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The Impact of Environmental Chemicals on the Gut Microbiome

Karen Chiu,*,† Genoa Warner,* Romana A. Nowak,‡,§ Jodi A. Flaws,*,†,‡,1 and Wenyan Mei*,‡

*Department of Comparative Biosciences, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, Illinois 61802, †Division of Nutritional Sciences, College of Agricultural, Consumer, and Environmental Sciences, ‡Carl R. Woese Institute for Genomic Biology, and §Department of Animal Sciences, College of Agricultural, Consumer, and Environmental Sciences, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

[1]To whom correspondence should be addressed at Department of Comparative Biosciences, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL 61802. E-mail: jflaws@illinois.edu.

ABSTRACT

Since the surge of microbiome research in the last decade, many studies have provided insight into the causes and consequences of changes in the gut microbiota. Among the multiple factors involved in regulating the microbiome, exogenous factors such as diet and environmental chemicals have been shown to alter the gut microbiome significantly. Although diet substantially contributes to changes in the gut microbiome, environmental chemicals are major contaminants in our food and are often overlooked. Herein, we summarize the current knowledge on major classes of environmental chemicals (bisphenols, phthalates, persistent organic pollutants, heavy metals, and pesticides) and their impact on the gut microbiome, which includes alterations in microbial composition, gene expression, function, and health effects in the host. We then discuss health-related implications of gut microbial changes, which include changes in metabolism, immunity, and neurological function.

Key words: environmental chemicals; gut microbiome; health risks.

Humans are exposed to hundreds of chemicals as evidenced by the fact that more than 300 environmental chemicals or their metabolites have been measured in human biological samples (CDC, 2017). Human exposure to these environmental chemicals is constant, and some of these chemicals have long half-lives in the body and environment. Chemicals such as bisphenols, phthalates, pesticides, persistent organic pollutants (POPs), and heavy metals have endocrine-disrupting effects that can alter hormonal metabolism. Many of these environmental chemicals are associated with adverse health outcomes, including male and female reproductive and developmental defects, type 2 diabetes, cardiovascular dysfunction, liver disease, obesity, thyroid disorders, and immune dysfunction (Chiang and Flaws, 2019; Hannon and Flaws, 2015; Jaishankar *et al.*, 2014; Nagy *et al.*, 2019; Rochester, 2013). The gut microbiome influences host metabolism, and thus, it may mediate some of the toxic effects of environmental chemicals (Martin *et al.*, 2019). With chronic exposure to a variety of environmental chemicals, it is vital to understand how the gut microbial community changes in response to environmental chemical exposures and the implications of such changes on health outcomes.

In this review, we summarize the known impact of environmental chemical exposure on the gut microbiome, with a

specific focus on the effects of bisphenols, phthalates, POPs, heavy metals, and pesticides on the gut microbiome. These chemical classes were included in the review because exposure to these chemicals is frequent in humans, and increasing evidence suggests they alter gut microbiota composition. In addition to summarizing the impact of these chemicals on altering the gut microbiome, we also summarize alterations in gene expression, functional changes, and health implications associated with these gut microbiome changes.

BISPHENOLS AND THE GUT MICROBIOME

Bisphenol A (BPA), a plastic monomer and high-volume industrial chemical, is one of the most widely studied endocrine-disrupting chemicals. Extensive research has shown that BPA is a reproductive toxicant, a neurotoxicant, and an obesogen, likely due to its affinity to multiple hormone receptors in the body (Patisaul, 2020; Vom Saal *et al.*, 2012; Ziv-Gal and Flaws, 2016).

Recent animal studies of developmental and adult exposure to BPA demonstrate that BPA can alter the gut microbiota of a variety of species in a sex-specific manner (Table 1). For example, male mice exposed to BPA have increased *Prevotellaceae* (Javurek *et al.*, 2016), bacteria that are known to be involved in the mucosal barrier function (Wright *et al.*, 2000). However, female mice have no change in the relative abundance of *Prevotellaceae* (Javurek *et al.*, 2016). BPA exposure also upregulated the levels of *Akkermansia* and *Methanobrevibacter* in the gut microbiome of males. This is of concern because *Akkermansia*, which plays a role in butyrate production, is also elevated in human cancers (Baxter *et al.*, 2014; Weir *et al.*, 2013), implying that BPA-induced gut microbiome alterations may increase the risk of carcinogenesis. However, other species of *Akkermansia* have been shown to be beneficial for intestinal immunity, glucose metabolism, and lipid metabolism (Naito *et al.*, 2018). Furthermore, *Methanobrevibacter* is shown to heighten the host's ability to metabolize exogenous fuels, resulting in upregulated host energy intake and weight gain (Samuel and Gordon, 2006; Sweeney and Morton, 2013). This raises a strong possibility that BPA-induced weight gain is caused at least partially by BPA-induced changes in the gut microbiome. Overall, BPA exposure produces sex-specific outcomes on the gut microbiome, implying that BPA-exposed males and females may be at different risk for certain diseases.

In support of the disease-driving effect of BPA exposure, studies found that BPA-induced alterations in gut microbiota are often associated with several physiological disorders in the host (Table 1). BPA-induced microbial alterations are found to increase oxidative stress, which is a trigger to inflammation. *In vitro* studies with human colonic cell lines show increased oxidative stress in response to BPA treatment (Qu *et al.*, 2018; Zhao *et al.*, 2019). A study using the *in vitro* Simulator of the Human Intestinal Microbial Ecosystem (SHIME) system to predict the effects of BPA on the human gut also found increased expression of genes related to oxidative stress (Wang *et al.*, 2018b). Furthermore, developmental BPA exposure in mice and rabbits reduced the diversity of gut microbiota composition with a decrease in protective bacteria, such as short-chain fatty acid (SCFA) producers. This is accompanied by chronic intestinal and hepatic inflammation and metabolic disorder (Malaise *et al.*, 2017, 2018; Reddivari *et al.*, 2017). The mechanisms by which BPA executes its actions on the gut microbiome remain unclear. Interestingly, in comparison with the effects of the synthetic estrogen ethinylestradiol (EE), BPA caused many of the same microbial effects as EE on the gut, such as decreased relative abundance of Firmicutes and Proteobacteria, implying BPA may modify gut microbiota through an estrogenic mechanism (Javurek *et al.*, 2016, Liu *et al.*, 2016).

In addition to the effect on the gut, BPA treatment is known to affect brain development, behavior, and lipid and glucose metabolism (Collins *et al.*, 2012; Guan *et al.*, 2019; Nicholson *et al.*, 2012). As gut microbiota function is known to be important for both brain and metabolic health, it is tempting to speculate that BPA-induced gut microbiome alterations partially mediate the adverse effects of BPA on neurological and metabolic health. Although BPA studies reveal a strong effect of this chemical on altering gut microbiota composition (Catron *et al.*, 2019; Javurek *et al.*, 2016; Wang *et al.*, 2018b), studies that evaluate the contribution of such alterations to BPA-induced adverse neurological and metabolic health outcomes are critically needed.

Because the problematic endocrine disrupting properties of BPA have come to light, alternative bisphenols have increased in prevalence and use (Rochester and Bolden, 2015). Considerably less research has been performed on alternative bisphenols, despite that fact that some may be more developmentally toxic than BPA (Kinch *et al.*, 2015). A study examining the effects of bisphenol S (BPS), bisphenol F (BPF), bisphenol B (BPB), bisphenol AF (BPAF), as well as BPA on the gut microbiome in zebrafish embryos found that the least developmentally toxic bisphenols (BPA, BPS, and BPF) had the most substantial impacts on the microbial community (Catron *et al.*, 2019). In contrast, the most developmentally toxic bisphenols (BPB and BPAF) did not impact microbiota (Catron *et al.*, 2019). The observed developmental toxicity ranking mirrors bisphenol potency in estrogen receptor activation *in vitro*, implying a causal relationship between estrogenicity and microbiota disruption. Future studies should determine the effects of other bisphenol alternatives, such as BPS, BPF, BPB, and BPAF, on the gut microbiome using mouse or pig models for human research and examine if they lead to similar outcomes in mammals. Furthermore, more studies are needed to determine the mechanism by which the changes in the gut microbiome lead to neurological and metabolic health defects.

PHTHALATES AND THE GUT MICROBIOME

Phthalates are plasticizers and stabilizers found in vinyl flooring, clothing, detergents, personal care products, children's toys, medical equipment, and plastic packaging film (Babich and Osterhout, 2010; Wittassek *et al.*, 2011). Phthalates are commonly found in the environment as phthalate vapors or dust particles, but they are also found in food and beverages. Because phthalates are noncovalently bound to materials, they can easily leach into the environment. As a result, foodstuff is the primary source of phthalate exposure. Besides ingestion, other routes of exposure to phthalates include inhalation, dermal absorption, and intravenous exposure.

Recent studies in several species indicate that developmental phthalate exposure alters gut microbiota composition and may have significant health consequences (Table 2). Humans exposed to high levels of phthalates at birth (commonly through intravenous infusions) have altered gut microbiota, and these changes have been associated with enhanced immunoglobulin M responses against hepatitis B vaccine vaccination, suggesting that phthalate-induced gut microbial changes in early life may alter immune responses to vaccination (Yang *et al.*, 2019b). Mono-(2-ethylhexyl) phthalate (MEHP) exposure in pubertal mice shifts the gut microbiota composition, and this

Table 1. Bisphenols and the Gut Microbiome

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
BPA	Developmental	0, 0.2, 0.6, 1.7, 2.9, 5.7, 11.5, 23.0, or 45.0 μM in water environment	Zebrafish embryo	Not applicable	↑ *Chromatiaceae* ↓ *Neisseriaceae* (–) *Rheinheimera*, *Pseudomonas*, *Leptothrix*	• High variability between vehicle control groups in each experiment • BPA and BPF caused similar microbial community changes	Catron *et al.* (2019)
		50 μg/kg bw dams dosed orally from GD 15 to weaning	Mice	Male offspring	↓ *Bifidobacterium* ↑ *Bacteroidetes*	• BPA acted as an obesogen, induced inflammation, and altered immune responses • Supports link between alterations in the gut microbiome and metabolic disease	Malaise *et al.* (2017)
		50 μg/kg bw dams dosed orally from GD 15 to weaning	Mice	Female offspring	Not applicable	• BPA exposure induced defects in fecal antimicrobial activity and impaired protection of the gut • BPA treatment altered the gut-associated immune system and systemic immune response	Malaise *et al.* (2018)
		200 μg/kg bw dams dosed orally from GD 15 to PND 7	Rabbits	Male offspring	↓ *Bacteroidetes* ↓ *Ruminococcaceae* ↓ *Oscillospira* (dams)	• BPA-induced colonic and liver inflammation • BPA altered the colonic metabolome	Reddivari *et al.* (2017)
		50 mg/kg feed weight (approximately 10mg/kg bw) F0 dams exposed through chow 2 weeks before mating through PND 30 (weaning), F0 males exposed breeding through weaning	Mice	Both; yes	↑ *Mogibacteriaceae*, *Sutterella* spp., and Clostridiales in F0 females ↑ Mollicutes and *Prevotellaceae* compared in F0 males ↑ *Bifidobacterium*, *Mogibacteriaceae* in F1 females ↑ *Akkermansia*, *Methanobrevibacter* in F1 males	• BPA exposure causes some of the same effects on the gut as ethinylestradiol (EE) exposure and some unique effects compared with EE • Clear sex differences in the effects of BPA were evident in both generations • BPA-mediated changes in the gut microbiota were inversely related to specific amino acid, lipid, and xenobiotic metabolism/degradation in females • BPA-mediated changes in the gut were positively associated with changes in sulfur metabolism, insulin signaling pathway, and steroid hormone biosynthesis in males	Javurek *et al.* (2016)
	Juvenile	30 μg/kg BW gavaged from PND 28 to 56	Nonobese diabetic mice	Female	↑ Verrucomicrobia ↓ *Nitrospira*, OD1, AD3, and Gemmatimonadetes	• Bacterial alterations correlated with blood glucose levels and immune endpoints	Xu *et al.* (2019)
	Adult	0, 2, and 20 μg/L and 2 or 20 μg/L BPA + 100 μg/l nano-TiO_2 in water environment for 3 months	Zebrafish	Both; yes	↑ Actinobacteria at 2 μg/L ↑ *Lawsonia* ↓ *Hyphomicrobium*	• Coexposure to TiO_2 antagonized BPA effects at the low dose and synergized at the high dose • Similar microbiome effects of BPA in both sexes • Serotonin levels in the gut were decreased in BPA-exposed males	Chen *et al.* (2018b)

