

MINI REVIEW

# Microbial gut dysbiosis induced by xenobiotics in model organisms and the relevance of experimental criteria: a minireview

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## Abstract

The gut microbiota is a dynamic ecosystem involved in multiple physiological processes that affect host health. Several factors affect intestinal microbial communities including dietary exposure to xenobiotics, which is highly concerning due to their widespread distribution. Current knowledge of this topic comes from culture-dependent methods, 16S rRNA amplicon fingerprinting, and metagenomics, but a standardised procedures framework remains lacking. This minireview integrates 45 studies from a systematic search using terms related to gut microbiota and its disruption. Only publications encompassing dietary-oral exposure and experimental gut microbiota assessments were included. The results were divided and described according to the biological model used and the disruption observed in the gut microbiota. An overall dysbiotic effect was unclear due to the variety of contaminants and hosts evaluated and the experimental gaps between publications. More standardised experimental designs, including WGS and physiological tests, are needed to establish how a particular xenobiotic can alter the gut microbiota and how the results can be extrapolated.

**Keywords:** Xenobiotics; gut dysbiosis; gut microbiota; NGS sequencing

## Dietary exposure to xenobiotics in food and water

The gut microbiota maintains physiological processes that promote host health (Ayres, 2017). A typical vertebrate gastrointestinal tract contains an average of  $10^{13}$  microbial cells and approximately 3,000 microbial species in total (Li et al., 2014; Sender et al., 2016). The microorganisms that inhabit the intestine are classified into four major groups (ie. archaea, bacteria, viruses, and fungi) and organised into functional communities that vary in density and structure along the digestive tract (Hiippala et al., 2018; Milani et al., 2017). The variation among gut microbial communities could be associated to the function of the microbiota, which expresses more than 3.3 million genes related to metabolic regulation, biotransformation, nutrient absorption, molecule biosynthesis, and the modulation of immune responses and behaviour (Claus et al., 2016; Qin et al., 2012). Thus, gut microbiota functions are fundamental to the well-being of host organisms, yet all microbial communities are unique. This

uniqueness is established from birth and can be altered through life due to the diet, immune system, genotype, age, and lifestyle of the host and by external factors such as habitat characteristics and xenobiotic exposure (Jin et al., 2017).

Xenobiotics are chemical substances of synthetic origin that are generally not present in the environment (Abdelsalam et al., 2020; Stefanac et al., 2021). However, this term is flexible and can also include endobiotics and other naturally occurring substances if their concentrations are higher than average (Soucek, 2011). These compounds, such as environmental contaminants and pharmaceuticals, have been identified in various foods and interact with gut microbes (Garcia and Gotah, 2017; Koppel et al., 2017). Introducing xenobiotics into the environment due to natural and anthropogenic processes has resulted in growing concerns regarding their impacts on human and animal health.

The levels of residues in food items are beyond the scope of this study but may affect consumers by inducing allergic reactions, hormonal imbalances, and bacterial resistance to antibiotics (Pugajeva et al., 2019). Contaminated water also constitutes another source of xenobiotic exposure (Amoatey and Baawain, 2019). However, while the toxicity of xenobiotics and their effects on human health have been extensively reported (Rodríguez et al., 2021), evidence indicates that the toxicity of non-target gut microbiota due to dietary exposure could also affect host health (Claus et al., 2016; Jin et al., 2017). Due to the conserved metabolic pathways among animal models, their use in toxicological studies allows us to extrapolate the measurable effects of xenobiotic exposure to humans (Hansen, 2012). However, evaluations of the effects of xenobiotics on the intestinal microbiota must consider multiple factors, including the genetic individual variability of the host given that genetic variants and associated gene expression could control the composition of the gut microbiota (Bubier et al., 2021). Therefore, using model species in pre-clinical trials that use translational approaches to evaluate xenobiotic effects in the gastrointestinal tract could provide novel insights due to the integration of pathologies (Johnson and Greenwood-Van Meerveld, 2017; Robinson et al., 2019).

To summarise the known interactions between xenobiotics and the intestinal microbiota, we performed a systematic search in the PubMed database. Published articles were searched with the terms “effects,” “xenobiotics,” “gut microbiota,” “ecotoxicology,” “microbiota,” and “metagenomics” in different combinations. In all, 672 results were returned. Experimental approaches are required to assess possible changes in the composition and function of the intestinal microbiota (Franklin and Ericsson, 2017; Hörmannspurger et al., 2015) and microbiota dynamics (Ranjan et al., 2016). Thus, we selected the 77 papers encompassing experimental exposure assessments, of which 45 articles deal exclusively with dietary-oral exposure and gut microbiota assessments (Table 1). Our search indicated that although the effects of xenobiotics are diverse, dysbiosis patterns, which are recurring changes in particular microbial groups due to exposure to xenobiotics, are present that may be related to the experimental organism and its core microbiota (Figure 1) such as (1) gut dysbiosis in the murine model, (2) gut dysbiosis in pollinators, (3) gut dysbiosis in fish models (eg. zebrafish and tilapia), and (4) some relevant cases of gut dysbiosis in poultry and insects. Moreover, when analysing studies with different experimental models, similar dysbiosis patterns were revealed that were mainly described using the 16S sequencing approach. In general, if these patterns are permanent or persist for extended periods, they may correlate with pathologies such as metabolic syndrome and obesity (Kocelak et al., 2013; Turnbaugh et al., 2006; Verdam et al., 2013) and cardiovascular (Lam et al., 2012, 2016) and gastrointestinal diseases (Becker et al., 2015; Gevers et al., 2014). However, microbial communities have an intrinsic ability to adapt to adverse conditions and recover without severe consequences to the host (Weiss and Hennet, 2017). In this regard, research on dietary xenobiotic exposure is highly relevant due to the underlying relationship between the gut microbiota and host health (Jin et al., 2017).

