# Placeholder ’cause old one was too cringey

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# Abstract

*Keywords*: microplastics, immunity, neuroinflammation

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# Introduction

First named by ([Thompson et al., 2004](#ref-thompsonLostSeaWhere2004)), microplastics are defined as particles with diameters from to , while nanoplastics have diameters smaller than .

# MP Transport and Crossing the Blood-Brain Barrier (BBB)

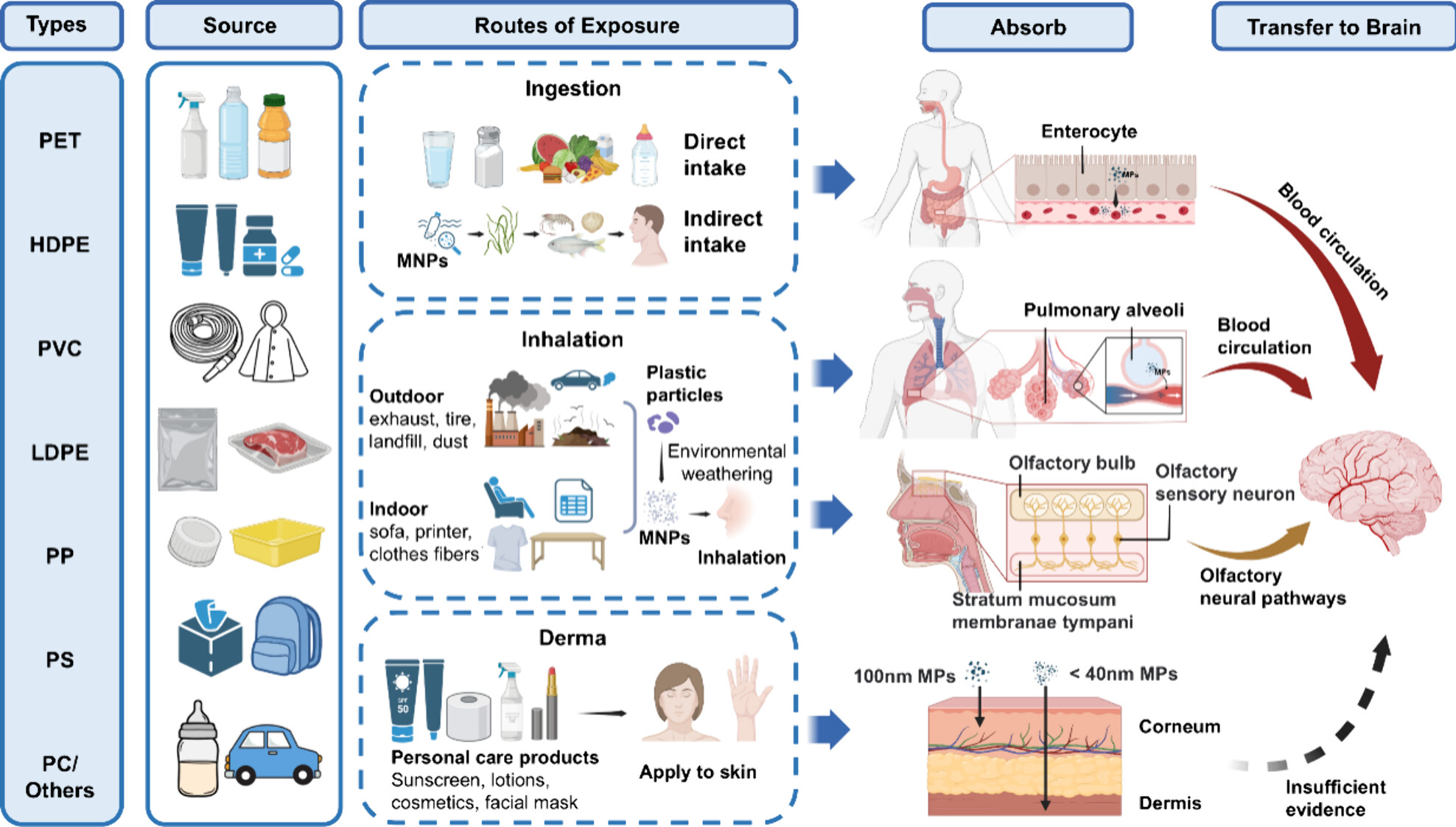
Lorem ipsum…

## Routes of Entry

Micro- and nanoplastics (MPs/NPs) enter the body via several primary routes of entry. The most prevalent pathways are ingestion—mainly from contaminated food and drinking water, which are almost everywhere in modern times—and inhalation—often from airborne particles such as indoor dust and synthetic clothing fibers. While dermal absorption remains a possibility, it is generally considered a less significant route. [Figure 1](#fig-entry-routes) depicts in detail how MNPs travel to the brain from outside. Recent research discovered that nanoplastics appear to be the most dangerous in terms of systemic effects, as their diminutive size facilitates rapid entrance into the bloodstream and distribution throughout the body ([Kopatz et al., 2023](#ref-kopatzMicroNanoplasticsBreach2023)).

