Minireview

The intestinal microbiota as mediators between dietary contaminants and host health

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Impact Statement

Recognition of the intestinal microbiota as a critical component of host health is growing, and appreciation of the interactions between these microbiota and dietary contaminants is important to further the understanding of how contaminants impact the host. This review explores these interactions through considering the contaminant groups bisphenols, phthalates, and mycotoxins given their prevalence in food and livestock feed. Our work reviews existing evidence of contaminant–microbiota interactions to provide a reference for approaches to studying the phenomena, identifies gaps in the current literature surrounding these relationships, and draws attention to the difficulty in reproducing community perturbations due to contaminant exposures. This information serves as a call for researchers to expand on these relationships to better characterize the hazard posed by these contaminants, and guides researchers to areas requiring further attention.

Abstract

The gut microbiota sit at an important interface between the host and the environment, and are exposed to a multitude of nutritive and non-nutritive substances. These microbiota are critical to maintaining host health, but their supportive roles may be compromised in response to endogenous compounds. Numerous non-nutritive substances are introduced through contaminated foods, with three common groups of contaminants being bisphenols, phthalates, and mycotoxins. The former contaminants are commonly introduced through food and/or beverages packaged in plastic, while mycotoxins contaminate various crops used to feed livestock and humans alike. Each group of contaminants have been shown to shift microbial communities following exposure; however, specific patterns in microbial responses have yet to be identified, and little is known about the capacity of the microbiota to metabolize these contaminants. This review characterizes the state of existing research related to gut microbial responses to and biotransformation of bisphenols, phthalates, and mycotoxins. Collectively, we highlight the need to identify consistent, contaminant-specific responses in microbial shifts, whether these community alterations are a result of contaminant effects on the host or microbiota directly, and to identify the extent of contaminant biotransformation by microbiota, including if these transformations occur in physiologically relevant contexts.

Keywords: Microbiome, bisphenol A (BPA), phthalates, mycotoxins, endocrine disruptors

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Introduction

The trillions of bacteria, fungi, viruses, and other microbes that comprise the mammalian gut microbiome play a crucial role in regulating gut health, and their activity can be influenced by a range of ingested substances.[1] A healthy gut microbiome aids in digestion, trains the immune system, and prevents colonization by pathogenic microbes; however, this community is exposed to and affected by nutritive and non-nutritive substances ingested by the host. Non-nutritive, unintended additions to food are called dietary contaminants, and they can be natural or anthropogenic in origin. These chemicals enter food at various stages of processing, from crops grown in contaminated soil to leachate from food contact materials. In addition, a subset of dietary contaminants can interfere with hormone function, earning the overlapping classification as endocrine-disrupting chemicals (EDCs). Following ingestion by the host, dietary contaminants have the potential to modify the microbial community, such as altering the concentration of microorganisms in the cecal and colonic regions of the gastrointestinal (GI) tract, potentially increasing host susceptibility to gut inflammation or colonization by pathogens. Gut flora may also metabolize these chemicals to various products with new toxicological relevance. This bidirectional relationship makes the gut microbiome an important target of dietary exposures, influencing host health through mechanisms distinct from host metabolism. This review focuses on bisphenols (BPs), phthalates, and mycotoxins as three common groups of dietary contaminants and EDCs, and discusses how they interact with gut microbiota, including a summary

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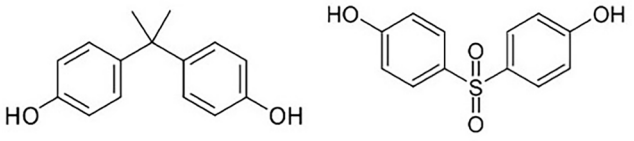

Figure 1. Bisphenol A (left) and Bisphenol S (right) [Public domain images].

of common methods used to study these relationships and recommendations for addressing knowledge gaps.

Background on microbiota

Bacteria are the primary interest for most investigations into the gut microbiome, and are predominantly represented by the phyla Bacillota and Bacteroidetes in the human gut.[1] Efforts to characterize the gut microbiomes of humans and other animals, and to establish their overlap, are an ongoing front in microbiome research as demonstrated by works like those of Gill *et al*.[2] and Hugenholtz and de Vos.[3] A dynamic community, the gut microbiome is shaped and molded by a vast amount of exposures. Changes characterized by the loss of beneficial microorganisms, overgrowth of harmful microorganisms, or loss of community diversity are referred to as dysbiosis and can be harmful to host health.[4] Agents known to change the microbiome community to the detriment of the host include broad spectrum antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors (PPIs), and dietary factors such high simple sugar and/or dietary fat intake.[5,6] Food contaminants also have the potential to cause dysbiosis, even if only inducing slight perturbations, and are now being studied to determine their influence on an individual's gut microbial profile and health consequences.

Background on BPs

The BPs are a class of diphenylmethane derivatives distinguished by their two hydroxyphenyl functionalities, with two examples shown in Figure 1, and used primarily to produce polycarbonate plastics and epoxy resins. BP products take the form of food packaging materials, safety equipment, medical devices, thermal paper, and more. Bisphenol A (BPA) and its analogs have been used in food contact materials since the 1960s and can migrate into food from these materials, making ingestion the primary exposure route for BPs.[7] The current tolerable daily intake (TDI) established by the European Food Safety Authority (EFSA) for BPA is 4 µg/kg bodyweight per day, but EFSA has proposed to lower this TDI.[8,9] Dermal absorption of BPs is also possible, and may represent a unique occupational exposure via thermal paper for cashiers, who reportedly have higher urinary BPA and BPS levels than the general population.[10,11] Because of their ubiquity in consumer products, BPA, BPS, and BPF have been detected in 95.7%, 89.4%, and 66.5% of randomly selected urine samples, respectively, from the 2013–2014 National Health and Nutrition Examination Survey.[12] Human exposure to BPs is common and recurring in industrialized countries, and increases in BP production draw attention to their health effects.

BPA has been labeled as an EDC due to its hormone receptor binding activity, such as disrupting ERα-mediated extranuclear (nongenomic) signals.[13–15] The analogs BPS and BPF are reportedly of the same magnitude as BPA for several hormonal effects, and the nongenomic estrogenic activity of BPA and BPS are comparable to estradiol (E_2).[16,17] Data on BPA in human studies are limited, but higher concentrations of urinary BPA were associated with increased but nonsignificant chance of poor sperm characteristics and DNA damage in men recruited from an infertility clinic.[18] BPA and BPS have also been implicated in epigenetic dysregulation in reproductive tissues of rodents.[19–21] A recent histopathology study on Sprague Dawley (SD) rats conducted at the National Center for Toxicological Research (NCTR) concluded BPA caused no adverse effects below 25,000 µg/kg bw/day in the core study on in-life and terminal endpoints; however, organ-specific investigations by grantee researchers using tissue samples from the study mice suggest low-dose BPA exposure may affect the development of organ systems like the brain and reproductive tissues.[22]

To consider BPs in the context of gut–microbial interactions, their toxicokinetic fate must be understood. Across mammalian species, BPA is readily absorbed through the small intestine after ingestion and converted primarily to BPA-glucuronide (BPA-G) through first-pass metabolism.[23–25] In rodents, studies administering radiolabeled BPA consistently find BPA eliminates primarily (80% recovered radioactivity) through feces as the parent compound, with some BPA-G detected in urine.[26] Glucuronidated compounds that are transported by bile back to the GI tract, such as sex hormones, morphine, naphthol, and BPA, can be deconjugated by various bacteria of the mammalian gut featuring β-glucuronidases.[27,28] Rodents primarily direct BP-conjugates through biliary excretion, where the BPs can be deconjugated by microbiota and reabsorbed, undergoing enterohepatic circulation.[28,29] An abstraction of enterohepatic circulation concerning exogenous compounds and bile acids is shown in Figure 2. Studies involving human volunteers who ingested deuterated-BPA (d-BPA) instead find near-complete elimination of BPA by 24 h, very low bioavailability of the parent compound (~1%), and near-total recovery of the d-BPA dose as BPA-G in urine.[24,30] As of yet, no human BP toxicokinetic studies analyzed volunteers' feces for BP elimination; however, toxicokinetic studies in humans regarding a heavier analog, BPS, recover only ~50% of a deuterated-BPS dose in urine, suggesting partial elimination through feces as an explanation.[31,32] An explanation for this divergence may be due to differences in molecular weight thresholds for biliary excretion between rodents and humans.[30] A physiologically based pharmacokinetic model of BPs determined BPS was glucuronidated at the lowest rate of the compared analogs, and incorporating enterohepatic circulation increased the correlation between measured and modeled concentration-time profiles for BPS.[33] One knowledge gap regarding the BPs is the elimination of weightier BP analogs. The heavier analogs like BPS and BP conjugates may eliminate through feces, but could also be deconjugated and modified by gut microbiota along that path, which would be a departure from our current understanding of BP toxicokinetics.