### Dysbiosis and gut physiology

A well-balanced gut ecosystem promotes feedback among the microbial species that reside within, which in turn regulates mucous epithelial immunity. For instance, anti-bacterial peptides secreted by mucous

**Table 1.** Overview of the main features of the studies that have evaluated gut dysbiosis due to xenobiotic dietary-oral exposure.

Xenobiotic	Methodology	Exposure period (d)	Mi alterations	ERC	HH evaluation	Me evaluation	GBI evaluation	References
Murine model								
Aflatoxin B1	16S (V3, V4)	28	No consistent effect patterns	-	-	-	-	Wang et al., 2016
Aflatoxin B1	16S (V3, V4)	28	↑ <i>Alloprevotella</i> spp. ↑ Firmicutes ↑ Anaerotruncus ↑ Clostridiales *	X	-	-	-	Liew et al., 2019
Arsenic	16S (V4)	28	↑ <i>Akkermansia</i> ↓ <i>Dorea</i> (females); ↑ (males)	-	-	-	-	Chi et al., 2016
Arsenic	16S (V4)	42	↓ <i>Adlercreutzia</i> ↑ <i>Akkermansia</i> ↑ <i>Clostridium</i> ↓ <i>Epulopiscium</i> *	X	X	X	-	Gaulke et al., 2018
Benzo-a-pyrene	16S (V4)	28	↑ Bacteroidaceae ↑ Porphyromonadaceae ↑ Paraprevotellaceae ↓ Lactobacillaceae *	-	X	-	-	Rivière et al., 2016
Bisphenol A	GULDA (qPCR)	28	↓ Firmicutes	-	X	X	X	Malaisé et al., 2017
Cadmium, lead	16S (V5,V6)	56	↓ Lachnospiraceae ↑ Erysipelotrichaceae ↑ <i>Turicibacter</i> ↑ <i>Barneselia</i> *	X	-	-	-	Breton et al., 2013a
Glyphosate	Cultured methods	SC: 42, C: 84	↓ Bacteroidetes ↓ Firmicutes ↓ <i>Corynebacterium</i> ↓ <i>Lactobacillus</i>	X	X	-	-	Aitbali et al., 2018

Table 1. Continued

Glyphosate	16S (V2, V3, V4, V6, V7, V8, V9)	673	↑ Bacteroidetes family S24-7 ↓ Lactobacillaceae	-	-	-	-	Lozano et al., 2018
Glyphosate	16S(V3, V4)	126	↑ <i>Prevotella</i> ↓ <i>Lactobacillus</i>	X	-	-	-	Mao et al., 2018
Glyphosate	16S(V3)	14	Very limited effects	-	X	X	-	Nielsen et al., 2018a
Glyphosate	16S (V3, V4)	34	↑ Bacteroidetes ↓ Firmicutes	X	X	X	-	Dechartres et al., 2019
Glyphosate	16S (V3, V4)	35	↓ Firmicutes ↓ <i>Lactobacillus</i> ↑ <i>Fusobacteria</i> ↑ <i>Ruminococcus_1</i> *	-	X	X	-	Tang et al., 2020
Glyphosate	Shotgun	90	↑ <i>Eggerthella</i> spp. ↑ <i>Shinella zoogloeoides</i> ↑ <i>Acinetobacter johnsonii</i> ↑ <i>Akkermansia municipihila</i>	X	X	X	-	Mesnage et al., 2021
Manganese	16S (V4)	91	↑ Firmicutes (males); ↓ (females) ↓ Bacteroidetes (males)	-	X	X	-	Chi et al., 2017
Methyl mercury	16S (V3, V4)	1 dose	↓ Bacteroidetes ↓ Proteobacteria ↑ Firmicutes	-	X	X	-	Lin et al., 2020
Methylimidazolium ionic liquids	16S (V4)	126	↓ <i>Parasutterella</i> ↑ Lachnospiracea ↑ <i>Coriobacteriaceae</i> spp.	X	X	X	-	Young et al., 2020
Neochamaejasmin A	16S (V4,V5)	90	↑ <i>Pseudoflavonifractor</i> ↑ Ruminococaceae ↑ <i>Lachnospira</i>	-	-	-	-	Yan et al., 2015
Perfluorooctane sulfonic acid	16S (V3, V4)	7	↑ Turicibacterales ↓ <i>Bacteroides acidifaciens</i> ↑ Cyanobacteria *	X	X	X	-	Lai et al., 2018

Table 1. Continued

Polybrominated diphenyl ethers	16S (V4)	4	↑ <i>Akkermansia muciphila</i> ↑ <i>Erysipelotrichia</i> ↑ <i>Allobaculum</i> spp. ↓ <i>Coriobacteriia</i> *	–	X	X	–	Li et al., 2018
Polybrominated diphenyl ethers	Transcriptomics	4	Metabolism enterotypes comparisons	–	X	–	–	Li et al., 2018
Silver NPs	16S (V4)	28	↑ Lachnospiraceae ↑ S24–7 ↓ Bacteroidetes	X	X	X	–	van den Brule et al., 2016
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Shotgun	LS: 92, RS: 30, SS: 28	↑ Enterobacteriaceae	X	–	–	–	Stedtfeld et al., 2017
Toxic metals	16S(V4)	5	↑ Proteobacteria (all except Cd) ↑ Verrucomicrobia (Cd, Co, Cr; ↓Ni) ↓ S24–7 (Ni) ↑ Enterobacteriaceae (Ni)	–	–	–	–	Richardson et al., 2018
Triazine	16S(V3, V4)	1 dose	↑ Firmicutes ↑ <i>Coriobacteriia</i> ↓ Lachnospiraceae ↓ Ruminococcaceae *	–	X	X	–	Zhan et al., 2018
Trichloroethylene	RT PCR	Uterus: 21, lactancy: 21, drinking water: 154 and 259	↓ Firmicutes ↓ Bacteroidetes ↑ <i>Lactobacillus</i> ↑ <i>Bifidobacterium</i>	X	X	X	–	Khare et al., 2019
Pollinators model								
Atrazine	16S (V4)	1 dose	↑ <i>Effusibacillus</i> ↑ <i>Serratia</i> spp. ↑ <i>Pseudomonas</i> spp. ↓ <i>Clostridium</i>	–	X	X	–	Wang et al., 2020

