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Full Length Article

Microbiota and organophosphates

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ABSTRACT

Organophosphates (OPs) are important toxic compounds commonly used for a variety of purposes in agriculture, industry and household settings. Consumption of these compounds affects several central nervous system functions. Some of the most recognised consequences of organophosphate pesticide exposure in humans include neonatal developmental abnormalities, endocrine disruption, neurodegeneration, neuroinflammation and cancer. In addition, neurobehavioral and emotional deficits following OP exposure have been reported.

It would be of great value to discover a therapeutic strategy which produces a protective effect against these neurotoxic compounds. Moreover, a growing body of preclinical data suggests that the microbiota may affect metabolism and neurotoxic outcomes through exposure to OPs.

The human gut is colonised by a broad variety of microorganisms. This huge number of bacteria and other microorganisms which survive by colonising the gastrointestinal tract is defined as “gut microbiota”. The gut microbiome plays a profound role in metabolic processing, energy production, immune and cognitive development and homeostasis. The effects are not only localized in the gut, but also influence many other organs, such as the brain through the microbiome-gut-brain axis. Therefore, given the gut microbiota’s key role in host homeostasis, this microbiota may be altered or modified temporarily by factors such as antibiotics, diet and toxins such as pesticides.

The aim of this review is to examine scientific articles concerning the impact of microbiota in OP toxicity. Studies focussed on the possible contribution the microbiota has on variable host pharmacokinetic responses such as absorption and biotransformation of xenobiotics will be evaluated. Microbiome manipulation by antibiotic or probiotic administration and faecal transplantation are experimental approaches recently proposed as treatments for several diseases.

Finally, microbiota manipulation as a possible therapeutic strategy in order to reduce OP toxicity will be discussed.

1. Organophosphates (OPs)

Organophosphates (OPs), such as chlorpyrifos (CPF), dichlorvos, monocrotophos, malathion or parathion (PT) among others, are extensively used as pesticides in agricultural, industrial and household settings (Costa, 2018). Due to their widespread availability and the high-intensity use, OPs are the pesticides which are most often associated with morbidity and mortality either through accidental exposure, or via suicidal attempts (Rohlman et al., 2011). According to the World Health Organization (WHO, 2001), about 3 million people worldwide are exposed to OPs each year, leading to 300,000 deaths.

1.1. Risks associated with OP exposure

a) *Acute toxicity*

The immediate adverse effects of acute overexposure to OPs are related to their capacity to inhibit the activity of acetylcholinesterase (AChE), leading to the accumulation of acetylcholine (ACh) at cholinergic synapses and neuromuscular junctions (Kwong, 2002). The

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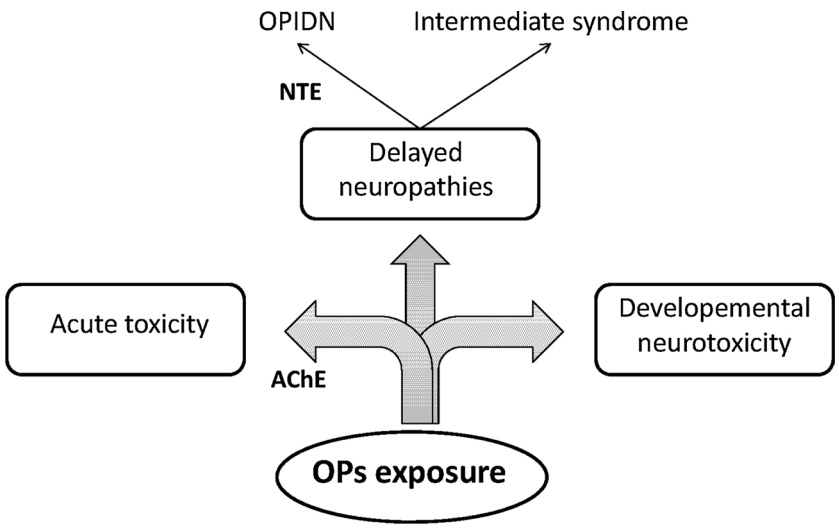

Fig. 1. Effects of OP exposition.
Legend: This figure represents some of the effects of the OP exposition in humans. (Abbreviations: AChE: acetylcholinesterase; OP: organophosphate; OPIDN: OP-induced delayed neuropathy; NTE: neuropathy target esterase).

overstimulation of nerves and muscles observed in patient suffering from OP intoxication produces autonomic dysfunction (increased sweating, hypersalivation, miosis, diarrhea, profound bronchial secretion,…), neuromuscular junctions disorders (weakness, fasciculations, twitching,…), and various CNS effects (dizziness, respiratory failure, convulsions, coma) (Lotti, 2010; Petersen and Round, 2014). Those signs and symptoms, known as the cholinergic syndrome, usually subside within 24–48 h. Some of the interventions employed to prevent acute symptoms of toxicity are treatment with anticholinergic drugs (e.g. atropine) or drugs that reverse the AChE inhibition such as oximes (e.g. 2-PAM).

It has been demonstrated that several OPs need to be bioactivated as oxygen analogs (oxons) in order to induce toxicity. For example, chlorpyrifos or diazinon toxicity is determined by a balance between cytochrome P450 isoenzymes or paraoxonase-1 (PON-1) bioactivation and detoxification processes catalyzed mainly by aryl esterases of the oxonase type, which can metabolize oxons to acids or alcohols and diethyl or dimethyl phosphate (Dardiotis et al., 2019; Hernández et al., 2013). Given that these metabolic reactions play a key role in the toxicology of OPs, an alternative approach to treating OP intoxication has included the use of enzymes that limit their metabolism to active compounds or accelerate their detoxification.

a) *Delayed Neuropathies*

When eventual signs of acute toxicity subside, several delayed physical and neurological conditions not clearly related to the inhibition of AChE can appear. Although the pathway and related mechanisms are still unknown, probably the best described delayed manifestation of OP poisoning is the intermediate syndrome, characterized by weakness, respiratory paresis and transient extrapyramidal symptoms several days following first contact with the OP (Costa et al., 2013). Occasionally, OP poisoning in humans is associated with another delayed neurological condition called OP-induced delayed neuropathy (OPIDN), characterised by cramping pain and paraesthesia of the extremities followed by weakness of the distal limb muscles. OPIDN has been associated with the inhibition by OPs of the neuropathy target esterase (NTE) (Lotti and Moretto, 2005). Nowadays, the discovery of an effective intervention targeting the delayed effects and long-term neurological consequences of OP exposure presents a great challenge.