Table 1. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
						• Changes in gut microbes related to oxidative stress	
		12–18 μg/kg feed weight in dog food contaminated with BPA can lining, 14 days	Dogs, gonadectomized	Both; yes but small *n*	↓ *Bacteroides* spp., Streptophyta, *Erysipelotrichaceae*, and *Flexispira* spp ↑ *Bacteroides ovatus*, [*Prevotella* spp.], [*Ruminococcus* spp.], and *Cetobacterium somerae*	• Exposure to BPA led to an increase in serum BPA levels • Some diet by sex interactions observed, but hard to interpret with small sample size • Bacteria known to metabolize bisphenols were suppressed with BPA treatment	Koestel *et al.* (2017)
		2000 μg/L in water environment for 5 weeks	Zebrafish	Male, age not specified	BPA altered microbial community; no analysis of statistical significance between groups	• BPA exposure caused similar changes in the gut as EE • Untreated male and female zebrafish have similar gut microbiota	Liu *et al.* (2017)
	In vitro	0–400 μM for 24 h	HCT116 human colon cancer cells	Not applicable	Not applicable	• BPA treatment decreased cell viability, caused oxidative damage due to ROS accumulation, disrupted mitochondrial function, and promoted apoptosis	Qu *et al.* (2018)
		25, 250, and 2500 μg/L in nutritional medium for 10 days	*In vitro* Simulator of the Human Intestinal Microbial Ecosystem	Not applicable	BPA ↓ microbial community richness at low doses and increased it at high dose; no analysis of statistical significance between groups ↑ *Microbacterium* and *Alcaligenes*	• BPA exposure increased genes related to oxidative stress and altered expression of estrogen receptors • BPA is metabolized in the system	Wang *et al.* (2018b)
		0–400 μM for 24 h	LS174T human colonic goblet cells	Not applicable	Not applicable	• BPA affected the secretory function of intestinal goblet cells by inducing mitochondrial dysfunction, oxidative stress, and apoptosis	Zhao *et al.* (2018)
Other bisphenols	Developmental	BPAF (0, 0.2, 0.6, 1.8, 5.2, 15.3, or 45.0 μM), BPB (0, 0.6, 1.7, 5.1, 15.0, or 44.0 μM), BPF (0, 0.2, 0.6, 1.8, 5.2, 15.3, 45.0 μM), BPS (0, 0.2, 0.6, 1.8, 5.2, 15.3, 45.0 μM) in water environment for 10 days	Zebrafish embryo	Not applicable	↓ *Neisseriaceae* (BPS) ↑ *Cryomorphaceae* (BPS) ↑ *Chromatiaceae* (BPF) ↓ *Neisseriaceae* (BPF)	• Exposure to the least developmentally toxic bisphenols impacted microbiota the most (BPS, BPA, BPF); the most developmentally toxic bisphenols did not impact microbiota (BPB, BPAF) • Similar microbial changes for BPA and BPF exposure, unique profile for BPS exposure • High variability between vehicle control groups in each experiment	Catron *et al.* (2019)

Table 2. Phthalates and the Gut Microbiome

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
DEHP	Birth	Newborns who did not receive intravenous infusion (control) vs newborns with respiratory distress who were given intravenous infusions	Newborn infants	Both sexes were used; however, sex differences were not assessed as both sexes were combined for analyses	↓ *Rothia* spp. and *Bifidobacterium longum*	• DEHP exposure at medically relevant doses altered the gut microbiota and decreased β-diversity, which may change immune responses in later life	Yang *et al.* (2019b)
DEP, methylparaben, triclosan	From birth to PND 62 and 191	0.1735, 0.105, and 0.05 mg/kg/day	Sprague Dawley rats	Female	↑ Bacteroidetes (*Prevotella*), Elusimicrobia in PND 62 ↓ Firmicutes (*Bacilli*) in PND 62	• Postnatal exposure to environmentally relevant doses of the chemicals from birth to adolescence (PND 62) in rats modified the gut microbiota • Microbiota differences diminished by adulthood (PND 181)	Hu *et al.* (2016)
MEHP	4-week exposure starting at puberty (4 weeks old)	0 or 0.05 mg/kg MEHP with normal diet or high-fat diet	4-week-old C57Bl/6 mice	Male	↑ Firmicutes; *Intestinimonas*, *Holdemanella*, *Coprobacter*, and *Parasutterella* ↓ Verrucomicrobia; *Akkermansia*, *Tannerella*, and *Alloprevotella* genus	• Postnatal exposure to 0.05 mg/kg MEHP altered gut microbiota and induced adipocyte hypertrophy and cholesterol overloading, deposition, and transportation	Wang *et al.* (2019a)
DEHP	Pubertal exposure for 7 and 14 days	0,1, or 10 mg/kg/day (oral gavage every other day)0, 10, or 100 μM DEHP in cecal contents (*in vitro*)	6- to 8-week-old C57Bl/6 mice	Female	↑ *Lachnoclostridium* (*in vivo*) ↓ *Akkermansia*, *Odoribacter*, and *Clostridium sensu stricto* (*in vivo*) ↑ *Alistipes*, *Paenibacillus*, and *Lachnoclostridium* (*in vitro* cultured cecal microbiota)	• Decreased fecal α-diversity in control compared with 7-day-DEHP group • Increased production of *p*-cresol in 7-day-DEHP treatment groups (10 and 100 μM) compared with control • Decreased butyrate synthesis in 7-day exposure of 100 μM DEHP	Lei *et al.* (2019)
DMP, DEP, and DBP combined	Not Available	500 mg/l	Asian carp species silver (*Hypophthalmichthys molitrix*) and bighead (*Hypophthalmichthys Nobilis*)	Not applicable	*Achromobacter aegrifaciens*, *Pseudomonas japonica*, *Bacillus subtilis*, and *Pseudomonas putida* isolated and enriched	• Isolated bacteria found in Asian carp eliminated phthalates from experimental systems	Kolb *et al.* (2019)

Abbreviations: DBP, dibutyl phthalate; DEHP, di-2-ethylhexyl phthalate; DEP, diethyl phthalate; DMP, dimethyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate.

was accompanied by adipocyte hypertrophy and cholesterol overloading (Wang *et al.*, 2019a), implying a causal relationship between MEHP-induced gut microbiota changes and impaired lipid metabolism. Subchronic exposure to di-2-ethylhexyl phthalate (DEHP) in female mice enhanced the production of *p*-cresol, which inhibits the synthesis of butyrate (Lei *et al.*, 2019). Given that butyrate is a microbial metabolite essential for intestinal homeostasis (Parada Venegas *et al.*, 2019), immune regulation (Correa-Oliveira *et al.*, 2016), and neurological function (Bourassa *et al.*, 2016), exposure to DEHP may lead to intestinal defects, immune dysfunction, and neurobehavioral impairments. The known effects of phthalates on gut microbiota in humans, rodents, and aquatic fishes are summarized in Table 2. Future studies should continue to examine whether phthalate exposure alters the gut microbiome via microbiome sequencing. In addition to sequencing studies, future studies should determine which gut microbes degrade phthalates and inoculate a single strain of bacteria into gnotobiotic animals to determine the function of that microbe.

POPs AND THE GUT MICROBIOME

Persistent organic pollutants are organic chemicals that contain hydrophobic and lipophilic properties and can be carried long distances through the air and water. Because these toxic chemicals are resistant to environmental degradation, POPs and their by-products can biomagnify and bioaccumulate in the ecosystem. Few POPs occur naturally in the environment. Instead, most POPs are synthesized for agricultural and industrial use, such as pesticides/insecticides, fast-food packaging, nonstick coatings for cookware, and heat exchange fluids.

Accumulating evidence indicates that POPs are toxic to human health and are linked to reproductive disorders, neurobehavioral impairments, and immune dysfunction (Li *et al.*, 2006; Siwen *et al.*, 2013). With increasing recognition of the roles of the gut microbiota on the immune system and knowing that the gut is the largest immune organ, recent studies have begun to investigate the impact of POP exposure on the gut microbiota and the potential roles it may have on health and disease. Specifically, these studies have investigated the impact of POP exposure on the gut microbiota during the developmental, juvenile, and adult stages in a variety of animals, including mice, fish, and humans (Table 3). In this section, we discuss highly studied POPs, including polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), perfluorochemicals (PFCs), and polybrominated diphenyl ethers (PBDEs), polychlorinated dibenzo-*p*-dioxins (PCDDs), and the impact these chemicals have on the gut microbiome.

Polychlorinated Biphenyls

Polychlorinated biphenyls were commercially used in thermal insulation materials, floor finishes, and electrical equipment before being banned in 1979 in the United States. However, PCBs persist in the environment and contaminate the food supply. Therefore, a primary route of exposure is by ingestion of PCBs. Developmental exposure to PCBs in the maternal diet significantly increased gut permeability and immune factors (*Il6*) in the murine ileum compared with control (Rude *et al.*, 2019). Gene expression of inflammatory markers (*Il6*, *IL1β*, and *IL22*) in the colon was also increased in PCB-exposed mice compared with control (Rude *et al.*, 2019). In addition to these functional changes in gastrointestinal (GI) physiology and immunology, PCB exposure markedly decreased the relative abundance of Proteobacteria, *Bacteroidales* family S7-25, and *Alistipes* compared with control (Rude *et al.*, 2019). These findings support that PCB exposure impacts GI physiology, modifies the gut microbiota composition, and alters mucosal immune responses.

In adult male mice, exposure to PCB-126 reduced cecal α-diversity and increased the Firmicutes to Bacteroidetes ratio (F/B ratio) (Petriello *et al.*, 2018). High F/B ratio has been observed in adult, obese populations in mice (Ley *et al.*, 2005) and humans (Ley *et al.*, 2006), implying that PCB-126 exposure may increase the risk of developing obesity. However, associations between the gut microbiome, specifically F/B ratio, and obesity are uncertain as Sze and collaborators revisited and reanalyzed 10 studies and determined that the association between F/B ratio and obesity was relatively weak (Sze and Schloss, 2016). Upon further analysis, the studies included in their analyses had small sample sizes and large interpersonal variation (Sze and Schloss, 2016). PCB exposure also increased intestinal inflammation as demonstrated by increased *hepcidin (Hemp)* and *Tnfa* in the colon and *Il-6* and *Il-18* in the jejunum (Petriello *et al.*, 2018). Furthermore, research in fish indicates that PCB-induced intestinal microbiota changes involve aryl hydrocarbon receptor (AhR) signaling (Chen *et al.*, 2018b; Gao *et al.*, 2018b; Ji and Qu, 2019).

Interestingly, a few studies suggest that the effect of PCBs on gut microbiota may be age-dependent. Acute PCB exposure in aging mice (11–13 months) decreased the relative abundance of Proteobacteria phyla (Choi *et al.*, 2013). This is in contrast to the effects of PCB exposure during development exposure through the maternal diet, which increased Proteobacteria (Rude *et al.*, 2019). It is important to note that the exposure methods in the studies were slightly different, which is a limitation. However, it is known that the gut microbiome changes with age (Cresci and Bawden, 2015).