Table 1. Continued

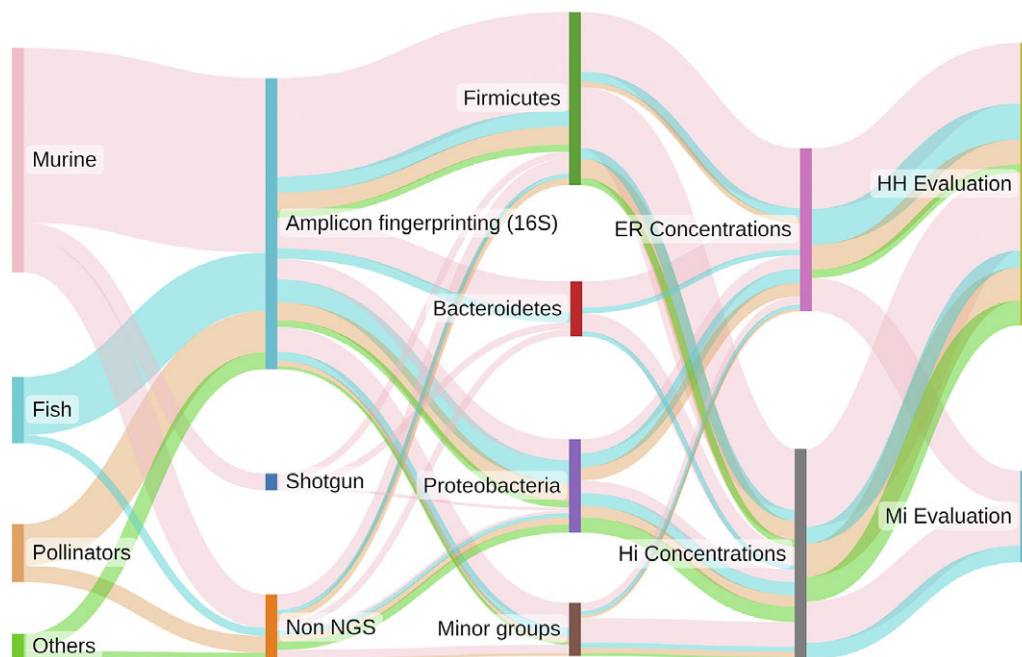
Chlorpyrifos	PCR with 16S rRNA primers	1 dose	<i>Lactobacillus plantarum</i> ISO metabolism	-	X	-	-	Daisley et al., 2018
Glyphosate	16S (V3, V4)	5	↑ Acidobacteria ↑ Gemmatimonadaceae ↑ Sphingobacteriales ↑ Thermoleophilia *	X	X	-	-	Dai et al., 2018
Glyphosate	qPCR	W: 5, NEWS: 2	↓ <i>Snodgrassella alvi</i> ↓ <i>Bifidobacterium</i> ↓ <i>Lactobacillus Firm-4</i> ↓ <i>Lactobacillus Firm-5</i> *	X	X	-	-	Motta et al., 2018
Glyphosate	qPCR	15	↓ <i>Snodgrassella alvi</i> ↓ <i>Gilliamella apicola</i> ↑ <i>Lactobacillus</i> spp.	-	X	X	-	Blot et al., 2019
Pesticides	16S	18	↓ <i>Lactobacillus</i> spp. ↓ <i>Bifidobacterium</i> spp. ↓ Alphaproteobacteria ↑ <i>Gilliamella apicola</i> *	-	X	-	-	Rouzé et al., 2019
Spinosad, cooper sulphate	16S(V4, V5)	1	↑ <i>Gilliamella</i>	X	X	X	-	Botina et al., 2019
Fish model								
Alpha-cypermethrin	16S	7	↑ Fusobacteria ↓ Proteobacteria	X	X	X	-	Cheng et al., 2022
Benzo [a] pyrene	16S (V3, V4)	15	↑ Firmicutes ↓ Proteobacteria	-	X	X	-	Xie et al., 2020
Carbendazim	16S (V3, V4)	21	↓ Bacteroidetes ↓ Firmicutes ↓ Proteobacteria	X	X	X	-	Bao et al., 2020
Dyethylhexyl phtalate	16S (V4, V5)	60	↓ Fusobacteria ↑ Proteobacteria ↓ Tenericutes	-	-	-	-	Buerger et al., 2020

Table 1. Continued

Methyl mercury	16S (V4)	30	↑ Xanthomonadaceae ↑ <i>Rhodobacter</i> ↑ Planctomycetes ↓ <i>Cetobacterium</i>	X	X	X	–	Nielsen et al., 2018b
Tebuconazole, difenoconazole	16S (V3, V4)	21	↑ Bacteroidetes ↑ Firmicutes ↑ Proteobacteria	–	X	X	–	Jiang et al., 2021
Tetracycline	16S (V3, V4)	60	↓ Bacteroidetes ↓ Firmicutes ↑ Proteobacteria	X	X	X	–	Keerthisinghe et al., 2020
TiO <sub>2</sub> NPs	Cultured methods	14	↓ <i>Aeromonas</i> spp. ↓ <i>Lactobacillus</i> spp. ↓ <i>Pseudomonas</i> spp.	X	X	X	–	Sherif et al., 2021
Water-soluble crude oil components + chemical dispersant	16S (V3, V4)	96 h	↓ Fusobacteria ↑ Proteobacteria	–	–	–	–	González-Penagos et al., 2020
Others								
Arsenic	16S (V4)	14	↑ <i>Bacillus</i> ↓ <i>Geobacter</i> ↑ <i>Ochrobactrum</i> ↓ <i>Staphylococcus</i> *	X	X	–	–	Wang et al., 2019
Cadmium	Transcriptomics	30	↑ Archaea ↓ Bacteria ↓ Eukaryotes ↓ Virus	–	X	–	–	Yang et al., 2018
Mercuric chloride	16S (V3, V4)	30, 60, 90	↑ Proteobacteria ↓ Spirochaetes ↑ Tenericutes	–	X	–	–	Zhou et al., 2020

Abbreviations: C, chronic; ERC, environmentally realistic concentrations; GBI, gut barrier integrity; HH, host health; LS, long-term study; m, mouse; Me, metabolites; Mi, microbiota; NEW, newly emerged workers; NPs, nanoparticles; r, rat; RS, recovery study; SC, sub-chronic; SS, short-term study; W, worker bees.