Figure 1

Environmental Sources and MNPs’ Pathways to the Brain



*Note*. This diagram showcases the types of plastics, where they come from, and how they enter the body. The American Plastics Industry Association created the SPI code (SPI-Code) to provide a standard method for classifying plastics. Nanoplastics are best at traversing through the BBB into the brain due to their diminutive size. Reprinted from Ma, Q., Lei, J., Pang, Y., Shen, Y., & Zhang, T. (2025). Neurotoxicity of Micro- and Nanoplastics: A Comprehensive Review of Central Nervous System Impacts. Environment & Health. https://doi.org/10.1021/envhealth.5c00087.

## Blood-Brain Barrier Structure

The central nervous system (CNS) has a sophisticated shield called the Blood-Brain Barrier (BBB) that separates brain matter from the rest of the body. This structure is formed by specialized cerebral endothelial cells connected by tight junctions, along with pericytes and astrocytes ([McConnell & Mishra, 2022](#ref-mcconnellCellsBloodbrainBarrier2022)). The BBB effectively limits the passage of foreign substances, pathogens, and large molecules from the circulatory system past the outer brain layer, which helps maintain the neural microenvironment’s homeostasis.

## Translocation Hypotheses

There are many hypotheses regarding the MNPs’ route through the BBB. One such route is paracellular diffusion, which in theory could allow even smallest nanoplastic particles to pass, although this pathway is heavily restricted ([Campbell et al., 2012](#X004f712ec1095099a0c1c2348f1de96e549812f); [Winiarska et al., 2024](#ref-winiarskaPotentialImpactNano2024)). A more probable mechanism is endocytosis—where NPs are internalized by the brain endothelial cells and subsequently exocytosed into the brain interstitial fluid ([Hamed et al., 2022](#ref-hamedNeurotoxicEffectsDifferent2022)). A third, highly discussed hypothesis is the “Trojan Horse effect”. This scenario presumes that MNPs are first phagocytized by circulating immune cells, which then act as vectors to carry them across the BBB ([Li et al., 2025](#ref-liNewEvidenceMechanisms2025)).

## Associated Toxicants

A critical factor that exacerbates MNP-related neurotoxicity is associated toxicants. MNPs, due to their high surface-to-volume ratio, readily absorb chemical additives and environmental pollutants, (e.g., benzo[a]pyrene, okadaic acid) ([Yan et al., 2023](#Xe629b25df5763d94ad90b0417c5c121df366051)). These chemicals also have the capability to disrupt the BBB and impair tight junction integrity, thereby allowing the plastic particles easier access to the brain tissue and synergizing the overall neurotoxic effect. ([Cheng et al., 2023](#ref-chengEffectsAdsorbedBenzoapyrene2023))

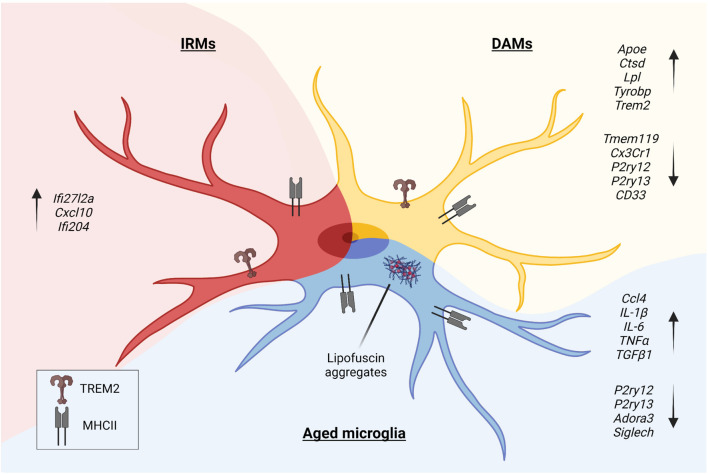
# Microglial Activation and Neuroinflammation

## The Role of Microglia

Microglial cells are the brain’s resident macrophages and the primary immune cells of the CNS. In their resting state, microglia adopt a branched morphology, actively surveying the microenvironment for pathogens, damaged cells, or misfolded proteins ([Wake et al., 2011](#ref-wakeFunctionsMicrogliaCentral2011)). When activated, these cells will rapidly undergo functional and morphological transformation, proliferate, migrate to the injury site, and engage in immunological activies—i.e., phagocytosis, antigen presentation, and the release of signaling molecules ([Yang et al., 2010](#ref-yangRoleMicrogliaCentral2010)). [Figure 2](#fig-microglia-states) showcases different transformations of microglial cells. The neuroinflammation is marked by thechronic, uncontrolled activation of cells like microglia, which leads to persistent neurotoxicity and neuronal damage ([Muzio et al., 2021](#X8c4db74612eb4359854825ace8f5a75bc5d1444)).

