid-rich organisms over polar environments. By emphasizing lipophilicity as a defining property, researchers can predict the ecological footprint and bioaccumulative potential of plastics, offering critical insights for environmental policies and plastic pollution mitigation.

Plastic bioaccumulation in adipose tissue – documented in both humans and animals – is a pressing concern [91–95]. Adipose tissue, being lipid-rich, readily attracts hydrophobic substances like microplastics, nanoplastics, and chemical additives such as bisphenols and phthalates. These compounds, often classified as obesogens [96], disrupt endocrine function and metabolism, contributing to weight gain and storage disorders. Their accumulation is linked to oxidative stress, chronic inflammation, and even accelerated aging, with additional risks for morbidities such as insulin resistance, cardiovascular diseases, and impaired cellular repair mechanisms. These disruptions can affect energy storage and utilization in organisms, further compromising health and survival.

The persistence of plastics in adipose tissue highlights their role as reservoirs for toxic substances that degrade slowly, releasing pollutants over time. This raises concerns about their long-term health impacts on individual organisms and ecosystems. Addressing these risks is critical to mitigating the broader implications of plastic pollution.

Foods rich in fatty tissue, like salo, a cured pork fat delicacy central to some Eastern European diets, may pose similar risks due to the bioaccumulation of hydrophobic pollutants. Fatty parts of animals and fish act as reservoirs for microplastics, persistent organic pollutants (POPs), and heavy metals such as mercury [97–100]. Regular consumption of such foods, especially from contaminated sources, can contribute to oxidative stress, inflammation, and accelerated aging. While salo holds deep cultural and culinary importance, it is essential to consider sourcing it from less-contaminated environments and consuming it in moderation to reduce health risks.

By understanding the bioaccumulation of plastics in fatty tissues, from environmental persistence to dietary implications, researchers and policymakers can develop targeted strategies to address the global challenges of plastic pollution while promoting informed dietary choices and safeguarding public health.

Bioavailable plastic, exogenic fatty acids, and the brain.

The human brain is approximately 60% fat, making it one of the fattiest organs in the body [101]. This high fat content plays a crucial role in brain function as it helps form the myelin sheath that insulates neurons, facilitates communication between cells, and supports the structural integrity of the brain's membranes.

Research suggests that the fats in our brains, particularly in the neocortex, played a crucial role in the evolution of human intelligence. The variety of fat molecules found in the human neocortex, the brain region responsible for advanced cognitive functions such as language, evolved at an exceptionally fast rate after the human–ape split [102, 103].

Approximately 20–30% of the brain's total weight is composed of myelin, a crucial component that functions as insulation around nerve fibers, much like the coating around electrical wires [104]. By reducing electrical resistance and minimizing signal loss, myelin enables nerve impulses (action potentials) to travel rapidly and efficiently along axons. This high-speed signal transmission is vital for fundamental processes such as movement, sensation, and cognition. Structurally, myelin is a complex mixture of lipids (fats) and proteins, with lipids making up about 70–80% of its composition [105]. These lipids are essential for maintaining the integrity and functionality of the myelin sheath [106]. Fig. 3 illustrates the structures of the major fatty acids involved in the synthesis of myelin.

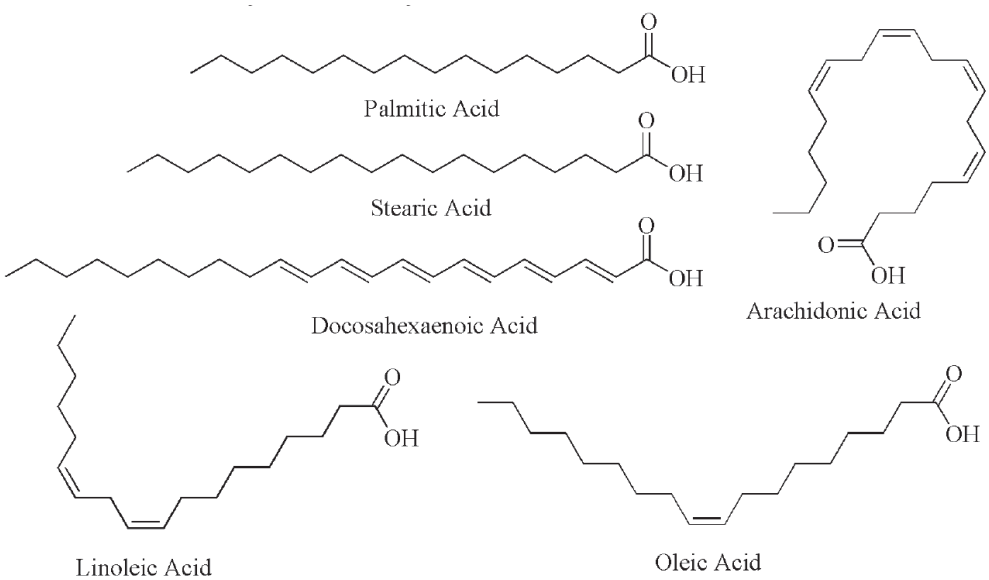


Fig. 3. Structures of the major fatty acids involved in the synthesis of myelin.