\*Other microbial groups changes were found.

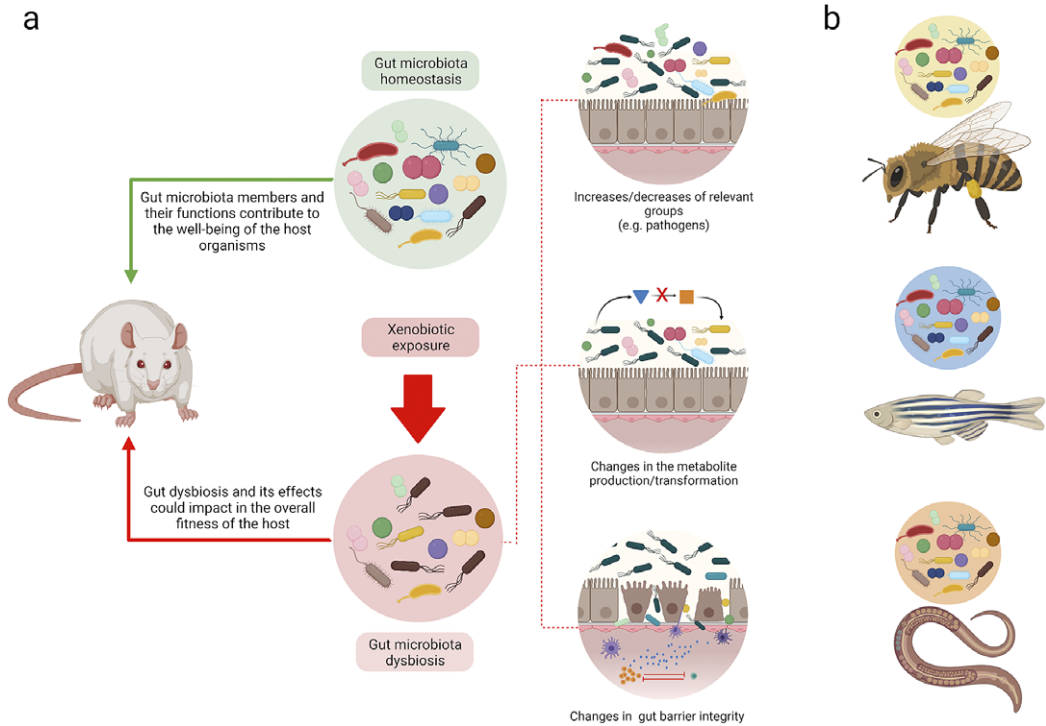


**Figure 1.** Relative frequencies of 45 studies with dietary-oral exposure and gut microbiota evaluations published between 2013 and 2022. Information on the kind of experimental organism, methodological approach to the microbiota evaluation, main bacterial groups that are affected after exposure, range of experimental concentrations (ER Concentration [environmentally realistic concentration] vs. Hi Concentration [high concentration when assessing action modes]), and evaluations of host health (HH Evaluation [host health evaluation] vs. Mi Evaluation [microbiota evaluation only]). The figure was made with sankeymatic.

membranes influence the composition of gut microbiota, and this communication is essential to maintain the integrity of the epithelial barrier and the immunological niche. However, xenobiotics and other antigens in food may interact with epithelial mucous and trigger pathological states associated with dysbiosis, which is defined as the loss of microbiota homeostasis that is characteristic of inflammatory, metabolic, neurological, and autoimmune diseases and disorders (DeGruttola et al., 2016). Changes in feedback processes may or may not induce inflammatory responses, although they can modify the permeability of the epithelial barrier and permit the translocation of bacteria from the intestinal lumen to the circulatory system. This disrupts cytokine production, T cell pro-inflammatory proliferation, and T cell anti-inflammatory inhibition, which provokes intestinal immunological niche dysfunction that ultimately results in a chronic inflammatory state within the host (Pagliari et al., 2017; Tilg et al., 2020).

Although epithelium-microbiota interactions that maintain homeostasis are highly complex, exposure to xenobiotics can result in distinctive dysbiotic patterns (Figure 2a). For instance, a decrease in the abundance of *Bifidobacterium* spp. and Firmicutes bacteria, particularly those of the Clostridiaceae family, precedes inflammatory conditions and may possibly play an important role in the development of obesity due to the overexpression of pro-inflammatory cytokines, which interrupts insulin signalling (Malaisé et al., 2017). These alterations lead to the reduction of anti-microbial activities and the disruption of IgA synthesis, a critical component that supports the integrity of the epithelial barrier. Additionally, xenobiotic-induced changes have been reported in the abundance of butyrate-producing bacteria, which are considered to be energy sources for epithelial cells in the colon that promote proliferation and differentiation (Weiss and Hennet, 2017). In this regard, members of the Lactobacillaceae family are reportedly the most affected by exposure to benzo- $\alpha$ -pyrene, glyphosate, and arsenic (Aitbali et al., 2018; Gaulke et al., 2018; Ribi re et al., 2016; Tang et al., 2020). Also,





**Figure 2.** Understanding homeostasis and dysbiosis in different biological models. (a) Summary of the loss of gut homeostasis due to xenobiotic exposure. The feedback between the gut microbiota and host could promote host health. Alternatively, at the onset of dysbiosis due to xenobiotic exposure, different mechanisms may be elicited that may result in different outcomes that affect the host. (b) Although gut microbiota studies have been performed with different species, extrapolating the results among them is not viable. Each model has its own genetic, metabolic, and gut microbiome particularities. The figure was made with Biorender.

changes in Bacteroidetes and Proteobacteria (Zhou et al., 2020) have also been associated with pro-inflammatory conditions that are similar to those observed with Paraprevotellaceae, Desulfovibrionaceae (Ribi re et al., 2016), and Enterobacteriaceae (Stedtfeld et al., 2017). Of note, few studies incorporate evaluations of metabolite and gut barrier integrity changes, and most of these only discuss these effects (Table 1).

