ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 March 7; 30(9): 994-1260

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 30 Number 9 March 7, 2024

EDITORIAL

GUIDELINES

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Clinical Trials Study

World Journal of Gastroenterology

Weekly Volume 30 Number 9 March 7, 2024

Contents

LETTER TO THE EDITOR

World Journal of Gastroenterology

Weekly Volume 30 Number 9 March 7, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Pal Miheller, MD, PhD, Assistant Professor, Department of Surgery, Transplantation and Gastroenterology, Head of Gastroenterology, Semmelweis University, Budapest H-1088, Pest, Hungary.miheller.pal@semmelweis.hu

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJG* as 4.3; Quartile category: Q2. The *WJG*'s CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

PUBLICATION DATE
March 7, 2024

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
https://www.shca.org.cn
https://www.zs-hospital.sh.cn

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2024 March 7; 30(9): 1011-1017

DOI: 10.3748/wjg.v30.i9.1011

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Impact of microplastics and nanoplastics on liver health: Current understanding and future research directions

Chun-Cheng Chiang, Hsuan Yeh, Ruei-Feng Shiu, Wei-Chun Chin, Tzung-Hai Yen

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Wu L, China

Received: January 10, 2024
Peer-review started: January 10, 2024
First decision: January 19, 2024
Revised: January 26, 2024
Accepted: February 18, 2024
Article in press: February 18, 2024
Published online: March 7, 2024

Chun-Cheng Chiang, Hsuan Yeh, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213, United States

Chun-Cheng Chiang, Pittsburgh Liver Research Center, University of Pittsburgh, Pittsburgh, PA 15213, United States

Chun-Cheng Chiang, Division of Experimental Pathology, Department of Pathology, University of Pittsburgh, Pittsburgh, PA 15213, United States

Hsuan Yeh, Division of Endocrinology, Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA 15213, United States

Ruei-Feng Shiu, Center of Excellence for The Oceans, National Taiwan Ocean University, Keelung 20224, Taiwan

Ruei-Feng Shiu, Institute of Marine Environment and Ecology, National Taiwan Ocean University, Keelung 20224, Taiwan

Wei-Chun Chin, Department of Materials Science and Engineering, University of California Merced, Merced, CA 95343, United States

Tzung-Hai Yen, Department of Nephrology, Clinical Poison Center, Chang Gung Memorial Hospital, Taoyuan 333, Taiwan

Tzung-Hai Yen, College of Medicine, Chang Gung University, Taoyuan 333, Taiwan

Corresponding author: Tzung-Hai Yen, MD, PhD, Doctor, Professor, Department of Nephrology, Clinical Poison Center, Chang Gung Memorial Hospital, Linkou, No. 5 Fu-Hsing Street, Taoyuan 333, Taiwan. m19570@cgmh.org.tw

Abstract

With continuous population and economic growth in the 21st century, plastic pollution is a major global issue. However, the health concern of microplastics/nanoplastics (MPs/NPs) decomposed from plastic wastes has drawn public attention only in the recent decade. This article summarizes recent works dedicated to understanding the impact of MPs/NPs on the liver-the largest digestive organ, which is one of the primary routes that MPs/NPs enter human bodies. The interrelated mechanisms including oxidative stress, hepatocyte energy re-distribution, cell death and autophagy, as well as immune responses and inflammation, were also featured. In addition, the disturbance of microbiome

and gut-liver axis, and the association with clinical diseases such as metabolic dysfunction-associated fatty liver disease, steatohepatitis, liver fibrosis, and cirrhosis were briefly discussed. Finally, we discussed potential directions in regard to this trending topic, highlighted current challenges in research, and proposed possible solutions.

Key Words: Microplastics; Nanoplastics; Liver; Reactive oxidative species; Cell death; Autophagy; Innate immunity; Metabolic dysfunction-associated fatty liver disease; Gut-liver axis

Core Tip: The liver is heavily impacted by exposure to microplastics/nanoplastics (MPs/NPs). This editorial not only summarized the key molecular and cellular events in the liver triggered by MPs/NPs but also highlighted prospective research directions including translational and clinical studies for further investigation in this field.

Citation: Chiang CC, Yeh H, Shiu RF, Chin WC, Yen TH. Impact of microplastics and nanoplastics on liver health: Current understanding and future research directions. *World J Gastroenterol* 2024; 30(9): 1011-1017
URL: https://www.wjgnet.com/1007-9327/full/v30/i9/1011.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i9.1011

INTRODUCTION

Plastic pollution has become one of the greatest challenges in the 21st century. The growing use of plastic materials nowadays has caused a serious burden not only to the environment but to human health. Microplastics (MPs, typically < 5 mm) and nanoplastics (NPs, typically < 1 μm) are small plastic particles manufactured by industry or degraded by physical and chemical processes[1,2]. These particles are now ubiquitously observed in the soil, drinking water, and even the air we breathe[3]. Furthermore, plastic particles can also enter the food chain and be biomagnified, which finally will return to our dining table and accumulate in the human body[4]. Despite a potential threat to human health, this critical issue has only attracted public awareness in recent years. Recent studies have indicated the occurrence and accumulation of MPs in the human body including blood, lungs, liver, and even in human placenta, which received considerable attention[5]. However, biomonitoring, translational, and clinical studies of human body burdens of MPs/NPs are still in their infancy.

