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Commentary: Tissue accumulation of microplastics in mice and biomarker responses suggest widespread health risks of exposure

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A commentary on

Tissue accumulation of microplastics in mice and biomarker responses suggest widespread health risks of exposure
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Microplastics, whether purposely manufactured in the form of micro-particles or produced via fragmentation of larger pieces, are widespread in the environment (Auta et al., 2017). Microplastics could be taken up by a large number of marine species, and could potentially serve as carriers or could biomagnify other persistent organic environmental pollutants (Galloway et al., 2017). As microplastics are chemically inert, it is not intuitively clear if these could have a detrimental effect when ingested by marine species beyond possibly a congestion of the gut. In recent years, a good number of studies have indeed demonstrated that microplastics (either pristine or dye-conjugated) exert detectable acute and toxic effects on marine invertebrate and fishes under controlled laboratory settings (see **Table 1** for a non-exhaustive summary). Microplastics are taken up and could accumulate in the gills and gut tissues of mussels and oysters (von Moos et al., 2012; Van Cauwenberghe et al., 2015; Paul-Pont et al., 2016; Sussarellu et al., 2016), with histopathology and stress responses documented with the former and reproductive deficiencies noted for the latter, as well as other marine invertebrates (Wright et al., 2013). More recent work has also documented adverse effects of microplastic ingestion in aquatic vertebrates such as the zebrafish (Lu et al., 2016; Chen et al., 2017). Ren's laboratory, for example, reported that 5 and 20 μm polystyrene micro-particles accumulate in gills, gut tissues and in the liver of zebrafish (Lu et al., 2016). Analysis of the fish liver revealed histological signs of inflammation and lipid accumulation, with elevation of oxidative stress marker enzymes and changes in the metabolomics profile.

MICROPLASTICS INGESTION AND ADVERSE EFFECTS IN MOUSE

The same group has now reported a similar analysis in a mammalian species (Deng et al., 2017). Ingested by the mice through drinking water, 5 and 20 μm polystyrene micro-particles elicited somewhat similar pathological and physiological changes in mice. These, particularly the 5 μm micro-particles, could be detected in histological sections of the gut, liver and kidney. Again, the authors reported that focused analysis on liver tissues revealed signs of inflammation, accumulation of lipid droplets, elevation of oxidative stress markers, defects in energy metabolism, and altered metabolomics. An inference on potential neurotoxicity of the micro-particles was also made based

TABLE 1 | A summary of histopathology and/or physiological perturbations observed in recent laboratory experiments with microplastics treatment of marine invertebrates, zebrafish and mouse.

Model organism	Nature of microplastics	Tissue accumulation and cellular uptake	Toxicity, pathology and physiological perturbations	References
MARINE INVERTEBRATES				
Zoo-plankton *Calanus helgolandicus*	Polystyrene microspheres 20 μm, 75 particles/mL	Ingestion and egestion	Significant decrease in algal feeding.	Cole et al., 2013, 2015
Daphnia magna	Polystyrene microspheres 100 nm and 2 μm, 1 mg/mL	Ingestion and egestion	Reduced feeding rate.	Rist et al., 2017
Polychaete worm (*Arenicola marina*)	Sediments spiked with microscopic unplasticised polyvinylchloride (UPVC), 0–5% by weight	Ingestion and egestion	Reduced feeding activity.	Wright et al., 2013
		Increased phagocytic activity of immune cells.		
		Significant reduction (50%) of energy reserve.		
Mussels (*Mytilus edulis*)	High-density polyethylene microspheres 0–80 μm, 2.5 g/L	Cellular uptake in gills and digestive tract	Granulocytoma formation.	von Moos et al., 2012
		Heterophagosome formation in intestinal epithelium.		
	Polystyrene microspheres 2 μm and 6 μm, 32 μg/L	Accumulation in gills and intestinal epithelium	Hemocyte infiltration into intestine and digestive gland and tissue pathology.	Paul-Pont et al., 2016
		Increase in ROS levels in hemocytes.		
			Elevation of anti-oxidation enzyme activity.	
Crab (*Carcinus maenas*)	Polystyrene microspheres 8 μm, 10^6–10^7 microspheres/L		Transient lowering of branchial function (based on oxygen consumption) and changes in hemolymph Na^+, Ca^{2+}.	Watts et al., 2014
Oyster (*Crassostrea gigas*)	Polystyrene microspheres 2 μm and 6 μm, 0.023 mg/L	Ingestion and detection in stomach, intestine	Increased in algal consumption and absorption efficiency.	Sussarellu et al., 2016
			Decreased in oocyte number, diameter and sperm velocity, decreased offspring.	
			Significant shift of energy allocation from reproduction to structural growth.	
FISH				
Zebrafish (*Danio rerio*)	Polystyrene microspheres 70 nm, 5 μm and 20 μm, 20 mg/L	Accumulation in gills, gut and liver (only the 5 μm particles)	Liver histopathology (signs of inflammation and lipid accumulation).	Lu et al., 2016
			Elevation of oxidative stress marker enzymes.	
			Changes in liver metabolomics profile.	
	Polystyrene "nanoplastics" 50 nm, 1 mg/L		Inhibition of larvae locomotion Inhibited acetylcholinesterase activity and upregulate cytoskeletal markers	Chen et al., 2017
MAMMAL				
Mouse (*Mus musculus*)	Polystyrene microspheres 5 μm and 20, 0.01–0.5 mg/day	Accumulation in gut, liver and kidney	Signs of inflammation and lipid accumulation in liver.	Deng et al., 2017
			Altered lipid profile and impairment of energy metabolism (reduction in ATP levels).	
			Increased liver oxidative stress markers, decreased acetylcholinesterase.	