Recently, a study identified that it is possible to attenuate PCB-induced gut microbiota changes in mice through exercise (Choi *et al.*, 2013). However, more studies are needed to address and provide solutions on how to attenuate or prevent PCB-induced gut microbiota changes that are associated with increased gut permeability, intestinal inflammation, and cognitive dysfunction.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are naturally found in the environment and are generated when burning wood, oil, and gas. Compared with PCBs, not many studies have investigated the impact of PAHs on the gut microbiota. One study used the *in vitro* SHIME system to show that PAH exposure in the colonic microbiome biotransforms PAHs to acquire more estrogenic activity than the parent compounds (Van de Wiele *et al.*, 2005). Although these estrogenic metabolites have similar estrogenicity equivalent to 0.31–2.70 nmol 17α-ethynylestradiol (EE2), further examination needs to be conducted on the actual PAH metabolites. A study in Atlantic cod exposed to PAH-contaminated waters showed different microbial communities compared with Atlantic cod residing in uncontaminated waters. PAH-exposed Atlantic cod contains PAH-degrading bacteria such as *Novosphingobium*, *Sphingobium*, and *Sphingomonas*, which are not present in unexposed Atlantic cod (Walter *et al.*, 2019). More studies are needed in models such as mice or rats to determine if these changes also occur in mammals and how we can attenuate the changes in the gut microbiome.

Table 3. Persistent Organic Pollutants and the Gut Microbiome

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
PCB mixture	Developmental	0, 0.1, 1, or 6 mg/kg/day starting 2 weeks before gestation and continuing through PND 21	Congenic wildtype (WT) (75% C57BL/6 and 25% Sv129) DM mice (mutations in *FMR1* and *RyR*)	No sex effects were observed, so all the data are combined and represented as equal proportions of males and females	↑ Proteobacteria phylum, specifically within the Deltaproteobacteria and Betaproteobacteria class ↑ Deferribacteres phylum was identified in DM mice compared with WT mice following exposure to 1 mg/kg/day PCB dose ↓ Proteobacteria, *Bacteroidales* family S7-25, and *Alistipes* in WT mice exposed to PCB compared with control	• Increased gut permeability in juvenile double mutant (DM) and WT mice • Genes of some inflammatory markers were significantly altered in treatment groups (regIIIgamma) of the same genotype. • Gut microbiota were altered significantly when comparing WT and DM mice. However, PCB exposure also altered gut microbiota in WT mice when compared with control	Rude *et al.* (2019)
PCB-126	Adult, 7 weeks old	0 or 1 μmol/kg/day at weeks 2 and 4	Ldlr−/− mice	Male	↓ α-Diversity in cecum ↑ Firmicutes to Bacteroidetes ratio (F/B ratio)	• PCB126 exposure altered the gut microbiota and host metabolism • Increased intestinal and systemic inflammation	Petriello *et al.* (2018)
Atrazine, estradiol, PCB126, PCB153	Adult (4 months)	DMSO or 1.0 μg/l of environmental pollutant mixture	Zebrafish	Males and females Sex-specific xenobiotic responses	↑ *Aeromonas* in females	• Estrogen receptor and aryl hydrocarbon receptor regulated the gut microbiota and host metabolism • PCB exposure increased *Aeromonas* in females, but not males. The increase in *Aeromonas* was also positively correlated with oxidative damage • *Histophilus*, *Mannheimia*, and *Blastococcus* were positively correlated with the integrity of the intestinal epithelial barrier • PCB exposure in males, but not females significantly decreased serotonin levels and tight junction protein 2 compared with control	Chen *et al.* (2018b)
PCB congeners (PCB153, PCB138, PCB180)	Adults 11–13 months of age	Exercise for 5 days followed by 2 days of oral exposure to PCB mixture (150 μmol/kg)	C57Bl/6J mice	Males	↓ Proteobacteria (*Pseudomonas plecoglossicida* strain CGMCC 2093, *P. plecoglossicida* strain R18, *Pseudomonas putida* strain SRI156)	• PCB exposure altered gut microbiome, but voluntary exercise attenuated PCB-induced changes in gut microbiome • PCB exposure decreased the abundance of 1133 bacterial taxa and increased the	Choi *et al.* (2013)

Table 3. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
					and Firmicutes (*Streptococcus infantis*) phyla ↑ *Candidatus aquirestis calciphila* (fold change 1.9), *Staphylococcus epidermidis* (fold change 1.7), *Bacteroides thetaiotaomicron* strain 8669 (fold change 1.6), *Tropheryma whipplei* (fold change 1.5), *Corynebacteriaceae*, *Verrucomicrobiaceae*, *Ulvophyceae*, *Porphyromonadaceae*	abundance of 90 taxa compared with control	
PAH parent compounds: naphthalene, phenanthrene, pyrene, and benzo(*a*)pyrene	*In vitro*	62.5 nmol	*In vitro* SHIME	Not applicable	Not specified	• The microbiome in colon biotransformed PAH to have estrogenic activity	Van de Wiele *et al.* (2005)
PAH	Information not available	No exposure to oil (northern Norway area) or 0.01 ppm exposure to oil (southern Norway area)	Atlantic cod (Gadus Morhua)	Not applicable	Clean water fish: Fusobacteria and Proteobacteria were the most abundant, followed by Firmicutes and Bacteroidetes. Fish exposed to oil-contaminated waters showed dominance in Firmicutes, followed by Proteobacteria, Bacteroidetes, and Fusobacteria. Vibrionales was the most abundant order identified	• Fish guts from a clean area had a lower microbial community richness compared with the fish guts from oil contaminated waters	Walter *et al.* (2019)
PFBS	*In utero* exposure (eggs exposed to PFBS)	0, 1.0, 2.9, 9.5 μg/l for the entire lifecycle	Marine medaka	Males and females Greater bioaccumulation of PFBS in males than females at all doses (1.0, 2.9, and 9.5 μg/l) Males had greater inflammatory responses than females Females exposed to PFBS had impaired lipid metabolism	Intestines of F0-exposed males: ↑ *Cetobacterium* (2.9 μg/l) compared with control ↓ *Vibrio* in F1 females after exposure of F0 parents to 9.5 μg/l PDBS ↑ *Planctomyces* and *Lutimonas* F1 intestines after parental exposure to 9.5 μg/l PFBS	• PFBS exposure affected gut microbiota in fertile adults, and this persisted in the offspring • *Cetobacterium* was significantly and positively correlated with host TJP2 expression, a biomarker of epithelial barrier integrity	Chen *et al.* (2018a)
PFAS: F-53B	Adult, 6 weeks old	0, 1, 3, or 10 μg/l for 10 weeks	C57Bl/6 mice	Males and females F-53B did not cause a sex-dependent effect	↓ Abundance of Firmicutes ↑ Verrucomicrobia after	• MUC2 protein decreased in response to PFAS, but transcription increased in	Pan *et al.* (2019)

Table 3. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
				in mice from an immune perspective	subchronic exposure. *Bacteroides* had no change. *Akkermansia* increased significantly in males but did not change significantly in females; *Parabacteroides* decreased significantly in females but showed no variation in males	response to PFAS, possibly due to a compensatory phenomenon • PFAS increased LPS in serum; increased MCP-1 markedly in males and females after treatment in colon; *Tlr4*, *NFkB*, *Il1*- TNF-α protein also upregulated. At 10 μg, PFAS increased CD83 dendritic cells and decreased sIgA levels in the colon • F-53B exposure decreased mucous production and decreased gene expression of ion transporters in both males and females.	
BDE-47	*In utero* and lactational exposure	0, 0.002, and 0.2 mg/kg BDE-47 from GD 6 to PND 21. Male mice selected to be either on normal diet or HFD for 14 weeks	Primigravida female ICR mice	Only male mice were selected for analysis	↓ α-Diversity in fecal extracts ↑ In the relative abundances of *Parasutterella* and *Gemella* ↓ In the relative abundances of *Christensenellaceae*, *Atopostipes*, and *Bacillus* ↑ In relative abundances of *Candidatus saccharimonas*, Ruminococcaceae, *Staphylococcus*, *Gemella*, *Eubacterium*, *Corynebacterium*, *Paenalcaligenes* when compared with normal diet + vehicle group	• Exposure to BDE-47 reduced alpha diversity in fecal extracts, altered microbial composition, and impaired metabolic functions, including impaired glucose homeostasis, hepatic steatosis, and injury	Wang *et al.* (2018a)
BDE-47 or BDE-99	Adult, 9 weeks old	0 or 100 μmol/kg/day for 4 days	C57Bl/6 mice (conventional and germ-free)	Males	PBDE exposure altered 23 gut microbial taxa	• PBDE exposure in the intestinal microbiome decreased branched-chain and aromatic amino acid metabolites	Scoville *et al.* (2019)
OBS	Adult, 6 weeks old	0, 0.1, 1, or 10 μg/l	ICR mice	Males	Not applicable	• No microbiome data—but the authors reported decreased mucus secretion and gut barrier dysfunction in treatment groups compared with control. Hepatic transcriptomics and metabolomics showed lipid metabolism disorders	Wang *et al.* (2019b)
HCH	Adult	N/A	Mothers-humans	Males and females were combined for analyses, so sex differences were not determined	↓ In microbial diversity in colostrum with ↑ HC levels. Proteobacteria and Firmicutes were main phyla in colostrum.	• HCH altered microbial composition in human colostrum and the colonization of the infant gut	Tang *et al.* (2019)

Table 3. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
					Microbial diversity at the genus level differed between samples (dose-dependent)		
Endosulfan	Adult, 8 weeks old	0, 0.5, or 3.5 mg/kg/day for 2 weeks	ICR mice	Male	Not applicable	• Endosulfan exposure-induced liver injury and disrupted amino acid, lipid, and gut microbiota metabolism	Zhang *et al.* (2017)
TCDD	Juvenile, 4 weeks old	0 or 30 μg/kg/day every 4 days for 28 days	Gnotobiotic C57Bl/6	Female	↑ Segmented filamentous bacteria (SFB)↓ *Bacteroides fragilis*	• TCDD-induced host response was significantly modulated by the presence of SFB in the gut microbiome	Stedtfeld *et al.* (2017b)
TCDD	Juvenile, PND 28, 29	0–30 μg/kg/day for 28 and 92 days with the latter having a 30-day recovery period	C57Bl/6 mice	Female	↑ *Enterobacteriaceae*	• TCDD exposure enriched ARG and MGE-harboring members of *Enterobacteriaceae* in the gut microbiome	Stedtfeld *et al.* (2017c)
TCDD	Adult, 5–8 weeks old	0, 0.1, 1.0, and 10 μg/kg/day for 4 days	B6C3F1 mice	Female	Expression of SFB in mouse ileum	• Addition of activated carbon decreased the bioavailability of TCDD in the host and may have influenced the gut microbiome	Stedtfeld *et al.* (2017a)
TCDD	Adult, 6 and 7 weeks old	0 or 6 μg/kg biweekly for 26 weeks	CD-1 mice in a prediabetic hyperglycemic state via streptozotocin intraperitoneal injection	Male	↑ Firmicutes ↓ Bacteroidetes ↑ *Lactobacillaceae* and *Desulfovibrionaceae* ↓ *Prevotellaceae* and Actinobacteria cluster ACK M1	• Dysregulated gut microbiome may have contributed to liver and immune toxicity	Lefever *et al.* (2016)
TCDD, PhIP, HBD, B[*a*]P, deltamethrin, and PAHs	Adults	0.005, 0.90, 2.60, 5, 21, and 38 μg/ml	Human *in vitro* cultured feces TC7 cells (clone of parenteral Caco-2 epithelial cell line)	Not applicable	Not applicable	• Pollutant disturbance may have promoted inflammation with the release of IL-8 from intestinal epithelial cells	Defois *et al.* (2018)
TCDF	Adult (8 weeks old)	0 or 24 μg/kg/day for 5 days	C57Bl/6J mice	Males	↓ F/B ratio ↑ In *Butyrivibrio* spp. and *Flavobacteria* ↓ In *Oscillibacter* and Clostridia ↓ SFB	• Changes in microbiota were associated with marked increases in bile acids, SCFA, altered liver function, increased intestinal inflammation, and inhibited signaling of FXR, a key regulator of fat and glucose metabolism	Zhang *et al.* (2015a)

Abbreviations: α-HBCD, α-hexabromocyclododecane; γ-HBCD, γ-hexabromocyclododecane; BDE-47, 2,2′,4,4′-tratrabromodiphenyl ether; DMSO, dimethyl sulfoxide; F-53B, 6:2 chlorinated polyfluorinated ether sulfonate; FXR, farnesoid X receptor; HCH, hexachlorocyclohexane; OBS, sodium *p*-perfluorous nonenoxybenzene sulfonate; PAH, polycyclic aromatic hydrocarbons; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyls; PFAS, per- and polyfluoroalkylated substances; PFBS, perfluorobutane sulfonate; SCFA, short-chain fatty acid; SHIME, Simulator of the Human Intestinal Microbial Ecosystem; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDF, 2,3,7,8-tetrachloro dibenzofuran.