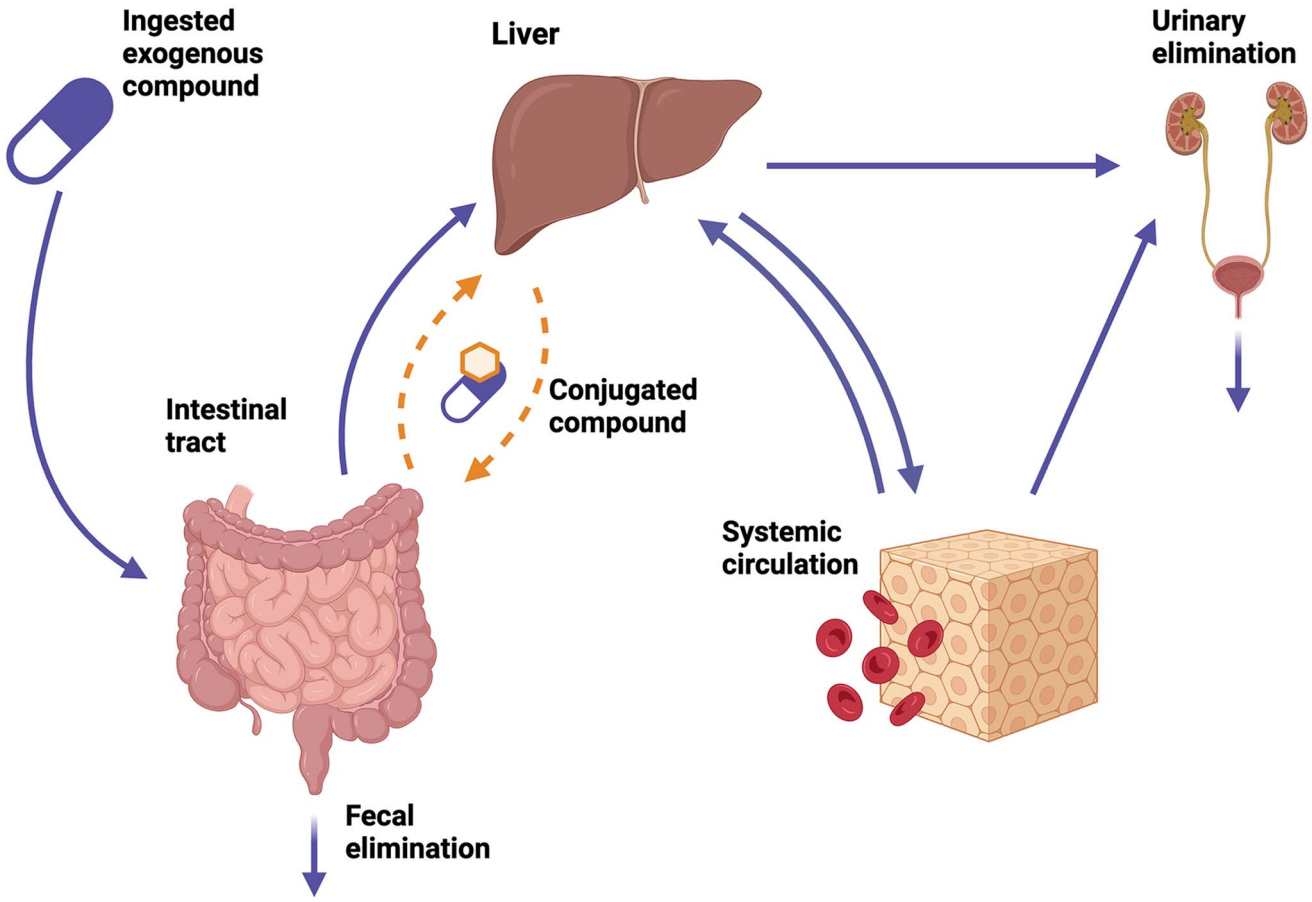

Figure 2. Abstraction of the enterohepatic circulation of exogenous compounds. The solid purple arrows represent the typical flows of an ingested drug or contaminant. The dashed orange arrows indicate the recycling of certain conjugated compounds. Created with BioRender.com.

Background on phthalates

In 2014, an estimated 70% of the 8.4 million tons of globally produced plastics contained phthalates, a heterogeneous group of chemicals used in a wide array of consumer and industrial products.[30,34] Phthalates vary in their molecular weight, a property which dictates their specific industrial application; low-molecular weight (LMW) phthalates such as dimethyl phthalate (DMP) and diethyl phthalate (DEP) (Figure 3) are used in aerosolized products as solvents and/or fragrance carriers, whereas high-molecular weight (HMW) phthalates such as diisononyl phthalate and Bis(2-Ethylhexyl) phthalate (DEHP) (Figure 3) are used as plasticizers mainly, but also as components of bindings and building materials.[36] Alarmingly, HMW phthalates may be found in products used to both package and process food, and have historically been used in plastic products which may otherwise come in contact with the mouth, such as plastic children's toys.[36] Given the tendency of phthalates to leech from the product of which they are a component of, oral exposure and ingestion of the contaminants represents an exposure route of toxicological relevance.[36] Phthalates of both categories, HMW and LMW, are considered as EDCs and toxic to reproductive health, though the compounds have been shown to adversely influence indices of metabolic, intestinal, and immune system health and have further been shown to adversely affect the health of organs both inside and outside of the reproductive system.[37–42] Driven by concerns of accidental oral exposures as well as then-novel research documenting their reproductive toxicity, the United States instituted the Consumer Product Safety Improvement Act of 2008 (CPSIA), banning the use of Bis(2-ethylhexyl) phthalate, dibutyl phthalate, benzyl butyl phthalate (DEHP, DBP, and BBP, respectively) in children's toys or child care products which contain more than 0.1% by weight of the respective phthalates after their production; an interim ban on diisononyl phthalate (DiNP) was instituted at this time, made permanent in 2017.[37,43]

Beyond usage and application in industry, the molecular weight of a given phthalate further determines its toxicokinetic properties and is thus central to its metabolic fate, following accidental exposures in humans.[44] Following oral exposure, ubiquitous hydrolysis of both HMW and LMW phthalates to their monoester constituents in the lumen of the small intestine occurs, a product of non-specific esterases and lipases.[45,46] Once hydrolyzed, luminal monoester absorption decreases as the molecular weight of the parent compound increases.[46] Little to no unhydrolyzed diesters are absorbed in the lumen of the small intestine, though small amounts of compounds may be absorbed in this manner in cases of high exposures.[46] Following intestinal absorption

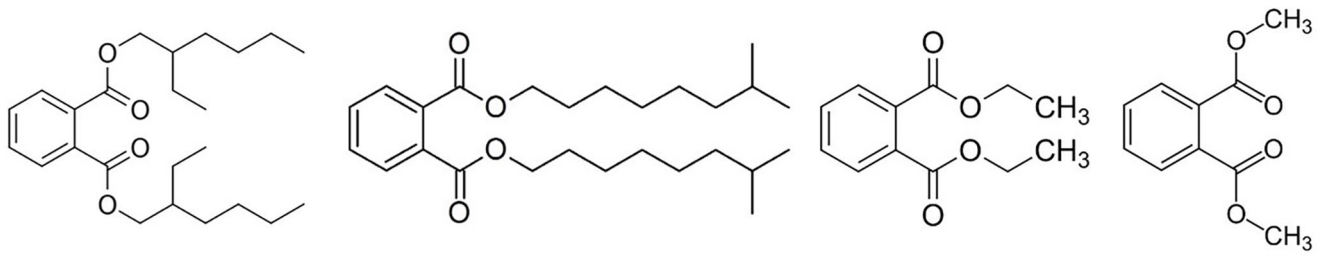

Figure 3. 2D structures of commonly used phthalates, in order from left to right: Bis(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP), diethyl phthalate (DEP) and dimethyl phthalate (DMP) [Public Domain Images].

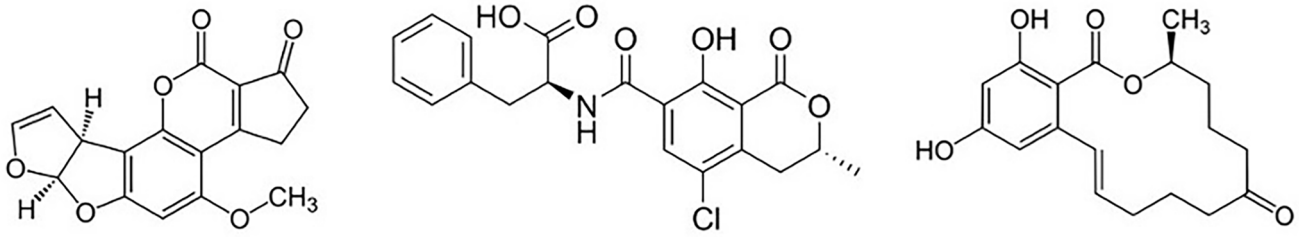

Figure 4. Mycotoxins from left to right: aflatoxin B1, ochratoxin A, zearalenone [Public Domain Images].

and flux from the basolateral membrane, monoesters of phthalates are transported to and taken up by the liver; the more hydrophobic phthalates undergo multiple biotransformations via hepatic microsomal systems and can further be conjugated with glucuronic acid and excreted in the urine.[45,47] Contrarily, monoesters derived from low-weight phthalates are primarily excreted as untransformed metabolites in urine, exhibiting low degrees of biotransformation once they reach the liver.[47,48] Proceeding such transformations, metabolites are excreted in urine and/or feces, again dictated by the molecular weight of the phthalate in question; a greater proportion of HMW phthalate metabolites are excreted in feces compared with LMW phthalates where most metabolites (~80%) have been shown to be excreted in urine.[49] Weight-specific toxicokinetic patterns are further apparent following inhalation, dermal, and intravenous phthalate exposures. As the focus of our review is centered around interactions of dietary contaminants with microorganism constituents of the microbiome, we will not cover such routes of exposure in detail in this review.[49]

Accidental oral ingestion of phthalate-contaminated foods is thought to be the principal means of phthalate exposure in humans, and most commonly is a product of HMW phthalate contamination, as materials that contain foods are usually manufactured with phthalate-containing plastics.[36] Discussed above, HMW phthalates are hydrolyzed to a lesser degree than LMW phthalates, potentiating traversal of HMW phthalates from the upper GI tract to the colon, unperturbed.[46] Whether or not the phthalates interact with and/or are metabolized by colonic microorganisms is a question that is ongoing, but remains a gap in the literature to date. Further investigations into this relationship would provide important, toxicological insight into the nature of phthalate-mediated adverse health effects, as a consequence of microbiome dynamics.

Background on mycotoxins

Mycotoxins are secondary metabolites of various fungi that can contaminate crops, foodstuffs, and grain feeds, with the capacity for acute toxicity and long-term effects on human and livestock health. Approximately 300–400 mycotoxins have been identified, with prior analyses showing over 70% of grain samples are contaminated with at least one of these compounds.[50,51] The World Health Organization warns that most mycotoxins are chemically stable, survive food processing, and can contaminate crops both pre- and post-harvest.[52] The more prevalent of these contaminants include aflatoxins, ochratoxin, and zearalenone (ZEN), with their representative forms depicted in Figure 4.[53]

Aflatoxins are produced primarily by *Aspergillus flavus* and *Aspergillus parasiticus*, with aflatoxin B1 (AFB1) believed to be the most potent compared with aflatoxin B2 (AFB2) and aflatoxin (AFM1).[54,55] These molds and their metabolites are prevalent in cereals, oilseeds, spices, and tree nuts, with AFM1 even found in milk of animals that ingest contaminated feed.[52] Acute ingestion of aflatoxin at low doses causes a range of digestive discomfort and symptoms, while high doses can cause death due to extreme liver damage.[52,54] Chronic aflatoxin exposure can cause hepatotoxicity, immunotoxicity, and hepatocellular carcinomas.[54,56,57] Specifically, AFB1 and AFM1 are absorbed from the intestines and metabolically activated in the liver into a genotoxic epoxide which forms a DNA adduct on the antitumor TP53 gene, but can also bind to proteins and RNA.[52,54] Aflatoxin is eliminated from humans through urine and feces in metabolite forms AFM1, AFQ1, and AFB-N7-guanine, with the AFQ1 form primarily excreted through feces.[58] Aflatoxins are an archetype of mycotoxins, demonstrating acute and chronic toxicity as well as carcinogenicity following ingestion.