on changes in liver acetylcholinesterase (AChE) activity (Note: This point in the paper is confusing, as the authors stated in the text that AChE activity "decreased" after exposure to microplastics, but the data presented showed it to be elevated instead). On the whole, although the changes reported were moderate, they were statistically significant.

IMPLICATIONS AND PERSPECTIVES

What is the significance of the findings of Deng et al.? On one hand, findings indicating that microplastics could accumulate in the tissues of marine vertebrates and even mammals at the apex of the trophic pyramid have important ecological implications, but these should be interpreted with some caution. For one, the relatively low abundance of microplastics in the ecological environment would likely not result in significant tissue accumulation via direct assimilation in larger organisms, but transfer across trophic levels and biomagnification along the food chain is a much touted possibility. There is no unequivocal evidence for the latter mechanisms pertaining to microplastics, largely because it is very difficult, given the heterogeneity and low abundance, to adequately assess microplastic distribution and bioaccumulation in the wild. One should bear in mind that the quantity of microplastics used in laboratory experiments are typically several magnitudes above environment abundance (Connors et al., 2017). In Deng et al.'s experimental setups, the lowest dose administered at 0.01 mg/day corresponded to $\sim 10^5$ of the 5 μm particles, a number that is likely 3–4 magnitudes above ecological abundance. Even the consumption of oysters which rather high accumulation of microplastics (Galloway and Lewis, 2016) would hardly approach the amounts used in the experiments.

How do microplastics elicit the adverse effects seen in mouse liver and the zebrafish liver in the earlier report (Lu et al., 2016)? To reach the liver, the ingested microplastics would need to somehow negotiate the gut-vascular barrier (Spadoni et al., 2015) or be taken up by intestinal enterocytes and transported across the epithelial mucosal lining in a manner akin to transcytosis of macromolecules. Thereafter, these have to enter the circulation via penetration of the vessel lining of endothelial cells and pericytes. Uptake of microplastics by gill and gut cells (von Moos et al., 2012) and translocation of ingested microplastic into the circulation (Browne et al., 2008) has been shown for the mussel *Mytilus edulis*, but not for the oyster (Sussarellu et al., 2016). How these microplastics negotiate the gut-vascular barrier and threshold concentrations at which this would effective occur are important questions that call for further investigation.

What about the toxicological/pathological perturbations measured in the liver? The data presented in Deng et al. are somewhat consistent with an acute injury-type inflammatory response, likely against circulating and liver tissue-accumulated microplastics, which would be accompanied by ROS elevation in adhering immune cells and a countering anti-oxidation response by the hepatocytes. This sort of acute inflammatory response is also evident in mussel tissues, as demonstrated by hemocyte infiltration and increase ROS (von Moos et al., 2012). The reduction in ATP and the formation of lipid droplets are indicative of changes in energy and lipid metabolism that accompanies mammalian liver injury and inflammation. The degree of injury was however not clear as common liver function tests were not performed. The metabolomics changes are difficult to interpret, and not particular useful except to support the notion that metabolic adaptations to injury and inflammation have likely occurred in liver tissues. Any claim of potential neurotoxicity based on changes in liver AChE is premature. If any, this is likely limited to the enteric nervous system as the blood-brain barrier presents a much more formidable obstacle for any plausible central nervous system accumulation of microplastics. The lack of any behavioral tests also precludes such a claim. The effect of ingested microplastics on longer term changes in feeding behavior and fecundity as previously observed for invertebrates (Wright et al., 2013; Sussarellu et al., 2016; Rist et al., 2017) were not investigated. These are more important parameters to assess pertaining to chronic exposure to any xenobiotic.

On the whole, the findings of Deng et al. (2017) were made under conditions that mimic a massive overdose of microplastics and the results seen are limited to what might resemble a tissue limited acute inflammatory response. Documenting the fact that such responses could be elicited by the presumably chemically inert pristine microplastics is not without value, but the suggestion of "widespread health risks of (microplastics) exposure" cannot be taken without some reservations.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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