Oleic acid is a mono-unsaturated fatty acid that contributes to the fluidity and stability of myelin membranes; palmitic acid is a saturated fatty acid that plays a role in the structural integrity of myelin; stearic acid is another saturated fatty acid important for maintaining the compactness of myelin; arachidonic acid is a polyunsaturated fatty acid involved in signaling and maintaining membrane dynamics; docosahexaenoic acid is an omega-3 fatty acid essential for neural development and myelin repair; while linoleic acid is an omega-6 fatty acid that supports the synthesis of other essential lipids in myelin [107]. These fatty acids are further assembled into phospholipids and glycolipids (Fig. 4) which serve as key building blocks of cell membranes and myelin sheaths [108].

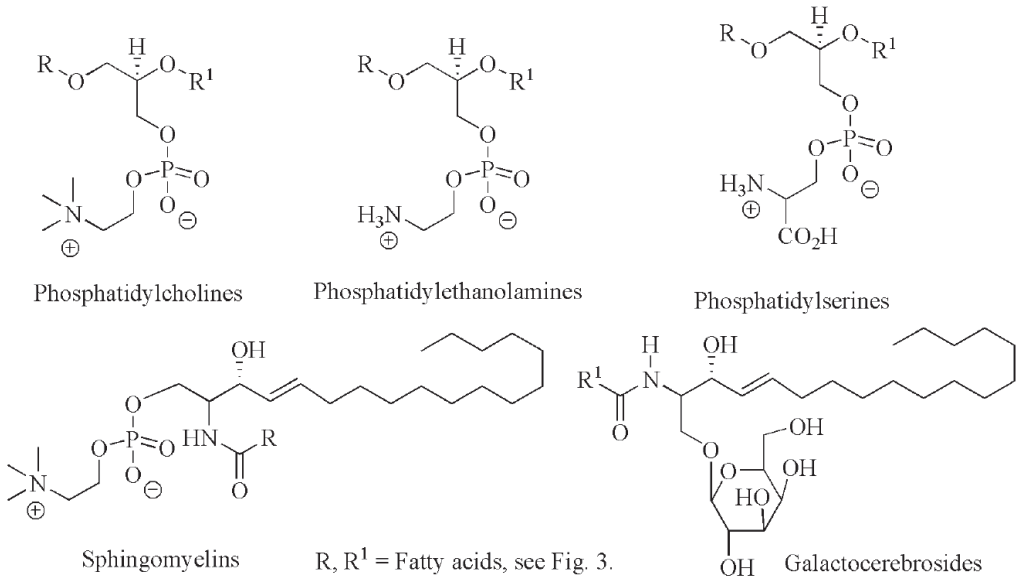


Fig. 4. Essential building blocks of cell membranes and myelin sheaths.

The accumulation of nanoplastics in the brains of various species, including humans, has been thoroughly documented and raises significant concerns. Studies show that the brain, due to its high fat content, serves as the most prevalent site for plastic deposition within the body. Comparisons of plastic amounts in the brain and other organs of the same individual highlight this striking propensity. This bioaccumulation has severe consequences as it has been linked to numerous neurodegenerative diseases [82, 109–114]. A recent study on decedent brains revealed that the largest relative proportions of plastic were found in individuals diagnosed with dementia, suggesting a potential correlation between plastic accumulation and cognitive disorders [115]. The mechanisms underlying the effects of nanoplastics on the brain remain unclear but are likely multifaceted. One hypothesis posits that nanoplastics trigger oxidative stress and immune responses, leading to elevated levels of inflammatory mediators. This cascade reduces the expression and function of regulatory proteins while increasing inhibitory protein expression. Such disruptions result in lipid peroxidation, DNA damage, misfolded protein accumulation, activation of apoptosis pathways, and neuroinflammation [23, 110]. Another explanation considers the possibility that nanoplastics suppress the expression of neurotransmitter-related genes and reduce antioxidant enzyme activity despite increased expression of proteins involved in oxidative stress in specific brain regions and neural cells. This interference disrupts the production and function of proteins crucial for neural development and the structural plasticity of the central nervous system [110,111].