Ochratoxins are produced during crop storage by *Aspergillus* and *Penicillium* species, and are known to contaminate cereals, coffee beans, spices, vine fruits, and wine and grape juice.[59] OTA distributes primarily throughout the kidneys, liver, muscle, and fat before elimination through both urinary and fecal routes.[60] Reabsorption from the intestines following biliary excretion and from kidney tubules contributes to OTA's long half-life and is also variable between species.[60] The primary effect of OTA ingestion is kidney damage, with evidence of renal carcinogenicity in animal models.[52,61] OTA may also target the developing central nervous system as a teratogen and has been associated with some human nephropathies, but its effects on human health are poorly characterized and debated.[61,62]

ZEN is an estrogenic compound mainly produced by *Fusarium graminearum* strains in cool, humid conditions, with ZEN contamination occurring in both pre- and post-harvest time frames.[50,57] Farm animals such as cows, sheep, pigs, and poultry are exposed through contaminated feed, whereas humans are exposed through direct plant consumption, breakfast cereals, and some animal products, such as eggs and milk.[3,63,64] Following ingestion, ZEN is similarly well absorbed in rats, rabbits, and humans and circulates between the intestines, blood, and bile.[65] The two primary biotransformation pathways proposed for ZEN are (1) hydroxylation into α- and β-zearalenol (α-ZEL, β-ZEL), and (2) conjugation with glucuronic acid, and additional metabolites include the similarly named α- and β-zearalanol (α-ZAL & β-ZAL); however, their relative estrogenicity and elimination via urine fluctuate between species.[50] Short-term ingestion of ZEN often results in no visible symptoms, as ZEN toxicity is low, but long-term exposure may cause reproductive disorders.[57] ZEN shows stronger affinity for ERα than ERβ.[66] While adverse effects due to acute ZEN exposure are of low concern, enterohepatic circulation and repeated consumption of contaminated animal products pose a risk of chronic exposure.

Complicating mycotoxin exposures are the "masked mycotoxins," conjugates produced by host plants in defense against xenobiotics. These conjugated mycotoxins remain in plant tissues through food or livestock feed processing but are not screened for and are thus "masked."[67] Because of this masking, exposure estimates to mycotoxins like ZEN, deoxynivalenol, and OTA, do not account for the full dose of mycotoxins ingested and may underestimate their risk.[67] The survivability of glucuronidated forms of ZEN (ZEN14Glc), α-ZEL (α-ZEL14Glc), and β-ZEL (β-ZEL14Glc), was assessed using a system of *in vitro* digestive compartments simulating stomach acid breakdown, absorption by intestinal epithelia, and modification by anaerobic microbiota from human feces.[68] Both the unmodified and glucuronidated compounds survived the stomach compartment, and while unmodified ZEN and its alpha and beta versions were absorbed by the intestinal epithelia, the ZEN glucuronides went unabsorbed but were deconjugated (97% reduction of dose) by the fecal microbiota.[68] While unmodified mycotoxins like ZEN can be absorbed, masked mycotoxins survive digestion and absorption by the host, but are modified by colonic microbiota to release the parent mycotoxin.

Search methodology

A literature search was conducted in PubMed to determine what is known about dietary xenoestrogens in the context of the gut microbiome, alongside what the most prevalent methods are for studying gut microbial communities. To begin this process, four search queries were constructed to gather information about (1) the compound class toxicokinetics, (2) gut microbiome exposure to the compounds, (3) microbiota–compound interactivity, and (4) estrogenic specifications for compounds. The search queries were tailored to each class of compounds included in the review and applied to PubMed. The initial search was restricted to English-language articles from the past decade, before expanding to include articles from back to the 1980s detailing early studies on toxicokinetics of these compounds, and their biodegradation by environmental microbiota. The search queries and query-specific results in square brackets are listed in Supplement 1. Of the initial 974 total results, filtering by abstract for relevance produced 165 articles for further consideration. Screening by text reading arrived at 63 articles contributing to background information and 54 articles considered in the results section regarding microbiota–compound interactions, with an overlap of 5 articles. An additional 5 articles were manually sought out to expand the background on microbiota. Overall, 117 studies, prior reviews, and reports were included in this review.

Microbial biodegradation of BPs

BP degradation by microbiota was initially studied from the perspective of environmental contamination, focusing on microbial consortia from wastewater treatment facilities, rivers, and soils. These studies identified BP biodegradation under aerobic and anaerobic conditions by various genera, including *Pseudomonas* and *Bacillus* species, and inspired the hypothesis gut microbiota could exhibit the same activity.[69,70] Also noteworthy is the implication of the xenobiotic-metabolizing superfamily Cytochrome P450 and ammonia monooxygenase as enzymes which appear to play a role in BP biodegradation, but this activity was identified in wastewater sludge microbiota and *Escherichia coli*, and has not been assessed in gut microbiota.[71,72]

BP-induced microbial community changes

Beyond environmental pollution, BPs' status as dietary contaminants introduces a concern for interaction with gut microbiota. The kinds of interactions considered are contaminant-induced changes in microbial community structure, biotransformation of the contaminant, and signaling effects resulting from the contaminant, as conveyed in Figure 5. Several studies reflecting the more recent interest in BPA–microbiota interactions are summarized below, exploring multiple models for investigating this relationship. Even the offspring of individuals who ingest BPA are at risk, as BPA has been shown to pass through the placental barrier and accumulate in the fetal gut.[73] A study on BPA in diet using California mice (*Peromyscus californicus*) sought to identify

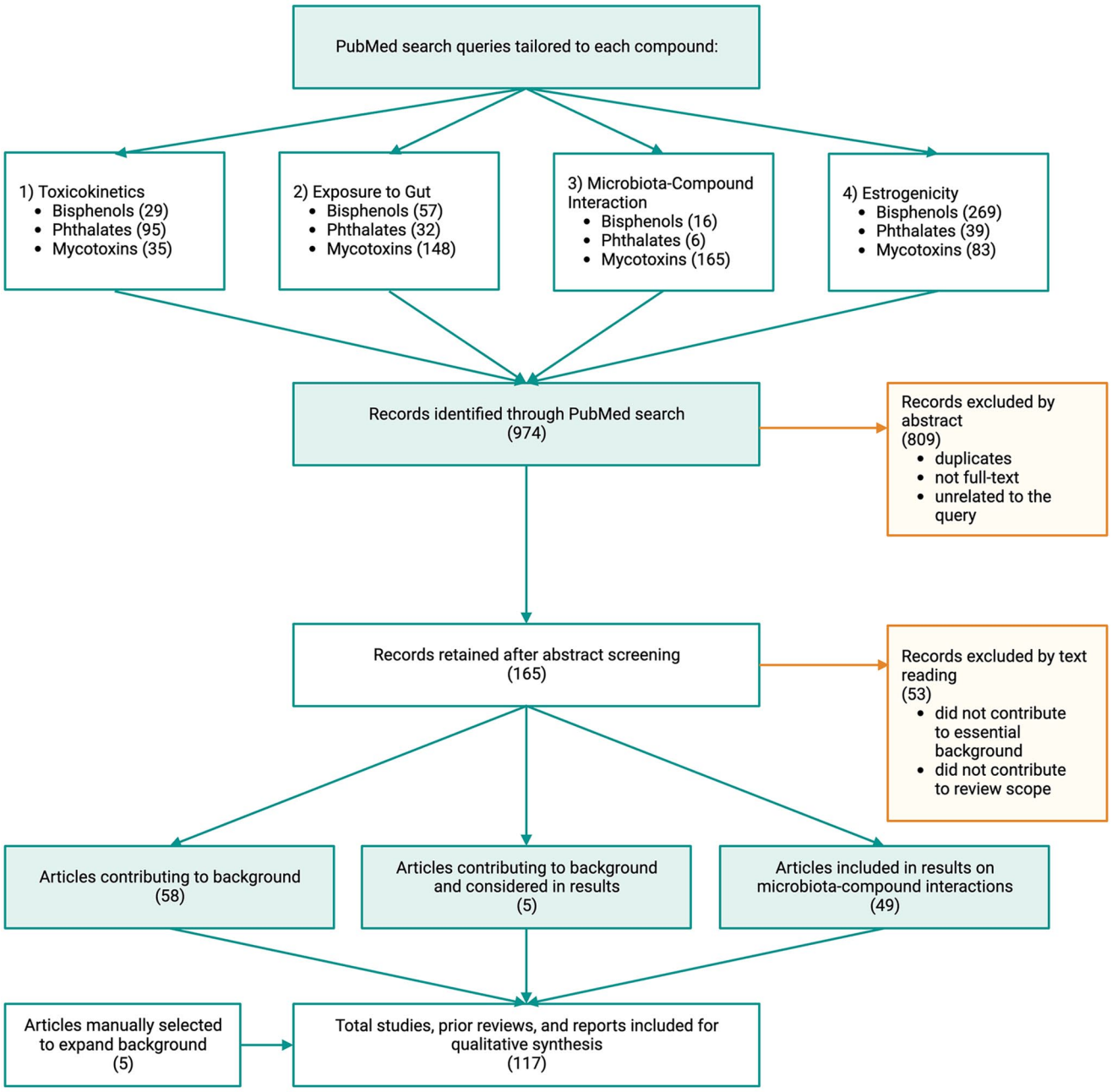

Figure 5. Flowchart of papers included in the review. Created with BioRender.com.

changes to the gut microbiome in exposed parents and offspring. Parent mice were placed on a control diet or 50 mg/kg feed weight BPA-supplemented diet prior to breeding, and offspring were exposed pre-conception through weaning via maternal exposure.[74] Principal Coordinates Analysis (PCoA) and linear discriminant analysis effect size (LEfSe) on the 16S rRNA gene sequencing of microbial communities did not find overt treatment-based patterns in bacterial classes, but LEfSe did identify microbes associated with specific sex, generation, and treatment intersections (see Table 1, row 1).[74] This study is representative of other microbiome investigations in that treatment effects are likely to be subtle and require a nuanced view of the various sample characteristics, and also highlights the need to better characterize sex-specific effects of BPA on host microbiota (Figure 6).

An investigation into intestinal inflammation from perinatal BPA exposure sought to identify alterations to the offspring's gut microbiome as the cause. Pregnant Dutch-belted rabbits were orally exposed to either 0 or 200 µg/kg BW/day BPA to create a gestational and lactational (collectively "perinatal") exposure scenario for the offspring.[75] Fecal samples from dams and offspring were collected weekly, and serum, colon, and liver samples were taken after euthanasia on postnatal week 6.[75] The microbiota of the rabbits were profiled via 16S rRNA gene sequencing and revealed Bacteroidota and Bacilliota as the two dominant bacterial phyla across all sample types and treatments.[75] Beta diversity levels showed distinct clustering by treatment when considering feces, colon, and cecum independently, but no significant differences were detected between

Table 1. Intestinal microbiota abundance changes following contaminant exposure.