Perfluorochemicals

Perfluorochemicals are commercially used in nonstick cookware, food packaging, and stain-resistant carpets. Although little is known about the impact of perfluorochemicals on the gut microbiome, a few studies have examined per- and polyfluoroalkylated substance (PFAS) and per- and polyfluorobutane substance (PFBS) exposure *in utero* and during adult stages of life (Table 3). Male fish exposed to PFBS (0, 1.0, 2.9, 9.5 μg/l) had an increased abundance of *Cetobacterium* compared with control male fish. The increase in *Cetobacterium* was positively correlated with altered tight junction protein expression, a marker of epithelial barrier integrity (Chen *et al.*, 2018a). In addition to experiencing alteration of gut microbiota composition and expression of tight junction proteins, males had hyperactive inflammatory responses (Chen *et al.*, 2018a). In contrast to males, PFBS-treated female fish only had slightly increased inflammatory responses, but had severely impaired lipid metabolism as demonstrated by their decreased levels of triglycerides and free fatty acids (Chen *et al.*, 2018a). The alteration in gut microbiota in fertile adults persisted in the offspring. These offspring had increased mortality, especially at higher doses of exposure compared with controls (Chen *et al.*, 2018a). These data suggest that PFC exposure alters the gut microbiome in a sex-dependent manner in fish, and this comes with sex-dependent health outcomes. In addition, the data suggest that gut microbiota alterations and the adverse effects on gut homeostasis, such as increased inflammation, upregulated oxidative stress, and a compromised intestinal epithelial barrier, can be carried over to the next generation.

Unfortunately, there are conflicting results on whether the results observed in fish are translatable to mammals such as mice. PFBS exposure in mouse adipose cells showed that triglyceride levels were increased compared with control (Qi *et al.*, 2018). In contrast, PFC exposure, specifically perfluorooctanesulfonic acid (PFOS) exposure, increased triglyceride levels in mice, whereas PFC exposure, specifically PFBS, decreased triglyceride levels in fish (Wang *et al.*, 2015). Major reasons for these conflicting results include the use of distinct models and species, different PFCs, and research performed outside a living organism versus within a living organism. Another limitation of the study on PFBS exposure is that fish were not exposed to environmentally relevant doses (Chen *et al.*, 2018a). The study used doses in the μg/l range (0, 1, 2.9, and 9.5 μg/l) (Chen *et al.*, 2018a). European adults are exposed to 0.03–3.72 ng/kg/day PFBS (EFSA, 2012; EPA, 2018), and Americans are exposed to roughly 4.2 ng/ml PFBS (Olsen *et al.*, 2017). Although the study in fish did not use environmentally relevant doses, it is still beneficial to study high doses above relevant exposures because these chemicals can bioaccumulate in the body.

Chlorinated polyfluorinated ether sulfonate or F-53B/(6:2) is another perfluorochemical commonly used in electroplating wastewater in China (Siwen *et al.*, 2013). F-53B exposure in adult mice decreased the abundance of Firmicutes and increased the abundance of Verrucomicrobia in both male and female mice (Pan *et al.*, 2019). F-53B exposure also caused sex-specific responses in the gut microbiota. For example, treated male mice had a significant increase in *Akkermansia* compared with control male mice, but treatment did not cause any variation in female mice. Treated female mice had a significant decrease in *Parabacteroides* compared with control female mice, but this did not occur in male mice (Wang *et al.*, 2019c). In addition to sex-specific gut microbial deviations, both male and female mice had significantly decreased mucus production and gene expression of ion transporters at the highest dose of F-53B exposure (Pan *et al.*, 2019). The potential link between these changes and gut microbiome alterations remain unclear. The different responses of the gut microbiome in males and females to F-53B exposure may explain sex differences in the effects of F-53B exposure on health outcomes.

Polybrominated Diphenyl Ethers

BDE-47 and BDE-99 are 2 PBDEs commonly used as flame retardants in building materials, furniture, airplanes, polyurethane foams, and electronics. Exposure to PBDEs *in utero* and adulthood perturbs the gut microbiome. Specifically, BDE-47 exposure *in utero* and during lactation reduced diversity of gut microbiota composition and impaired glucose homeostasis in male mice (Wang *et al.*, 2018a). In adult male mice, BDE-47 and BDE-99 exposure altered 23 gut microbial taxa and amino acid and carbohydrate metabolism (Scoville *et al.*, 2019). Specifically, BDE-treated mice had decreased branched-chain and aromatic amino acid metabolites compared with controls. Although these previous studies provide important information, they both used male mice only. It is important to study the female sex as well and compare that to the male sex because males and females have different hormone profiles, which can affect the impact of environmental chemicals on the entire body, including the gastrointestinal and reproductive tracts. Overall, these studies indicate that exposure to PBDEs can alter gut microbiome and impair metabolism. It would be interesting to know if PBDE-induced gut microbiome alterations mediate some aspects of the metabolic disorders in PBDEs-treated animal models.

Polychlorinated Dibenzo-*p*-Dioxins

Polychlorinated dibenzo-*p*-dioxins are naturally formed from volcanic eruptions and forest fires. However, human activities create the most dioxins by manufacturing pesticides and burning organic materials, such as fossil fuels and garbage. Exposure to dioxins can occur through inhalation, ingestion, and dermal absorption. Two dioxins that have been studied are 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and 2,3,7,8-tetrachlorodibenzofuran (TCDF).

In a series of studies carried out by the same laboratory, conventional, and gnotobiotic female mice were orally dosed with vehicle control or TCDD to assess the effects of TCDD on the gut microbiota (Stedtfeld *et al.*, 2017a,b,c). In the first study, conventional female mice treated with TCDD showed increased *Enterobacteriaceae* compared with control mice (Stedtfeld *et al.*, 2017c). Gut microbiota alterations due to TCDD treatment were associated with an increase in the reservoir of antibiotic-resistant genes in the gut microbiome. In a second study, gnotobiotic mice of the same sex (female) were colonized with and without segmented filamentous bacteria (SFB) and polysaccharide A (Stedtfeld *et al.*, 2017b). SFB is an immune activator, whereas polysaccharide A is a background immune suppressor. TCDD treatment increased SFB and decreased *Bacteroides fragilis* compared with control. Thus, the TCDD-induced host response was significantly impacted by the presence of SFB in the gut microbiome (Stedtfeld *et al.*, 2017b). The addition of activated carbon decreased the bioavailability of TCDD and obliterated the expression of the SFB 16S rRNA gene (Stedtfeld *et al.*, 2017a). Activated carbon had minimal influences on the murine gut microbiome and affected the relative abundance of *Lactobacillaceae* and 2 other minor groups. TCDD exposure had

drastic effects on the gut microbiome, and activated carbon attenuated the changes in the gut microbiome (Stedtfeld *et al.*, 2017a). Altogether, these studies indicate that TCDD causes alterations in the gut microbiota, which are associated with antibiotic resistance; however, the presence of activated carbon reduces TCDD exposure and possibly antibiotic resistance.

Chronic TCDD exposure in adult male mice also caused alterations in gut microbiota. The dysregulation in the gut microbiome may have contributed to immune toxicities, and this aligns with several studies that examined the effects of TCDD on immune responses. An *in vitro* study cultured human fecal suspensions with TCDD. Following TCDD-gut microbiota interaction, fecal suspensions were processed for its cellular supernatant and incubated with intestinal epithelial cells to measure immune responses (Defois *et al.*, 2018). TCDF exposure increased IL-8 secretion from intestinal epithelial cells, suggesting that dioxin disturbance may promote inflammation and is immunotoxic (Zhang *et al.*, 2015a). Beyond associative changes in gut microbiome with the immune system, changes in the gut microbiota due to TCDD exposure link to liver toxicity as there were marked increases in bile acids and SCFAs and decreases in farnesoid X receptor signaling (Wang *et al.*, 2019b; Zhang *et al.*, 2017). Ultimately, these studies suggest that dioxin exposure disrupts both gut microbiome and lipid and glucose metabolism. Whether there is a causal relationship between dioxin-induced alterations in gut microbiome and metabolic disorder remains to be studied.

HEAVY METALS AND THE GUT MICROBIOME

Heavy metals are natural, high-density elements found in the Earth's crust and are highly toxic even at low concentrations. Like POPs, heavy metals bioaccumulate in some organisms and further increase the burden of heavy metals. Several studies have examined the impact of heavy metals, such as lead, cadmium, arsenic, and mercury on the gut microbiome (Table 4). In mice, lead exposure reduced diversity of gut microbiota and altered the metabolism of many pathways, including vitamin E, bile acid, and nitrogen metabolism (Gao *et al.*, 2017c).

Exposures to cadmium altered the gut microbiota in frogs (Ya *et al.*, 2019), fish (Chang *et al.*, 2019), and mice (Breton *et al.*, 2013, Zhang *et al.*, 2015b) (Table 4). However, whether there are sex-specific changes remains to be determined because previous *in vivo* studies either did not examine sex differences or used only male or female animals.

Exposure to arsenic and its impact on the gut microbiome have been studied in mice and humans. Arsenic exposure has been shown to alter the gut microbiota in various strains of mice during neonatal, juvenile, and adult stages (Table 4). These alterations were also associated with changes in the metabolism of lipids, vitamin E, bile acids, oxidative stress, and detoxification. Arsenic exposure also presents a problem in humans through ingestion of contaminated waters. An adult human study in a Bangladesh population reported that arsenic exposure altered the gut microbiome and resulted in an overproduction of genus *Citrobacter* (Wu *et al.*, 2019). Depending on the species, *Citrobacter* can result in various health problems such as urinary tract infections, respiratory diseases, inflamed gastrointestinal tract, and sepsis in immunocompromised individuals. Analysis showed a significant association between arsenic exposure in water, *Citrobacter*, and vascular intima-media thickness (IMT). IMT is accessed by measuring the distance of the luminal-intima to the medial-adventitia of the carotid artery by ultrasound. High IMT increases risk of developing cardiovascular diseases, specifically atherosclerosis. Ultimately, IMT is used as a subclinical marker for atherosclerosis (Simova, 2015). Thus, the data on arsenic exposure suggest that the altered gut microbiome may play an essential role in the development of atherosclerosis, possibly through a microbiota-derived metabolite called trimethylamine *N*-oxide (TMAO) (Jonsson and Bäckhed, 2017; Lindskog Jonsson *et al.*, 2018). TMAO disrupts bile acid synthesis and metabolism, which is associated with atherosclerosis due to the buildup of cholesterol (Ding *et al.*, 2018). Overall, having a stable microbiome, which includes the presence of *Faecalibacterium*, may reduce arsenic toxicity and arsenic-related diseases (Coryell *et al.*, 2018).