Among these, the liver is a major organ of the reticuloendothelial system, also known as the monocyte-phagocytic system, which contains gatekeeper cells like sinusoidal endothelial cells or Kupffer cells, capable of clearing foreign particles in blood circulation[6]. In addition, enterohepatic circulation includes the transportation of substances absorbed by enterocytes through portal flow and the passage of bile into the intestine *via* the biliary tracts[7]. This re-entry cycle can cause repeated exposure of MPs/NPs to hepatocytes and sequelae in the liver. Although *in vitro* and *in vivo* studies have demonstrated possible mechanisms that MPs can affect liver health (Figure 1), human studies are currently limited.

OXIDATIVE STRESS

MPs/NPs can either generate extracellular reactive oxygen species (ROS) by weathering degradation like light or heat[8], or intracellular ROS by disrupting the mitochondrial membrane integrity and potential after internalization[3]. The redox imbalance can further cause DNA damage and genotoxicity, protein oxidation and misfolding, and lipid peroxidation with membrane instability. Metabolic dysfunction-associated fatty liver disease (MAFLD), or metabolic dysfunction-associated steatotic liver disease is a liver manifestation of metabolic syndrome which affects nearly one-third of the global adult population[9]. The theory of multiple blows is currently a recognized pathogenesis of MAFLD[10,11]. Although multiple hits like diet, obesity, insulin resistance, genetic factors, and gut dysbiosis have been found to contribute to MAFLD pathogenesis, environmental toxins or pollutants were barely mentioned in previous literature[12,13]. Recently, multiple models have demonstrated that the liver can be insulted by MPs through ROS generation, directly or indirectly resulting in MAFLD. In zebrafish models, combined exposure to a high-fat diet and MPs increased oxidative stress and upregulated lipogenic and inflammatory gene expression, which led to steatotic liver and altered behaviors [14]. Co-exposure of MPs with antibiotic pollutants in zebrafish exhibited significantly higher levels of lipid accumulation and inflammation in conjunction with oxidative stress production in their livers[15]. In mice, single-cell transcriptome analysis revealed that MPs triggered Kupffer cell and T cell activation in the high-fat diet context[16]. The study also showed MPs regulated PPAR signaling, chemical carcinogenesis-ROS pathways, and complement and blood coagulation cascade in the liver. In human pluripotent stem cell-derived liver organoids, MPs increased the gene and protein expression of hepatic HNF4A and CYP2E1, which control lipid metabolism, insulin signaling, and mitochondrial function [17]. The upregulation of the cytochrome p450 enzyme, CYP2E1, is responsible for the phase I metabolism of the liver and

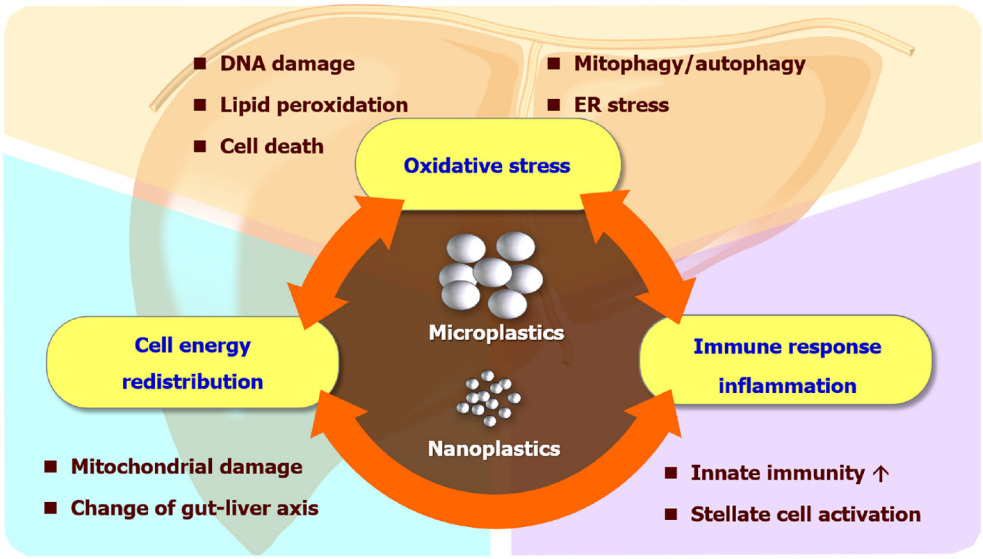

Figure 1 An overview of interrelated mechanisms behind the microplastics and nanoplastics-induced hepatotoxicity. ER: Endoplasmic reticulum.

is highly linked to the occurrence of oxidative stress. Activated Kupffer cells can form extracellular traps of MPs/NPs, driving hepatocellular epithelial-mesenchymal transition and pro-inflammatory cytokine production through the ROS signaling pathway[18].