Throughout the last decade, growing efforts have been made to discover more regarding the neurotoxicity of prolonged exposure to low levels of OPs, not only occupationally, but also in the general population through residues present in food and drinking water (Costa, 2018). Neurobehavioral problems in psychomotor speed, executive function, visuospatial ability and working and visual memory have been observed following low-level exposure to organophosphate pesticides in an occupational setting (Muñoz-Quezada et al., 2016; Ross et al., 2013). Previous animal studies conducted in our lab have shown that long-term effects such as anxiety or spatial memory impairment arise 6 months following subacute exposure to CPF (López-Granero et al., 2016, 2013). Moreover, an increase in impulsivity six months and one year after CPF exposure and when AChE activity is recovered has also been observed (Cardona et al., 2011, 2006). In fact, acylpeptide hydrolase activity seems to be a more sensitive biomarker for acute low-level exposure than AChE (Cardona et al., 2013). The most plausible hypothesis is that repeated exposure to low levels of OPs for prolonged periods of times provokes an accumulation of this compound in the body leading to adverse health effects (Naughton and Terry, 2018). However, the mechanisms of chronic low-level exposure to producing these symptoms are not well understood yet.

a) *Developmental neurotoxicity*

Another adverse health effect associated with subacute exposure to OPs is developmental neurotoxicity. It has been demonstrated in animal models that prenatal exposure to CPF causes changes in locomotor skills and cognitive performance (Chen et al., 2012; Levin et al., 2002). This adverse effect has been also observed in humans. Epidemiological studies showed that prenatal or early postnatal exposure to OPs is related to behavioural impairment in attention, learning and memory (González-Alzaga et al., 2014; Hernández et al., 2016; Sapbamrer and Hongsibsong, 2019) or even a reduced IQ score, in the case of the chlorpyrifos exposure (Rauh et al., 2011). Based on adverse effects following low-level exposure to chlorpyrifos in developing children, the possibility of strongly restricting its use should be reconsidered by the Environmental Protection Agency (EPA) (Fig. 1).

1.2. Mechanisms of OP toxicity

As previously mentioned, the inhibition of AChE plays a key role in OP toxicity. Nevertheless, preclinical studies have shown that OP-induced toxicity appears in animals at concentrations lower than the threshold for AChE inhibition. It has thus been suggested that other

modes of action may play a role in OP neurotoxicity (Burke et al., 2017; Naughton and Terry, 2018). The scientific community has consequently invested greater effort into describing and increasing knowledge of alternative non-cholinergic OP mechanisms (Costa, 2018; Terry, 2012). Prior studies in our lab have demonstrated that acyl peptide hydrolase seems to be more sensitive to inhibition by OPs than AChE (Cardona et al., 2013; López-Granero et al., 2013). Finally, oxidative stress and neuroinflammation have been intensively investigated as additional OP pathways.

Studies have shown that oxidative stress occurs both *in vitro* and *in vivo* after exposure to OPs (Pearson and Patel, 2016). For example, *in vivo* studies have demonstrated that exposure to CPF, paraoxon or diisopropylphorofluoridate elevates oxidative stress through an increase in lipid peroxidation or alteration in antioxidant and scavenging systems in rat tissues (Jafari et al., 2012; López-Granero et al., 2013; Ojha et al., 2011; Zaja-Milatovic et al., 2009). Similarly, malathion administration changes the antioxidant status of the cells and increases the peroxidation of the lipid membrane (Akbel et al., 2018). In addition, it has been demonstrated that acephate upregulates inflammatory cytokines in vivo (Singh and Jiang, 2003) and CPF induces inflammatory responses, increasing IL-6 and glial fibrillary acidic protein (GFAP) levels in cultured astrocytes (Mense et al., 2006). These studies suggest that oxidative stress and neuroinflammation might be important mechanisms underlying OP neurotoxicity, although further studies are required to search for functional links between these changes and OP-related neurobehavioral deficits.

1.3. Data gaps in OP neurotoxicity

Deleterious health effects caused by OPs have been documented in both adults and children (Reiss et al., 2015; Rohlman et al., 2011) for decades; an increased risk of a variety of chronic illnesses including respiratory (e.g., chronic obstructive respiratory disease), metabolic (e.g., obesity, diabetes) and neurodegenerative diseases such as Alzheimer's or Parkinson's have been reported after OP exposure (Chakraborty et al., 2009; Hancock et al., 2008; Sánchez-Santed et al., 2016; Slotkin, 2011). In addition, neurobehavioral and emotional deficits in response to OP exposure have been reported in preclinical and clinical studies. Animal studies have shown that CPF or malathion may lead to anxiety-like behaviour (Chen et al., 2011; Hashjin et al., 2013; López-Crespo et al., 2007). Occupational studies have also indicated that farmers exposed to OPs showed higher risks of developing symptoms related to anxiety and mood disorders, even following low-level exposure (Harrison and Mackenzie Ross, 2016; Koh et al., 2017). These data indicate the importance of OPs as causal patterns in the development of mental disorders.

Novel therapeutic approaches are required to counteract the harmful effect that OP exposure has on health, since there are currently no ideal therapeutic methods available. Some of the new potential OP targets described below could be vital in the designing of therapeutic strategies to combat OP toxicity. Given the role of human microbiota on diseases observed after contact to OP, the interaction of OPs with the microbiome is stimulating a lot of interest in the scientific community.

2. Microbiota and microbiome-gut-brain axis

Recently, microbiota has been a central focus in modern biomedical research. In fact, the last five years have seen a considerable rise in studies evaluating the role of microbiota on health, presenting the microbiota as a remarkable symbiotic partner critical to the maintenance of human health (Fond et al., 2015).

2.1. Microbiota

The gastrointestinal (GI) tract has been described as being home to more than 100 trillion microscopic bacteria (10^{14} or 100,000,000,000,000 cells) and hosting more than 70% of all bodily flora (Vyas and Ranganathan, 2012). The term 'gut microbiota' refers to the collection of microorganisms, mainly bacteria, which colonise the GI tract (Neish, 2009). The ratio between human cells and microbiota is close to 1:1 (Sender et al., 2016). The adult microbiome includes approximately 30 species of *Bifidobacterium*, 52 species of *Lactobacillus*, and others, such as *Streptococcus* and *Enterococcus* (Wallace et al., 2011), where *Firmicutes* and *Bacteroidetes* largely dominate, as well as *Actinobacteria* and *Proteobacteria* (Thursby and Juge, 2017).

2.2. Factors that alter microbiota

Although microbiota colonisation begins at birth, this process actually starts during the gestational period, given that a diverse range of microbes have been found in amniotic fluid, the placenta, umbilical cord blood, and foetal membranes (Dunn et al., 2017). Following parturition, the gut microbiota is refined and modified until adult-like communities reach homeostasis in their diversity when the child is around 2 years old (Ohland and Jobin, 2015). However, microbiota composition represented throughout adult life is shaped by a number of factors including mode of delivery (vaginal or caesarean section), breastfeeding or bottle-feeding, diet, some medications (particularly antibiotics), exposure to viral or bacterial infections, stress and others habits such as smoking (Kochhar and Martin, 2015; Martín et al., 2003; Rea et al., 2017; Savin et al., 2018). Other factors that alter the microbiota both in stability, diversity, composition, and/or metabolism of gut bacteria are several GI pathologies, commonly known as dysbiosis (Chassard et al., 2012; Rajilić-Stojanović et al., 2011). Dysbiosis is characterized by an imbalance in intestinal microorganisms with an increase in *Firmicutes phylum* and decrease in *Bacteroidetes phylum* (Shreiner et al., 2015).