Figure 2

Different Activation States of Microglia



*Note*. Microglia experience morphologic and phenotypic/functional changes upon activation. Shown in this drawing are Disease-Associated Microglia (DAMs), Injury-Responsive Microglia (IRMs), and aged microglia, each representing a distinct activation state. Reprinted from Muzio, L., Viotti, A., & Martino, G. (2021). Microglia in Neuroinflammation and Neurodegeneration: From Understanding to Therapy. Frontiers in Neuroscience, 15, 742065. https://doi.org/10.3389/fnins.2021.742065.

## Direct Activation Mechanism

One primary hypothesized mechanism involves the direct interaction of ultra-fine plastic particles (nanoplastics) with microglia. As discussed in the previous section, NPs are believed capable of crossing the BBB and being taken up via phagocytosis by nearby microglial cells. Being non-degradable, these particles persist within the microglial lysosome, which leads to a phenomenon coined “frustrated phagocytosis” ([Ishida et al., 2019](#ref-ishidaLivecellImagingMacrophage2019)). The inability to clear the foreign material results in chronic lysosomal stress and damage—akin to choking themselves to death ([Mularski et al., 2018](#Xc075ecd0603de099cd0d3801a41cc8bb5d7a187)). Persistent internal stress like this drives a sustained microglial activation state that remains even in the absence of a live pathogen.

## Inflammasome Pathway

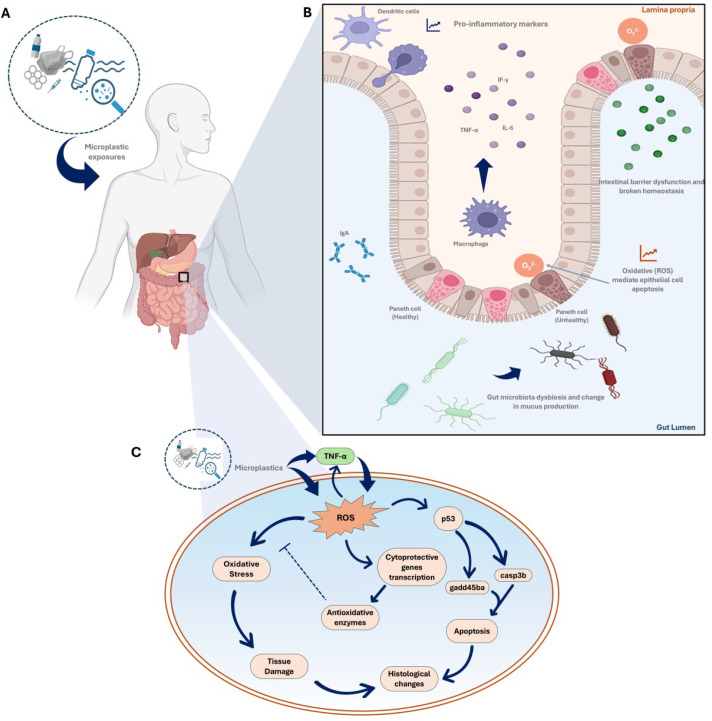
As a direct consequence of frustrated phagocytosis, an important flammatory signaling cascade would be triggered: the the NLRP3 Inflammasome. This complex is an intracellular receptor that senses danger signals, such as lysosomal rupture and the formation of reactive oxygen species (ROS), both of which are common outcomes of MP/NP internalisation by body cells. Activation of the NLRP3 inflammasome leads to the cleavage of pro-caspase-1 into active caspase-1. This activated enzyme, in turn, will cause the maturation and release of highly pro-inflammatory cytokines, namely, Interleukin-1 (IL-1) and Interleukin-18 (IL-18) ([Harrison, 2013](#ref-harrisonChiasmaRochePartner2013); [Matousek et al., 2012](#X592a8f7e9822be7b2d667d2b74ce1e90f1cedb8)). Said cytokines further propagates the inflammatory signal, recruiting additional immune cells and intensifying the neuroinflammatory cycle—therefore directly contributing to neuronal injury ([Delantoni et al., 2023](#X7e07edb5dcf956124458476de0bb8c859e947f0)).