The effects of mercury exposure on the microbiome have been studied in various species including mice, rats, chickens, fish, and humans during the adult stage (Table 4). The forms of mercury included in this literature review are the following: methylmercury (MeHg), monomethylmercury (MMHg), and mercuric chloride ($MgCl_2$). Exposure to MeHg damaged the GI tract and altered the gut microbiota and its metabolites (Bridges *et al.*, 2018, Lin *et al.*, 2020). However, nutrition may provide some protection from MeHg toxicities. For example, supplementation of selenium reversed some changes in the gut microbiota of MeHg-poisoned rats so that the gut microbiota presented more like the control group (Liu *et al.*, 2019). Protein addition also seems to enhance MMHg metabolism *in vitro* (Guo *et al.*, 2018). Similar to MeHg, $MgCl_2$ damaged the GI tract and resulted in thickened muscle walls, decreased goblet cells, widened submucosa, and necrotic enterocytes in the cecum of mice and chickens (Ruan *et al.*, 2019; Zhou *et al.*, 2020). In addition to changes in the morphology of the cecum and cecal microbiome, $MgCl_2$ exposure was associated with altered metabolism of vitamin C, aldarate, xenobiotics, and PAHs (Zhou *et al.*, 2020).

Although a myriad of studies have examined the effects of heavy metals on the gut microbiome, many of these microbiome studies only reported descriptive changes in the makeup of the gut microbiota and used only 1 type of sex or combined both sexes in their analyses (Table 4). In the future, it is important to conduct research beyond characterizing the gut microbiota to evaluate the effects of heavy metals on other aspects of health, such as metabolism and reproduction. Experiments that are designed to investigate the sex-dependent effects and multigenerational or transgenerational effects as a result of heavy metal exposure are especially important.

PESTICIDES AND THE GUT MICROBIOME

Pesticides, which include insecticides, herbicides, and fungicides, are used globally to aid in food production. Although pesticides are generally highly toxic to target species through mechanisms that may not affect humans and most nontarget species, many pesticides are toxic to humans and wildlife through other mechanisms, including endocrine disruption (Mnif *et al.*, 2011). Recent studies on environmentally relevant doses of pesticides have revealed the long-term consequences of the environmental metabolites of legacy pesticides (Liang *et al.*, 2019; Liu *et al.*, 2016) as well as the harms of their replacements, especially on nontarget organ systems including the gut. As scientists are beginning to understand the complex functions of the gut microbiome, the literature on the effects of pesticides on gut microbiota has significantly expanded in the past 3 years (Table 5).

Both pure glyphosate and various glyphosate-based herbicide (GBH) formulations alter the bacterial makeup of the gut microbiome in rodents (Aitbali *et al.*, 2018; Dechartres *et al.*,

Table 4. Heavy Metals and the Gut Microbiome

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
Lead	Perinatal	32 ppm until 40 weeks of age in maternal drinking water	Mice	Male and female Pb exposure was highly correlated with increased adult body weight in male, but not female offspring	Bacteroidetes and Firmicutes shifted in response to Pb exposure	• Lead exposure impacted the gut microbiota	Wu *et al.* (2016)
Lead	Juvenile (6 weeks old)	100 and 500 ppm for 8 weeks in drinking water	Balb/c mice	Female	↓ Lachnospiraceae ↑ Lactobacillaceae and Erysipelotrichaceae Within Erysipelotrichaceae family, *Turicibacter*, *Blautia*, *Barnesiella*, and *Alistipes* were higher in treatment group compared with control ↓ Genus diversity in treatment group than control	• Lead exposure impacted the gut microbiota	Breton *et al.* (2013)
Lead	Adult, 7 weeks old	10 ppm for 13 weeks in drinking water	C57Bl/6 mice	Female	Lead exposure reduced phylogenetic diversity ↓ Clostridiales, Lachnospiraceae, and Ruminococcaceae	• Lead exposure altered the gut microbiome and significantly affected vitamin E, bile acid, nitrogen metabolism, oxidative stress, and detoxification mechanisms	Gao *et al.* (2017c)
Cadmium	Larval stage	0, 5, 100, and 200 μg/l from Gosner stage 26 to 38	*Bufo gargarizans* larvae	Not specified	↑ Relative abundance of Proteobacteria ↓ Relative abundance of Bacteroidetes and Firmicutes	• Chronic cadmium exposure caused significant intestinal damage and gut microbiota changes	Ya *et al.* (2019)
Cadmium	Juvenile	0, 50, and 500 μg Cd/l in drinking water for 4 weeks	*Cyprinus carpio*	Not applicable	↓ Fusobacteria, *Cetobacterium*, and *Akkermansia muciniphila* ↑ Firmicutes	• Cd exposure decreased diversity of gut microbiota	Chang *et al.* (2019)
Cadmium	Juvenile (5 weeks old)	10 ppm in drinking water for 10 weeks	C57Bl/6 mice	Male	↓ Relative abundance of Firmicutes and γ-Proteobacteria Quantity of Firmicutes decreased significantly in the cecum contents after 10 weeks of Cd exposure	• Cd increased liver TG, FFA, and TG levels; mRNA of key genes in de novo FFA synthesis and transport pathways and TG synthesis in mice • Cd exposure dysregulated Cd exposure and altered the gut microbiome in mice	Zhang *et al.* (2015b)
Cadmium	Juvenile (6 weeks old)	20 and 100 ppm for 8 weeks in drinking water	Balb/c mice	Female	↓ Lachnospiraceae ↑ Lactobacillaceae ↑ Erysipelotrichaceae → *Turicibacter*, *Blautia*, *Barneselia*, and *Allistipes* were higher in heavy metal-treated groups than in control	• Heavy metal exposure altered gut microbiota and may interfere with gut homeostasis	Breton *et al.* (2013)

Table 4. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
Arsenic	Neonatal (PND 10)	0.05 mg/kg bw	CD-1 mice	Female	↓ Bacteroidetes ↑ *Eubacterium plexicaudatum*, *Lachnoclostridium*, and *Mucispirillum schaedleri*, *Deferribacteres*	• Arsenic exposure resulted in a distinct bacterial population and gut-associated immune status	Gokulan *et al.* (2018)
Arsenic and zinc	Juvenile	Zinc restriction and 0, 50, 500 ppb inorganic arsenic in drinking water for 6 weeks	C57BL/6 mice	Female	↑ *Shewanella*, *Rheinheimera*, and *Bifidobacterium* ↓ *Herpetosiphonales*	• Zinc deficiency was associated with reductions in the host's and microbiome's ability to detoxify arsenic	Gaulke *et al.* (2018)
Arsenic	Juvenile	100 ppb for 13 weeks	C57Bl/6 mice	Female	↑ Verrucomicrobia ↓ Firmicutes	• Arsenic exposure altered the gut microbiome and its ability to carry out carbohydrate and pyruvate metabolism • Arsenic exposure increased oxidative stress response genes; increased vitamin biosynthesis genes; increased folic acid synthesis; altered LPS-related genes	Chi *et al.* (2017)
Arsenic	Juvenile (5 weeks old)	3 mg/l As, 5 mg/l Fe + 3 mg/l As, and 5 mg/l Fe	ICR mice	Male	↑ Firmicutes, Proteobacteria, Acidobacteria, Cyanobacteria ↓ Bacteroidetes and Saccharibacteria (TM7)	• Exposure to arsenicaltered the gut microbiota and the metabolic profiles of the mouse	Guo *et al.* (2014)
Arsenic	Juvenile (5 weeks old)	50 ppm in drinking water for 2 weeks	C57Bl/6 mice	Not specified	↓ Gut microbiota diversity but not significant	• Arsenic exposure was associated with bile acid molecular families	Li *et al.* (2019b)
Arsenic	Juvenile to adult (6–8 weeks old)	0, 10, or 250 ppb arsenite As(III) for 2, 5, or 10 weeks	C57Bl/6 Tac mice	Male	↑ Bacteroidetes, Clostridia ↓ Firmicutes, Bacteroides	• Arsenic exposure altered the gut microbiome and was linked to changes in amino acid metabolism	Dheer *et al.* (2015)
Arsenic	Adult, 7 weeks old	0, 250 ppb, and 1 ppm in drinking water	C57Bl/6 mice (with normal or disrupted gut microbiome)	Female	Not applicable	• Arsenic-induced gut alterations altered arsenic biotransformation and increased toxicity	Chi *et al.* (2019)
Arsenic	Adult, 8 weeks old	0 or 10 ppm for 4 weeks	C57Bl/6 mice	Female	↓ Cyanobacteria, Tenericutes ↑/↓ Firmicutes depending on class	• Arsenic exposure altered the gut microbiota • Metagenomic sequencing revealed that changes in gut microbiota were strongly associated with changes in bile acids, amino acid derivatives, lipids, fatty acids, isoflavones, indole derivatives, glucuronide, and carnitine	Lu *et al.* (2014a)

Table 4. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
Arsenic	Adult, 9 and 10 weeks old	0 or 10 ppm in drinking water for 4 weeks	C57Bl/6 mice (free of *Helicobacter*)	Not specified	Not applicable	• Arsenic exposure altered phospholipid, cholesterol, and tryptophan metabolism in the gut • Arsenic upregulated several unsaturated fatty acids	Xue *et al.* (2019)
Arsenic	Adult, 8 weeks old	0 or 10 ppm in drinking water for 4 weeks	C57Bl/6 mice, WT and IL10−/−	Females	↑ Bacteroidetes ↓ Firmicutes	• Significantly different gut microbiome phenotypes may have had an impact on arsenic biotransformation	Lu *et al.* (2014b)
Arsenic	Adult, 8 weeks old	10 ppm in drinking water for 4 weeks	C57Bl/6 mice	Male and female Microbiome of female mice treated with As was more significantly affected than male mice treated with As	Female-treated mice: ↓ *Dorea* ↑ *Akkermansia* These changes not observed in males	• Nitrogen, carbon, and sulfate metabolism were significantly altered in arsenic-treated males • The gut microbiome is distinct in males and females as well as treated and nontreated mice	Chi *et al.* (2016)
Arsenic	Adult, 7–13 weeks old	0, 25, or 100 ppm inorganic arsenic in drinking water for 2 weeks	Germ-free C57Bl/6 WT and AS3MT-KO mice	Male and female were combined for the analyses; therefore, sex differences were not determined	Presence of *Faecalibacterium prausnitzii* suggest this microbe provides protection by decreasing arsenic toxicity increasing butyrate synthesis	• As3mt and intact gut microbiome (along with the presence of *F. prausnitzii*) provided protection against arsenic toxicity in mice • Stable human gut microbiome transplanted in mice protected against arsenic-induced mortality	Coryell *et al.* (2018)
Arsenic	25- to 50-year-old adults	Not applicable	Humans	Male and female adults were included in the study but sex differences were not determined	Did not identify associations between arsenic exposure and the composition of the gut microbiome after correcting for multiple testing	• Significant association of genus Citrobacter with IMT	Wu *et al.* (2019)
Methylmercury (MeHg)	Adult, 4 weeks old	0 or 10 μg/kg bw (oral dosing)	Sprague Dawley rats	Male	↓ Bacteroidetes and Proteobacteria; Lactobacillaceae, Bacteroidaceae, Streptococcaceae, and Sutterellaceae ↑ Firmicutes; *Desulfovibrionaceae*, *Helicobacteraceae*, *Peptococcaceae*, and *Rhodospirillaceae*	• MeHg exposure damaged intestinal villi and walls in the small and large intestines • MeHg exposure promoted inflammatory responses (increased IL-1β and IL-6; decreased IgE and BDNF) in treatment groups compared with control • MeHg exposure altered the metabolism of nucleotides, carbohydrates, amino acids, and lipids • MeHg altered the gut microbiome and metabolites	Lin *et al.* (2020)