2.3. Microbiome-gut-brain axis

The microbiome-gut-brain axis is a bidirectional communication network, in which communication occurs via three different pathways: neural (mainly through the vagus nerve), endocrine (cortisol) and immune (cytokines) (Bercik and Collins, 2014; De Palma et al., 2014). Additionally, bacterial products activate the enteric nervous system (Al-Nedawi et al., 2015) and stimulate afferent nerves and bacterial metabolites such as short chain fatty acids (SCFA) to provoke changes in behavior (Chichlowski and Rudolph, 2015). Gut microbiota can also be altered by several factors such as stress exposure, evidencing this bidirectional pathway (Molina-Torres et al., 2019). Moreover, the gut microbiota produces many metabolic substances which are affected by the individual's diet (Blaut and Clavel, 2007); microbiome-released metabolites may include several vitamins (folate, biotin), SCFA (propionate, butyrate, acetate) and neuroactive metabolites (serotonin, gamma-butyric acid), among others (Sharon et al., 2014). Hence, changes in the microbiota were highly correlated with the quantities of SCFAs, which are among the most important metabolites derived from the metabolic processes of the gut microbiota, coming from the anaerobic fermentation of dietary carbohydrates and some amino acids. Several studies have demonstrated that SFCAs cross the gut-blood and blood-brain barriers gaining access to the brain where they can accumulate and alter multiple neurophysiological processes, including neurotransmitter release and behaviour (Ohland et al., 2013). Thus, altering the diet can have significant effects on gut fermentation (Fig. 2).

2.4. Microbiome-gut brain axis and related disorders

Nowadays, it is widely recognised that the gut microbiome plays a significant role in different physiological functions, from energy metabolism to mental health (Moloney et al., 2016). The gut microbiome, for example, contributes to the early programming of epithelial barrier

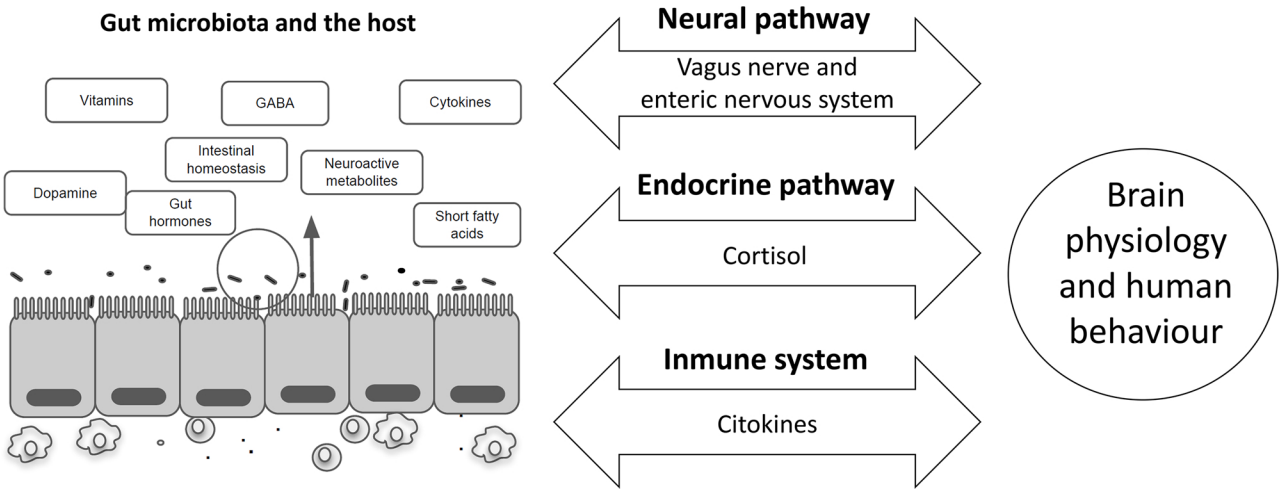

Fig. 2. Microbiota and gut brain axis.
Legend: Represents the interaction between the intestinal microbiota and the host, the pathways of action resulting in an effect into the brain physiology and human behaviour. Intestinal epithelial cells (grey coloured) are arranged forming the intestinal barrier interacting with the microorganisms of the microbiota (small circles and bacillus structures black coloured) that are in the intestinal lumen. Under the intestinal cells there are a variety of inmune cells (white cells represented under the intestinal cells). (Abbreviations: GABA: gamma-Aminobutyric acid).

function, angiogenesis, and innate and host immune function (Rodríguez-Fandiño et al., 2010). Therefore, experimental and clinical studies give support to the fact that alterations in the pattern of GI colonization have long-term consequences on immune function (Nash et al., 2017). Several studies have shown the important influence that the gut microbiota have on brain physiology and behaviour (Carabotti et al., 2015; Cryan and Dinan, 2012; Dinan et al., 2014) through a variety of mechanisms (Chichlowski and Rudolph, 2015). Recent studies have shown that intestinal homeostasis may directly affect brain functioning, and consequently modulate affection, motivation and higher cognitive functions (Borre et al., 2014; Carabotti et al., 2015; Cryan and Dinan, 2012). These modulations, both emotional and cognitive, occur through microbiome-gut brain axis.

2.5. Gut microbiota on gut brain modulation

Several experimental approaches have been used to study the modulatory effects of gut microbiota on gut–brain interactions, including gut microbial manipulation with antibiotics, probiotics, prebiotics, paraprobiotics, symbiotics and faecal transplantations (Mayer et al., 2015). A probiotic is defined as a live bacterium which produces health benefits in the host when administered in an adequate quantity (WHO, 2001), the most commonly used being *Lactobacilli*, *Bifidobacteria* and *Saccharomyces boulardii* (Hardy et al., 2013). Prebiotics are defined as non-viable food components associated with modulation of the microbiota, that are beneficial on the host's health (Hoseinifar et al., 2014; Roberfroid et al., 2010). Compounds which potentially enhance the growth of administered or commensal probiotic microbes are typically referred to as prebiotics. Paraprobiotics or ghost probiotics are non-living probiotic strains, resulting from exposure to high temperatures or irradiation, or some probiotic fractions (Taverniti and Guglielmetti, 2011).

The use of probiotics and prebiotics is considered to be a therapeutic way of restoring the microbiota in various situations, such as following an antibiotic treatment or in patients with GI diseases that produce dysbiosis. Some probiotic bacteria have even received great attention due to their ability to reduce the toxicity of several environmental contaminants, including heavy metals and pesticides (Feng et al., 2018).

3. Role of microbiota in OP toxicity

Emerging scientific evidence links gut microbiota dysbiosis with exposure to environmental agents such as OPs. This relationship has been evaluated in CPF mainly, both in pre-clinical and in vitro studies (Table 1).