HEPATOCYTE ENERGY DEPRIVATION

The energy metabolism affected by MPs/NPs is not merely limited to lipids. Exposure to MPs changes the purinergic metabolites in the liver, which suggests MPs can deplete the energy reserve of different organisms[19-21]. Additionally, the mRNA of ND5, an important protein subunit of the electron transport chain located at the inner membrane of mitochondria, was altered after exposure to NPs[22]. Since MPs/NPs can cause mitochondrial damage, it is expected that NPs interfere with the ability to produce ATPs and mobilize energy reserve, which is further echoed by liver and serum metabolite analyses related to tricarboxylic acid cycle and glycolysis[23,24]. Moreover, liver transcriptomic and metabolomic studies revealed MPs/NPs can perturb monosaccharide and lipid metabolism including pentose phosphate pathways and gluconeogenesis[25,26]. Not only do MPs/NPs inhibit building block synthesis and signal transduction, but they also damage intestinal function and suppress the absorption of nutrients[27]. Overall, these studies indicate that MPs/NPs can lead to energy deprivation in the liver.

CELL DEATH AND AUTOPHAGY

A multitude of evidence suggests MPs/NPs drive cell death including apoptosis, pyroptosis, and ferroptosis. MPs activated hepatic intrinsic apoptosis signaling p53/Bcl-2/Bax signaling[28] and meanwhile stimulated the compensatory antioxidant Nrf2/Keap1 pathway[29]. Besides, studies showed MPs/NPs induced apoptosis by activating protein kinase RNA-like endoplasmic reticulum kinase (PERK) and mitogen-activated protein kinase pathways[30,31]. In addition, MPs/NPs induced hepatocyte pyroptosis by increasing NLRP3/ASC and caspase-1-dependent pathway[32,33]. Furthermore, MPs induced lipid peroxidation in the liver, which regulates ferroptosis-related proteins such as TFRC, FTH1, and GPX4[32]. MPs/NPs can also lead to hepatocyte autophagy by altering autophagosome LC3 and p62 ratios[33-35], and mitophagy by PERK pathway with increased ER stress[31]. A recent study demonstrated MPs triggered apoptosis and necroptosis in mouse liver through the ROS/PTEN/PI3K/AKT axis with excessive autophagy flux[36].

IMMUNE RESPONSES AND INFLAMMATION

MPs/NPs promote inflammation and stimulate innate immune responses. After the 30 d exposure to MPs, the mouse liver showed severe vacuolar degeneration, hepatocyte edema, and inflammatory cell infiltration[29]. MPs/NPs increase cytokine expression and induce enzymatic activity related to inflammation[37,38]. The nuclear factor-kappaB (NF-κB) pathway is activated, which furthers the inflammatory response in the liver[39]. Exposure to MPs can recruit neutrophils, macrophages, and natural killer cells to the liver[39,40]. Among the infiltrative immune cells, Kupffer cells (liver-resident macrophages) play a central role in lipid metabolism and responses of hepatocytes to fat overload[41]. The activation of

Kupffer cells by engulfing MPs/NPs will affect lipid metabolism, oxidize free fatty acids, and then produce excessive ROS and result in liver damage[41-43]. Furthermore, MPs polarized hepatic macrophages to pro-inflammatory M1 type and facilitated extracellular trap formation of neutrophils and macrophages[18,39,40,44]. Notably, one recent study suggested that polyethylene MPs impede the innate immune response in the liver by disrupting the extracellular matrix [45]. The contradictory result to previous research may need more future studies to confirm and clarify the underlying mechanism.

FIBROSIS AND CIRRHOSIS

Most chronic hepatitis ultimately results in fibrosis and cirrhosis. One study showed that NPs can increase ROS and exacerbate high-fat diet-induced liver fibrosis[46]. Another study demonstrated the ROS generated by MPs can act on the TGF-β/Smad2/3 signaling axis in hepatocytes[18]. Also, ROS can cause DNA break and release from both hepatocyte nuclei and mitochondria, where in the cytoplasm the fragmented DNA sensing cGAS/STING cascade is triggered and the pro-fibrotic NF-κB pathway is activated[47]. In addition, co-exposure to cadmium and MPs promotes the extracellular release of ATP through the hemichannels of hepatocytes. The extracellular ATP activates hepatic stellate cells by interacting with P2X7 receptors and initiates fibrosis[48]. Interestingly, one retrospective study analyzing human liver tissue discovered six different MP polymers in the liver of individuals with cirrhosis, but not in those without underlying liver disease[49].