	Subject compound	Study	Model	Identification method	Dose and exposure	Contaminant-associated abundance changes (reported as notable or statistically significant)
1	BPA	Javurek *et al.*[74]	California mice; M/F; parents and offspring	16s rRNA gene sequencing	0, 50 mg BPA/kg feed weight; oral exposure through supplemented diet for parents, gestational and lactational exposure for offspring	↑*Sutterella* spp., *Clostridiales*, *Mogibacteriacae*, *Mollicutes*, *Prevotellaceae*, *Bifidobacterium* spp. ↓*Lactococcus* spp., *Desulfovibrio* spp., *Oxalobacter* spp.,
2	BPA	Reddivari *et al.*[75]	Dutch-belted rabbits; dams; M/F offspring	16s rRNA gene sequencing	0, 200 µg BPA/kg bw/day; oral exposure through carrot puree for parents, gestational and lactational exposure for offspring	↑*Methanobrevibacter* spp., *Dorea* spp., *Bilophila* spp., ↓*Bacteroides* spp., *Ruminococcus* spp., *Akkermansia* spp., *Odoribacter* spp., *Oscillospira* spp.,
3	BPA	Feng *et al.*[81]	CD-1 mice; male	16S rRNA gene sequencing	0, 50 µg BPA/kg bw/day; oral exposure through supplemented diet	↑*Proteobacteria*, ↓*Verrucomicrobiota*, *Akkermansia*,
4	BPA	Ni *et al.*[76]	C57BL/6 mice; M/F	16S rRNA gene sequencing	0, 50 mg BPA/kg bw/day; oral exposure through supplemented diet	↑Bacilliota, *Verrucomicrobiota*, *Proteobacteria* (in females), *Oscillibacter*, *Ruminiclostridium* 9, *Tyzzerella*, *Ruminococcaceae* NK4A214 group, *Desulfovibrio* ↓Bacteroidota, *Proteobacteria* (in males), *Alloprevotella*, *Muribaculum*, *Allobaculum*, *Ruminococcus* 1, *Parabacteroides*, *Akkermansia*, *Erysipelatoclostridium*, *Candidatus Soleaferrea*, *Christensenellaceae* R-7 group
5	DEHP	Lei *et al.*[98]	C57BL/6 mice; female	16S rRNA gene sequencing	0, 1 or 10 mg/kg bw/day	↑ *Lachnoclostridium* ↓ *Akkermansia*, *Odoribacter*, *Clostridium sensu stricto*
6	DEHP	Wang *et al.*[89]	Rats (Wistar, Sprague Dawley) and mice (BALB/c, C57BL/6 J); male; 4 weeks-old	16S rRNA gene sequencing	300, 1000, and 3000 mg DEHP/kg BW/day	↑*Runimococcaceae* and *Rikenellaceae* (Feces; BALB/c), *Oscillospira*, *Peptostreptococcaceae*, *Mycoplasma*, *Roseburia*, *Clostridiaceae*, *Sutterella*, *Clostridiales*, RF32, *Christensenellaceae*, *Blautia*, rc4-4 (Feces; SD rats), *Adlercreutzia*, *Eubacateriaceae* (Feces; Wistar rats), *Rikenellaceae* (cecal content; BALB/c), *Ruminococcus* (cecal contents; C57LB/6J), *Actinomyces*, *Arthrobacter* and *Porphyromonas* (cecal contents; SD rats), ↓*Bacteroides* (Feces; BALB/c), *Prevotella*, *Lachnospiraceae*, and *Desulfovibrio* (Feces; C57LB/6J), *Prevotella* (Feces; SD rats), *Coprococcus*, *Dehalobacteiaceae* (Feces; Wistar rats), S24-7 (cecal content; BALB/c), *ctinobacteria*, *Desulfovibrio*, *Allobaculum*, *Bifidobacterium*, *Lactobacillus*, *Prevotella*, *Adlercreutzia*, *Desulfovibrionaceae*, *Clostridiaceae* (cecal contents; C57LB/6J), *Bacteroides* (cecal contents; SD rats), *Desulfovibrionaceae* and *Ruminococcus* (Wistar rats)

(Continued)

Table 1. (Continued)

	Subject compound	Study	Model	Identification method	Dose and exposure	Contaminant-associated abundance changes (reported as notable or statistically significant)
7	DEHP	Yu *et al.*[91]	Sprague Dawley rats; female	16S rRNA gene sequencing	0.5 mg DEHP/kg bw/day	↑ *Akkermansia*, *Oscillibacter*, *Pseudoflavonifractor*, Unclassified_*Clostridiales*, Unclassified_*Desulfovibrionaceae*, Unclassified_*Lachnospiraceae*, and Unclassified_*Ruminococcaceae* ↓ *Acetivibrio*, *Alloprevotella*, *Barnesiella*, *Clostridium_IV*, *Clostridium_XIVa*, *Lachnospiracea_incertae_sedis*, *Lactobacillus*, *Prevotella*, *Roseburia*, *Ruminococcus*, and Unclassified_*Porphyromonadaceae*
8	DEHP	Yang *et al.*[97]	Human newborn infants	16S rRNA gene sequencing	DEHP-containing IVs (dose unknown; exposure confirmed through urinary metabolite concentrations)	↓*Rothia sp*. and *Bifidobacterium Longum*
9	DEHP	Zhao *et al.*[93]	Sprague Dawley rats	16S rRNA gene sequencing	500 mg DEHP/kg bw/day	Abundant genera of jejunal microbiome differed in rats treated with DEHP versus those in the control group; no significant changes at the genus level observed in the ileal or colonic microbiome
10	DBP	Zhang *et al.*[96]	Sprague Dawley rats; male; 8 week-old	16S rRNA gene sequencing	500 mg/kg of dibutyl phthalate/day	↑*Prevotella* spp. ↓*Corynebacterium* spp.
11	DBP	Xiong *et al.*[90]	C57BL/6J mice; male	16S rRNA gene sequencing	0, 0.1, and 1 mg/kg/day	↑ Bacilliota and α-proteobacteria (Phylum); *Prevotella*, *Desulfovibrio*, *Sutterella*, and *Bacteroides* (genus) ↓ Bacteroidota and Verrucomicrobia (phylum); *Oscillospira*, *Parabacteroides*, *Akkermansia*, *Odoribacter*, and *Helicobacter* (genus); decrease in diversity via Shannon/Simpson indices
12	DEHP	Su *et al.*[88]	C57BL/6J mice; male	16S rRNA gene sequencing	0, 0.05, and 5 mg DEHP/kg bw/day	↑ *Streptococcus* and *Butyrivibrio* ↓ *Lactobacillus*
13	DEHP	Adamovsky *et al.*[94]	Zebrafish; M/F	16S rRNA gene sequencing	0 or 3 mg DEHP/kg bw/day	↑ *Fusobacteria*, *Bacteroidetes*, and *Verrucomicrobia* ↓ *Verrucomicrobiae*, *Saccharibacteria*
14	DiNP	Chiu *et al.*[99]	CD-1 mice; Female	16S rRNA gene sequencing	20 µg, 200 µg, 2 mg, 20 mg or 200 mg/kg bw/day	↑ *Blautia*
15	DEHP	Wei *et al.*[92]	CD-1 (ICR) mice; male	16S rRNA gene sequencing	0, 5, and 25 mg DEHP/kg bw/day	↑ *Allobaculum* ↓ *Bacteroides*
16	AFB1, OTA	Sobral *et al.*[107]	*In vitro* digestion model involving Caco-2 cells coupled with human-derived colonic fermentation compartment	16S rRNA gene sequencing	Experimental "Snack" meals contaminated with 9 µg of AFB1, 9 µg of OTA or simultaneous contamination 6 µg of AFB1 and 6 µg of OTA	↓ *Bacteroidaceae*, *Ruminococcaceae* and *Lachnospiraceae*
17	ZEN, DON	Saenz *et al.*[64]	Fecal samples from weaned piglets	Metaproteomics	DON(low): 870 µg DON/kg feed, DON(high): 2493 µg DON/kg feed or ZEN(low): 679 µg ZEN/kg feed, ZEN(high): 1623 µg ZEN/kg feed	↑ Proteins associated with antioxidant capacity; Bacteroidetes phylum ↓ Proteins associated with carbohydrate metabolism; Bacillota phylum
18	ZEN	Zada *et al.*[105]	Bacterial isolates from food and rumen samples	16S rRNA gene sequencing	ZEN dissolved in DMSO for a final concentration of 25 ng/mL	↑ *Lactobacillus*, *Pseudomonas*

(Continued)

Table 1. (Continued)

	Subject compound	Study	Model	Identification method	Dose and exposure	Contaminant-associated abundance changes (reported as notable or statistically significant)
19	ZEN, DON	Reddy *et al.*[108]	Castrated 8-week-old male piglets; pigs; male – castrated; 8 weeks-old (piglets)	16S rRNA gene sequencing	DON and ZEN at 8 mg/kg feed and 0.8 mg/kg feed, respectively	↑ *Lactobacillus*, *Prevotella* ↓ *Clostridiaceae*, *Bulleidia*, *Clostridiales*
20	ZEN, DON	Le Sciellour *et al.*[109]	Pigs; M (castrated)/F	16S rRNA gene sequencing	DON- and ZEN-contaminated diet (3.02 mg DON/kg feed and 0.76 mg ZEN/kg feed) at day 113 and 134	↑ *Erysipelotrichaceae* ↓ *Ruminococcaceae*, *Streptococcaceae*, and *Veillonellaceae*
21	OTA	Izco *et al.*[110]	BALB/c mice	16S rRNA gene sequencing	OTA (0.21, 0.5, or 1.5 mg/kg bw)	↑ *Bacteroidetes* ↓ *Bacillota*
22	ZEN	Jia *et al.*[111]	Broiler chickens; M/F; 1 day-old	16S rRNA gene sequencing	2.5 mg/kg/bw ZEN, microbial inhibition, and microbial inhibition + 2.5 mg/kg/bw ZEN	↑ *Bacillota* ↓ Bacteroidota