However, an alternative hypothesis to consider is rooted in the foundational principles of organic chemistry. Plastics, which exhibit strength and rigidity at the macroscale, undergo a remarkable transformation as their size diminishes. As the size of these materials is reduced, they become increasingly flexible

and deformable, a phenomenon that is well documented [116,117]. This size reduction induces heightened instability in their crystalline structures, rendering the materials more susceptible to deformation and fracture under lower stress levels. Additionally, the significant surface-to-volume ratio characteristic of nanoplastics can lead to pronounced shifts in mechanical properties, including reductions in hardness and strength [118, 119]. Once nanoplastics reach a certain diminutive size, it can be argued that, despite retaining a similar chemical composition, the defining properties of the original plastic may be fundamentally altered or entirely lost. This raises a critical question, at what lower size limit can particles still be classified as nanoplastics? We also propose the importance of distinguishing between plastics as polymers and the degraded byproducts of their breakdown, i.e. oligomers that carry functional groups formed through the cleavage of C–C and C–H bonds in the parent polymer. Establishing such a conceptual framework could help clarify the evolving nature of plastics and their transformations across different scales.

Research indicates that PP particles in the 10–30 nm range can induce oxidative stress, reduce acetylcholinesterase activity, and promote α-synuclein aggregation [120]. These effects are linked to severe neurological outcomes, including cognitive decline, memory deficiency, Alzheimer's disease [121–123], and Parkinson's disease [124–127]. Considering that endogenous fatty acids and phospholipids measure between 1–4 nm, and that phospholipids naturally organize into bilayers – forming a typical membrane thickness of approximately 10 nm – we propose that the threshold distinguishing nanoplastics from oligomers should be set at around 10 nm. This distinction would provide a meaningful framework for understanding their biological and toxicological impacts.

Solvation-assisted desorption of approximately 10 nm PE oligomers is theoretically feasible within fatty tissue, a lipophilic matrix comprised primarily of triglycerides, phospholipids, and other lipophilic macromolecules. The translocation of, for example, PE oligomers from a surface into fatty tissue is thermodynamically favored, driven by the shift from a constrained, surface-bound state to a fully solvated environment. When adsorbed on a surface, the oligomer experiences limited, directional van der Waals interactions resulting in a comparatively unstable energetic state. Conversely, within fatty tissue at the human body temperature of ~37 °C, the oligomer engages in omnidirectional interactions with surrounding lipids leading to a significant enthalpy gain and a substantial increase in entropy, thus lowering its Gibbs' free energy. The entropy factor is particularly crucial as the increased freedom of movement in the solvated state significantly contributes to overall thermodynamic favorability. This transition, while spontaneous due to the favorable thermodynamic profile, necessitates overcoming an activation energy barrier, primarily the energy required to disrupt the surface constraint and initiate solvation. Therefore, while the process is not a zero-change event, the combined influence of the enthalpy gain, the substantial increase in entropy, and the physiological temperature within the human body provides a potent driving force for the oligomer's release and dissolution in the lipophilic matrix of fatty tissue.

From an organic chemistry perspective, some of these oligomers as part of plastics'

end-of-life products, are homologs of endogenous fatty acids like palmitic, stearic, oleic, and linoleic acids. These endogenous fatty acids are prevalent in membranes and the myelin sheath where they contribute to the synthesis of phospholipids and other lipophilic macromolecules.

Due to known enzyme promiscuity [128–130], plastic-derived exogenous fatty acids can be utilized in the biosynthesis of phosphor- and glycolipids and subsequently incorporated into membranes and myelin sheaths. Specifically, enzymes such as acyl-CoA synthetases [131], glycerol-3-phosphate acyltransferases [132], lysophosphatidylcholine acyltransferases [133], and sphingosine N-acyltransferases [134] may take up these exogenous fatty acids as substrates, thus altering the lipid composition of cellular structures. In particular, this could affect membrane fluidity, stability, and function, potentially disrupting cellular processes.