One of the first studies evaluating this relationship was carried out by Cook and Shenoy in 2003 (Cook and Shenoy, 2003). The authors studied the intestinal transport of CPF in Sprague–Dawley rats using a rat perfusion model. Their results showed that 99% of orally administered CPF is absorbed by the small intestine. By means of DNA sequencing, Xia and cols. (Xia et al., 2013) found a lower proportion of *Proteobacteria* and a higher proportion of *Firmicutes* and *Lactobacillales* after CPF exposure in the midgut microbiota of the diamondback moth, *Plutella xylostella*.

The effect of CPF on intestinal permeability after chronic in utero and postnatal exposure has also been studied. Condette and colleagues (Joly Condette et al., 2014) evaluated the impact of in utero and postnatal oral low-dose CPF administration on gut epithelial permeability and bacterial translocation. Their results showed that chronic CPF-exposure during critical pre- and postnatal periods causes morphological changes in the intestinal epithelium and increases intestinal permeability and bacterial translocation which is associated with dysbiosis in the intestinal microbiota. Similar effects were observed for mature animals of 60 days old. In fact, exposure to CPF during gestation and early stages of growth development altered the pups' intestinal microbiota, producing an intestinal microbial dysbiosis associated with greater bacterial translocation to the liver. More specifically, the abundance of *Lactobacillus* was reduced significantly during CPF while the presence of *Clostridium* was increased (Condette et al., 2015). A different study from the same research group investigated the bacterial translocation from the intestinal tract of rats following CPF exposure. A total of 72 intestinal segments and extra-intestinal organs were obtained from 14 CPF exposed rats and bacterial translocation was confirmed for 7 of the 31 strains (22.6%) isolated from extra-intestinal sites. In addition, they showed that the most prevalent bacteria were *Staphylococcus aureus* (55.5%), *Enterococcus faecalis* (27.7%) and *Bacillus cereus* (9.8%) (Joly Condette et al., 2014). Collectively, these data suggest that prenatal and lactational exposure to CPF have both short-term and long-lasting impacts on the microbiota, indicating that exposure in infancy should be avoided.

Joly Condette et al. also investigated the effects of chronic exposure

Table 1
Relationship between microbiota and OPs toxicity.

Reference	Animal model	In vitro procedure	OP	Main findings
(Cook and Shenoy, 2003)	Sprague–Dawley rats		Oral CPF	99% of orally administered CPF is absorbed by the small intestine
(Joly Condette et al., 2014)	13 pregnant females Hannover Wistar		Chronic CPF in utero	Morphological changes in the intestinal epithelium, increases intestinal permeability and bacterial translocation
(Condette et al., 2015)	17 pregnant females Hannover Wistar and pups		Prenatal chronic oral CPF and in pups during lactational and in food	Changes in the histological structures intestinal microbial dysbiosis: low *Lactobacillus* counts and high *Clostridium* counts. Increased bacterial translocation in the spleen and liver.
(Joly Condette et al., 2014)	15 pregnant females Hannover Wistar and pups		Prenatal chronic oral CPF and in pups during lactational and in food	Bacterial translocation (22,6%). The most prevalent bacteria were *Staphylococcus aureus* (55.5 %), *Enterococcus faecalis* (27.7 %) and *Bacillus cereus* (9.8 %).
(Zhao et al., 2016)	Male mice (Mus musculus KM, ten-week-old)		Chronic CPF	Increase *Bacteroidetes* / Decrease *Firmicutes*
(Fang et al., 2018)	36 adult male Wistar tats		Chronic oral CPF	Reduction in the counts of *Aerococcus, Brevundimonas* and *Trichococcus* in normal-fat fed rats, and *Olsenella, Clostridium, sensu stricto, Amphibacillus, Enterorhabdus* and *Alloprevotella* in high-fat fed rats
(Vismaya and Rajini, 2014)	Adult male Wistar rats		Chronic oral MCP	Small intestine affected and the enzymes involved in digestion.
(Gao et al., 2017)	C57BL/6 mice		Chronic Diazinon in water	*Lachnospiraceae* family decreased in both male and female animals. *Ruminococcaceae, Clostridiaceae* and *Erysipelotrichaceae* decreased in female animals.
(Xia et al., 2013)	*Plutella xylostella.*		CPF	Increase *Firmicutes* and *Lactobacillales.* Decrease *Proteobacteria*
(Joly et al., 2013)		SHIME	CPF	Increase *Enterococcus* and *Bacteroides.* Decrease *Bifidobacteria* and *Lactobacilli*
(Reygner et al., 2016a)		SHIME and conventional bacterial culture	Chronic CPF	Increase *Enterobacteria, Bacteroides* Decrease *Bifidobacteria*
(Gao et al., 2018)	C57BL/6 mice		Malathion	Increase *Clostridium* population. Depleted *Blautia, Roseburia, Christensenellaceae* and *Planococcaceae*

to CPF on intestinal microbiota using an *in vitro* model, the Simulator of the Human Intestinal Microbial Ecosystem (SHIME), finding that CPF exposure was associated with an increase in the total cultured bacterial count showing microbiota dysbiosis. Specifically, they observed an increase in *Enterococcus* and *Bacteroides* which was accompanied by a decrease in the numbers of *Bifidobacteria* and *Lactobacilli* (Joly et al., 2013). Similar results were also found following 30 days of chronic exposure to a low dose of CPF using the same model, with an increase in *Enterobacteria*, *Bacteroides* and *Clostridia* counts, and a decrease in *Bifidobacteria* counts being observed. A decrease in *Lactobacilli* was not found in this case, although *lactic acid bacteria* was evaluated rather than *Lactobacilli* alone (Reygner et al., 2016a). Nevertheless, another research group observed an increase in *lactic acid bacteria* counts, therefore these strains could possibly tolerate high concentrations of CPF (Cho et al., 2009).

Zhao and collaborators investigated the toxic effects of CPF on the gut-microbiome and urine metabolome in mice. Their results showed an unsteady microbiota characterised by an increase in *Bacteroidetes* at the expense of *Firmicutes* in the CPF group (Zhao et al., 2016).

Recently, it has been demonstrated that CPF exposure altered gut microbiota in a diet-specific manner (Fang et al., 2018). CPF reduces *Aerococcus, Brevundimonas* and *Trichococcus* in rats fed a normal-fat diet, and *Olsenella, Clostridium, sensu stricto, Amphibacillus, Enterorhabdus* and *Alloprevotella* in rats fed a high-fat diet. Moreover, CPF exposure induced changes in the populations of SCFA-producing bacteria in both groups. For example, SCFA-producing *Allobaculum* and *Roseburia* were significantly more prominent in rats fed normal levels of fat, whereas there were significantly less *Bacteroides* in high-fat fed rats. Those bacteria and also SCFA producing bacteria has been associated with obesity and diabetes (Baothman et al., 2016). Therefore, CPF could be considered a stressor producing dysbiosis (Mazzon et al., 2002).