FUTURE RESEARCH DIRECTIONS

The pathogenesis of MPs/NPs may appear challenging and complicated offering a lot of research opportunities. Microbiome research has become one of the popular topics in the recent decade. Several studies have uncovered that MPs/NPs disturb the homeostasis of gut microbiota, which affects hepatic fat accumulation and steatohepatitis[15,50,51]. In zebrafish models, the abundance of Bacteroidetes and Proteobacteria decreased significantly and the abundance of Firmicutes increased significantly by polystyrene MPs[15,52]. On the contrary, polystyrene MP exposure decreased the relative abundances of Firmicutes and a-Proteobacteria in mouse intestines[51]. Conflicting results in different species require future studies for validation. However, high throughput sequencing of the 16S rRNA gene V3-V4 region revealed a significant change in the richness and diversity of gut microbiota in both polystyrene MP-exposed zebrafish and mice [51,52]. MPs/NPs-related dysbiosis may be a "second hit" or be sensitized by other factors to cause intestinal barrier dysfunction (leaky gut) and liver inflammation[53-56]. In addition, MPs/NPs can leach out additives, flame retardants, dyes, and other organic compounds. The adsorbability, large surface area, and biodistribution characteristics of MPs/NPs also can accentuate the bioaccumulation and toxicity of heavy metals and organic compounds (Trojan-horse effect)[57, 58]. This effect on hepatocytes is not only found in cell line experiments and model organisms[28,33,59-61] but also discovered in liver organoids from human embryonic stem cells and patient-derived-induced pluripotent stem cells[62, 63], which may provide a powerful strategy for personalized toxicology evaluation. Furthermore, microfluidic technology has kept evolving in recent years with more efficient approaches for the identification, separation, and quantification of MPs[64]. Microfluidics is also widely applied to isolation, analysis, and parallel manipulation of single cells[65,66]. Combining these two research fields with microfluidics may take its advantage of manipulating small volumes of samples within micrometer-scale structures with a point-of-care potential. Lastly, the "long-term uncontrolled inflammation" by MPs/NPs can be a cause of tumor induction. Although one epidemiological study suggested polyvinyl chloride MPs exposure may increase the risk of liver cancers[67], it is uncertain whether the carcinogenic effect is caused by MPs or vinyl chloride monomer *per se*. Nevertheless, the more prominent existence of different MPs in cirrhotic patients than in healthy subjects implies that MPs/NPs may play a more important role in pre-cancerous lesions[49]. More pre-clinical and population-based research evidence is needed to delineate the correlation between MPs/NPs and liver cancers.

CONCLUSION

While trying to close the knowledge gap for plastic pollution, scientists are facing some specific challenges. The discrepant results among studies can be owing to various characterizations of MPs/NPs or different experimental protocols. Future experimental designs need to take the type, size, shape, and surface groups of MPs/NPs into consideration. It is also imperative to set exposure concentration and duration comparable to the realistic environment. Standardization of the materials and methods may yield more consistent results. Moreover, the current literature lacks clinical and epidemiological studies. Conducting human population studies can elucidate the association between the MPs/NPs exposure and health outcomes. With advanced analytical technologies, new experimental models, and well-informed interdisciplinary research collaborations, we expect to gain deeper insight into the risk of MPs/NPs to liver health, which will benefit the development of mitigation strategies and policies.

FOOTNOTES

Author contributions: Chiang CC, Yeh H, Shiu RF, Chin WC and Yen TH contributed to this paper; Yen TH designed the overall concept and outline of the manuscript; Shiu RF and Chin WC contributed to the discussion of the manuscript; Chiang CC and Yeh H contributed to the writing, and editing the manuscript, illustrations, and review of literature.

Supported by Chang Gung Memorial Hospital, No. CMRPG3N0621.

Conflict-of-interest statement: Chun-Cheng Chiang, Hsuan Yeh, Ruei-Feng Shiu, Wei-Chun Chin and Tzung-Hai Yen have nothing to disclose.

Country/Territory of origin: Taiwan

ORCID number: Chun-Cheng Chiang 0000-0001-8105-2512; Hsuan Yeh 0000-0002-4926-8433; Wei-Chun Chin 0000-0003-4881-9085; Tzung-Hai Yen 0000-0002-0907-1505.

Corresponding Author's Membership in Professional Societies: Taiwan Society of Nephrology.