The incorporation of exogenous fatty acids into myelin, particularly within the brain, has the potential to significantly impact myelin turnover and remodeling [135]. Given myelin's highly specialized structure and composition, finely tuned to support neural function, even subtle variations in fatty acid characteristics, such as chain length, saturation, or functional groups, could disrupt its precisely tuned properties [136]. Thus, disruption by incorporation of exogenous fatty acids may compromise myelin's structural integrity and insulating properties, subsequently affecting axonal conduction and neural signaling. Furthermore, the dynamic nature of myelin lipid turnover suggests that exogenous fatty acids could alter the rates of lipid synthesis, degradation, and recycling. For instance, increased susceptibility to oxidation in these exogenous fatty acids might accelerate lipid turnover due to oxidative damage, while inefficient integration could slow the process. Myelin remodeling, crucial for development, learning, and repair, relies on specific lipid availability; suboptimal exogenous fatty acids could hinder this process, affecting brain plasticity and recovery [137]. While some exogenous fatty acids, such as certain omega-3 analogs, may exhibit neuroprotective effects, the overall impact of replacing endogenous fatty acids depends on their specific properties. Consequently, these replacements could either integrate seamlessly or disrupt the delicate balance essential for myelin's structure and function, further research to elucidate these complex dynamics and their implications for neural health is necessitated.

Additives, leaching, and hormonal dysfunction.

Plastics, beyond their synthetic polymer base, commonly incorporate a diverse array of additives and fillers/reinforcements to enhance performance characteristics. These include antioxidants, stabilizers, plasticizers such as bisphenol A and phthalates, flame retardants, colorants, inorganic particles, and organic and inorganic fibers. Furthermore, residual functionalized monomers and oligomers of the starting materials are frequently present within the plastic matrix [138–140].

Quantifying the number of additives employed in plastics is challenging due to the breadth and dynamic nature of the industry. However, available data indicates that thousands of chemicals are utilized in plastic production with studies suggesting figures exceeding 10,000 [139]. Notably, the availability and quality of safety data for these chemicals are highly variable. The complex and often opaque composition of plastics further hinders

accurate quantification [141]. Consequently, while a definitive number remains elusive, it is evident that a substantial proportion of these chemicals lack adequate safety data, underscoring the complexity of this issue and its potential detrimental effects on both the environment and human health [32, 33, 142–144].

The leaching of additive chemicals from plastics into the human body represents a significant health concern with pathways including ingestion, dermal absorption, inhalation, and medical device exposure. Within food systems, additives migrate from plastic packaging and utensils, particularly under conditions of heat, acidity, or prolonged contact with fatty substances, leading to ingestion and systemic exposure [145–147]. Similarly, dermal contact with plasticized products facilitates the absorption of additives through the skin, a process exacerbated prolonged exposure. Inhalation of volatile additives and micro-/nanoplastics from indoor environments and heated plastics provides another route of entry, while the use of plastic medical devices introduces direct exposure to internal tissues and fluids. Environmental contamination by micro-/nanoplastics further contributes to ingestion and inhalation exposures. The extent of leaching is influenced by factors such as temperature, pH, food/liquid composition, contact time, plastic type, and additive characteristics. Consequently, the potential for endocrine disruption, reproductive toxicity, and other adverse health effects necessitates further research into the complex dynamics of additive leaching and its implications for human health [148–150].

Due to their widespread use in plastics and resins and demonstrated endocrine-disrupting properties, bisphenols A, S, and F (Fig. 5) are among the most prevalent and concerning bisphenols for potential adverse human health effects [151].

Bisphenols exert their endocrine-disrupting effects through multiple mechanisms, including acting as estrogen receptor agonists, mimicking endogenous estrogens or behaving as antagonists, or blocking estrogen as well as interfering with other hormone receptors, disrupting enzyme activity, inducing epigenetic modifications, or causing oxidative stress and inflammation thereby disrupting normal hormonal signaling and cellular function [152].

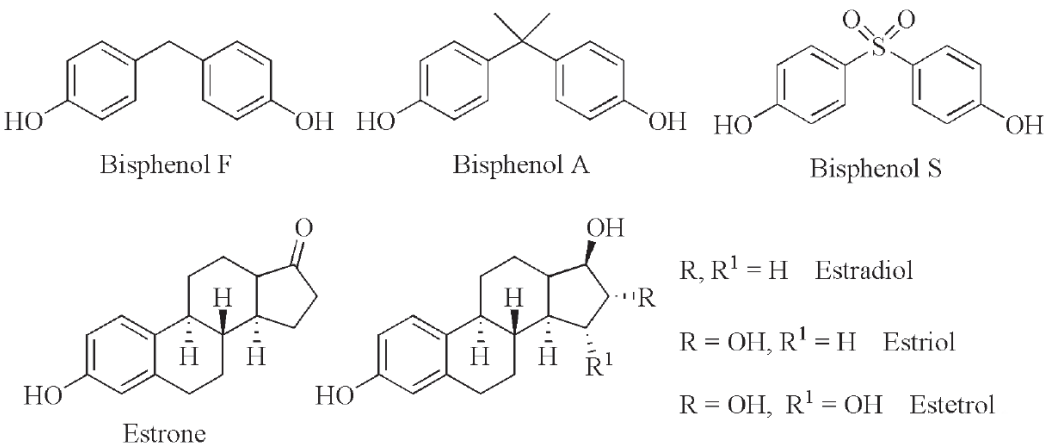


Fig. 5. Chemical structures of the most prevalent bisphenols and major endogenous estrogens.