While a large number of investigations are focussed on CPF, studies evaluating the role of other OPs over microbiota are scarce. Monocrotophos (MCP) is a broad spectrum systemic OP highly consumed in India. Vismaya and Rajini (Vismaya and Rajini, 2014) observed that multiple oral doses of MCP affected both the structure and functions of the small intestine in rats and also disrupted normal intestinal motility and the enzymes involved in digestion.

The impact of exposure to malathion, another OP, on gut microbiome development in C57BL/6 mice was investigated (Gao et al., 2018). It was found that malathion altered the gut microbiome developmental trajectory and quorum sensing, as well as related physiological processes such as motility and pathogenicity. Specifically, an increase in pathogenic bacteria such as the *Clostridium* population was observed. On the other hand, *Blautia*, *Roseburia*, *Christensenellaceae* and *Planococcaceae* were totally depleted following malathion exposure.

Using the same animal model, the effect of other OP on gut microbiome composition and its metabolic functions were also investigated by Gao and colleagues (Gao et al., 2017). Results showed that diazinon (DZN) altered the gut microbiome community structure, functional metagenome and metabolic profiles of the gut microbiome in a sex-specific manner. Precisely, several genera of the *Lachnospiraceae* family decreased in both male and female animals. *Lachnospiraceae* is involved in the production of SCFAs, and reduced levels of *Lachnospiraceae* have been observed in patients with depressive disorders (Jiang et al., 2015). Additionally, in females, *Ruminococcaceae*, *Clostridiaceae* and *Erysipelotrichaceae* decreased after exposure to DZN. Moreover, the prevalence of several potentially pathogenic bacterias such as *Burkholderiales*, *Erysipelotrichaceae* and *Coprobacillus* were only observed in treated male mice. This data may point to the potential role of the gut microbiome in producing different neurotoxicity effects in male and female animals.

The research cited above shows that several OPs, such as CPF, caused dysbiosis both in childhood and adulthood. CPF also altered gut microbiota in a diet-specific manner; moreover, DNZ also altered gut microbiota in a sex-specific manner, and both effects seem to be related to the production of SCFAs. Therefore, gut microbiota dysbiosis should be taken into consideration when evaluating the neurotoxicity of these compounds.

4. Manipulation of microbiota over OP toxicity

In spite of increasing data highlighting dysbiosis after OP exposure, there is limited evidence concerning the effects of microbiota manipulation on OP toxicity.

As previously mentioned, several strategies have been employed to alter or temporarily modify the microbiome through the administration of different diets, antibiotics, prebiotics or probiotics or even by faecal transplantation (Fond et al., 2015).

Inulin has been used to test whether supplementation with prebiotics from gestation to adulthood, through a modulation of microbiota composition, alleviates CPF induced metabolic disorders (Reygner et al., 2016b). In that study rats were exposed from pregnancy to weaning to two doses of CPF either alone or in association with inulin. CPF decreased the *Firmicutes* population and increased the general population of bacteria and the total SCFA production was observed in groups that received a prebiotic.

The protective effect of inulin subsequent to CPF exposure has been also investigated using *in vitro* models (Réquilé et al., 2018). A reduction in the *Enterococcus* count and an increase in SCFAs, without affecting the *Bifidobacterium* and *Lactobacillus* counts, was observed in the CPF group pre-treated with inulin. According to these findings, the dysbiosis and metabolic imbalance in the intestinal environment observed after CPF exposure could be prevented by co-treatment with inulin.

Probiotics have also been used to reduce OP toxicity. Trinder et al. (2016) found that *Lactobacillus* bacteria is able to bind, but not metabolise, OP pesticides and reduce intestinal absorption in vitro. Interestingly, pre-treatment with *Lactobacillus rhamnosus* reduced mortality and growth deficits in Drosophila exposed to CPF. Other *Lactobacillus* strains such as *Lactobacillus casei* reduced the DZN induced cytotoxicity in vitro (Bagherpour Shamloo et al., 2016).

Another microbiota modulation that has been evaluated is faecal transplantation, the effect of which on mice has also been assessed following MCP exposure. Velmurugan et al. (2017) carried out a complete research project with human samples obtained from people exposed to several OPs and a BALB/c mice strain exposed to MCP with the aim of understanding the role of gut microbiota in OP-induced glucose impairment. Their results showed an increase in the SCFA acetic acid after OP exposure that correlated with impaired glucose tolerance condition. In addition, the recipients of faecal microbiota from MCP-fed animals exhibited significant glucose intolerance in comparison to recipients of control microbiota.

This combined data highlights the relevance of gut microbiota modulation in the reduction of OP toxicity through the re-establishment of homeostasis. However, there is limited data available, so future research should evaluate the efficacy of prebiotics and probiotics to prevent OP toxicity.

5. Conclusions

As previously outlined, OPs are widely used as pesticides. In light of the harmful health effects of OPs that have been documented in humans, governments have increased environmental concern regarding their use. Of particular interest in this review is the finding that low level OP exposure produces emotional and cognitive effects (Harrison and Mackenzie Ross, 2016; Reiss et al., 2015) even when AChE was recovered (Cardona et al., 2011). Thus, alternative methods for AChE inhibition need to be studied.

In recent years, a growing body of literature has studied how the gut microbiome can contribute to several nervous system disorders

including autism, depression, anxiety, and stress, and how microbiome-related products could modulate these disorders (Roman et al., 2018a, 2018b; van de Wouw et al., 2018). Regarding OPs, it has been shown that the gut microbiome is significantly altered following OP exposure, suggesting that perturbation of the gut microbiome contributes to the neurotoxicity of organophosphate pesticides. There could be multiple specific pathways, since an altered gut microbiome affects the physiological properties of the gut permeability and many biological processes, including the production of important metabolites such as vitamins and SCFAs.

The manipulation of the microbiota using probiotics, prebiotics or faecal transplant revealed interesting results concerning the effects of OP exposure in different *in vitro* and preclinical studies. However, further analyses are required to fully characterise the impact of OPs on microbiota. The use of new approaches such as next generation sequencing targeting 16S rRNA in order to characterise the microbiota and integrate metabolic and biochemical analysis could facilitate a more detailed explanation on the whole process of OPs intoxication and its current clinical symptoms.

Declaration of Competing Interest

All the authors declare that they have no conflict of interest.

References

Akbel, E., Arslan-Acaroz, D., Demirel, H.H., Kucukkurt, I., Ince, S., 2018. The subchronic exposure to malathion, an organophosphate pesticide, causes lipid peroxidation, oxidative stress, and tissue damage in rats: the protective role of resveratrol. Toxicol. Res. (Camb). 7, 503–512. https://doi.org/10.1039/c8tx00030a.