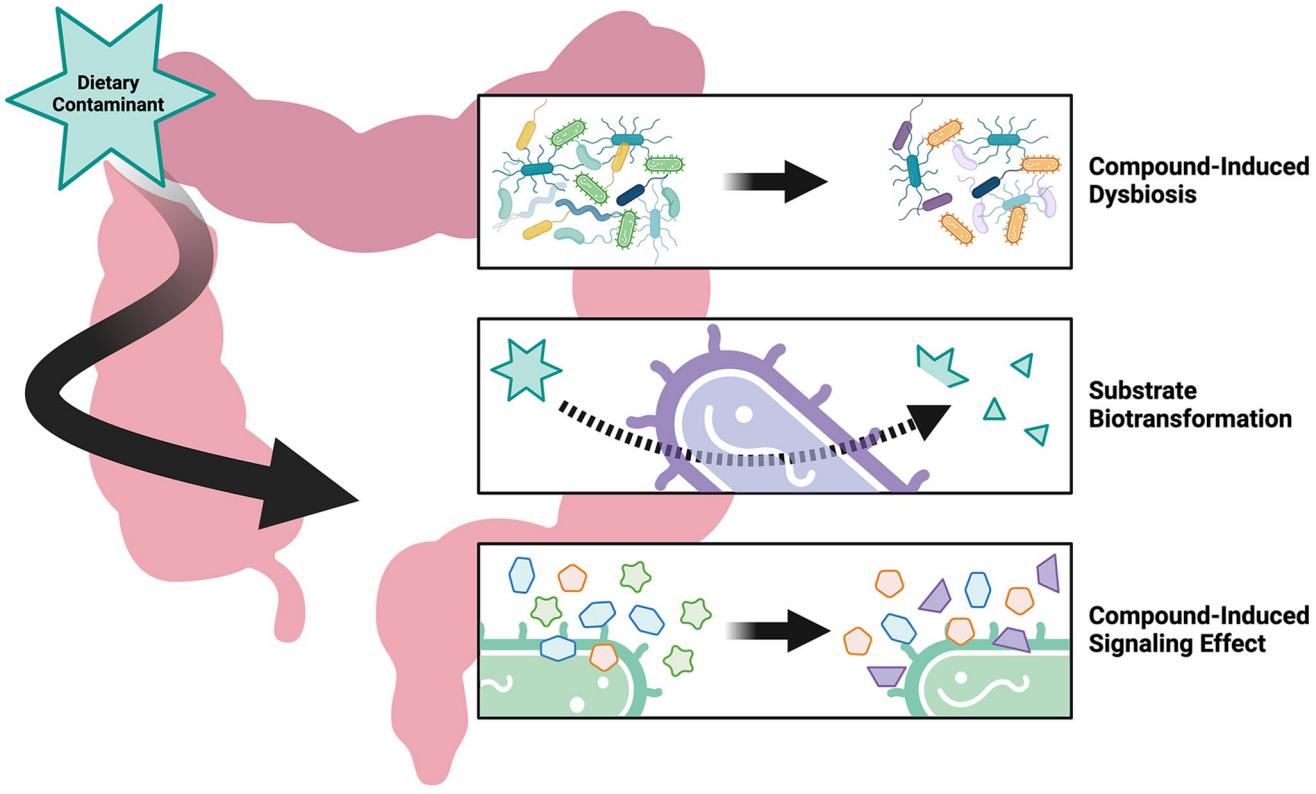

Figure 6. Abstraction of the contaminant–microbiota bidirectional relationship. Created with BioRender.com.

exposed and control offspring using a PERMANOVA on the weighted UniFrac distances.[75] A LEfSe identified differentially-abundant microbes between BPA-exposed and control dams and offspring, for each sample type (see Table 1; Study 2). In addition, there was a significant reduction in acetic and propionic acid levels in feces from BPA-exposed offspring.[75] Furthermore, BPA exposure induced colonic and liver inflammation in dams and pups, and while this inflammation and the microbial dysbiosis were both associated with BPA, the authors recommended further studies to determine if the dysbiosis was a consequence of the inflammation or direct action from BPA.[75] Also related to GI inflammation, BPA has been shown to exacerbate dextran sodium sulfate-induced colonic inflammation in mice.[76] In female ovariectomized C57BL/6 mice, 50 µg/kg bw/day BPA ingestion reduced fecal levels of tryptophan and of

microbially derived metabolites of aromatic amino acids, demonstrating BPA alters gut microbial metabolic profiles.[76] Of note, serotonin and its metabolite hydroxy indoleacetic acid (HIAA), which are important to intestinal function, were among the metabolites reduced by BPA treatment, and taken with the disease measures may indicate a mechanism by which BPA worsens colonic disease.[76]

Exploring the effects of BPs on human gut microbiota generally involves bioreactor systems inoculated with either whole communities from a fecal sample or select, representative strains. The simulator of human intestinal microbial ecosystem (SHIME) consists of five bioreactors representing the stomach, small intestine, and the ascending, transverse, and descending colon, wherein the compartments simulate the passage of material through the GI tract and only the colonic compartments receive bacterial inoculation.[77] To study BPA bioavailability and effects following digestion, a SHIME was inoculated with an antibiotic-free human fecal sample and exposed to 25, 250, and 2500 µg/L BPA for 10 days each. HPLC analysis found BPA concentrations for the three doses decreased significantly by 28.7%, 44.6%, and 61%, respectively, between the stomach and the small intestine.[77] Smaller, gradual decreases in BPA bioaccessibility occurred between each subsequent chamber for the higher two doses.[77] The main phyla identified in the colon compartments were Bacilliota, Bacteroidota, *Proteobacteria*, and *Actinomycetota*, and BPA exposure reduced community richness in all three compartments according to Chao1 and Ace indexes, except for the higher two doses in the descending colon, which instead increased richness.[77] Analysis using the Shannon index revealed BPA exposure increased diversity in the first two colon compartments but decreased in the descending colon, and furthermore, BPA exposure reduced community differences between the colon compartments compared with the control SHIME.[77] The authors also reported BPA exposure increased the abundance of possible BPA-degrading genera, such as *Lactobacillus* and *Alcaligenes*.[77] In summary of the SHIME experiment, GI digestion decreased BPA bioavailability as hypothesized, and the remaining BPA from multiple dosing levels altered microbial community composition compared with control bioreactors, with several human-associated gut microbiota enriched supporting their role as BPA degraders.[77] Another study used a bioreactor approach to explore bacterial activity and function in extended simplified human intestinal microbiota (SIHUMIx), composed of eight representative species from the human microbiome, acclimated in brain–heart infusion medium before exposure to 45 µM BPS.[78] The authors found BPS did not alter growth or total biomass, nor did it alter short-chain fatty acid levels.[78] Metaproteomics were used to identify relative abundances of species, which were similar in all bioreactors on day 7 (the day of BPS or DMSO addition), differed by treatment on day 8, and reached a similar state between treatments by day 14.[78] The results indicated no long-term effect from BPS treatment, and the differences between day 14 abundances and those of the adaptation phase (d1-7) may be attributed to DMSO solvent.[78] It is worth mentioning the SIHUMIx does not contain the typical microbiota responsive to BP treatment, *Akkermansia* and Bacilliota members, and being composed of only eight species, may not be the best model when assessing subtle effects of a contaminant on whole community structure.

López-Moreno *et al.* (2021) sought to identify human gut microbes that could metabolize BPA in the interest of probiotic BPA detoxification. Ten microbial isolates from the feces of 0–1-year-old infants and 6–8-year-old children were incubated in BHI/MRS medium spiked with BPA concentrations ranging from 0.5 to 50 ppm.[79] Subsequently, BPA-tolerant strains were incubated in pure cultures for additional identification and characterization methods (such as catalase activity, gram staining, and motility tests).[79] They found the BPA-tolerant isolates were predominantly related to the *Bacillus* genus, and *Bacillus sp*. AM1 could best tolerate higher BPA concentrations but could not grow in BPS-enriched medium, suggesting its BPA-degrading pathways may not translate to BPS.[79] This was the first article to identify BPA-degrading microbial isolates from human fecal samples and describe the plausible degradation pathways, corroborating the importance of the Bacilliota phylum and *Bacillus* genus in this process with a review of bacteria-mediated BPA degradation by Zhang et al.[70]

Regarding multiple BP analogs, zebrafish were used to compare the degree of microbial dysbiosis caused by the different compounds. The zebrafish microbiome is complex and contains similar enzymes and biochemical pathways as mammalian microbiota, despite the former being dominated by *Proteobacteria* and the latter primarily featuring Bacilliota and Bacteroidota.[80] Zebrafish embryos were incubated with BP doses from 0 to 45 µM (adjusted per compound) to assess the developmental toxicity and behavioral effects of BPA, BPAF, BPB, BPF, and BPS, as informed by prior toxicity data on BPs in zebrafish from the iCSS ToxCast Dashboard.[80] The developmental toxicity assessment using 11 estrogen receptor (ER)-based toxicity assays ranked the descending potency of the BPs as BPAF > BPB > BPF, BPA > BPS, with corresponding no observed effect concentrations (NOEC) as follows: 1.8, 5.1, 15.3, 11.5, and 45 µM.[80] From 16S rRNA gene sequencing, the researchers observed moderate variation in community structures among DMSO vehicle controls, but non-metric multidimensional scaling (NMDS) analyses still detected significant concentration-dependent changes in microbial community structure due to BPS, BPA, and BPF (ANOSIM $p < 0.05$).[80] The summary of community structure assessments revealed BP developmental toxicity was inversely related to microbial disruption.

Beyond just gut health, growing interest in gut–organ axes has encouraged investigations into how dietary contaminants impact target organs by way of modifying gut function. A study on male CD-1 mice fed a diet supplemented with 50 µg/kg bw/day BPA for 24 weeks was focused on how BPA impacts liver health through its interactions with gut microbiota. The dose was comparable to the pre-2015 TDI set by the EFSA, and the study found significant increases in liver weight, liver proportion of bodyweight, fat accumulation in liver cells, total cholesterol, and total triglycerides in BPA-exposed animals compared with controls.[81] Analyses on 16S rRNA gene sequencing of microbiota from collected feces found BPA-exposed mice had fewer observed species and lower alpha diversity Shannon index scores, with significant differences summarized in Table 1 (row 3).[81] The study

also found increased lipopolysaccharide (LPS) level and liver inflammation via the TLR4/NF-κB pathway in BPA-exposed animals, and all results taken together support an association between BPA, gut microbial community disruption, and liver steatosis.[81] Considering next the gut–microbiota-brain axis, a study by Ni *et al.* (2021) found dietary intake of 50 mg/kg bw/day BPA induced cognitive impairment of male C57BL/6 mice, increased neuroinflammation, and altered gut microbiota composition. After 12 weeks of feeding, starting from 7-week-old mice, males exposed to BPA had poorer performance on various cognitive tests compared with controls, but female performance was unaffected.[82] In addition, BPA exposure reduced the level of Claudin-1, a tight-junction marker, in the blood–brain barrier (BBB) and colonic tight-junctions of male mice, and lower BPA doses fed to male mice similarly reduce mRNA levels of several BBB and colonic tight-junction markers.[82] 16S rRNA sequencing of cecal feces found significantly reduced alpha diversity along the Chao1, Ace, Shannon, and Simpson indices in BPA-exposed males only compared with controls, and BPA exposure also caused discrimination in beta-diversity in male mice.[82] Table 1 (Study 4) lists the microbial taxa whose relative abundance were significantly increased or decreased relative to BPA exposure, as identified by LEfSe. Spearman correlation analysis found, in general, that BPA-reduced bacterial taxa were positively correlated with the behavioral test results, while BPA-enriched bacteria were negatively correlated with these same results, and these correlations held true for tight-junction-related gene expression, learning and memory-associated gene expression, and short chain fatty acid (SCFA) levels.[82] The results from Feng *et al.* (2020) and Ni *et al.* (2021) display clear associations between BPA disruption of gut microbial communities and negative health effects on the liver and brain; however, further studies are required to confirm if these organ toxicities actually result from gut microbial disruption or direct action of BPA.