Literature data indicates that bisphenol exposure can impact both male and female fetuses and infants, with effects varying significantly due to the sex-specific roles of hormones during development [153–155]. Both sexes are extremely vulnerable to developmental and biological impacts due to the sensitivity of hormonal balance during the early stages of life.

In males, prenatal and early postnatal exposure to bisphenols has been shown to disrupt the development of the male reproductive system, leading to reduced sperm count and impaired sperm motility. This disruption arises from bisphenols' interference with testosterone production and function, which is critical for spermatogenesis, and these effects are attributed to their endocrine-disrupting properties. Exposure to bisphenols can also cause hormonal imbalances, manifesting as reduced testosterone levels and changes in secondary sexual characteristics, described as "emasculating" effects that are linked to bisphenols' interactions with androgen receptors. Additionally, altered anogenital distance (AGD), a sexually dimorphic trait influenced by prenatal androgen levels, may be shortened in male infants exposed to bisphenols, suggesting disrupted androgen signaling during critical developmental periods. Moreover, prenatal bisphenol exposure has been associated with abnormal prostate gland development, potentially increasing the risk of prostate-related health issues in adulthood, likely due to disruptions in hormonal pathways during prostate formation [156–158].

In females, bisphenol exposure can interfere with estrogen signaling and affect ovarian development, egg maturation, and the formation of the reproductive tract. Such disruptions potentially result in long-term reproductive health problems. Prenatal bisphenol exposure may also accelerate puberty, resulting in early menarche and associated health concerns, and it may negatively affect fertility, increasing the risk of conditions such as polycystic ovary syndrome. Although less studied, it is hypothesized that bisphenols could alter the estrogen–androgen balance, potentially increasing musculature in females due to disrupted hormonal signaling. Furthermore, since bisphenols' interference with estrogen pathways may impair ovarian development and egg maturation, this can potentially result in infertility. Bisphenol exposure is decisive if it coincides with sensitive developmental windows and the effects of bisphenols can be enduring and potentially span multiple generations. Further research is required to fully understand the complex and multifaceted effects of bisphenol exposure on human development [159–161].

Phthalates, like bisphenols, are endocrine-disrupting chemicals, but their effects differ slightly in scope and mechanism. While both can interfere with hormonal processes, phthalates are particularly known for their anti-androgenic effects, i.e. they block or reduce the action of male hormones like testosterone [162–164].

Phthalates (Fig. 6) generally need to have a lipophilic aliphatic part in addition to their aromatic ring and carbonyl groups to function as effective endocrine disruptors, including their anti-androgenic activity. The lipophilic aliphatic chains, such as ethyl, hexyl, butyl, or benzyl groups, contribute to the hydrophobic nature of phthalates, allowing them to easily interact with lipid-rich environments like cell membranes. This property is critical for their ability to penetrate biological systems and bind to hormone receptors or disrupt enzyme

function. The aromatic ring, as well as contributing to chemical stability, also contributes to interaction with specific molecular targets, e.g. in binding to receptor sites or enzymes involved in hormonal signaling. The carbonyls of the ester groups are essential for chemical reactivity and contribute to the ability of phthalates to interact with biological molecules such as proteins, receptors, or enzymes involved in endocrine system regulation. While these structural elements make phthalates highly effective as plasticizers, they also enable the endocrine-disrupting properties [165,166] and the combination of these structural elements allows phthalates to interfere with hormonal balance and signaling in various ways despite phthalates being structurally different from natural hormones like testosterone and estrogen [167].