# Indirect Disruption via Gut-Brain Axis

Microglial activation does not require direct entry of plastic particles into the brain. Exposure in peripheral sites, particularly the gut (via ingestion) and the lungs (via inhalation), can be sufficient to drive a state of systemic inflammation. As MNPs invade and damage the intestinal and pulmonary barriers, gut bacteria and associated toxins will translocate into the bloodstream. This systemic inflammatory state results in the establishment of neuro-immune link (gut-brain axis) ([Kalyan et al., 2022](#X8aac5304898f8d6b298a94f1cf67b376bb3965d)). As such, inflammatory signals (such as pro-inflmmatory cytokines), even without crossing the BBB themselves, can signal through endothelial cells and other immune cells, or directly diffuse across the BBB, practically acting as “danger messages” that trigger an indirect, secondary activation of the quiescent microglial population and extend the peripheral damage into the CNS ([Bora et al., 2024](#ref-boraMicroplasticsHumanHealth2024); [Hoogland et al., 2015](#X542999c159c4319fc9bb0895037e02ed832cecc)). [Figure 3](#fig-gut-brain-axis) demonstrates the this complicated cascade, alongside the gut-brain axis.

Figure 3

Interactions Between MNPs and Human Gut



*Note*. Figure (A) shows the entry of MNPs into the body. Figure (B) is the inflammatory response caused by the invasion of MNPs—marked by the release of pro-inflammatory cytokines such as TNF- and IL-6. Figure (C) outlines the pathways of oxidative stress activated by MNP-induced inflammation. Reprinted from Bora, S. S., Gogoi, R., Sharma, M. R., Anshu, Borah, M. P., Deka, P., Bora, J., Naorem, R. S., Das, J., & Teli, A. B. (2024). Microplastics and human health: Unveiling the gut microbiome disruption and chronic disease risks. Frontiers in Cellular and Infection Microbiology, 14, 1492759. https://doi.org/10.3389/fcimb.2024.1492759.

# Consequences and Future Directions

# References

Bora, S. S., Gogoi, R., Sharma, M. R., Anshu, Borah, M. P., Deka, P., Bora, J., Naorem, R. S., Das, J., & Teli, A. B. (2024). Microplastics and human health: Unveiling the gut microbiome disruption and chronic disease risks. *Frontiers in Cellular and Infection Microbiology*, *14*, 1492759. <https://doi.org/10.3389/fcimb.2024.1492759>

Campbell, C. S. J., Contreras-Rojas, L. R., Delgado-Charro, M. B., & Guy, R. H. (2012). Objective assessment of nanoparticle disposition in mammalian skin after topical exposure. *Journal of Controlled Release*, *162*(1), 201–207. <https://doi.org/10.1016/j.jconrel.2012.06.024>

Cheng, S., Ye, Z., Wang, X., Lian, C., Shang, Y., & Liu, H. (2023). The effects of adsorbed benzo(a)pyrene on dynamic behavior of polystyrene nanoplastics through phospholipid membrane: A molecular simulation study. *Colloids and Surfaces B: Biointerfaces*, *224*, 113211. <https://doi.org/10.1016/j.colsurfb.2023.113211>

Delantoni, A., Sarafopoulos, A., Giannouli, N., & Rafailidis, V. (2023). Maxillofacial inflammations visualized with ultrasonography. Description of the imaging features and literature review based on a characteristic case series. *Journal of Ultrasonography*, *23*(93), e80–e89. <https://doi.org/10.15557/jou.2023.0015>

Hamed, M., Martyniuk, C. J., Naguib, M., Lee, J.-S., & Sayed, A. E.-D. H. (2022). Neurotoxic effects of different sizes of plastics (nano, micro, and macro) on juvenile common carp (Cyprinus carpio). *Frontiers in Molecular Neuroscience*, *15*. <https://doi.org/10.3389/fnmol.2022.1028364>

Harrison, C. (2013). Chiasma and Roche partner in oral peptide drug delivery. *Nature Reviews Drug Discovery*, *12*(4), 255–255. <https://doi.org/10.1038/nrd3989>

Hoogland, I. C. M., Houbolt, C., van Westerloo, D. J., van Gool, W. A., & van de Beek, D. (2015). Systemic inflammation and microglial activation: Systematic review of animal experiments. *Journal of Neuroinflammation*, *12*, 114. <https://doi.org/10.1186/s12974-015-0332-6>