Changes in the intestinal architecture constitute a primary focus of multiple experiments that have aimed to evaluate the effects of dietary xenobiotics at a systemic level. In a murine model, the modification of intestinal structures was related to different inflammatory states that were the result of polynuclear and inflammatory cell (IL-6, IL-6 $\beta$ ) infiltration due to oral methylmercury exposure (Lin et al., 2020). Furthermore, evidence of changes to epithelial tissues in regions of the small and large intestines have been reported with benzo[a]pyrene (Lin et al., 2020; Ribi re et al., 2016), in addition to reductions in villi height, modifications to the proportions between these structures, and changes in crypt depth due to glyphosate exposure (Tang et al., 2020). In the worst-case scenario, a full depletion of epithelial tissue has been reported (Ribi re et al., 2016). In poultry exposed to mercuric chloride, a complete absence of villi in some intestinal regions and cell infiltrations in the *stratum propri* zone associated with inflammatory effects have been found (Zhou et al., 2020). In addition to the intestines, the kidneys and liver have been evaluated with histological analyses, and evidence of glyphosate dose-dependent lesions has been found in the latter (Mesnage et al., 2021). These effects are similar to those observed in other biological models. However, dysbiosis patterns are unique for each model due to genetic, metabolic, and gut niche particularities (Figure 2b).

### Linking gut dysbiosis and physiological effects due to xenobiotics

The murine model has been widely used in pharmaceutical and medical research. Twenty-seven of the studies included in this review employed rodents (Table 1). However, when evaluating and analysing gut dysbiosis, some key aspects must be considered to better understand the processes involved. For instance, the inherent variability within the microbiomes of the same species, particularly with regard to resident microorganisms, depends on the physiology of the digestive system; therefore, the identification and standardisation of external factors capable of modifying microbial communities should be considered (Franklin and Ericsson, 2017; Hugenholtz and de Vos, 2018). In this sense, knowledge gaps also need to be considered. However, one of the main limitations appears to be that functional predictions of metabolic routes and affected genes are only possible at the in-silico level without a subsequent step to evaluate systemic effects. Complete studies should evaluate the general effects associated with gut dysbiosis using biochemical approaches to determine specific biomarkers and histopathology techniques and, if possible, to evaluate mechanistic approaches in terms of immunology, behaviour, and survival rates.

Only 6 of 45 papers included a biochemistry analysis of blood serum. In these experiments, molecules related to inflammatory processes were quantified, including inflammatory and neurotrophic factors (Lin et al., 2020), interleukins (Nielsen et al., 2018a), and C-reactive protein (van den Brule et al., 2016). In the same way, molecules associated with lipid metabolism (one of the most important routes affected by gut dysbiosis), adiponectin (Gaulke et al., 2018), and triglycerides (Lai et al., 2018) were determined and quantified. The results from these analyses allow xenobiotic concentrations in the bloodstream to be determined (Zhan et al., 2018). Histopathological techniques were used in 5 out of 45 studies. The intestine was the target organ in these approaches, and the main aim of these studies was to identify structural changes in different intestinal regions as well as the infiltration of inflammatory cells (Lin et al., 2020; Mesnage et al., 2021; Ribière et al., 2016; Tang et al., 2020; Zhou et al., 2020). Finally, some organism-level changes were considered in the experimental approaches such as behavioural changes due to the critical role of the gut–brain axis (Aitbali et al., 2018; Dechartres et al., 2019) and survival rates after exposure to xenobiotics (Lee et al., 2020; Motta et al., 2018; Wang et al., 2020). In the previous experiments, omics tools were used to explore these changes, including metabolomics to evaluate changes in gut and faeces metabolites (Chi et al., 2017; Lin et al., 2020; Nielsen et al., 2018b), transcriptomics (Wang et al., 2020; Yang et al., 2018), and proteomics (Li and Cui, 2018; Yang et al., 2018).

Only 7 of 45 studies in this review dealt with the effects of pesticides on pollinators (Blot et al., 2019; Botina et al., 2019; Dai et al., 2018; Daisley et al., 2018; Motta et al., 2018; Rouzé et al., 2019; Wang et al., 2020). This topic is of particular importance because the ecological roles of pollinators appear to be threatened by non-target exposure to xenobiotics (Cullen et al., 2019). Likewise, the prevalence of contaminants in water bodies highlights the importance of studies that assess the effects of using fishes as research models. In this study, eight publications employed fish models, of which most were zebrafish (Bao et al., 2020; Buerger et al., 2020; Cheng et al., 2022; González-Penagos et al., 2020; Jiang et al., 2021; Keerthisinghe et al., 2020; Sherif et al., 2021; Xie et al., 2020). In addition, other studies considered other organisms such as spiders (Yang et al., 2018), arthropods (Wang et al., 2019), and poultry (Zhou et al., 2020).

### *Gut dysbiosis in the murine model*

Most mammal studies that have assessed the impacts of xenobiotics on gut microbiota have been conducted in murine models. However, even if the same species is used in different studies, various biological factors could induce variability among responses. In addition, some responses have shown a pollutant-type dependency. Nevertheless, some evidence has emerged indicating possible patterns at the taxonomic level. This is the case of the Firmicutes phyla. In this phyla, changes in abundance that are mainly due to changes in the abundance of the Lachnospiraceae family have been associated with heavy metals (Breton et al., 2013b). Similarly, Lactobacillaceae abundance has shown responsiveness to exposure to methylmercury (Lin et al., 2020), benzo[a]pyrene (Ribière et al., 2016), glyphosate and its commercial formulations (Aitbali et al., 2018; Mao et al., 2018; Tang et al., 2020), and trichloroethylene

(Khare et al., 2019). Interestingly, these bacteria are essential for butyrate synthesis. Butyrate is related to gut barrier integrity and is a source of energy for epithelial cells in the colon (Silva et al., 2020).