Al-Nedawi, K., Mian, M.F., Hossain, N., Karimi, K., Mao, Y.-K., Forsythe, P., Min, K.K., Stanisz, A.M., Kunze, W.A., Bienenstock, J., 2015. Gut commensal microvesicles reproduce parent bacterial signals to host immune and enteric nervous systems. FASEB J. 29, 684–695. https://doi.org/10.1096/fj.14-259721.

Bagherpour Shamloo, H., Golkari, S., Faghfoori, Z., Movassaghpour, A., Lotfi, H., Barzegari, A., Yari Khosroushahi, A., 2016. Lactobacillus casei decreases organophosphorus pesticide diazinon cytotoxicity in human HUVEC cell line. Adv. Pharm. Bull. 6, 201–210. https://doi.org/10.15171/apb.2016.028.

Baothman, O.A., Zamzami, M.A., Taher, I., Abubaker, J., Abu-Farha, M., 2016. The role of Gut Microbiota in the development of obesity and Diabetes. Lipids Health Dis. 15, 108. https://doi.org/10.1186/s12944-016-0278-4.

Bercik, P., Collins, S.M., 2014. The effects of inflammation, infection and antibiotics on the microbiota-gut-brain axis. Adv. Exp. Med. Biol. 817, 279–289. https://doi.org/10.1007/978-1-4939-0897-4_13.

Blaut, M., Clavel, T., 2007. Metabolic diversity of the intestinal microbiota: implications for health and disease. J. Nutr. 137, 751S–755S.

Borre, Y.E., Moloney, R.D., Clarke, G., Dinan, T.G., Cryan, J.F., 2014. The impact of microbiota on brain and behavior: mechanisms & therapeutic potential. Adv. Exp. Med. Biol. 817, 373–403. https://doi.org/10.1007/978-1-4939-0897-4_17.

Burke, R.D., Todd, S.W., Lumsden, E., Mullins, R.J., Mamczarz, J., Fawcett, W.P., Gullapalli, R.P., Randall, W.R., Pereira, E.F.R., Albuquerque, E.X., 2017. Developmental neurotoxicity of the organophosphorus insecticide chlorpyrifos: from clinical findings to preclinical models and potential mechanisms. J. Neurochem. 142 (Suppl), 162–177. https://doi.org/10.1111/jnc.14077.

Carabotti, M., Scirocco, A., Maselli, M.A., Severi, C., 2015. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann. Gastroenterol. Q. Publ. Hell. Soc. Gastroenterol. 28, 203–209.

Cardona, D., López-Crespo, G., Sánchez-Amate, M.C., Flores, P., Sánchez-Santed, F., 2011. Impulsivity as long-term sequelae after chlorpyrifos intoxication: time course and individual differences. Neurotox. Res. 19. https://doi.org/10.1007/s12640-009-9149-3.

Cardona, D., López-Grancha, M., López-Crespo, G., Nieto-Escamez, F., Sánchez-Santed, F., Flores, P., 2006. Vulnerability of long-term neurotoxicity of chlorpyrifos: effect on schedule-induced polydipsia and a delay discounting task. Psychopharmacology (Berl.) 189, 47–57. https://doi.org/10.1007/s00213-006-0547-4.

Cardona, D., López-Granero, C., Cañadas, F., Llorens, J., Flores, P., Pancetti, F., Sánchez-Santed, F., 2013. Dose-dependent regional brain acetylcholinesterase and acylpeptide hydrolase inhibition without cell death after chlorpyrifos administration. J. Toxicol. Sci. 38, 193–203. https://doi.org/10.2131/jts.38.193.

Chakraborty, S., Mukherjee, S., Roychoudhury, S., Siddique, S., Lahiri, T., Ray, M.R., 2009. Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India. J. Occup. Health 51, 488–497.

Chassard, C., Dapoigny, M., Scott, K.P., Crouzet, L., Del'homme, C., Marquet, P., Martin, J.C., Pickering, G., Ardid, D., Eschalier, A., Dubray, C., Flint, H.J., Bernalier-Donadille, A., 2012. Functional dysbiosis within the gut microbiota of patients with constipated-irritable bowel syndrome. Aliment. Pharmacol. Ther. 35, 828–838. https://doi.org/10.1111/j.1365-2036.2012.05007.x.

Chen, W.-Q., Yuan, L., Xue, R., Li, Y.-F., Su, R.-B., Zhang, Y.-Z., Li, J., 2011. Repeated exposure to chlorpyrifos alters the performance of adolescent male rats in animal models of depression and anxiety. Neurotoxicology 32, 355–361. https://doi.org/10.1016/J.NEURO.2011.03.008.

Chen, X.-P., Chen, W.-Z., Wang, F.-S., Liu, J.-X., 2012. Selective cognitive impairments are related to selective hippocampus and prefrontal cortex deficits after prenatal chlorpyrifos exposure. Brain Res. 1474, 19–28. https://doi.org/10.1016/j.brainres.2012.07.036.

Chichlowski, M., Rudolph, C., 2015. Visceral pain and gastrointestinal microbiome. J. Neurogastroenterol. Motil. 21, 172–181. https://doi.org/10.5056/jnm15025.

Cho, K.M., Math, R.K., Islam, S.M.A., Lim, W.J., Hong, S.Y., Kim, J.M., Yun, M.G., Cho, J.J., Yun, H.D., 2009. Biodegradation of chlorpyrifos by lactic acid Bacteria during kimchi fermentation. J. Agric. Food Chem. 57, 1882–1889. https://doi.org/10.1021/jf803649z.

Condette, C.J., Bach, V., Mayeur, C., Gay-Quéheillard, J., Khorsi-Cauet, H., 2015. Chlorpyrifos exposure during perinatal period impacts intestinal microbiota associated with delay of maturation of digestive tract in rats. J. Pediatr. Gastroenterol. Nutr. 61, 1. https://doi.org/10.1097/MPG.0000000000000734.

Cook, T.J., Shenoy, S.S., 2003. Intestinal permeability of chlorpyrifos using the single-pass intestinal perfusion method in the rat. Toxicology 184, 125–133. https://doi.org/10.1016/S0300-483X(02)00555-3.

Costa, L.G., 2018. Organophosphorus compounds at 80: some old and new issues. Toxicol. Sci. 162, 24–35. https://doi.org/10.1093/toxsci/kfx266.

Costa, L.G., Giordano, G., Cole, T.B., Marsillach, J., Furlong, C.E., 2013. Paraoxonase 1 (PON1) as a genetic determinant of susceptibility to organophosphate toxicity. Toxicology 307, 115–122. https://doi.org/10.1016/j.tox.2012.07.011.

Cryan, Dinan, 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 13, 701–712. https://doi.org/10.1038/nrn3346.

Dardiotis, E., Aloizou, A.-M., Siokas, V., Tsouris, Z., Rikos, D., Marogianni, C., Aschner, M., Kovatsi, L., Bogdanos, D.P., Tsatsakis, A., 2019. Paraoxonase-1 genetic polymorphisms in organophosphate metabolism. Toxicology 411, 24–31. https://doi.org/10.1016/J.TOX.2018.10.012.