Table 4. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
Methylmercury	Pregnant mothers	Not applicable	Human (recruited from Greenville, South Carolina), $n = 17$	Females	Microbial richness (α- and β-diversity) was not markedly changed for gut microbiota with high and low concentrations of mercury in hair and stool	• MeHg concentrations in stool likely do not reflect biotransformation by the gut microbiota • 17 bacterial genera were associated with Hg in stool and hair	Rothenberg *et al.* (2016)
Methylmercury	Pregnant mothers	Not applicable	Humans (recruited from only from South Caroline)	Females	Not applicable	• Gut microbiome composition differed between high and low MeHg concentrations in blood in stool during early gestation • α-Diversity decreased with MeHg exposure in late gestation compared with early gestation • Several taxa were correlated with MeHg biomarkers, but associations of taxa and MeHg exposure differed depending on whether sample was collected during early or late gestation	Rothenberg *et al.* (2019)
Methylmercury	Adult	Fathead minnow (FHM): control (0.02 μg/g), 0.72 μg/g, 5.50 μg/g Hg dry weight for twice a day for 30 days Mice: control (0.02 μg/g), 0.43 μg/g, 4.39 μg/g Hg dry weight in diet for twice a day for 30 days	FHM CD-1 mice	FHMs: males and females Mice: males	Dominant phyla in low MeHg group: Planctomycetes (*Pirellula* and *Planctomyces* genera), Fusobacteria (*Cetobacterium*) ↓ *Cetobacterium* in high MeHg group compared with control ↑ *Aeromonas*, *Acinetobacter*, and an unclassified member of the Neisseriaceae family	• MeHg exposure increased microbes associated with xenobiotic metabolism and increased microbes related to immune suppression compared with control • FHM: increased putrescine, L-serine, and glycerol; decreased stearic acid, palmitic acid, oleic acid, and L-glutamine • Mice and FHM exposed to MeHg had decreased fatty acids in palmitic, oleic, and stearic acids and increased glycerol, the backbone of triglycerides. Gene expression of enzymes in were also dysregulated, indicating that fatty acid dyshomeostasis	Bridges *et al.* (2018)
Methylmercury	Adult, 8 weeks old	0 or 4 mg/kg bw MeHg by intragastric gavage for 4 weeks every other day Some of the MeHg-poisoned rats were given 2.74 mg/kg bw sodium selenite	Sprague Dawley rats	Males	↓ Cyanobacteria and Bacteroidetes in MeHg treatment groups compared with control; Firmicutes in MeHg + sodium selenite compared with MeHg group ↑ Firmicutes in MeHg treatment groups compared with control; Bacteroidetes in MeHg + sodium selenite compared with MeHg	• MeHg exposure altered the gut microbiota compared with control; however, sodium selenite supplementation reversed some of the changes in the gut microbiota, suggesting that selenium may reduce toxicity and improve intestinal health	Liu *et al.* (2019)

Table 4. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
Methylmercury	Adults, 18–80 years old	Subjects were asked to consume 3 fish meals per week for 2 weeks	Human (recruited from the University of Rochester Medical Center community, $n = 37$)	Males and females Sex differences not specified because males and females were combined for analyses	Not applicable	• Elimination rates in subjects prescribed antibiotics ($n = 2$) showed significant decreases in MeHg compared with control subjects who did not take antibiotics, suggesting the gut microbiome plays a role in the metabolism of MeHg	Caito *et al.* (2018)
Monomethylmercury	Not applicable	10 ng/g	*In vitro* experiment with human fecal samples ($n = 2$)	Not specified	Not applicable	• Microbes, such as *Sutterella parvirubra* and *Acidaminococcus intestini*, play a role in MMHg degradation, but the extent of MMHg metabolism is highly dependent on nutrients such as carbohydrates and proteins *in vitro* • Compared with control, MMHg metabolism is enhanced with the addition of protein	Guo *et al.* (2018)
Mercuric chloride ($HgCl_2$)	Chicks, 1 day old	0 or 150 ppm in drinking water for 30, 60, and 90 days	Hyline chicken	Male	Day 30 results: ↑ Proteobacteria, Tenericutes Day 60 results: ↑ Tenericutes Day 90 results: ↓ Spirochaetes	• $HgCl_2$ exposure decreased growth performance and altered cecal and colonic morphology on days 60 and 90 compared with control • Species richness increased in Hg groups compared with control after 30 days of exposure but decreased after 90 days of exposure in the cecum • Functional profiling of microbial communities showed $HgCl_2$ exposure for 60 days increased genes related to ascorbate and aldarate metabolism, xenobiotic metabolism by cytochrome P450, and PAH degradation • $HgCl_2$ exposure for 30 days may affect infectious bacterial diseases • No significant functional changes in chickens exposed to $HgCl_2$ for 90 days	Zhou *et al.* (2020)
Mercuric chloride	Adult, 8 weeks old	0 or 2 mg/kg bw $HgCl_2$ for 90 days	Kunming mice	Female	↑ *Butyricimonas*, *Dehalobacterium*, *Coprococcus*, *Oscillospira*, and *Bilophila* ↓ *Sporosarcina*, *Jeotgalicoccus*, *Staphylococcus*, and *Acinetobacter*	• $HgCl_2$ exposure decreased body weight, caused histopathological lesions in the cecum, and altered cecal microbiota	Ruan *et al.* (2019)

Abbreviations: As, arsenic; Cd, cadmium; IMT, intima-media thickness; MeHg, methylmercury; $MgCl_2$, mercuric chloride; MMHg, monomethylmercury; PAH, polycyclic aromatic hydrocarbons: Pb, lead; WT, wildtype.

Table 5. Pesticides and the Gut Microbiome

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
Aldicarb (I)	Adult	2 ppm (approximately 0.3 mg/kg bw/day) in drinking water for 13 weeks beginning at 8 weeks of age	C57BL/6 mice	Male	↓ *Christensenellaceae*, *Coriobacteriaceae*, Bacillales, *Anaerostipes*, *Roseburia* ↑ Erysipelotrichaceae, *Clostridium*	• Exposure to aldicarb increased pathogenicity of gut bacteria—increased genes for virulence, adhesion, and bacteriocins • Lipid profile and lipid metabolism altered in feces of treated mice compared with control • Aldicarb increased antioxidant gene expression, suggesting increased oxidative stress • Aldicarb increased DNA damage response gene expression, suggesting increased DNA damage • Brain metabolome/energy metabolism altered in response to aldicarb	Gao *et al.* (2019)
Aminomethylphosphonic acid (AMPA; glyphosate metabolite)	Adult	1.5 or 7.5 mM in sugar syrup or cotreatment with equal amounts of AMPA and glyphosate for 15 days	Honeybee	Female	None	• AMPA did not alter gut microbiome	Blot *et al.* (2019)
Atrazine (H)	Developmental	200 μg/l in water environment for 6 days or in *ex vivo* culture of whole gut for 6 days	Cuban tree frog	Male and female, but sex differences not discussed	None	• Atrazine exposure did not cause significant alterations in gut bacteria in tadpoles and adults • Gut microbiome changes are not likely the route through which atrazine affects tolerance to amphibian fungal infections	Knutie *et al.* (2018)
	Adult	1.0 μg/l atrazine dose (0.42 μg/l measured) in water environment starting at 4.5 months of age for 7 days	Zebrafish	Both; yes	↑ *Acinetobacter* (females) ↓ *Streptococcus* (females) ↑ *Capnocytophaga* (males and females)	• Atrazine exposure decreased body weight and gonadal weight in females • Atrazine caused sex-dependent alterations of the microbiome at phyla level • Atrazine-induced inflammation and oxidative stress in male intestines	Chen *et al.* (2018b)
Azoxystrobin (F)	Adult	0.1–5 mg/kg azoxystrobin in dry soil environment for 28 days	*Enchytraeus crypticus*	Not discussed	↓ Proteobacteria (low dose) ↑ Proteobacteria (high dose)	• Different effects on gut microbiota observed at different doses of azoxystrobin • Changes in gut were different from the changes in soil, suggesting gut changes were due to direct ingestion of azoxystrobin	Zhang *et al.* (2019a)
Carbendazim (F)	Adult	100 or 500 mg/kg orally via diet for 4 weeks starting at 7 weeks of age	ICR mice	Male	↓ Bacteroidetes ↑ Firmicutes, Actinobacteria, Proteobacteria	• Gut alterations occurred after 1 week of treatment, reduced richness and diversity of microbiota • Treatment caused inflammation, hepatic lipid metabolism disorder, and liver damage	Jin *et al.* (2015)

Table 5. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
	Adult	0.2–5 mg/kg orally via drinking water for 14 weeks starting at 6 weeks of age	C57BL/6 mice	Male	↓ Bacteroidetes, Verrucomicrobia ↑ Actinobacteria, Bacteroidetes	• Treatment altered gut microbiota, starting after 1 week of exposure • Treatment altered lipid synthesis and metabolism, causing hyperlipidemia and inflammation	Jin *et al.* (2018)
Chlorothalonil (F)	Adult	Chlorothalonil: 10 μg/l in 30% sucrose solution for 6 weeks	Honeybees	Both; however, sex differences were not assessed as both sexes were combined for analyses	↓ *Lactobacillaceae*	• Chlorothalonil had the strongest effect on the microbial community of 3 pesticides studied • Chlorothalonil altered structure and function of gut microbiome including altered gene expression	Kakumanu *et al.* (2016)
Chlorpyrifos (I)	Developmental	1 mg/kg bw/day by oral gavage from GD 0 to PND 21 (dams) and PND 21–60 (pups)	Hannover Wistar rats	Male (unclear)	↑ *Bacteroides* ↓ *Lactobacillus*, *Bifidobacterium*	• Similar changes in microbiome observed between SHIME and rats • SHIME overestimated effects observed in rats	Joly *et al.* (2013)
	Developmental	1 or 5 mg/kg bw/day by oral gavage from GD 0 to PND 21 (dams) and PND 21–60 (pups)	Wistar rats	Male	↓ *Lactobacillus* ↑ *Clostridium*, *Staphylococcus*	• Exposure significantly decreased body mass and body length vs controls • Exposure delayed maturation of intestinal barriers • Strongest effects of chlorpyrifos on the gut were observed at weaning	Joly Condette *et al.* (2015)
	Developmental	1 or 3.5 mg/kg gavage to dams from GD 1 until PND 21, gavage to pups from PND 21 to 60; inulin cotreatment	Wistar rats	Male	↓ Firmicutes, *Clostridium coccoides* (CPF only)	• Inulin supplementation alleviated some of the negative effects of prenatal chlorpyrifos treatment on the microbiome	Reygner *et al.* (2016a)
	Adult	0.3 mg/kg by gavage daily 25 weeks starting at 4 weeks of age or 20 weeks starting at 9 weeks of age with normal- or high-fat diet	Wistar rats	Male	Effects varies for all treatment groups	• Chlorpyrifos treatment had the strongest effect in the newly weaned mice fed a high-fat diet • Diet strongly affected the gut microbiome • Chlorpyrifos altered gut-brain communication	Liang *et al.* (2019)
	Adult	0.3 or 3 mg/kg by gavage daily for 9 weeks starting at 9 weeks of age with normal- or high-fat diet	Wistar rats	Male	↓ *Aerococcus*, *Brevundimonas*, *Trichococcus* (normal diet) ↓ *Olsenella*, *Clostridium sensu stricto* 1, *Amphibacillus*, *Enterorhabdus*, and *Alloprevotella* (high-fat diet)	• Low dose with normal diet significantly increased body weight, whereas high-fat diet had no effect on body weight • Chlorpyrifos-induced diet-specific effects on the microbiome • Insulin levels were decreased under all treatment conditions with bacterial changes related to glucose metabolism	Fang *et al.* (2018)