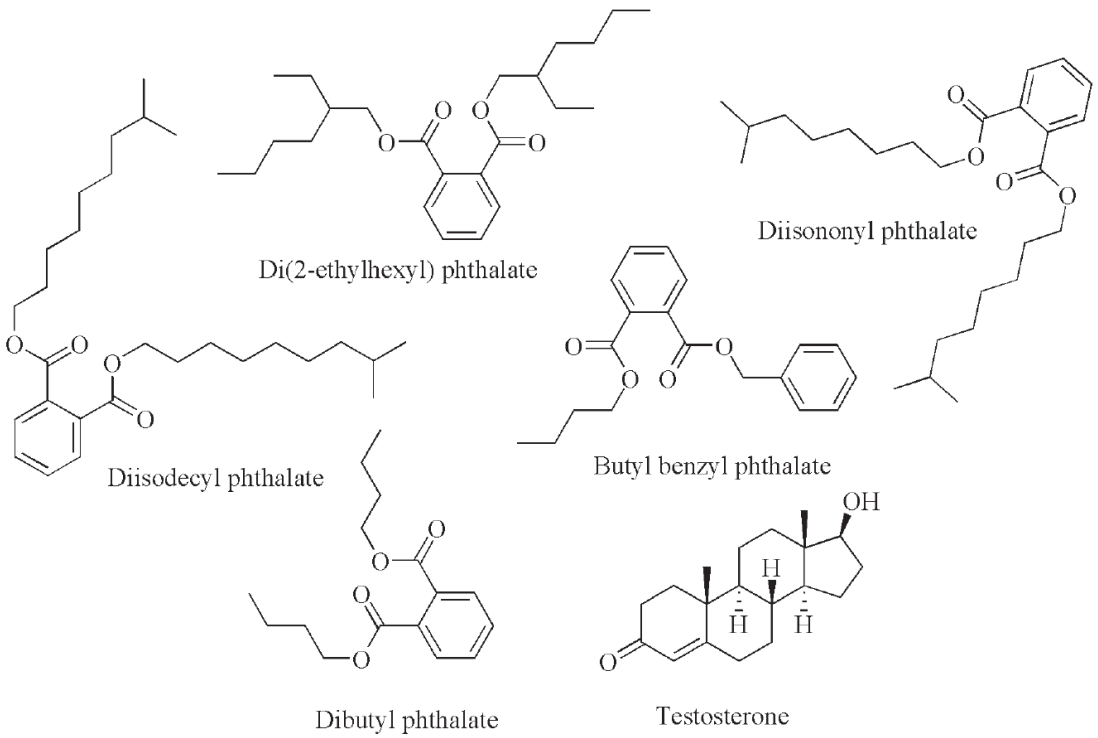


Fig. 6. Chemical structures of most prevalent *ortho*-phthalates and the androgen testosterone.

In male babies, prenatal exposure to phthalates has been linked to disrupted development of the male reproductive system. This includes reduced testosterone levels, altered AGD, and potential impacts on testicular descent and penile development. Such changes may lead to fertility issues later in life including reduced sperm count and motility. The anti-androgenic properties of phthalates are a key factor in these effects [168–170]. In female babies, phthalates can disrupt estrogen signaling, potentially affecting ovarian development and reproductive tract formation. [171–173]. While less studied, there is evidence suggesting that phthalates

may also influence the timing of puberty and increase the risk of reproductive health issues, such as reduced fertility or hormonal imbalances [174–176]. Overall, while both bisphenols and phthalates disrupt hormonal systems, phthalates are more strongly associated with anti-androgenic effects, whereas bisphenols often mimic estrogen. Of particular note, the timing and level of exposure to these leached additives are critical in determining the severity of their impacts. Phthalates primarily act as anti-androgens, i.e. they interfere with male hormones like testosterone rather than mimicking estrogen directly. Unlike bisphenols, which have a phenol group that allows them to mimic estrogen, phthalates lack this structural feature. However, phthalates can still disrupt hormonal signaling by binding to hormone receptors or altering hormone production. Interestingly, some studies suggest that phthalates may have weak estrogenic activity under certain conditions, but their primary mode of action is through blocking androgen receptors and reducing testosterone synthesis [177]. This is why their effects are often more pronounced in disrupting male reproductive development such as altering AGD and impairing testicular function.