In the previously mentioned studies (Aitbali et al., 2018; Khare et al., 2019; Lin et al., 2020; Tang et al., 2020), decreases in Firmicutes abundance were observed, whereas in experiments conducted with polybrominated diphenyl ethers (Li et al., 2018) and bisphenol A (Malaisé et al., 2017), increases in Firmicutes abundance were observed after exposure. Furthermore, Chi et al. (2017) demonstrated that changes in Firmicutes abundance were sex-dependent due to manganese exposure, with increases and decreases observed in males and females, respectively. Likewise, Lozano et al. (2018) described changes in Lactobacillaceae abundance associated with exposure to roundup, although they were only present in females. However, although several studies in murine models indicate changes in this phylum, Wang et al. (2016) reported that no significant changes in the abundance of this group were observed after exposure to aflatoxin B1. Similarly, the phylum Bacteroidetes also presents different outcomes depending on the exposure. Pollutants, such as trichloroethylene (Khare et al., 2019), aflatoxin B1 (Liew et al., 2019), methylmercury (Lin et al., 2020), benzo[a]pyrene (Ribi re et al., 2016), and glyphosate (Dechartres et al., 2019; Nielsen et al., 2018a), could promote positive or negative changes in Bacteroidetes abundance that are mainly associated with changes in *Bacteroides* abundance. It is worth noting that both Firmicutes and Bacteroidetes play important roles within mammalian microbiota ecosystems. It has been reported that imbalances in their abundance have been involved in different intestinal disorders while also being associated with an obesogenic phenotype (Buerger et al., 2020; Lozano et al., 2018).

Dysbiotic changes may also be linked to physiological effects that affect the overall fitness of the host, with manifestations such as changes in body composition, survival rates, immune conditions, metabolic production, and behaviour as well as additional transgenerational effects. Changes in metabolism may be identified through blood biochemistry and metabolomics analyses, which can also help to identify biotransformations of target xenobiotics and the synthesis of enzymes and transport molecules such as the ones associated with bile acid metabolism (Li et al., 2018). Metabolic changes can also be identified by the production of neurotransmitters such as serine, GABBA, L-tyrosine, and aspartic acid (Lin et al., 2020). Other impacts of xenobiotic exposure have been associated with changes in oxidative stress and glutathione (GSH), glutathione peroxidase (GSH-Px), and adiponectin levels (Gaulke et al., 2018; Tang et al., 2020). Also, studies evaluating inflammatory processes have reported changes in the production of metabolites, such as IL-33, IFN-gamma, and IL-3, and changes in cytokine levels (eg. IL-12, IL-17F, GM-CSF, eotaxin, and MIP-1- $\alpha$  chemokine) that are directly associated with intestinal immunoregulation (Khare et al., 2019). Furthermore, exposure to glyphosate-based herbicides promotes changes in the gut microbiota that result in anxiogenic and depressive behaviour in murine models (Aitbali et al., 2018), which confirms that chemical pollutants can alter animal social behaviour at individual and group levels (Michelangeli et al., 2022). Moreover, exposure to bisphenol A induced a significant and gradual increase in weight over the experimental period, even without changes in the food intake rate (Malais e et al., 2017). This outcome is one of the main reasons to classify bisphenol A as an obesogen toxicant and thus one of the most studied endocrine-disrupting xenobiotics (Chiu et al., 2020). Body composition measurements are determining factors that must be considered when attempting to understand the overall impact that a xenobiotic compound may have on an organism.

### ***Gut dysbiosis in insect pollinators***

Worldwide, ecotoxicological research on pollinating insects arises from their inevitable chronic exposure to pesticides and the fundamental roles they play within ecosystems (Cullen et al., 2019). Pollinating insects play critical roles in plant reproduction cycles, which can influence biodiversity and ecosystem services with impacts that transcend agriculture (Lautenbach et al., 2012; Potts et al., 2016). Recent studies have shown the effects on gut microbiota due to exposure to glyphosate (Blot et al., 2019; Dai et al., 2018; Motta et al., 2018), spinosad and cooper sulphate (Botina et al., 2019), chlorpyrifos (Daisley et al., 2018), atrazine (Wang et al., 2020), fipronil, imidacloprid, thiamethoxam, and coumaphos (Rouz e et al., 2019). However, similar

to what has been observed with murine models, major changes in the abundance of Proteobacteria, Firmicutes, and Actinobacteria have been reported, although patterns are difficult to identify given that responses are likely dependent on exposure conditions. For instance, glyphosate exposure has been linked to microbiota changes, such as those observed within the Actinobacteria phylum that are characterised by a reduced abundance of *Bifidobacterium* spp. (Blot et al., 2019), or changes in Firmicutes abundance that are mostly driven by the increased abundance of Clostridia, Ruminococcaceae (Dai et al., 2018), *Staphylococcus* spp., and *Lactobacillus* spp. (Blot et al., 2019). Motta et al. (2018) reported a decrease in the abundance of *Lactobacillus* spp. In this sense, it is unclear if the role of *Lactobacillus* spp. is just as relevant as it is in the murine model. However, these studies are mostly based on 16S rRNA (Dai et al., 2018), and thus fail to include detailed taxonomic identifications or even functional inferences. Despite these limitations, when the studies have also included qPCR techniques, they have been able to identify specific species of interest. For example, within the Proteobacteria phylum, it was observed that glyphosate exposure promoted a decrease in the abundance of *Snodgrassella alvi*, which is a characteristic member of the core microbiota of bees (Blot et al., 2019; Motta et al., 2018). Remarkably, bees with conventional microbiota that have been exposed to glyphosate exhibited an overall susceptibility to opportunistic pathogens (Motta et al., 2018). Other studies have reported changes in the abundance of *Gilliamella apicola*, a dominant gut Gamma-proteobacteria in honey bees and bumblebees, after exposure to pesticides such as fipronil, spinosad, and glyphosate (Blot et al., 2019; Botina et al., 2019; Motta et al., 2018; Rouzé et al., 2019).