S-Editor: Fan JR
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Lambert S**, Wagner M. Characterisation of nanoplastics during the degradation of polystyrene. *Chemosphere* 2016; **145**: 265-268 [PMID: 26688263 DOI: 10.1016/j.chemosphere.2015.11.078]
2 **Koelmans AA**, Besseling E, Shim WJ. Nanoplastics in the Aquatic Environment. Critical Review. In: Bergmann M, Gutow L, Klages M, editors. Marine Anthropogenic Litter. Cham: Springer International Publishing, 2015: 325-340
3 **Khan A**, Jia Z. Recent insights into uptake, toxicity, and molecular targets of microplastics and nanoplastics relevant to human health impacts. *iScience* 2023; **26**: 106061 [PMID: 36818296 DOI: 10.1016/j.isci.2023.106061]
4 **Xu JL**, Lin X, Wang JJ, Gowen AA. A review of potential human health impacts of micro- and nanoplastics exposure. *Sci Total Environ* 2022; **851**: 158111 [PMID: 35987230 DOI: 10.1016/j.scitotenv.2022.158111]
5 **Auguet T**, Bertran L, Barrientos-Riosalido A, Fabregat B, Villar B, Aguilar C, Sabench F. Are Ingested or Inhaled Microplastics Involved in Nonalcoholic Fatty Liver Disease? *Int J Environ Res Public Health* 2022; **19** [PMID: 36294076 DOI: 10.3390/ijerph192013495]
6 **Kalyane D**, Maheshwari R, Raval N, Chauhan AS, Tekade RK. Chapter 9 - Transportation and Biointeraction Properties in Nanomaterials Across Biological Systems. In: Tekade RK, editor Basic Fundamentals of Drug Delivery: Academic Press, 2019: 343-368
7 **Grasela TH**, Lukacova V, Morris DN, Clark RD, Andrews KA, Bolger MB. 4.04 - Human PK Prediction and Modeling. In: Chackalamannil S, Rotella D, Ward SE, editors. Comprehensive Medicinal Chemistry III. Oxford: Elsevier, 2017: 51-82
8 **Pannetier P**, Cachot J, Clérandeau C, Faure F, Van Arkel K, de Alencastro LF, Levasseur C, Sciacca F, Bourgeois JP, Morin B. Toxicity assessment of pollutants sorbed on environmental sample microplastics collected on beaches: Part I-adverse effects on fish cell line. *Environ Pollut* 2019; **248**: 1088-1097 [PMID: 30871891 DOI: 10.1016/j.envpol.2018.12.091]
9 **Devarbhavi H**, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. *J Hepatol* 2023; **79**: 516-537 [PMID: 36990226 DOI: 10.1016/j.jhep.2023.03.017]
10 **Buzzetti E**, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism* 2016; **65**: 1038-1048 [PMID: 26823198 DOI: 10.1016/j.metabol.2015.12.012]
11 **Tilg H**, Adolph TE, Moschen AR. Multiple Parallel Hits Hypothesis in Nonalcoholic Fatty Liver Disease: Revisited After a Decade. *Hepatology* 2021; **73**: 833-842 [PMID: 32780879 DOI: 10.1002/hep.31518]
12 **Ramírez-Mejía MM**, Qi X, Abenavoli L, Romero-Gómez M, Eslam M, Méndez-Sánchez N. Metabolic dysfunction: The silenced connection with fatty liver disease. *Ann Hepatol* 2023; **28**: 101138 [PMID: 37468095 DOI: 10.1016/j.aohep.2023.101138]
13 **Klaunig JE**, Li X, Wang Z. Role of xenobiotics in the induction and progression of fatty liver disease. *Toxicol Res (Camb)* 2018; **7**: 664-680 [PMID: 30090613 DOI: 10.1039/c7tx00326a]
14 **Boopathi S**, Haridevamuthu B, Mendonca E, Gandhi A, Priya PS, Alkahtani S, Al-Johani NS, Arokiyaraj S, Guru A, Arockiaraj J, Malafaia G. Combined effects of a high-fat diet and polyethylene microplastic exposure induce impaired lipid metabolism and locomotor behavior in larvae and adult zebrafish. *Sci Total Environ* 2023; **902**: 165988 [PMID: 37549705 DOI: 10.1016/j.scitotenv.2023.165988]
15 **Zhou W**, Shi W, Du X, Han Y, Tang Y, Ri S, Ju K, Kim T, Huang L, Zhang W, Yu Y, Tian D, Chen L, Wu Z, Liu G. Assessment of Nonalcoholic Fatty Liver Disease Symptoms and Gut-Liver Axis Status in Zebrafish after Exposure to Polystyrene Microplastics and Oxytetracycline, Alone and in Combination. *Environ Health Perspect* 2023; **131**: 47006 [PMID: 37027337 DOI: 10.1289/EHP11600]
16 **Liu W**, Li M, Guo H, Wei S, Xu W, Yan Y, Shi Y, Xu Z, Chang K, Wei G, Zhao S. Single-cell transcriptome analysis of liver immune microenvironment changes induced by microplastics in mice with non-alcoholic fatty liver. *Sci Total Environ* 2024; **912**: 168308 [PMID: 37977403 DOI: 10.1016/j.scitotenv.2023.168308]
17 **Cheng W**, Li X, Zhou Y, Yu H, Xie Y, Guo H, Wang H, Li Y, Feng Y, Wang Y. Polystyrene microplastics induce hepatotoxicity and disrupt