Table 5. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
	Adult	1 mg/kg by gavage daily for 30 days beginning at 12 weeks of age	Chinese Kunming mice	Male	↓ Firmicutes, *Lactobacillaceae* ↑ Bacteroidetes, *Bacteroidaceae*	• Treatment altered gut microbial composition • Observed gut changes were correlated with changes in metabolites • Treatment caused intestinal inflammation and abnormal intestinal permeability	Zhao *et al.* (2016)
	Adult	30–100 μg/l in water environment for 21 days	Zebrafish	Male	↓ Proteobacteria	• Treatment altered expression of oxidative stress genes suggesting increased oxidative stress • Treatment caused changes in glucose and lipid metabolism in the liver	Li *et al.* (2019a)
	Adult	5 mg/kg by gavage daily at 4 weeks of age for 12 weeks with normal- or high-fat diet	C57BL/6 and CD-1 (ICR) mice	Male	↑ Proteobacteria ↓ Bacteroidetes	• Treatment increased gut permeability, causing inflammation, and increased lipopolysaccharide levels • Treatment caused obesity in normal diet mice • Diet and strain did not significantly alter results	Liang *et al.* (2019)
	In vitro	1 mg per day for 30 days	SHIME	Not applicable	↑ *Enterococcus*, *Bacteroides* ↓ *Lactobacillus*, *Bifidobacterium* (no stats)	• Similar changes in microbiome observed between SHIME and rats	Joly *et al.* (2013)
	In vitro	3.5 mg/day injection in media into SHIME reactor for 30 days; cells treated with SHIME supernatant for 6 or 24 h; inulin cotreatment	SHIME and Caco-2/TC7 human intestinal cells	Not applicable	↓ *Lactobacillus*, *Bifidobacterium*	• Inulin cotreatment partially reversed CPF-induced gut alterations and increased SCFA production in the SHIME • Cotreatment impacted tight junction gene expression and inhibited proinflammatory signaling in the Caco-2/TC7 intestinal cell line	Réquilé *et al.* (2018)
	In vitro	1 mg/day in oil to SHIME for 30 days	SHIME human *in vitro*	Not applicable	↑ *Enterobacteria*, *Bacteroides*, Clostridia ↓ *Bifidobacterium*	• Treatment altered the microbial community in the SHIME • Effects varies between compartments and was strongest for culturable bacteria • Changes in SCFA and lactate levels also observed	Reygner *et al.* (2016a)
Coumaphos (I)	Adult	Treated strips following manufacturer's instructions for 6 weeks	Honeybees	Males and females were used; however, sex differences were not assessed because both sexes were combined for analyses	↑ Burkholderiales, Bifidobacteriales	• Treatment altered bacterial community • No changes in fungal communities were observed due to coumaphos exposure	Kakumanu *et al.* (2016)

Table 5. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
	Adult	650 μg/kg in sugar syrup for 24–34 h of interior worker bees	Honeybees	Female	↓ *Lactobacillus*, *Bifidobacterium*	• Honeybee gut microbiota varied by season • Gut microbiota exhibited similar changes due to different pesticides, suggesting a shared general mechanism	Rouzé *et al.* (2019)
Diazinon (I)	Adult	4 mg/l in drinking water for 13 weeks starting at 8 weeks of age	C57BL/6 mice	Male and female Guts of males were more disrupted than females Genes involved in synthesis of neurotransmitters altered by diazinon in males more significantly than females	↓ *Lachnospiraceae* (both) ↑ Burkholderiales, Bacteroidetes (male) ↓ Firmicutes (male) ↓ *Ruminococcaceae*, *Clostridiaceae*, and *Erysipelotrichaceae* (female)	• Perturbation of the gut may contribute to the neurotoxicity of organophosphate pesticides	Gao *et al.* (2017b)
	Adult	4 mg/l in drinking water for 13 weeks starting at 8 weeks of age	C57BL/6 mice	Male	N/A	• Treatment altered gut metatranscriptome and quorum sensing system • Treatment-activated stress response pathways and altered energy metabolism of gut microbiota	Gao *et al.* (2017a)
Diethyl phosphate (metabolite of CPF + others) (I)	Adult	0.08 or 0.13 mg/kg by gavage daily for 20 weeks starting at 8 weeks of age	Wistar rats	Male	↑ *Paraprevotella*, *Parabacteroides*, *Alloprevotella*, *Helicobacter*	• Treatment increased pathogenic bacteria levels • Treatment resulted in increased estradiol, decreased triglycerides, and enrichment of SCFA	Yang *et al.* (2019a)
Epoxiconazole (F)	Adult	4 or 100 mg/kg via diet for 90 days starting at 9 weeks of age	Sprague Dawley rats	Female	↓ Firmicutes ↑ Bacteroidetes, Proteobacteria	• Treatment altered the abundance and composition of gut microbiota	Xu *et al.* (2014)
Fipronil (I)	Adult	0.25 or 1.0 μg/kg in sugar syrup for 24–34 h of interior worker bees	Honeybees	Female	↓ *Lactobacillus*, *Bifidobacterium* ↑ *Gilliamella apicola*, *Snodgrassella alvi*	• The high dose was lethal • Honeybee gut microbiota varied by season • Gut microbiota exhibited similar changes due to different pesticides, suggesting a shared general mechanism	Rouzé *et al.* (2019)
Glyphosate-based herbicide (GBH)	Developmental	5 mg/kg/day oral dose via biscuits daily from GD 10 to PND 22 (weaning)	Sprague Dawley rats	Female	↑ Bacteroidetes ↓ Firmicutes	• Treatment altered maternal behavior; Roundup-treated dams spent significantly more time licking pups compared with control • Glyphosate and Roundup altered the microbiome of the dams at PND 22 differently	Dechartres *et al.* (2019)

Table 5. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
	Developmental	1.75 mg/kg bw/day in drinking water to dams from GD 6 through weaning (PND 28); pups dosed in drinking water following weaning for 6 or 13 weeks	Sprague Dawley rats	Both; however, sex differences were not assessed because both sexes were combined for analyses	↑ *Prevotella*, *Mucispirillum*, *Parabacteroides*, *Veillonella* ↓*Lactobacillus*, *Aggregatibacter* (pups)	• No effect of treatment on the dams' microbiome • Different effects observed between Roundup vs glyphosate treatment in the pups • Microbiome composition changed at different sample times in pups before puberty	Mao *et al.* (2018)
	Adult	250 or 500 mg/kg bw/day dose by gavage beginning at 1 month of age for 1 day, 6 weeks, or 12 weeks	Swiss mice	Male	↓ *Lactobacillus* ↓ Bacteroidetes ↓ *Corynebacterium* ↓ Firmicutes	• Subchronic and chronic exposure increased anxious and depressive behaviors at both doses • Subchronic and chronic exposure decreased intestinal bacterial count	Aitbali *et al.* (2018)
	Adult	0.00022 to 3.6 g/l in cultured bacteria from caecum of wild turtles	Hawaiian green turtles	Both; however, sex differences were not assessed because both sexes were combined for analyses	↓ *Pantoea*, *Proteus*, *Shigella*, *Staphylococcus*	• Glyphosate significantly decreased bacterial density at all doses	Kittle *et al.* (2018)
	Adult	0.1 ppb, 400 ppm, or 5000 ppm in tap water for 673 days (50 ng/l, 0.1 g/l, and 2.25 g/l of glyphosate, respectively)	Sprague Dawley rats	Male and female Treated females showed significant differences in gut microbial composition compared with controls and treated males	↑ Bacteroidetes (females) ↓ *Lactobacillaceae* (females)	• GBH exposure produced sex-specific gut microbiota composition • Very small study, but unique in treatment length	Lozano *et al.* (2018)
	In vitro	Bacterial strains from rat feces were treated with 0.1 ppb, 400 ppm, or 5000 ppm in media for 24 h	Sprague Dawley rats	Not applicable	↓ *Bifidobacteria*, *Clostridia*, *Enterococci* (male, highest 2 doses)	• Treatment altered levels of select bacterial strains • *In vivo* microbiome disturbances following Roundup treatment may be due to direct bactericidal action • Highly tolerant strain of *Escherichia coli* observed in culture	Lozano *et al.* (2018)
	In vitro	0.075–5 mg/ml in media for up to 5 days	Many bacterial strains from poultry	Not applicable	Pathogenic bacteria *Salmonella* and *Clostridium* were highly resistant to treatment Beneficial bacteria *Enterococcus*, *Bacillus*, *Bifidobacterium*, and *Lactobacillus* were reduced as well as *Campylobacter*	• Pathogenic bacteria were resistant to glyphosate, whereas beneficial bacteria were moderate to highly susceptible to resistance • Glyphosate was toxic to the gut microbiome • Glyphosate was associated with an increase in diseases mediated by *Clostridium botulinum*	Shehata *et al.* (2013)

Table 5. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
Glyphosate (H)	Developmental	0.8, 4, and 20 mg/l in diet from days 2 to 5 after grafting (larval stage)	Honeybees	Both; however, sex differences were not assessed because both sexes were combined for analyses	↑ Firmicutes, Clostridia, γ-Proteobacteria, Clostridiales, *Lachnospiraceae*, *Prevotellaceae*, and *Ruminococcaceae*	• Glyphosate-exposed larvae had lower survival and lower weights compared with controls • Glyphosate (20 mg/l) exposure significantly decreased diversity in intestinal bacteria in newly emerged bees	Dai *et al.* (2018)
	Developmental	5 mg/kg/day oral dose via biscuits daily from GD 10 to PND 22 (weaning)	Sprague Dawley rats	Female	↑ Bacteroidetes ↓ Firmicutes, *Butyricicoccus*	• Glyphosate had fewer effects on the microbiome than Roundup	Dechartres *et al.* (2019)
	Developmental	1.75 mg/kg bw/day in drinking water to dams from GD 6 through weaning (PND 28); pups dosed in drinking water following weaning for 6 or 13 weeks	Sprague Dawley rats	Both; however, sex differences were not assessed because both sexes were combined for analyses	↑ *Prevotella*, *Mucispirillum*, *Blautia* ↓ *Lactobacillus*, *Aggregatibacter*, *Streptococcus*, *Rothia*	• No effect of treatment on the dams' microbiome • Different effects observed between Roundup vs glyphosate treatment in pups • Microbiome composition changed at different sample times in pups before puberty	Mao *et al.* (2018)
	Adult	5 or 10 mg/l for 5 days of adult workers; 1 mM for 2 days or 0.1 mM for 5 days of newly hatched workers	Honeybees	Female	↓ *S. alvi*, *Bifidobacterium*, *Lactobacillus* (5 mg) ↑ *G. apicola* (5 mg)	• Exposure decreased total bacteria in adults • Stronger effects observed for the 5 mg group than the 10 mg group • Exposure interfered with gut colonization in newly hatched bees • Glyphosate increased susceptibility of newly hatched bees to bacterial pathogen	Motta *et al.* (2018)
	Adult	1.5 or 7.5 mM in sugar syrup for 15 days; infection with parasite	Honeybees	Female	↓ *S. alvi* ↓ *G. apicola* ↑ *Lactobacillus*	• No synergism observed between glyphosate and *Nosema ceranae* • Glyphosate strongly affected gut microbiota	Blot *et al.* (2019)
	In vitro	1, 10, 100 μg/ml in rumen fluid cultured in DAISY incubators for 48 h	Nonlactating Holstein-Friesian cow rumen fluid	Not applicable	↓ *Entodinium* spp., *Diplodinium* spp., *Epidinium* spp., *Ophryoscolex* spp., *Dasytricha* spp.	• Effects of glyphosate were strongest with fiber-rich diet • Glyphosate exposure increased the population of pathogenic species • High dose of glyphosate led to increased production of botulinum neurotoxin in cultures incubated with *C. botulinum*	Ackermann *et al.* (2015)
Hexachlorocyclohexane (HCH, all isomers) (I)		Colostrum samples collected from eastern China	Human breast milk	Not applicable	↑ *Pseudomonas*, *Proteus* ↓ *Enterococcus*	• Different microbial populations were identified in breast milk containing higher levels of HCH isomers • More contaminated milk contained more Pseudomonas, bacteria known to break down HCH	Tang *et al.* (2019)