Aside from the direct effects on host fitness, such as dose-dependent survival rates, Wang et al. (2020) reported that changes in gut microbiota derived from atrazine exposure could exert inherited effects on the progeny, which suggests that legacy microbiota could provide protective effects due to the enrichment of *Serratia marcescens* and *Pseudomonas protegens*, which are associated with atrazine metabolism. In this sense, research using biological models with short reproductive cycles, like insect pollinators, allows for the crucial aspects of the overall effects of a particular xenobiotic to be assessed at higher organisational levels. Examples of these assessments include survival rate analysis, linking dysbiosis with disease and xenobiotic exposure, and evaluating transgenerational effects due to inherited microbiota with population-level consequences.

### **Gut dysbiosis in fishes**

Although there is an increase in publications related to gut microbiota dysbiosis, studies using aquatic organisms, such as fishes or amphibians, are scarce compared to murine model investigations (Evariste et al., 2019). Among aquatic model organisms used in dysbiosis experiments, fish models stand out, particularly the zebrafish model. Zebrafish are particularly interesting models due to the homology of their genome and intestinal structure and functionality with those of mammals (Howe et al., 2013; Lickwar et al., 2017). Zebrafish have been used to evaluate changes in microbial richness and diversity, the general structure of the microbiota, and possible disruptions in the intestinal tract due to aquatic exposure to environmental pollutants (Zhong et al., 2022). For instance, carbendazim exposure elicited decreases in the abundance of Firmicutes, Bacteroidetes, and some members of  $\alpha$ - and  $\gamma$ -Proteobacteria (Bao et al., 2020), which is similar to what has been reported with tetracycline exposure (Keerthisinghe et al., 2020). In contrast with these changes, exposure to diethylhexyl phthalate and benzo[a]pyrene increased the abundance of Proteobacteria and Firmicutes, respectively (Buerger et al., 2020; Xie et al., 2020). Another group with significant changes in abundance is Fusobacteria. In this taxa, exposure to  $\alpha$ -cypermethrin promoted an increase of specific taxa (Cheng et al., 2022), in contrast to the observations described by Buerger et al. (2020) and Jiang et al. (2021) in which exposure to diethylhexyl phthalate and triazole fungicides decreased the abundance of Fusobacteria.

As with the murine model, different authors have indicated that changes in the Firmicutes:Bacteroidetes ratio in the gut microbiota serve as an obesity biomarker in zebrafish. These studies detected changes in body weight after exposure to carbendazim (Bao et al., 2020) and diethylhexyl phthalate (Buerger et al., 2020). Also, in the study conducted by Xie et al. (2020), the associations between zebrafish

gut microbiota and inflammatory responses after benzo[a]pyrene exposure were described, emphasising increases of IL1 $\beta$  cytokine, IL6, IL8, and Ifn1 protein, which could be related to the inherent genetic background of the zebrafish intestine.

Another fish species widely used in xenobiotic experiments is the Nile tilapia (*Oreochromis niloticus*). However, only Sherif et al. (2021) explored changes within the *Aeromonas*, *Lactobacillus*, and *Pseudomonas* genera after exposure to titanium dioxide nanoparticles, which induced higher mortalities when fish were challenged with *Aeromonas hydrophila*. However, the study relies on traditional bacterial counting and not on molecular approaches or technologies.

## Gut microbiota study criteria

### *Experimental considerations*

An experimental design for assessing alterations in the gut microbiota must consider key aspects to produce accurate results. Among these is establishing the proper population size for statistical purposes. However, socio-ecological restrictions must be also considered to determine the proper group size within a specific space (Shülke and Ostner, 2012). This is crucial in rodents and other social species, such as zebrafish, which are gregarious animals that establish complex relationships within their groups (Green, 1966). These dynamics, specifically any dominance hierarchy, play an essential role in feeding behaviour and could affect stress responses, as some of the main characteristics of dominance include chasing, fighting, and avoidance behaviour (Mondragón et al., 1987). The feeding strategy is another relevant variable that must be defined in these studies, especially considering that subordinate organisms take longer to feed than dominant organisms. In rodents, *ad libitum* feeding is typically employed. However, this method makes it difficult to control xenobiotic dosing, and differences in feeding could also influence the susceptibility to these compounds (Hart et al., 1995). An alternative that compensates for ingestion differences, is timed feeding, which grants animals illimitable access to food in a specific period and considers the social dynamics within a group (Carey and Merrill, 2012). These feeding periods can be flexible and may depend on the experimental species and their biological rhythms. Timed feeding can synchronise many behavioural variables such as anticipatory food activity (Sato et al., 2006). Dietary exposure to xenobiotics must also be addressed. For instance, in studies using murine models, ensuring that the proper concentration of xenobiotics is supplied is achieved by orally gavaged dosing, but employing this method may not be feasible with other organisms such as fish and invertebrates. Nevertheless, it is important to consider possible stress arising from the methodology employed.

Other considerations must also be considered when establishing a dysbiosis experimental design. The sampling protocol for gut content must be standardised to yield comparable results, as the composition and dynamics of the microbiota depend on specific target (tissue and/or organ) conditions such as the enzymes involved in nutrient metabolism, the molecular patterns associated with cell-surface attachment, and the ability to avoid immune responses from the host (Adak and Khan, 2019). In turn, these factors are related to specific gastrointestinal tract regions. Therefore, this is also applicable to establishing comparisons between histological analyses that are mainly due to the microanatomy of every intestinal region and each species (Mowat and Agace, 2014). Only a few studies include autocritiques on possible experimental artefacts that will help to improve future experiments such as the importance of estimating exposure periods and origin of the recollected samples to extract microbial DNA (Chi et al., 2016), sample size, and bioinformatic parameters (Wang et al., 2016).