Summary of microbiota–BP interactions

Literature from the past two decades supports the assertion that BPs alter gut microbial community structures and metabolomic profiles, and that colonic microbiota can modify or degrade BPs to varying degrees. However, more research is needed to identify consistent patterns of community alterations due to BPs, as only minor findings are replicated between studies. Reduced *Akkermansia* and Bacteroidota members' relative abundance compared with controls was associated with BPA between multiple mouse studies and one study on rabbits. Increased relative abundance for Bacilliota phylum members was associated with BPA treatment in several experiments, one finding that multiple Bacilliota members were among the most BP-tolerant species.[79] Paired with studies on environmental biodegradation of BPA, *Bacillus* members may be BP degraders and should be explored further in the gut microbiome. Beyond these observations, there is a lack in reproduced results regarding BPA-induced alterations to microbial communities, likely due to large interspecies and even interindividual variations in gut microbial composition. There is insufficient data for other BP analogs to determine patterns in gut microbial alterations.

Microbial biodegradation of phthalates

An inverse relationship exists between the weight of a given phthalate and the extent of its hydrolysis in the lumen of the small intestine; as such, the possibility of HMW phthalate–microbiota interactions may exist.[46] Indeed, the capacity of phthalates to interact with microorganisms outside of the mammalian microbiome is evident. Phthalate-degrading bacteria play crucial roles in remediating bodies of water, soil, and sewage systems contaminated with the chemicals, particularly as abiotic methods are slow acting and phthalates are remarkably resilient once they leach into the said environments.[83] BBP, for instance, has an estimated half-life of over 100 years.[84] Consequences of long-standing phthalate contamination of soil, for example, include impairments in nitrogen fixation and proliferation of phthalate-degrading microorganisms at the expense of net microbial diversity.[85–87]

Phthalate-induced microbial community changes

Substantially less is known about phthalate interactions with microorganism constituents of the mammalian microbiome. Much of the *in vivo* evidence to date points to alterations in microbial diversity and accompanying physiological consequences, such as metabolic derangement,[88–92] reproductive organ toxicity,[35,36] and impairments in adaptive immunity.[94] In a multi-rodent study (Wistar Rats, SD rats, BALB/c Mice and C57BL/6J Mice; $n = 6$ rodents/experimental group or $n = 24$ rodents per cohort) DEHP was administered at doses of 0, 300, 1000 or 3000 mg/kg/bw/day for 30 days; following sacrifice, organ, and tissue samples were collected, biochemical analyses were performed quantifying testosterone, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and serum cytokines, cecal/fecal SCFAs were measured, and 16S rDNA sequencing was performed with paired-end sequencing to assess microbiota diversity.[89] Physiological effects of DEHP administration were dose dependent and largely confined to SD rats, but included increases in inflammatory cytokines and cholesterol levels, reductions in serum testosterone, reductions in SCFA production, increased liver and body weight, and decreased reproductive organ weight. Microbiota-specific outcomes were less dependent on rodent species and included an increased Bacilliota/Bacteroidota ratio associated with bodyweight gain, and increased abundance of genera in fecal/cecal samples associated with metabolic derangement.[89] While DEHP-mediated effects on microbial dysbiosis and accompanying physiological impairments were observed in SD rats in the prior study, Su *et al.* (2022) observed similar changes in mice ($n = 24$) following DEHP administration for 14 weeks with two representative doses of DEHP (0.05 and 5 mg/kg of body weight). Although the span of time was longer than the work of Wang *et al.* (2020) the authors further observed body weight increases, hepatic fatty acid accumulation, increased serum insulin, and increased mRNA encoding proinflammatory cytokines.[88] Accompanying impacts of

DEHP administration on the microbiome manifested as phylum and genus-level changes (Table 1, row 12).[88] Elsewhere, rodent models of DEHP exposure show alterations in cholesterol metabolism and bile acid activity in SD rats, outcomes thought to be traced to an increased ratio of Bacilliota/Bacteroidota as well as species-specific correlations with metabolites involved in bile acid and fatty acid metabolism.[91] To date, limited evidence of phthalate-mediated metabolic impairments with accompanying dysbiosis exist with respect to phthalates outside of DEHP, though Xiong *et al.* (2020) showed impaired lipid metabolism, inflammation, and accompanying gut microbiota disturbance following 10-week administration of DBP to C57BL/6J mice. More specifically, the authors noted liver weight and bodyweight increases with accompanying increases to blood lipid and plasma liver enzyme levels, phylum, and genus-level community shifts (Table 1, row 11).[90] Interestingly, this finding parallels the work of Su *et al.* (2022), whereby longer-term DEHP administration (14 weeks) resulted in similar changes to metabolic indices of health with respect to liver health and fatty acid flux in C57BL/6J mice; given that the multirodent work of Wang *et al.* (2020) showed no such changes in C57BL/6J mice over 4 weeks of DEHP administration, an experimental framework of long-term, lower-dose phthalate administration at least in mice may be necessitated when studying dysbiosis-mediated impacts on multiorgan metabolism. Interestingly, the work of Deng *et al.* (2020) showed that 30-day exposure of microplastics alone or microplastics incubated with phthalate mixtures (DEHP, DBP, DMP, DEP) to mice resulted in accumulation of phthalates and microplastics in intestinal tissue (179.89 ± 14.78, 142.42 ± 9.52, 124.95 ± 8.02, and 106.41 ± 8.58 ng/g dry weight of DEHP, DBP, DMP, and DEP, respectively), increased intestinal permeability indices in phthalate/phthalate + microplastic groups, decreased microbial diversity with accompanying metabolites associated with intestinal injury, and altered lipid and energy metabolism.[95]

Multiple studies highlight dysbiosis accompanying phthalate-mediated reproductive toxicity. Compared with those receiving corn oil only, those at postnatal (PN) day 21 administered 500 mg/kg/bw/day DEHP showed histological damage to testicular and intestinal tissue, impaired steroid hormone production, and oxidative stress with accompanying microbial dysbiosis.[93] Differences in jejunal microbiome contents (Table 1, row 9) were seen between treatment and control animals, though no significant differences were observed in ileal or colon contents between groups.[93] Elsewhere, DBP administered at a dose of 500 mg/kg/bw/day was given gestationally to female SD rats; male offspring born to DBP-exposed mothers exhibited deleteriously formed reproductive organs coupled with marked differences in the abundance of various bacterial genera (Table 1, row 10) compared with offspring receiving corn oil controls.[96] The multi-species (Wistar Rats, SD rats, BALB/c Mice and C57BL/6J Mice) work of Wang *et al.*[89] discussed previously showed that DEHP-exposed SD rats exhibited dose-dependent decreases in reproductive organ weights and serum testosterone concentration. Importantly, the authors did not note any significant associations of the observed dysbiosis with the measured reproductive outcomes, in contrast to the associations observed between measured metabolic outcomes.[89] In conjunction with the aforementioned physiological effects, Zhang *et al.*[96] observed a concomitant increase in genera associated with poor testicular function and reduced sperm motility, in the offspring of DBP-exposed mothers compared with control offspring. A more focused association was theorized in the work of Zhao *et al.* (2020) discussed above; following exposure to DEHP, prepubertal male SD rats had jejunum-specific effects with respect to histological damage, oxidative stress, Nrf2 mRNA abundance, and dysbiosis. Coupled with observed reproductive outcomes, the authors speculated that localized jejunal dysbiosis may contribute to DEHP-mediated oxidative stress in the intestine, resulting in increased gut permeability, and subsequent reproductive toxicity *in vivo*. Interestingly, studies elsewhere report that the microbiome influenced the expression of genes encoding steroidogenesis, though these results were independent of phthalate exposure.[93]

Several studies have investigated the relationship of DEHP exposures to dysbiosis and accompanying immune system outcomes. In an experiment examining microbiome composition and immune response to vaccination in human neonates receiving either DEHP-containing IVs or no IVs at all, the authors found that DEHP-exposed neonates exhibited higher urinary concentrations of phthalate metabolites, altered microbiome diversity, and significantly greater anti-HBsAg-IgM response.[97] Control neonates showed a greater abundance of species considered to be "normal" with respect to the developing infant microbiome (Table 1, row 8), compared with those receiving IVs with DEHP. While this study is limited through its small sample size ($n = 25$), it provides evidence of DEHP-mediated impairments in infant immune response as a byproduct of transient dysbiosis.[97] This association is strengthened by controls implemented by the authors of the study, ensuring that the dysbiotic outcomes were, indeed, likely due to transient exposure to the phthalate. To date, only one *in vivo* investigation exists which assesses adaptive immunity in tandem with dysbiosis and phthalate administration; Adamovsky *et al.*[94] exposed male and female zebrafish to daily DEHP (3 mg/kg/bw/day) for two months and found DEHP led to upregulation of gene networks associated with T-cell receptors and associated cytokines, all of which are implicated in diseases such as Chron's and which play roles in neutralization of pathogens and maintenance of the intestinal epithelial barrier. Phylum level increases in Fusobacteria, Bacteroidota and Verrucomicrobia were further observed, leading to the researchers to speculate that the microbiome-mediated shifts could underpin the immune-system dysregulation observed.[94] Importantly, the authors of this study did not note any adverse effects of DEHP on bodyweight or intestinal histopathology, which contrasts much of the rodent-specific research mentioned previously; such a finding further highlights the drastic, interspecies differences seen following phthalate exposure, particularly as the dose administered in this study was designed to mimic daily human exposures.[94] Taken together, DEHP at least may play a role in dysbiosis-mediated immune dysfunction though analysis across different species with respect to this pathophysiological endpoint is necessitated, particularly one which utilizes differing phthalate doses, mixtures, and time points.