De Palma, G., Collins, S.M., Bercik, P., Verdu, E.F., 2014. The microbiota-gut-brain axis in gastrointestinal disorders: stressed bugs, stressed brain or both? J. Physiol. 592, 2989–2997. https://doi.org/10.1113/jphysiol.2014.273995.

Dinan, T.G., Borre, Y.E., Cryan, J.F., 2014. Genomics of schizophrenia: time to consider the gut microbiome? Mol. Psychiatry 19, 1252–1257. https://doi.org/10.1038/mp.2014.93.

Dunn, A.B., Jordan, S., Baker, B.J., Carlson, N.S., 2017. The maternal infant microbiome: considerations for labor and birth. MCN Am. J. Matern. Child Nurs. 42, 318. https://doi.org/10.1097/NMC.0000000000000373.

Fang, B., Li, J.W., Zhang, M., Ren, F.Z., Pang, G.F., 2018. Chronic chlorpyrifos exposure elicits diet-specific effects on metabolism and the gut microbiome in rats. Food Chem. Toxicol. 111, 144–152. https://doi.org/10.1016/j.fct.2017.11.001.

Feng, P., Ye, Z., Kakade, A., Virk, A., Li, X., Liu, P., 2018. A review on gut remediation of selected environmental contaminants: possible roles of probiotics and gut microbiota. Nutrients 11, 22. https://doi.org/10.3390/nu11010022.

Fond, G., Boukouaci, W., Chevalier, G., Regnault, A., Eberl, G., Hamdani, N., Dickerson, F., Macgregor, A., Boyer, L., Dargel, A., Oliveira, J., Tamouza, R., Leboyer, M., 2015. The "psychomicrobiotic": targeting microbiota in major psychiatric disorders: a systematic review. Pathol. Biol. 63, 35–42. https://doi.org/10.1016/j.patbio.2014.10.003.

Gao, B., Bian, X., Mahbub, R., Lu, K., 2017. Sex-specific effects of organophosphate diazinon on the gut microbiome and its metabolic functions. Environ. Health Perspect. 125, 198–206. https://doi.org/10.1289/EHP202.

Gao, B., Chi, L., Tu, P., Bian, X., Thomas, J., Ru, H., Lu, K., 2018. The organophosphate malathion disturbs gut microbiome development and the quorum-Sensing system. Toxicol. Lett. 283, 52–57. https://doi.org/10.1016/j.toxlet.2017.10.023.

González-Alzaga, B., Lacasaña, M., Aguilar-Garduño, C., Rodríguez-Barranco, M., Ballester, F., Rebagliato, M., Hernández, A.F., 2014. A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure. Toxicol. Lett. 230, 104–121. https://doi.org/10.1016/j.toxlet.2013.11.019.

Hancock, D.B., Martin, E.R., Mayhew, G.M., Stajich, J.M., Jewett, R., Stacy, M.A., Scott, B.L., Vance, J.M., Scott, W.K., 2008. Pesticide exposure and risk of Parkinson's disease: a family-based case-control study. BMC Neurol. 8, 6. https://doi.org/10.1186/1471-2377-8-6.

Hardy, H., Harris, J., Lyon, E., Beal, J., Foey, A.D., 2013. Probiotics, prebiotics and immunomodulation of gut mucosal defences: homeostasis and immunopathology. Nutrients 5, 1869–1912. https://doi.org/10.3390/nu5061869.

Harrison, V., Mackenzie Ross, S., 2016. Anxiety and depression following cumulative low-level exposure to organophosphate pesticides. Environ. Res. 151, 528–536. https://doi.org/10.1016/J.ENVRES.2016.08.020.

Hashjin, G.S., Dizaj, F.S., Attaran, H., Koohi, M.K., 2013. Malathion induces anxiety in the male adult mouse. Arch. Med. Sci. 9, 368–371. https://doi.org/10.5114/aoms.2013.33174.

Hernández, A.F., Gil, F., Lacasaña, M., Rodríguez-Barranco, M., Tsatsakis, A.M., Requena, M., Parrón, T., Alarcón, R., 2013. Pesticide exposure and genetic variation in xenobiotic-metabolizing enzymes interact to induce biochemical liver damage. Food Chem. Toxicol. 61, 144–151. https://doi.org/10.1016/J.FCT.2013.05.012.

Hernández, A.F., González-Alzaga, B., López-Flores, I., Lacasaña, M., 2016. Systematic reviews on neurodevelopmental and neurodegenerative disorders linked to pesticide exposure: methodological features and impact on risk assessment. Environ. Int. 92–93, 657–679. https://doi.org/10.1016/J.ENVINT.2016.01.020.

Hoseinifar, S.H., Soleimani, N., Ringø, E., 2014. Effects of dietary fructo-oligosaccharide supplementation on the growth performance, haemato-immunological parameters, gut microbiota and stress resistance of common carp (Cyprinus carpio) fry. Br. J.