lipid metabolism in the liver organoids. *Sci Total Environ* 2022; **806**: 150328 [PMID: 34571217 DOI: 10.1016/j.scitotenv.2021.150328]
18 **Wang S**, Chen L, Shi X, Wang Y, Xu S. Polystyrene microplastics-induced macrophage extracellular traps contributes to liver fibrotic injury by activating ROS/TGF-β/Smad2/3 signaling axis. *Environ Pollut* 2023; **324**: 121388 [PMID: 36871749 DOI: 10.1016/j.envpol.2023.121388]
19 **Deng Y**, Zhang Y, Lemos B, Ren H. Tissue accumulation of microplastics in mice and biomarker responses suggest widespread health risks of exposure. *Sci Rep* 2017; **7**: 46687 [PMID: 28436478 DOI: 10.1038/srep46687]
20 **Lu Y**, Zhang Y, Deng Y, Jiang W, Zhao Y, Geng J, Ding L, Ren H. Uptake and Accumulation of Polystyrene Microplastics in Zebrafish (Danio rerio) and Toxic Effects in Liver. *Environ Sci Technol* 2016; **50**: 4054-4060 [PMID: 26950772 DOI: 10.1021/acs.est.6b00183]
21 **Wright SL**, Rowe D, Thompson RC, Galloway TS. Microplastic ingestion decreases energy reserves in marine worms. *Curr Biol* 2013; **23**: R1031-R1033 [PMID: 24309274 DOI: 10.1016/j.cub.2013.10.068]
22 **Brandts I**, Teles M, Tvarijonaviciute A, Pereira ML, Martins MA, Tort L, Oliveira M. Effects of polymethylmethacrylate nanoplastics on Dicentrarchus labrax. *Genomics* 2018; **110**: 435-441 [PMID: 30316739 DOI: 10.1016/j.ygeno.2018.10.006]
23 **Ye G**, Zhang X, Liu X, Liao X, Zhang H, Yan C, Lin Y, Huang Q. Polystyrene microplastics induce metabolic disturbances in marine medaka (Oryzias melastigmas) liver. *Sci Total Environ* 2021; **782**: 146885
24 **Wei L**, Liao P, Wu H, Li X, Pei F, Li W, Wu Y. Toxicological effects of cinnabar in rats by NMR-based metabolic profiling of urine and serum. *Toxicol Appl Pharmacol* 2008; **227**: 417-429 [PMID: 18164359 DOI: 10.1016/j.taap.2007.11.015]
25 **Luo T**, Wang C, Pan Z, Jin C, Fu Z, Jin Y. Maternal Polystyrene Microplastic Exposure during Gestation and Lactation Altered Metabolic Homeostasis in the Dams and Their F1 and F2 Offspring. *Environ Sci Technol* 2019; **53**: 10978-10992 [PMID: 31448906 DOI: 10.1021/acs.est.9b03191]
26 **Wang C**, Hou M, Shang K, Wang H, Wang J. Microplastics (Polystyrene) Exposure Induces Metabolic Changes in the Liver of Rare Minnow (Gobiocypris rarus). *Molecules* 2022; **27** [PMID: 35163849 DOI: 10.3390/molecules27030584]
27 **Tataranni PA**, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E. Effects of glucocorticoids on energy metabolism and food intake in humans. *Am J Physiol* 1996; **271**: E317-E325 [PMID: 8770026 DOI: 10.1152/ajpendo.1996.271.2.E317]
28 **Sheng S**, Han N, Wei Y, Wang J, Han W, Xing B, Xing M, Zhang W. Liver Injury Induced by Exposure to Polystyrene Microplastics Alone or in Combination with Cadmium in Mice Is Mediated by Oxidative Stress and Apoptosis. *Biol Trace Elem Res* 2023 [PMID: 37736782 DOI: 10.1007/s12011-023-03835-5]
29 **Li S**, Shi M, Wang Y, Xiao Y, Cai D, Xiao F. Keap1-Nrf2 pathway up-regulation *via* hydrogen sulfide mitigates polystyrene microplastics induced-hepatotoxic effects. *J Hazard Mater* 2021; **402**: 123933 [PMID: 33254827 DOI: 10.1016/j.jhazmat.2020.123933]
30 **Hu Q**, Wang H, He C, Jin Y, Fu Z. Polystyrene nanoparticles trigger the activation of p38 MAPK and apoptosis *via* inducing oxidative stress in zebrafish and macrophage cells. *Environ Pollut* 2021; **269**: 116075 [PMID: 33316494 DOI: 10.1016/j.envpol.2020.116075]
31 **Pan L**, Yu D, Zhang Y, Zhu C, Yin Q, Hu Y, Zhang X, Yue R, Xiong X. Polystyrene microplastics-triggered mitophagy and oxidative burst *via* activation of PERK pathway. *Sci Total Environ* 2021; **781**: 146753 [DOI: 10.1016/j.scitotenv.2021.146753]
32 **Mu Y**, Sun J, Li Z, Zhang W, Liu Z, Li C, Peng C, Cui G, Shao H, Du Z. Activation of pyroptosis and ferroptosis is involved in the hepatotoxicity induced by polystyrene microplastics in mice. *Chemosphere* 2022; **291**: 132944 [PMID: 34793849 DOI: 10.1016/j.chemosphere.2021.132944]
33 **Zhong G**, Rao G, Tang L, Wu S, Tang Z, Huang R, Ruan Z, Hu L. Combined effect of arsenic and polystyrene-nanoplastics at environmentally relevant concentrations in mice liver: Activation of apoptosis, pyroptosis and excessive autophagy. *Chemosphere* 2022; **300**: 134566 [PMID: 35413363 DOI: 10.1016/j.chemosphere.2022.134566]
34 **Kaloyianni M**, Bobori DC, Xanthopoulou D, Malioufa G, Sampsonidis I, Kalogiannis S, Feidantsis K, Kastrinaki G, Dimitriadi A, Koumoundouros G, Lambropoulou DA, Kyzas GZ, Bikiaris DN. Toxicity and Functional Tissue Responses of Two Freshwater Fish after Exposure to Polystyrene Microplastics. *Toxics* 2021; **9** [PMID: 34822680 DOI: 10.3390/toxics9110289]
35 **Missawi O**, Venditti M, Cappello T, Zitouni N, Marco G, Boughattas I, Bousserrhine N, Belbekhouche S, Minucci S, Maisano M, Banni M. Autophagic event and metabolomic disorders unveil cellular toxicity of environmental microplastics on marine polychaete Hediste diversicolor. *Environ Pollut* 2022; **302**: 119106 [PMID: 35248622 DOI: 10.1016/j.envpol.2022.119106]
36 **Wang S**, Wu H, Shi X, Wang Y, Xu S. Polystyrene microplastics with different sizes induce the apoptosis and necroptosis in liver through the PTEN/PI3K/AKT/autophagy axis. *Sci Total Environ* 2023; **899**: 165461 [PMID: 37451460 DOI: 10.1016/j.scitotenv.2023.165461]
37 **Yu P**, Liu Z, Wu D, Chen M, Lv W, Zhao Y. Accumulation of polystyrene microplastics in juvenile Eriocheir sinensis and oxidative stress effects in the liver. *Aquat Toxicol* 2018; **200**: 28-36 [PMID: 29709883 DOI: 10.1016/j.aquatox.2018.04.015]
38 **Silvestre F**. Signaling pathways of oxidative stress in aquatic organisms exposed to xenobiotics. *J Exp Zool A Ecol Integr Physiol* 2020; **333**: 436-448 [PMID: 32216128 DOI: 10.1002/jez.2356]
39 **Zhao L**, Shi W, Hu F, Song X, Cheng Z, Zhou J. Prolonged oral ingestion of microplastics induced inflammation in the liver tissues of C57BL/6J mice through polarization of macrophages and increased infiltration of natural killer cells. *Ecotoxicol Environ Saf* 2021; **227**: 112882 [PMID: 34700168 DOI: 10.1016/j.ecoenv.2021.112882]
40 **Ma S**, Xiao Y, Zhang X, Xu Y, Zhu K, Zhang K, Li X, Zhou H, Chen G, Guo X. Dietary exposure to polystyrene microplastics exacerbates liver damage in fulminant hepatic failure *via* ROS production and neutrophil extracellular trap formation. *Sci Total Environ* 2024; **907**: 167403 [PMID: 37820799 DOI: 10.1016/j.scitotenv.2023.167403]
41 **Diehl KL**, Vorac J, Hofmann K, Meiser P, Unterweger I, Kuerschner L, Weighardt H, Förster I, Thiele C. Kupffer Cells Sense Free Fatty Acids and Regulate Hepatic Lipid Metabolism in High-Fat Diet and Inflammation. *Cells* 2020; **9** [PMID: 33050035 DOI: 10.3390/cells9102258]
42 **Rudolph J**, Völkl M, Jérôme V, Scheibel T, Freitag R. Noxic effects of polystyrene microparticles on murine macrophages and epithelial cells. *Sci Rep* 2021; **11**: 15702 [PMID: 34344948 DOI: 10.1038/s41598-021-95073-9]
43 **Prata JC**. Microplastics and human health: Integrating pharmacokinetics. *Crit Rev Environ Sci Technol* 2023; **53**: 1489-1511 [DOI: 10.1080/10643389.2023.2195798]
44 **Yin K**, Wang D, Zhang Y, Lu H, Hou L, Guo T, Zhao H, Xing M. Polystyrene microplastics promote liver inflammation by inducing the formation of macrophages extracellular traps. *J Hazard Mater* 2023; **452**: 131236 [PMID: 36958159 DOI: 10.1016/j.jhazmat.2023.131236]
45 **Huang H**, Hou J, Liao Y, Wei F, Xing B. Polyethylene microplastics impede the innate immune response by disrupting the extracellular matrix and signaling transduction. *iScience* 2023; **26**: 107390 [PMID: 37554443 DOI: 10.1016/j.isci.2023.107390]
46 **Li L**, Xu M, He C, Wang H, Hu Q. Polystyrene nanoplastics potentiate the development of hepatic fibrosis in high fat diet fed mice. *Environ Toxicol* 2022; **37**: 362-372 [PMID: 34755918 DOI: 10.1002/tox.23404]