Compared with evidence of phthalate-mediated dysbiosis, less is known about microbial degradation of phthalates *in vivo*, though emerging evidence suggests that DEHP is degraded.[98] Lei *et al.* (2019) exposed 6–8-week-old female mice to DEHP and analyzed day 7 + 14 microbial diversity, using fecal-derived 16S RNA sequencing with subsequent operational taxonomic unit (OTU) categorization, and looked at *in vitro* stool samples from the animals after inoculation with DEHP; in both contexts, LC-MS was used to quantify metabolomic changes following phthalate exposure. The results showed increased diversity following DEHP exposure *in vivo* with an increased abundance of *Lachno Clostridium* genus, a species implicated in neurological disorders; MEHP was present in both samples, implying microbial degradation of the phthalate.[98] Lei and colleagues further mapped organism–metabolite correlations via KEGG pathways showing a connection between *clostridium* family and p-cresol production; importantly, production of p-cresol precursor by this bacterial family increased following addition of DEHP to anaerobic batch culture. DiNP administration over 14 days to adult female mice in occupationally and postnatally relevant doses (20 µg/kg/bw and 200 µg/kg/bw, respectively) led to minimal changes in relative abundance of microbiome species compared with control, with the principal change noted as an increase in the relative abundance in *Blautia* in the 20 µg/kg/bw/day DiNP group, though this change was also present in the control; the authors noted that the abundance of *Blautia* was more variable in the control mice, pointing to a more consistent effect of DiNP on relative abundance following exposure in this sample.[99] Importantly, authors used isolated genomic DNA coupled with 16S rRNA gene sequencing and polymerase chain reaction PCR amplification to identify three species capable of utilizing DiNP as a carbon source (*Proteus mirabilis strain ATCC 29,906, Desulfitobacterium hafniense DCB-2 and Paenibacillus barengoltzii strain NBRC 101,215*). Outside of *in vivo* studies in rodents, Kolb, O'Loughlin & Gsell (2019) characterized phthalate-degrading bacteria in the microbiomes of two species of Asian carp. The authors captured $n = 10$ carp from a polluted lake in the south side of Chicago, Illinois; following capture, the carp were dissected and samples of gill, scale, and feces were collected for analysis.[100] Enrichment studies using MSM and infusion of a variety of phthalates (DMP, DEP, and DBP) were undertaken with each anatomical/fecal sample and revealed degrading capacity of microbiome-derived *Bacillus subtilis* strain SK18, *Pseudomonas putida* strain SKTG1, and Consortium SK-1 (predominant genera *Rhodococcus* spp. (32.5%), Agrobacterium spp. (10.9%), *Achromobacter* spp. (9.4%), and *Hyphomicrobium* spp. (8.9%). Intriguingly, this finding provides some evidence of overlap between mammalian microbiome-derived isolates capable of degrading phthalate, and genera of phthalate-degrading isolates commonly seen in environments contaminated with the chemicals. While important, the aqueous environment from which the carp were captured should be taken into consideration, as the abundance of microorganisms which can degrade phthalates may increase in the presence of a high volume of phthalate pollution. Furthermore, species-specific metabolic and microbiota differences might influence carp microbiome composition in ways which could differ from that of, for example, rodents and humans. Nevertheless, the finding of environment-eukaryotic microbiome overlap with respect to phthalate-degrading microorganisms deserves further investigation in the context of other *in vivo* settings.

Summary of microbiota–phthalate interactions

The interaction of phthalates at large with the mammalian microbiome is best characterized as reductions in microbial diversity and reductions in the abundance of different species. Outside of the mammalian microbiome, the reductions in diversity seem to be at the expense of proliferation of phthalate-degrading microbes, an effect which can prove beneficial in situations which necessitate detoxification and bioremediation of various ecosystems. Such an effect is not known to appear in humans, though whether or not this is due to lack of phthalate-degrading microorganisms *in vivo* or due to a lack of research surrounding this relationship remains yet to be determined.

Microbial biodegradation of mycotoxins

Estimates of mycotoxin contamination in the global food supply are as high as 25% and their toxic effects necessitate their removal for the safety of both animal and human consumption.[101,102] Microorganism-mediated biodegradation and expulsion of mycotoxins and their metabolites is well-documented, and has been applied to large-scale food production and agriculture systems where mycotoxin contamination of foodstuffs is a realized threat.[103] Biodegradation and removal of toxins in this fashion is thought to hold an advantage over chemical or physical means of mycotoxin removal, as they better conform to agency-specific standards on quality and nutrition of processed foodstuffs.[102] Milling of maize, for example, can result in fractional volumes of mycotoxin remaining in the germ or bran of the plant, whereas bacterial biodegradation of some mycotoxins can result in complete breakdown of the compounds to harmless byproducts.[102] Broadly, the detoxification of mycotoxins in the food supply can be either through bacterially facilitated binding and sequestration, or through bacterially derived enzymatic degradation into less volatile compounds.[101] The latter system of detoxification is a product of ligninolytic enzyme systems, bacterial and fungal-derived enzymes with broad substrate specificity such as laccase, lignin peroxidase and/or manganese peroxidase.[104]

Mycotoxin-induced microbial community changes

Outside of their practical applications in decontamination of foodstuffs and agricultural feed, microorganisms of the mammalian microbiome are affected by and can interact with various mycotoxins. Characterization of ZEN biodegradation using bacterial isolates from food and rumen samples showed Lactobacillus genus-derived *Bacillus subtilis* and several substrains of the *Pseudomonas* genus to degrade the mycotoxin (Table 1, row 18). ELISA/HPLC

comparisons were used to initially characterize degradation of the mycotoxin and 16S RNA sequencing plus phylogenetic analysis was used to hone in on specific species.[105] Daud *et al.* (2020) analyzed 14 bacterial strains derived from the human colon to characterize their degradative capacities with respect to both food-derived mycotoxins and masked (conjugated) mycotoxins. Following anaerobic culture and exposure to treatment, total hydrolysis of the masked conjugate of Deoxynivalenol (DON), DON-Glc was observed in B. adolescentis *DSM* 20083 and B. fibrisolvens 16/4, while partial hydrolysis was observed with several other strains (*Roseburia intestinalis, Eubacterium rectale, Lactobacillus plantarum, Prevotella copri).*[106] Sobral *et al.* (2022) coupled an *in vitro*, semi-dynamic digestion model with one of colonic fermentation to characterize human microbial interaction/digestion of AFB1 and OTA as constituents of contaminated foods. While AFB1 in particular significantly reduced Caco-2 cell viability, a significant portion of both mycotoxins (32.7–48.4% of AFB1 and 27.6–47.2% of OTA) remained undigested, highlighting the potential for microbial interactions.[107] Furthermore, *in vitro* analysis of colonic fermentation showed that AFB1 and OTA contaminated meals led to lower abundances of families *Bacteroidaceae, Ruminococcaceae* and *Lachnospiraceae* compared with control.[107]

In vivo evidence points to dysbiotic effects of various mycotoxins, with potential microorganism involvement in biotransformation and detoxification. ZEN, as well as DON administered to pigs resulted in genus-level changes (Table 1, row 19); 16S rRNA sequencing resulted in two dominant *Lactobacillus* OTUs persisting in the colon contents of pigs exposed to ZEN or DON, signifying that *lactobacillus* genus could play a role in detoxification of the contaminants.[108] A longer term, lower dose exposure to ZEN and DON in pigs resulted in family level, fecal microbiome changes at both 119 and 140 days of age (Table 1, row 20).[109] Interestingly, fecal microbiome contents returned to baseline in the treatment groups following a three-week period of no exposure.[108] The effect of both DON and ZEN on microbial composition and function of the small intestine was characterized in weaned piglets; Saenz *et al*.[64] used metaproteomic analysis of global microbial protein composition to show reductions in proteins associated with carbohydrate metabolism but increased proteins associated with antioxidant capacity of the bacteria, both with respect to protein anabolism (pentose phosphate pathway) and translated product (thioredoxin). Microbial alterations were observed after DON exposure (Table 1, row 17), while ZEN exposure resulted in a similar, non-significant trend. Collective results from these findings point to dysbiosis after mycotoxin exposure resulting in involvement of pathways necessary to respond to oxidative stress.[64] Evidence of mycotoxin-mediated microbiome disturbance extends outside of porcine models. Fecal contents of mice exposed to sub-chronic doses of OTA for 28 days showed an increase in the relative abundance of phylum bacteroidetes and a decrease in relative abundance of phylum Bacillota.[110] In broiler chickens, ZEN was shown to increase the relative abundance of Bacillota and to decrease the relative abundance of Bacteroidota in the caecum compared with control.[111] Importantly, marked interspecies variation exists in such studies, necessitating a human-centric approach to microbial modeling of biotransformation when drawing conclusions related to specific health outcomes.[112]

Special attention should be paid to "masked" mycotoxins, mycotoxins conjugated by plant-specific phase II metabolic enzymes for vacuole sequestration prior to food processing.[68] Such conjugates remain stable in plant foods post-processing and have been shown to evade degradation in the digestive milieu of the stomach and small intestines.[68] Berthiller *et al.* (2011) modeled the digestive ability of the upper and lower GI tracts with respect to the glucose conjugate of DON, DON-3-β-d-glucoside; using *in vitro* characterization of digestive conditions as well as post-digestive exposure to bacterial species under optimal growth/incubation conditions followed by LC-MS/MS to confirm metabolites of DON-3-β-d-glucoside present at certain time points post bacterial incubation. DON-3-β-d-glucoside proved to be stable following exposure to HCL, pepsins, and human-derived recombinant glucosidase (cytosolic β-glucosidase; hCBG) but was shown to be efficiently cleaved by gut derived microorganisms *E. cloacae, E. durans, E. faecium, E. mundtii, L. plantarum and B. adolescentis* with up to 62% of DON released after 8 h of incubation.[113] In agreement with the prior study and using a similar *in vitro* model of digestion followed with bacterial incubation and LC/MS-confirmation of metabolites, Gratz *et al.* (2017) showed glucoside conjugates of common tricothene mycotoxins as well as glucuronidated ZEN remained unperturbed in this *in vitro* upper GI tract model. Further results from this study using fecal batch cultures from five human donors showed that masked compounds were fully metabolized by microorganisms; LC-MS/MS demonstrated full recovery of tricothenes, whereas only 30% of ZEN was recovered with the rest metabolized into unknown compounds.[68] Daud *et al.* (2020) did, indeed, show marked degradation of masked mycotoxins (DON-Glc, HT-2 Glc & NIV-Glc) by bacterial strains considered prevalent in the human intestinal microbiome. The degradative capacity of microbiota in this experiment was dose and strain specific, highlighting the heterogeneity of biotransformations in this regard.[106] Furthermore, the authors observed very little hydrolysis of a-glucosides, with the exception of dAS-Glc; this demonstrates the specificity of microbial metabolism with respect to differentially conjugated masked metabolites.[106] *In vitro*, masked mycotoxins appear to be deconjugated by microorganisms inherent to the human microbiome, allowing for the absorption of biotransformed products.