### *Sequencing strategies*

In this review, 35 of the 45 selected studies used the taxonomic 16S rRNA amplicon fingerprinting approach to evaluate changes in bacterial communities due to the dietary intake of xenobiotics (Table 1). Notably, the amplification of the V3 – V4 conserved region was the most frequently employed approach. The 16S method is widely used in gut dysbiosis studies due to its cost-effectiveness and various

bioinformatics tools. However, this method comes with some limitations that should be considered. These considerations include (1) a putative association of the 16S gene with taxa defined as operational taxonomic units and the resulting difficulty of assessment (Poretsky et al., 2014); (2) a lack of reproducibility as a result of different experimental variables, including sample management, the 16S gene variable region selected, and the bioinformatic pipelines employed (Han et al., 2020); and (3) an inability to establish reliable species or strain functional predictions (Ranjan et al., 2016).

The 16S rRNA amplicon fingerprinting method classifies the identified taxa from phylum to genus, with an observable decrease in specificity at the lower levels, making it particularly unreliable at the species level (similar to the difference in results obtained using OTUs vs. ASVs). In this sense, whole-genome sequencing (WGS) approaches, also known as metagenomics or shotgun sequencing, allows for more information to be retrieved from genera with low abundance (Durazzi et al., 2021). Moreover, WGS can be used to infer functional features such as the genes present and metabolic routes involved in responses to xenobiotic exposure (Mesnage et al., 2021; Stedtfeld et al., 2017). In addition to functional assessments, the WGS approach allows for diversity indexes to be more accurately estimated and for the taxonomic structures of complex microbial communities to be elucidated, taking into consideration species and even strains of bacteria, archaea, viruses, fungi, and protozoans (Han et al., 2020; Poretsky et al., 2014; Ranjan et al., 2016). For example, in a study by Mesnage et al. (2021), increases in the abundance of three species (*Eggerthella* isolate HGM04355, *Acinetobacter johnsonii*, and *Akkermansia muciphila*) were detected after glyphosate and MON 52276 exposure. Also, the authors characterised and quantified the abundance of the *EPSPS* gene encoding the target enzyme of this herbicide and performed a functional analysis using KO assignments specific to their biological model. However, exploring multivariate and multidimensional microbial communities with this approach is highly expensive for large-scale studies with deep sequencing. A more affordable alternative is to adjust the metagenomic sequencing depth according to the experimental hypothesis of the study, focusing on the required reads to detect the species, functions, and biomarkers expected as outcomes. In this regard, shallow shotgun sequencing is a viable option to determine common species and functional profiles in samples at a slightly higher cost than that of 16S fingerprinting without losing valuable information (Hillmann et al., 2018). Although the WGS method usually provides complete information about the structure and functionality of the microbiomes, this approach cannot necessarily be generalised, as particular changes may be required for specific depth adjustments. This was the case with the study of Stedtfeld et al. (2017), who were unable to determine variations in the abundance of antibiotic-resistance genes with lower abundance. They then used qPCR to overcome this limitation.

### ***Data analysis reproducibility***

The different methodological approaches used in microbiota experiments create substantial difficulty when integrating the resulting data of different studies. Restrictions when comparing outcomes stem from the different methods used to extract and store DNA/RNA material, the sequencing strategies and platforms used in each study, and the bioinformatics pipelines and databases employed. It is desirable to use a specific database to reference sequence assignments such as the Murine Microbiome Database (MMDB). However, it is also necessary to be able to compare among general databases to avoid size, updating, or management-related biases, which are mainly due to the search space or the quantity of undiscovered microbial groups, as this can lead to false positive and negative classifications, respectively (Ye et al., 2019). This also applies when exploring the effects of xenobiotic exposure that may induce changes associated with new or unclassified microbial groups, which may be dismissed because databases may not include abnormal or disturbed microbiota. In addition, a standardisation of available metadata is important to provide additional context for the samples and raw reads available in public repositories (Dundore-Arias et al., 2020). For some experiments, such as evaluations of dysbiosis under conditions of xenobiotic exposure, their outcomes require a clear workflow with sufficiently detailed information on the algorithms and parameters used for data processing in order to ensure

reproducibility. Thus, data accessibility is crucial for creating a robust conceptual framework to increase our understanding of the dynamics of microbiota changes due to xenobiotic exposure.

## Conclusions

The gut microbiota was explored as a dynamic interaction system, which can be perturbed due to xenobiotic exposure. According to the studies reviewed herein, impacts on specific gut microbial communities could be associated with pathologies and changes at intestinal, metabolic, and systemic levels. Thus, the overall health of the organism may be at stake due to xenobiotic exposure. In this sense, using bioinformatics tools and biological models is a relevant strategy to explore dysbiosis mechanisms. Murine models are the most studied in these experiments. Exploring the effects of xenobiotic exposure on the structure and composition of the gut microbiota from organisms that are exposed to several contaminants in natural environments, such as pollinators and fishes, could extend our knowledge of the main microbial groups that are susceptible to xenobiotics and the overall impacts that these compounds have. While 16S approaches could be used as exploratory approaches, more WGS and physiological studies with standardised and specific experimental designs are needed to understand how xenobiotics can perturb the gut microbiota and how the results may be extrapolated.

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**Data availability statement.** The data for this study are available from the corresponding author upon reasonable request.

**Author contribution.** Conceptualization: B.I.-M, B.Y.-R; Data curation: B.I.-M.; Funding acquisition: M.B.-L.; Supervision: B.Y.R.; Visualisation: B.I.-M., B.Y.-R.; Writing – original draft: B.I.-M.; Writing – review and editing: B.Y.-R., B.G.-G., M.B.-L., L.R.

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