Table 5. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
β-Hexachlorocyclohexane (I)	Adult	10 mg/kg daily by gavage for 8 weeks	C57BL/6 mice	Male	↑ Firmicutes, Proteobacteria ↓ Actinobacteria, Verrucomicrobia, Bacteroidetes	• Treatment altered gut microbiota composition • Treatment-activated bile acid synthesis, reduced ileal bile acid readsorption, and altered biliary bile acid profiles	Liu *et al.* (2017)
Imazalil (F)	Adult	100 or 1000 μg/l for 1, 7, or 21 days in aquatic environment at 6 months of age	Zebrafish	Male	↓ Proteobacteria, Bacteroidetes, *Alistipes*, *Akkermansia* ↑ Fusobacteria, Firmicutes	• Exposure increased microbiome diversity in gut • Treatment decreased mucin secretion in the gut, disrupted hepatic metabolism, and altered genes associated with glycolysis and lipid metabolism	Jin *et al.* (2017)
	Adult	0.1, 0.5, or 2.5 mg/kg bw/day orally via diet for 2, 5, or 15 weeks beginning at 6 weeks of age	C57BL/6 mice	Male	↓ Bacteroidetes	• Gut changes began by 2 weeks and stabilized by 15 weeks • Changes in cecal bacterial were abnormal and unpredictable • Chronic exposure disturbed intestinal barrier function and decreased mucus secretion • After 45 days of recovery after treatment finished, the colon only partially recovered	Jin *et al.* (2018)
	Adult	25, 50, or 100 mg/kg bw/day orally via diet for 4 weeks beginning at 6 weeks of age	ICR mice	Male	↓ Bacteroidetes, Firmicutes, Actinobacteria	• Exposure significantly reduced richness and diversity of cecal and fecal microbiota • Treatment-induced colonic inflammation	Jin *et al.* (2016)
Imidacloprid (I)	Adult	3.5 μg/kg in sugar syrup for 24–34 h to interior worker bees	Honeybees	Female	↓ *Lactobacillus*, *Bifidobacterium*	• Honeybee gut microbiota varies by season • Gut microbiota exhibited similar changes due to different pesticides, suggesting a shared general mechanism	Rouzé *et al.* (2019)
	Adult	500 μg/l in sugar syrup for 3 days to worker bees	Honeybees	Female	None	• Treatment was lethal to bees, but did not alter the microbiome	Raymann *et al.* (2018)
	Adult	10–100 μM in food (length of treatment not given)	*Drosophila melanogaster*	Female	↑ *Acetobacter*, *Lactobacillus*	• Nonlethal low dose treatment altered gut microbiota • Antibiotic treatment increased fly survival	Daisley *et al.* (2017)
Malathion (I)	Adult	2 mg/l (approximately 0.6 mg/kg BW/day) in drinking water for 13 weeks beginning at 8 weeks of age	C57BL/6 mice	Male	↑ *Corynebacterium*, *Clostridium* ↓ *Planococcaceae*, *Christensenellaceae*, *Anaerostipes*, *Blautia*, *Roseburia*	• Treatment altered expression of genes important for bacterial cell-to-cell communication (quorum sensing) and increased motility and pathogenicity-related genes (related to quorum sensing) • These changes may lead to pathogen invasion	Gao *et al.* (2018a)

Table 5. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
Monocrotophos (I)	Adult	28 μg/kg bw/day in drinking water for 180 days starting at 8 weeks of ages followed by fecal transplantation	*BALB/c* mice	Female	N/A	• Treatment-induced glucose intolerance • Recipients of fecal transplants from treated mice showed glucose intolerance compared with control transplants, suggesting these effects are mediated through gut microbiota	Velmurugan *et al.* (2017)
p,p′-Dichlorodiphenyldichloroethylene (metabolite of DDT, DDE) (I)	Adult	1 mg/kg bw/day daily by gavage for 8 weeks	C57BL/6 mice	Male	↑ Firmicutes, Proteobacteria ↓ Actinobacteria, Verrucomicrobia, Bacteroidetes	• Treatment altered gut microbiota composition • Treatment-activated bile acid synthesis, reduced ileal bile acid readsorption, and altered biliary bile acid profiles	Liu *et al.* (2017)
	Adult	2 mg/kg bw/day by gavage for 8 weeks beginning at 4 weeks of age; cotreatment and recovery with pectin	C57BL/6J mice	Male	↑ Bacteroidetes (cotreatment) ↓ Proteobacteria, Deferribacteres, Cyanobacteria (cotreatment)	• DDE treatment altered gut microbial composition • Pectin treatment altered gut microbiota during cotreatment and recovery periods • Cotreatment reduced the bioaccumulation of DDE in fatty tissues	Zhan *et al.* (2019)
Pentachlorophenol (I, H)	Juvenile	1, 50, or 100 μg/l in water environment for 28 days	Goldfish	Both; however, sex differences were not assessed because both sexes were combined for analyses	↑ Bacteroidetes ↓ Firmicutes	• Bioaccumulation in fish liver occurred during exposure • Exposure was not lethal but reduced body and liver weight and caused liver damage • Exposure significantly altered gut microbiome	Kan *et al.* (2015)
Permethrin (I)	Juvenile	34 mg/kg body weight gavage from PND 6 to 21, 4-month follow-up period	Wistar rats	Male	↑ *Lactobacillus*, *Bacteroides*, *Prevotella*, *Porphyromonas* (PND 21, 51)	• Treatment altered gut microbial communities and levels of SCFA	Nasuti *et al.* (2016)
	In vitro	3.2–0.00625 mg/ml in culture media	Many bacterial strains	Not applicable	N/A	• *Blautia producta* and *Bifidobacterium* were most sensitive to permethrin, and *E. coli* and *Pseudomonas aeruginosa* were least sensitive • Pathogenic bacteria were not very sensitive to treatment	Nasuti *et al.* (2016)
Propamocarb (F)	Adult	3–300 mg/l in drinking water (0.5–50 mg/kg bw/day) for 28 days starting at 6 weeks of age	ICR mice	Male	↓ Proteobacteria, Bacteroidetes (fecal) ↑↓ Firmicutes, Actinobacteria (fecal) ↓ Firmicutes, Proteobacteria, Actinobacteria, Tenericutes, *TM7* (cecal)	• Changes of gut bacterial populations in feces changed over time during treatment period • Different changes observed between fecal and cecal samples • Fecal metabolites were altered, indicating metabolic disturbance through or partly through the gut	Wu *et al.* (2018a)

Table 5. (continued)

Chemical	Exposure Window	Dose	Model	Sex & Sex Differences	Effect on Gut Microbiota	Conclusions	References
	Adult	1–10 mg/l in drinking water for 10 weeks beginning at 6 weeks of age	C57BL/6J mice	Male	↑ Bacteroidetes ↓ Firmicutes	• Some different changes observed between fecal and cecal microbiota • Fecal metabolites related to energy metabolism were altered	Wu *et al.* (2018b)
	Adult	100 and 1000 μg/l in water environment for 7 days	Zebrafish	Male	↑ Proteobacteria, Bacteroidetes, Firmicutes (1000 μg)	• Treatment significantly altered the gut microbiome in the 1000 μg treatment group • Treatment decreased gene expression and altered metabolites related to glycolysis and lipid metabolism	Zhang *et al.* (2019b)
Tau-fluvalinate (I)	Adult	Treated strips following manufacturer's instructions for 6 weeks	Honeybees	Male and female; sex differences not assessed because both sexes were combined for analyses	↓*Enterobacteriaceae*, *Caulobacteraceae*	• Treatment altered bacterial community • No changes in fungal communities were observed due to pesticide exposure	Kakumanu *et al.* (2016)
Thiamethoxam (I)	Adult	1.7 μg/kg in sugar syrup for 24–34 h of interior worker bees	Honeybees	Female	↓ *Lactobacillus*, *Bifidobacterium*, Alphaproteobacteria ↑ *G. apicola*	• Honeybee gut microbiota varied by season • Gut microbiota exhibited similar changes due to different pesticides, suggesting a shared general mechanism	Rouzé *et al.* (2019)
Trichlorfon (I)	Adult	12 μg/g bw single dose by oral gavage at 8 weeks of age, collected 24 h after dosing	Japanese quail	Male and female Female gut more impacted by treatment than male gut	↓ *Lactobacillus* ↑ Proteobacteria	• Treatment caused different changes in microbial populations in the cecum, large intestine, and feces	Crisol-Martinez *et al.* (2016)

Abbreviations: F, fungicide; H, herbicide; I, insecticide; SCFA, short-chain fatty acid; SHIME, Simulator of the Human Intestinal Microbial Ecosystem.

2019; Lozano *et al.*, 2018; Mao *et al.*, 2018) and honeybees (Blot *et al.*, 2019; Dai *et al.*, 2018; Motta *et al.*, 2018). In contrast, aminomethylphosphonic acid (AMPA), a glyphosate metabolite, does not alter the gut microbiome of exposed honeybees (Blot *et al.*, 2019). Collectively, these studies suggest that the parent compounds—not the metabolites—are responsible for the changes in the gut microbiome.

Extensive evidence indicates that the organophosphate chlorpyrifos affects microbial populations in male rodents and fish exposed during development and adulthood (Condette *et al.*, 2015; Li *et al.*, 2019a; Liang *et al.*, 2019; Reygner *et al.*, 2016b; Stunes *et al.*, 2017). Chlorpyrifos exposure additionally causes inflammation and oxidative stress in the gut (Li *et al.*, 2019a; Liang *et al.*, 2019; Zhao *et al.*, 2016). However, information on the effects of chlorpyrifos in females is lacking.

Few studies have examined the developmental effects of pesticide exposures beyond glyphosate and chlorpyrifos on the gut. However, studies in adults across multiple species using a wide range of insecticides, fungicides, and herbicides show alterations of the gut microbiome as well as other common effects, including altered lipid metabolism, inflammation, and oxidative stress (Table 5). The few studies that directly measured sex differences found differential alterations of gut microbiome between male and female animals following exposure to atrazine (Chen *et al.*, 2018b), diazinon (Gao *et al.*, 2017b), GBH (Lozano *et al.*, 2018), and trichlorfon (Crisol-Martinez *et al.*, 2016). However, there is disagreement on whether males or females have more alterations in the gut microbiome.

FUTURE DIRECTIONS

Collectively, the existing data suggest that exposure to environmental chemicals during various stages of life causes alterations in the gut microbiome and is associated with changes in health, including immune dysfunction, altered carbohydrate and lipid metabolism, and neurobehavioral impairments. Moreover, the effects of the environmental chemicals on gut microbiota highly depend on sex and age. A major question raised from the studies reviewed is whether, and to what extent, microbiota mediate the disease-causing effects of the environmental chemicals. The field of gut microbiome toxicology is still relatively new, which is why many studies have only reported changes in the gut microbiota composition and not on the mechanisms by which chemicals interfere with gut microbiota. In the future, it is important to characterize which microbes are present by sequencing the full length of 16S rRNA gene to correctly identify strains and species that are in the gut. A partial 16S rRNA sequencing, commonly on hypervariable regions 3 and 4 (V3 and V4), does not yield enough depth to give information on the species or strains of microbes. While partial 16S rRNA sequencing can give us some information on changes at higher taxonomic levels, this information is not enough because different strains of the same species can have different effects. For example, *Escherichia coli* O157: H7 is a disease-causing strain whereas *E. coli* Nissle 1917 is a probiotic strain (Wassenaar, 2016). In addition to identifying changes of gut bacteria at the species and strain levels, studies should also include metagenomic sequencing to study alterations of other microorganisms in the gut microbiome, which would provide insights into the functional changes in the gut microbiome. On the whole, future studies should examine the causal relationship between chemically induced changes in the gut microbiome and chemically induced adverse health outcomes. As such, research should supplement sequencing studies with mechanistic studies using conventional and gnotobiotic animal models, such as fish, mice, and pigs, because these models are essential for understanding the impact of environmental chemicals on the gut microbiome and the health consequences resulting from the altered gut microbiota (Nguyen *et al.*, 2015).

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