In contrast to testosterone, a steroid hormone with a four-ring structure, phthalates are simple diesters of phthalic acid. Phthalates exert their endocrine-disrupting effects primarily by interfering with androgen signaling rather than mimicking testosterone [178] to which they are structural dissimilar and are potent anti-androgens [179]. and their disruption of the endocrine system is due to their ability to inhibit testosterone function and production. *ortho*-Phthalates require a combination of structural features to effectively interact with biological systems. These include a lipophilic aliphatic part, an aromatic ring, and a carbonyl group. The lipophilic aliphatic chains enhance their hydrophobic nature, allowing them to interact with lipid-rich environments, such as cell membranes, facilitating their entry into biological systems. The aromatic ring contributes to their chemical stability and interaction with molecular targets such as hormone receptors and enzymes involved in hormonal signaling. The carbonyl of the ester functionalities is essential for their reactivity, allowing them to interact with biological molecules involved in endocrine processes. Phthalates also act by mechanisms such as androgen receptor interference whereby they block the binding of testosterone and other androgens to their receptors inhibiting normal androgen signaling pathways critical for reproductive development [180]. They can inhibit testosterone synthesis by disrupting enzymes involved in its production leading to reduced testosterone levels. Additionally, phthalates alter the expression of genes regulated by testosterone, affecting the development of androgen-dependent tissues [181]. These structural and functional characteristics explain their potent anti-androgenic activity and ability to disrupt male reproductive development, such as reducing anogenital distance, impairing testicular development, and altering secondary sexual characteristics. While phthalates differ greatly in structure from testosterone, their anti-androgenic effects arise from their ability to block and inhibit the hormonal processes regulated by androgens [182,183]. So, while phthalates don't mimic estrogen in the same way bisphenols do, they are potent endocrine disruptors with their own unique mechanisms of action.

CONCLUSIONS. The range of health problems associated with plastic, as outlined in this article, is far from exhaustive. Ongoing research continues to uncover new areas of concern and expand upon previously identified issues related to plastic exposure. Among the most alarming findings is the emerging evidence of a potential connection between plastic exposure and premature cognitive decline in older adults, potentially contributing to the onset or worsening of neurodegenerative diseases, including those linked to dementia. Moreover, chemicals leached from plastics, particularly endocrine disruptors, have been shown to cause hormonal imbalances, which may lead to the masculinization of female development and the feminization of male development. If left unaddressed, these impacts could culminate in a significant and largely unanticipated environmental health crisis.

This Perspective took a chemistry-based approach to enhance our understanding, explanation, and prediction of certain aspects of plastic-related health issues. Specifically, we introduced the concept of *bioavailable plastic* for plastic particles smaller than 2.5 μm capable of penetrating biological barriers. By examining the physicochemical properties of bioavailable plastic, it becomes evident that lipophilicity is the key property underpinning bioavailable plastic distribution within the human body and other organisms. We emphasize that plastics tend to accumulate in adipose tissues, including visceral and subcutaneous fat as well as the brain. Furthermore, we propose a mechanism of solvation-assisted desorption whereby oligomeric molecules released from plastics in fatty tissues generate mono- and dicarboxylic acids that mimic endogenous fatty acids. These exogenous fatty acids can integrate into the biosynthesis of phospholipids and glycolipids becoming part of cell membranes and myelin sheaths. These considerations may inspire meaningful research aimed at improving protection for neurological health in an increasingly plastic-laden environment; until then, the broader implications of such integration remain a significant concern. Understanding the mechanistic links between environmental exposure to bioavailable plastic and central nervous system disorders could pave the way for transformative policy changes and preventive measures aimed at safeguarding the health of future generations.

Although plastic is ubiquitous in our environment, nevertheless one can take proactive steps to reduce exposure and minimize potential health risks. One key recommendation is to limit the consumption of fatty animal products, particularly pig fat, known as salo. While salo holds significant cultural and culinary value, it appears to be one of the primary reservoirs for plastic particles smaller than 200 nm, i.e. it is a reservoir for bioavailable plastic. These particles are capable of penetrating biological barriers in humans. To mitigate risks, salo should be consumed in mindful moderation unless it is sourced from animals raised and produced in plastic-free environments. One simple and effective way to reduce microplastic intake is by switching from bottled water to filtered tap water, which can decrease annual microplastic consumption from 90,000 particles to just 4,000. Other key sources of microplastic intake include the use of plastic tea bags and improper food storage and heating. Plastic tea bags release nanoparticles during brewing, so opting for loose-leaf tea or tea bags made from natural materials is advisable. Heating food in plastic containers, especially in the microwave, can release substantial amounts of micro- and

nanoplastics. Using glass, ceramic, or stainless steel containers for storing and heating food can help avoid this issue. Additionally, choosing clothing made from natural fibers and using laundry bags designed to catch microfibers can reduce the release of microplastics during washing. Reducing reliance on single-use plastics, being mindful of personal care products that contain microbeads, and engaging in regular physical activities that promote sweating can also help minimize microplastic exposure as sweating can help cleanse the body of plastics that have already been ingested. Indeed, any activity that promotes sweating and not just physical exercise such as sauna sessions may aid in the elimination of bioavailable plastic. And while researchers are still investigating this process, the initial findings do suggest that sweating could play a significant role in helping the body expel these unwanted particles. By incorporating these practices into daily routines, one can help protect oneself from the potential health risks associated with microplastics. Lastly, staying informed about the latest research, educating others, and advocating for policies that promote sustainable materials and practices are crucial steps in reducing plastic pollution and protecting public health. By adopting these measures, we can minimize our exposure to microplastics and contribute to a healthier environment for ourselves and for future generations to come.