47 **Shen R**, Yang K, Cheng X, Guo C, Xing X, Sun H, Liu D, Liu X, Wang D. Accumulation of polystyrene microplastics induces liver fibrosis by activating cGAS/STING pathway. *Environ Pollut* 2022; **300**: 118986 [PMID: 35167931 DOI: 10.1016/j.envpol.2022.118986]

48 **Sun J**, Qu H, Ali W, Chen Y, Wang T, Ma Y, Yuan Y, Gu J, Bian J, Liu Z, Zou H. Co-exposure to cadmium and microplastics promotes liver fibrosis through the hemichannels -ATP-P2X7 pathway. *Chemosphere* 2023; **344**: 140372 [PMID: 37802476 DOI: 10.1016/j.chemosphere.2023.140372]

49 **Horvatits T**, Tamminga M, Liu B, Sebode M, Carambia A, Fischer L, Püschel K, Huber S, Fischer EK. Microplastics detected in cirrhotic liver tissue. *EBioMedicine* 2022; **82**: 104147 [PMID: 35835713 DOI: 10.1016/j.ebiom.2022.104147]

50 **Dong R**, Zhou C, Wang S, Yan Y, Jiang Q. Probiotics ameliorate polyethylene microplastics-induced liver injury by inhibition of oxidative stress in Nile tilapia (Oreochromis niloticus). *Fish Shellfish Immunol* 2022; **130**: 261-272 [PMID: 36122639 DOI: 10.1016/j.fsi.2022.09.022]

51 **Lu L**, Wan Z, Luo T, Fu Z, Jin Y. Polystyrene microplastics induce gut microbiota dysbiosis and hepatic lipid metabolism disorder in mice. *Sci Total Environ* 2018; **631-632**: 449-458 [PMID: 29529433 DOI: 10.1016/j.scitotenv.2018.03.051]

52 **Jin Y**, Xia J, Pan Z, Yang J, Wang W, Fu Z. Polystyrene microplastics induce microbiota dysbiosis and inflammation in the gut of adult zebrafish. *Environ Pollut* 2018; **235**: 322-329 [PMID: 29304465 DOI: 10.1016/j.envpol.2017.12.088]