The *in vitro* findings of full and partial recovery of unconjugated mycotoxins coupled with bacterial metabolism of the contaminants is supported by *in vivo* evidence, whereby animals exposed to conjugated mycotoxins results in recovery of unconjugated metabolites in their urinary/fecal matrices. Predominantly, *in vivo* assessment of masked mycotoxin metabolism has been carried out in porcine models and the existing evidence is largely centered around conjugates of DON (DON3G), ZEN (ZEN-14G), and T2 (T2-3G). Male crossbred piglets 28 days of age received time-dependent doses of PO (By mouth) DON and PO or intravenous DON-3G for 14 days (day 5, DON-3G PO; day 9, DON PO; day 13, DON-3G IV) followed by UHPLC-MS/MS analysis of metabolites in urine and fecal samples.[114] PO DON-3G administration led to urinary excretion of DON

as the principal metabolite (8–24H dose recovery 330 ± 130 nmol) with very little recovery of the conjugate itself (8–24H dose recovery 15 ± 4 nmol), in contrast to recovery of the intravenously administered conjugate (0–8H dose recovery 410 ± 27 nmol). Notably, little to no recovered DON-3G dose in either administrative scenario was detected in the feces matrix; in the context of oral intake this finding implies inter-metabolic conversion of masked conjugate DON-3G to DON prior to fecal excretion, though whether this transformation was microorganism-mediated cannot be deduced from this study alone.[114] In agreement with this finding, Broekhart *et al.* (2017) showed no hydrolysis of DON-3G to DON following IV administration as well as recovery of DON exclusively as a metabolite following PO administration.[115] The investigators used a combination of LC-MS/MS metabolite detection and dual catheter placement (*venus jugularis & vena porta*) to analyze pre- and post-systemic metabolism of the compounds following both oral and IV administration. Significantly, DON was the only metabolite detected in the portal plasma samples following PO DON-3G administration, lending credence to the notion that hydrolysis of DON-3G to DON occurs in the GI tract via microorganism or enzyme-mediated processes.[115] Furthermore, findings from this study suggested a lag time between DON-3G ingestion and DON absorption in pigs; as DON is principally absorbed in the proximal small intestine, this implies lower GI tract hydrolysis and absorption.[115] Both of the aforementioned studies are important in the context of human biotransformation of masked conjugates, since microorganisms shown to degrade DON-3G such as *L. Plantarum* are known to be present in the microbiota of both pigs and humans.[116] Masked conjugates of ZEN (ZEN-14-O-β-glucoside and ZEN-16-O-β-glucoside) were undetectable in urine or feces following oral administration to piglets, though ZEN was detectable in urine samples of pigs treated with ZEN-14-O-β-glucoside (40–62 ng/mL) and ZEN-16-O-β-glucoside (4.0–45 ng/mL treatment).[117] While this finding parallels those observed in porcine models of DON-3G oral ingestion, Binder *et al.* (2017) detected fecal and urinary metabolites of the masked conjugates themselves, highlighting bioavailabilities of 40–56% (Zen-14-Glc) and 31–39% (Zen-16-Glc). While this finding provides contrasting *in vivo* data compared with DON-3G in porcine models of oral exposure, differences in metabolism could be due to varying degrees of stability of the conjugates in the digestive milieu of the small intestine.[117] Unlike the studies of DON-3G, this model did not analyze samples of plasma from the portal vein, making assumptions of relative intestinal hydrolysis in this context impossible with the exception of extrapolations from *in vitro* models; this highlights the need for multi-compartmental analysis of metabolites, especially when assessing post-ileal microbial transformation.

Summary of microbiota–mycotoxin interactions

The current evidence surrounding microbial biodegradation of various mycotoxins points to established bacterial transformation outside of the GI tract, with robust species-specific biotransformation of the compounds by the microbiota. Less is known about the effects of certain mycotoxins in human models of bacterial transformation, as well as their byproducts on human health-related endpoints. Emerging evidence surrounding the propensity of masked mycotoxins to evade digestive breakdown necessitates the need for analyzing the potential of such compounds to be absorbed further down the digestive tract, as well as the frequency of such absorption with respect to various conjugates common in the human food supply chain.

Discussion

The health hazards posed by or suspected of many BP and phthalate compounds justify regulating their use in pathways that lead to food contact, while mycotoxins have long been a target of food safety due to their acute and chronic toxicity. The ability of these three groups of contaminants to alter the gut microbiome, and in turn be modified by it, even at lower doses emphasizes the need to reevaluate current exposure limits to these compounds.

Mammalian toxicokinetics of BPA generally feature rapid clearing of the BP as a glucuronide in urine and the parent compound in feces within 24–48 h of exposure, favoring the fecal route in rodents and urinary route in humans. The data available for BPs suggest greater bioavailability in the intestines for heavier analogs like BPS compared with BPA, and even suggest human elimination for BPs such as BPS and BPAF may take longer due to enterohepatic circulation, implying colonic bacteria are exposed to the heavier BPs and justifying a concern for microbiota–BP interactions. While BP exposure has demonstrated the ability to shift microbial communities from their baseline, there are no consistent patterns among studies on BP-induced alterations; however, the Bacilliota phylum and *Bacillus* genus members are associated with *in vivo* BPA treatment and environmental biodegradation, highlighting these organisms as potential BPA-degraders in the gut.

Phthalate toxicokinetics are separable by high- and low-molecular weight compounds, across several routes of exposure (oral, dermal, inhalation). While species-specific variations in metabolism exist in this regard, the principal characteristics governing initial first-pass metabolism and bioavailability are similar. In high doses, evidence suggests that HMW phthalates such as DEHP, DiNP, and DnBP eliminate largely through feces due to saturable intestinal absorption, leading to unmetabolized diesters (and monoesters) encountering microbiota downstream of the upper GI tract. Indeed, recent studies highlight dysbiosis occurring in conjunction with phthalate exposures, though only two to date document biotransformation of phthalates *in vivo*. Furthermore, whether or not dysbiosis accompanying exposure to various phthalates is a product of phthalate–microbial interactions or a symptom of the adverse physiological effects of the phthalate exposure itself is not clear. Clarification of this relationship may provide critical insight into metabolism of the contaminants outside of established patterns of inter-organ metabolism. Furthermore, microorganism-specific biodegradation of both unmetabolized phthalates and their metabolites necessitates further investigation due to the paucity of non-mammalian, environment-specific biodegradation shown in the literature.

The three mycotoxin groups, aflatoxins, ochratoxin, and ZEN compounds, collectively exhibit dual reliance on urinary and fecal routes for elimination. OTA and ZEN compounds both feature circulation between intestines, blood, and bile, prolonging their lifetime in the body relative to other mycotoxins. The aspect of these well-studied compounds requiring more attention are the masked mycotoxins, which remain intact and unabsorbed through the digestive process but can be deconjugated by intestinal microbiota, serving as a direct "delivery" of the parent mycotoxin to the gut microbiome. With the "masked" title referring to how these plant-conjugates of fungal metabolites are not screened for, this unaccounted for mycotoxin exposure could have clinical importance for humans and livestock, particularly in regard to gut microbial perturbations.

Knowledge gaps and recommendations

There is a common need to better understand the proportion of ingested doses of BPs, phthalates, and mycotoxins that reach intestinal microbiota. Prior toxicokinetic studies for BPA and BPS, for example, involve administration of a radiolabeled low dose of the compound; however, the hazard these compounds pose contraindicates this approach. Researchers might consider *in vitro* compartmental models to investigate dietary contaminant absorption by intestinal epithelia, conjugate transport into blood or bile from hepatocytes, and affinities for the transport receptors involved in these processes. There is also an absence of information on specific gut microbiota responsible for the metabolism and transformation of these contaminants, beyond the implication of Bacilliota members as BPA degraders. *In vitro* studies using donated human fecal material can elucidate key biodegraders and investigate the role these members play in the gut microbial community.

More information is needed on the toxicokinetics of the various BP analogs, as the majority of literature solely focuses on BPA with only limited data available for humans. These data would clarify the proportion of ingested BPs that reach the gut microbiota and inform investigations into microbiota–BP interactions. It is also imperative to understand the bioactivities and fates of the metabolic products of gut microbial metabolism, and if these modifications neutralize or bioactivate the products relative to the parent BPs.

Regarding phthalate exposure, available toxicokinetic data points to ADME dependent on molecular weight. Whether or not an appreciable amount of both hydrolyzed and/or unhydrolyzed phthalates interact with organs and tissue of the lower GI tract warrants further investigation. Evidence of phthalate-mediated dysbiosis *in vivo* suggests that some amount of phthalates reach the colon, though the extent of such a phenomenon is not clear nor is the identity of what metabolites may be reaching/interacting with the microbiota. In addition, marked differences between various species exist with respect to phthalate metabolism and dysbiosis as a function of phthalate exposure. Collectively, determination of the extent of hydrolyzed or intact phthalates that reach the lower GI tract could determine the biological importance of the gut microbiota as a means of contaminant–microorganism interaction. Furthermore, it would provide toxicokinetic evidence of interactions of phthalates and their metabolites, downstream of the upper GI tract. In this context, models should incorporate differing *in vivo* models due to interspecies variability with respect to phthalate metabolism. Furthermore, research should utilize both environmentally relevant doses of the contaminants as well as time periods long enough to mimic subacute exposures versus large-dose boluses to provide relevance to human exposure.

The need for more information on mycotoxins primarily centers on the masked mycotoxins. Conjugated forms of ZEN compounds persist through the digestive process, reaching the colon and gut microbiota intact. More information is needed to determine if this persistence is a universal trait of mycotoxin conjugates. If so, this would imply that current screenings for mycotoxins in food may not protect against cumulative exposure to these compounds. In this scenario, even exposures below acute toxic thresholds may still perturb the gut microbiome in those who consume them. Experimentally, *in vivo* models focus principally on conjugates of ZEN and DON and documentation of microorganism biotransformation of these compounds has largely been conducted in porcine and rodent animal models. Expanding the variety of conjugates in these investigations, and incorporating human cells and human-derived fecal microbiota in *in vitro* compartmental models, can resolve the mystery surrounding these mycotoxin conjugates.

Just as the gut microbiome continues to be a promising frontier in understanding nutrition and health, it is also necessary to reevaluate exposures to dietary contaminants through the lens of gut microbiota as mediators of health. The threat these contaminants pose to human health cannot be fully characterized without considering the bidirectional relationship these substances have with gut microbiota, and investigating these relationships may redefine acceptable exposure limits to the compounds in question.

AUTHORS' CONTRIBUTIONS

AC and ZB conducted the literature search, review, and writing of this manuscript. AJ and CA offered recommendations on the scope of the effort, provided edits and interpretations, and reviewed the manuscript.

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SUPPLEMENTAL MATERIAL

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