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БІОДОСТУПНИЙ ПЛАСТИК: ВІД КОГНІТИВНОГО ЗАНЕПАДУ У СТАРШИХ ЛЮДЕЙ ДО ГОРМОНАЛЬНИХ ЗБОЇВ У МОЛОДШИХ

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Присвята. Присвячується Кейсі та Каллі Мінз, відважним борцям за науку та здоров'я, за їхню натхненну діяльність у сфері переосмислення здорового способу життя та розширення можливостей людей контролювати власну метаболічну долю.

Мікро/нанопластики являють собою повсюдний екологічний забруднювач із потенційними негативними наслідками для всіх живих організмів. Постійні дослідження виявляють нові та розширюють існуючі занепокоєння щодо впливу пластику. Зокрема, з'являються докази зв'язку між впливом пластику та передчасним когнітивним занепадом у літніх людей, що потенційно сприяє розвитку або загостренню нейродегенеративних захворювань, пов'язаних із деменцією. Крім цього, хімічні речовини, отримані з пластику, є особливо руйнівними в ендокринному плані і пов'язані з гормональними порушеннями, що потенційно призводить до маскулінізації розвитку жінок та фемінізації розвитку чоловіків. Якщо ці наслідки не будуть пом'якшені, вони можуть спричинити значну та непередбачену екологічну кризу здоров'я.

У цій перспективній статті використано хімічний підхід для роз'яснення питань, пов'язаних зі здоров'ям, які виникають через пластик, вводячи поняття «біодоступний пластик» – це частинки розміром менше 2,5 мікронів, здатні проникати через біологічні бар'єри. Ми підкреслюємо ліпофільність як ключову фізико-хімічну властивість, що визначає розподіл цих частинок в організмах, наголошуючи на їхньому накопиченні в жировій тканині, включаючи мозок. Крім цього, ми пропонуємо механізм сольватаційно-асистованої десорбції, за яким олігомерні молекули, що вивільняються з пластику в жирових тканинах, утворюють моно- та дикарбонові кислоти, що імітують ендогенні жирні кислоти. Ці екзогенні жирні кислоти можуть інтегруватися в біосинтез фосфоліпідів та гліколіпідів, стаючи компонентами клітинних мембран та мієлінових оболонок. Ці міркування повинні стимулювати дослідження, спрямовані на захист неврологічного здоров'я в умовах все більш насиченого пластиком середовища, хоча ширші наслідки цієї інтеграції викликають значне занепокоєння. Механістичне розуміння зв'язку між впливом біодоступного пластику та розладами центральної нервової системи (ЦНС) є вирішальним для інформування трансформаційних політичних змін та профілактичних заходів, спрямованих на захист здоров'я майбутніх поколінь. Щоб надати читачам дієві стратегії для зменшення впливу пластику, ми пропонуємо кілька рекомендацій. Зокрема, рекомендовано обмежити споживання жирних продуктів тваринного походження, особливо свинячого сала. Хоча сало є культурно значущим продуктом, воно, напевно, є основним резервуаром біодоступних частинок пластику, особливо розміром менше 200 нм. Ці наночастинки, через їхню здатність проникати через біологічні бар'єри людини, становлять значний ризик. Цей огляд має на меті підкреслити критичну необхідність комплексних досліджень довгострокових наслідків мікропластику для здоров'я людини, висвітлюючи його повсюдне поширення та потенційні приховані небезпеки.

Ключові слова: біодоступний пластик, мікро-нанопластики, екологічні забруднювачі, екологічна криза здоров'я, системне забруднення, розподіл розмірів частинок, проникнення через біологічні бар'єри, когнітивний занепад, нейротоксичність, пластикові добавки, бісфеноли, фталати, гормональні порушення, ендокринна система, ліпофільність, ліпідо-опосередкований транспорт, накопичення в жировій тканині, сало (український солений жир), сольватаційно-асистована десорбція, ендогенні/екзогенні жирні кислоти.

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