53 **Okamura T**, Hamaguchi M, Hasegawa Y, Hashimoto Y, Majima S, Senmaru T, Ushigome E, Nakanishi N, Asano M, Yamazaki M, Sasano R, Nakanishi Y, Seno H, Takano H, Fukui M. Oral Exposure to Polystyrene Microplastics of Mice on a Normal or High-Fat Diet and Intestinal and Metabolic Outcomes. *Environ Health Perspect* 2023; **131**: 27006 [PMID: 36821708 DOI: 10.1289/EHP11072]

54 **Lv W**, Shen Y, Xu S, Wu B, Zhang Z, Liu S. Underestimated health risks: Dietary restriction magnify the intestinal barrier dysfunction and liver injury in mice induced by polystyrene microplastics. *Sci Total Environ* 2023; **898**: 165502 [PMID: 37451458 DOI: 10.1016/j.scitotenv.2023.165502]

55 **Luo T**, Wang D, Zhao Y, Li X, Yang G, Jin Y. Polystyrene microplastics exacerbate experimental colitis in mice tightly associated with the occurrence of hepatic inflammation. *Sci Total Environ* 2022; **844**: 156884 [PMID: 35752249 DOI: 10.1016/j.scitotenv.2022.156884]

56 **Zheng H**, Wang J, Wei X, Chang L, Liu S. Proinflammatory properties and lipid disturbance of polystyrene microplastics in the livers of mice with acute colitis. *Sci Total Environ* 2021; **750**: 143085 [PMID: 33182181 DOI: 10.1016/j.scitotenv.2020.143085]

57 **Hirt N**, Body-Malapel M. Immunotoxicity and intestinal effects of nano- and microplastics: a review of the literature. *Part Fibre Toxicol* 2020; **17**: 57 [PMID: 33183327 DOI: 10.1186/s12989-020-00387-7]

58 **Zhao WG**, Tian YM, Zhao P, Zhao LA, Jin C. [Research Progress on Trojan-horse Effect of Microplastics and Heavy Metals in Freshwater Environment]. *Huan Jing Ke Xue* 2023; **44**: 1244-1257 [PMID: 36922186 DOI: 10.13227/j.hjkx.202202118]

59 **Wang Q**, Chen G, Tian L, Kong C, Gao D, Chen Y, Junaid M, Wang J. Neuro- and hepato-toxicity of polystyrene nanoplastics and polybrominated diphenyl ethers on early life stages of zebrafish. *Sci Total Environ* 2023; **857**: 159567 [PMID: 36272476 DOI: 10.1016/j.scitotenv.2022.159567]

60 **Menéndez-Pedriza A**, Jaumot J, Bedia C. Lipidomic analysis of single and combined effects of polyethylene microplastics and polychlorinated biphenyls on human hepatoma cells. *J Hazard Mater* 2022; **421**: 126777 [PMID: 34364209 DOI: 10.1016/j.jhazmat.2021.126777]

61 **Luo T**, Weng Y, Huang Z, Zhao Y, Jin Y. Combined hepatotoxicity of imidacloprid and microplastics in adult zebrafish: Endpoints at gene transcription. *Comp Biochem Physiol C Toxicol Pharmacol* 2021; **246**: 109043 [PMID: 33862234 DOI: 10.1016/j.cbpc.2021.109043]

62 **Cheng W**, Zhou Y, Xie Y, Li Y, Zhou R, Wang H, Feng Y, Wang Y. Combined effect of polystyrene microplastics and bisphenol A on the human embryonic stem cells-derived liver organoids: The hepatotoxicity and lipid accumulation. *Sci Total Environ* 2023; **854**: 158585 [PMID: 36089014 DOI: 10.1016/j.scitotenv.2022.158585]

63 **Liang S**, Luo Y, Yi J, Feng L, Xu M, Yao R. Toxicity of microplastics and plastic additive co-exposure in liver Disse organoids from healthy donors and patient-derived induced pluripotent stem cells. 2022 Preprint. Available from: bioRxiv:2022.2009.2012.506301 [DOI: 10.1101/2022.09.12.506301]

64 **Ece E**, Hacıosmanoğlu N, Inci F. Microfluidics as a Ray of Hope for Microplastic Pollution. *Biosensors (Basel)* 2023; **13** [PMID: 36979544 DOI: 10.3390/bios13030332]

65 **Zare RN**, Kim S. Microfluidic platforms for single-cell analysis. *Annu Rev Biomed Eng* 2010; **12**: 187-201 [PMID: 20433347 DOI: 10.1146/annurev-bioeng-070909-105238]

66 **Liu L**, Zhang QH, Li RT. In Situ and Individual-Based Analysis of the Influence of Polystyrene Microplastics on Escherichia coli Conjugative Gene Transfer at the Single-Cell Level. *Environ Sci Technol* 2023; **57**: 15936-15944 [PMID: 37801563 DOI: 10.1021/acs.est.3c05476]

67 **Zarus GM**, Muianga C, Brenner S, Stallings K, Casillas G, Pohl HR, Mumtaz MM, Gehle K. Worker studies suggest unique liver carcinogenicity potential of polyvinyl chloride microplastics. *Am J Ind Med* 2023; **66**: 1033-1047 [PMID: 37742097 DOI: 10.1002/ajim.23540]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com