Ishida, T., Fujihara, N., Nishimura, T., Funabashi, H., Hirota, R., Ikeda, T., & Kuroda, A. (2019). Live-cell imaging of macrophage phagocytosis of asbestos fibers under fluorescence microscopy. *Genes and Environment*, *41*, 14. <https://doi.org/10.1186/s41021-019-0129-4>

Kalyan, M., Tousif, A. H., Sonali, S., Vichitra, C., Sunanda, T., Praveenraj, S. S., Ray, B., Gorantla, V. R., Rungratanawanich, W., Mahalakshmi, A. M., Qoronfleh, M. W., Monaghan, T. M., Song, B.-J., Essa, M. M., & Chidambaram, S. B. (2022). Role of Endogenous Lipopolysaccharides in Neurological Disorders. *Cells*, *11*(24), 4038. <https://doi.org/10.3390/cells11244038>

Kopatz, V., Wen, K., Kovács, T., Keimowitz, A. S., Pichler, V., Widder, J., Vethaak, A. D., Hollóczki, O., & Kenner, L. (2023). Micro- and Nanoplastics Breach the Blood–Brain Barrier (BBB): Biomolecular Corona’s Role Revealed. *Nanomaterials*, *13*(8), 1404. <https://doi.org/10.3390/nano13081404>

Li, X., Hu, S., Yu, Z., He, F., Zhao, X., & Liu, R. (2025). New Evidence for the Mechanisms of Nanoplastics Amplifying Cadmium Cytotoxicity: Trojan Horse Effect, Inflammatory Response, and Calcium Imbalance. *Environmental Science & Technology*, *59*(19), 9471–9485. <https://doi.org/10.1021/acs.est.5c01254>

Matousek, S. B., Ghosh, S., Shaftel, S. S., Kyrkanides, S., Olschowka, J. A., & O’Banion, M. K. (2012). Chronic IL-1β-mediated neuroinflammation mitigates amyloid pathology in a mouse model of Alzheimer’s disease without inducing overt neurodegeneration. *Journal of Neuroimmune Pharmacology*, *7*(1), 156–164. <https://doi.org/10.1007/s11481-011-9331-2>

McConnell, H. L., & Mishra, A. (2022). Cells of the Blood-brain Barrier: An Overview of the Neurovascular Unit in Health and Disease. *Methods in Molecular Biology (Clifton, N.J.)*, *2492*, 3–24. <https://doi.org/10.1007/978-1-0716-2289-6_1>

Mularski, A., Marie-Anaïs, F., Mazzolini, J., & Niedergang, F. (2018). Observing Frustrated Phagocytosis and Phagosome Formation and Closure Using Total Internal Reflection Fluorescence Microscopy (TIRFM). *Methods in Molecular Biology (Clifton, N.J.)*, *1784*, 165–175. <https://doi.org/10.1007/978-1-4939-7837-3_16>

Muzio, L., Viotti, A., & Martino, G. (2021). Microglia in Neuroinflammation and Neurodegeneration: From Understanding to Therapy. *Frontiers in Neuroscience*, *15*, 742065. <https://doi.org/10.3389/fnins.2021.742065>

Thompson, R. C., Olsen, Y., Mitchell, R. P., Davis, A., Rowland, S. J., John, A. W. G., McGonigle, D., & Russell, A. E. (2004). Lost at Sea: Where Is All the Plastic? *Science*, *304*(5672), 838–838. <https://doi.org/10.1126/science.1094559>

Wake, H., Moorhouse, A. J., & Nabekura, J. (2011). Functions of microglia in the central nervous system – beyond the immune response. *Neuron Glia Biology*, *7*(1), 47–53. <https://doi.org/10.1017/S1740925X12000063>

Winiarska, E., Jutel, M., & Zemelka-Wiacek, M. (2024). The potential impact of nano- and microplastics on human health: Understanding human health risks. *Environmental Research*, *251*, 118535. <https://doi.org/10.1016/j.envres.2024.118535>

Yan, L., Yu, Z., Lin, P., Qiu, S., He, L., Wu, Z., Ma, L., Gu, Y., He, L., Dai, Z., Zhou, C., Hong, P., & Li, C. (2023). Polystyrene nanoplastics promote the apoptosis in Caco-2 cells induced by okadaic acid more than microplastics. *Ecotoxicology and Environmental Safety*, *249*, 114375. <https://doi.org/10.1016/j.ecoenv.2022.114375>

Yang, I., Han, S. J., Kaur, G., Crane, C., & Parsa, A. T. (2010). The Role of Microglia in Central Nervous System Immunity and Glioma Immunology. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia*, *17*(1), 6–10. <https://doi.org/10.1016/j.jocn.2009.05.006>