Nutr. 112, 1296–1302. https://doi.org/10.1017/S0007114514002037.
Jafari, M., Salehi, M., Asgari, A., Ahmadi, S., Abbasnezhad, M., Hajihoosani, R., Hajigholamali, M., 2012. Effects of paraoxon on serum biochemical parameters and oxidative stress induction in various tissues of Wistar and Norway rats. Environ. Toxicol. Pharmacol. 34, 876–887. https://doi.org/10.1016/j.etap.2012.08.011.
Jiang, H., Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., Wang, W., Tang, W., Tan, Z., Shi, J., Li, L., Ruan, B., 2015. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav. Immun. 48, 186–194. https://doi.org/10.1016/j.bbi.2015.03.016.
Joly, C., Gay-Quéheillard, J., Léké, A., Chardon, K., Delanaud, S., Bach, V., Khorsi-Cauet, H., 2013. Impact of chronic exposure to low doses of chlorpyrifos on the intestinal microbiota in the Simulator of the Human Intestinal Microbial Ecosystem (SHIME) and in the rat. Environ. Sci. Pollut. Res. Int. 20, 2726–2734. https://doi.org/10.1007/s11356-012-1283-4.
Joly Condette, C., Khorsi-Cauet, H., Morlière, P., Zabijak, L., Reygner, J., Bach, V., Gay-Quéheillard, J., 2014. Increased gut permeability and bacterial translocation after chronic chlorpyrifos exposure in rats. PLoS One 9, e102217. https://doi.org/10.1371/journal.pone.0102217.
Kochhar, S., Martin, F.-P., 2015. Metabonomics and Gut Microbiota in Nutrition and Disease, 1st ed, Molecular and Integrative Toxicology. Springer Publishing Company.
Koh, S.-B., Kim, T.H., Min, S., Lee, K., Kang, D.R., Choi, J.R., 2017. Exposure to pesticide as a risk factor for depression: a population-based longitudinal study in Korea. Neurotoxicology 62, 181–185. https://doi.org/10.1016/J.NEURO.2017.07.005.
Kwong, T.C., 2002. Organophosphate pesticides: biochemistry and clinical toxicology. Ther. Drug Monit. 24, 144–149.
Levin, E.D., Addy, N., Baruah, A., Elias, A., Christopher, N.C., Seidler, F.J., Slotkin, T.A., 2002. Prenatal chlorpyrifos exposure in rats causes persistent behavioral alterations. Neurotoxicol. Teratol. 24, 733–741.
López-Crespo, G.A., Carvajal, F., Flores, P., Sánchez-Santed, F., Sánchez-Amate, M.C., 2007. Time course of biochemical and behavioural effects of a single high dose of chlorpyrifos. Neurotoxicology 28, 541–547. https://doi.org/10.1016/j.neuro.2007.01.013.
López-Granero, C., Cañadas, F., Cardona, D., Yu, Y., Giménez, E., Lozano, R., Avila, D.S., Aschner, M., Sánchez-Santed, F., 2013. Chlorpyrifos-, diisopropylphosphorofluoridate-, and parathion-induced behavioral and oxidative stress effects: are they mediated by analogous mechanisms of action? Toxicol. Sci. 131, 206–216. https://doi.org/10.1093/toxsci/kfs280.
López-Granero, C., Ruiz-Muñoz, A.M., Nieto-Escámez, F.A., Colomina, M.T., Aschner, M., Sánchez-Santed, F., 2016. Chronic dietary chlorpyrifos causes long-term spatial memory impairment and thigmotaxic behavior. Neurotoxicology 53, 85–92. https://doi.org/10.1016/j.neuro.2015.12.016.
Lotti, M., 2010. Clinical toxicology of anticholinesterase agents in humans. Hayes' Handb. Pestic. Toxicol. 1543–1589. https://doi.org/10.1016/B978-0-12-374367-1.00072-0.
Lotti, M., Moretto, A., 2005. Organophosphate-induced delayed polyneuropathy. Toxicol. Rev. 24, 37–49.
Martín, R., Langa, S., Reviriego, C., Jimínez, E., Marín, M.L., Xaus, J., Fernández, L., Rodríguez, J.M., 2003. Human milk is a source of lactic acid bacteria for the infant gut. J. Pediatr. 143, 754–758. https://doi.org/10.1016/j.jpeds.2003.09.028.
Mayer, E.A., Tillisch, K., Gupta, A., 2015. Gut/brain axis and the microbiota. J. Clin. Invest. 125. https://doi.org/10.1172/JCI76304.
Mazzon, E., Sturniolo, G.C., Puzzolo, D., Frisina, N., Fries, W., 2002. Effect of stress on the paracellular barrier in the rat ileum. Gut 51, 507–513.
Mense, S.M., Sengupta, A., Lan, C., Zhou, M., Bentsman, G., Volsky, D.J., Whyatt, R.M., Perera, F.P., Zhang, L., 2006. The common insecticides cyfluthrin and chlorpyrifos alter the expression of a subset of genes with diverse functions in primary human astrocytes. Toxicol. Sci. 93, 125–135. https://doi.org/10.1093/toxsci/kfl046.
Molina-Torres, G., Rodriguez-Arrastia, M., Roman, P., Sanchez-Labraca, N., Cardona, D., 2019. Stress and the gut microbiota-brain axis. Behav. Pharmacol. 30, 187–200. https://doi.org/10.1097/FBP.0000000000000478.
Moloney, R.D., Johnson, A.C., O'Mahony, S.M., Dinan, T.G., Greenwood-Van Meerveld, B., Cryan, J.F., 2016. Stress and the microbiota-gut-brain axis in visceral parelevance to irritable bowel syndrome. CNS Neurosci. Ther. 22, 102–117. https://doi.org/10.1111/cns.12490.
Muñoz-Quezada, M.T., Lucero, B.A., Iglesias, V.P., Muñoz, M.P., Cornejo, C.A., Achu, E., Baumert, B., Hanchey, A., Concha, C., Brito, A.M., Villalobos, M., 2016. Chronic exposure to organophosphate (OP) pesticides and neuropsychological functioning in farm workers: a review. Int. J. Occup. Environ. Health 22, 68–79. https://doi.org/10.1080/10773525.2015.1123848.
Nash, M.J., Frank, D.N., Friedman, J.E., 2017. Early Microbes Modify Immune System Development and Metabolic Homeostasis-The "Restaurant" Hypothesis Revisited. Front. Endocrinol. (Lausanne). 8, 349. https://doi.org/10.3389/fendo.2017.00349.
Naughton, S.X., Terry, A.V., 2018. Neurotoxicity in acute and repeated organophosphate exposure. Toxicology 408, 101–112. https://doi.org/10.1016/j.tox.2018.08.011.
Neish, A.S., 2009. Microbes in gastrointestinal health and disease. Gastroenterology 136, 65–80. https://doi.org/10.1053/j.gastro.2008.10.080.
Ohland, C.L., Jobin, C., 2015. Microbial activities and intestinal homeostasis: a delicate balance between health and disease. Cell. Mol. Gastroenterol. Hepatol. 1, 28–40. https://doi.org/10.1016/j.jcmgh.2014.11.004.
Ohland, C.L., Kish, L., Bell, H., Thiesen, A., Hotte, N., Pankiv, E., Madsen, K.L., 2013. Effects of Lactobacillus helveticus on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. Psychoneuroendocrinology 38, 1738–1747. https://doi.org/10.1016/j.psyneuen.2013.02.008.
Ojha, A., Yaduvanshi, S.K., Srivastava, N., 2011. Effect of combined exposure of commonly used organophosphate pesticides on lipid peroxidation and antioxidant enzymes in rat tissues. Pestic. Biochem. Physiol. 99, 148–156. https://doi.org/10.1016/J.PESTBP.2010.11.011.
Pearson, J.N., Patel, M., 2016. The role of oxidative stress in organophosphate and nerve agent toxicity. Ann. N. Y. Acad. Sci. 1378, 17–24. https://doi.org/10.1111/nyas.13115.
Petersen, C., Round, J.L., 2014. Defining dysbiosis and its influence on host immunity and disease. Cell. Microbiol. 16, 1024–1033. https://doi.org/10.1111/cmi.12308.
Rajilić-Stojanović, M., Biagi, E., Heilig, H.G.H.J., Kajander, K., Kekkonen, R.A., Tims, S., de Vos, W.M., 2011. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. Gastroenterology 141, 1792–1801. https://doi.org/10.1053/j.gastro.2011.07.043.
Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D.B., Whyatt, R., 2011. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ. Health Perspect. 119, 1196–1201. https://doi.org/10.1289/ehp.1003160.
Rea, K., Dinan, T.G., Cryan, J.F., 2017. The brain-gut axis contributes to neuroprogression in stress-related disorders. Mod. Trends Pharmacopsychiatry 31, 152–161. https://doi.org/10.1159/000470813.
Reiss, R., Chang, E.T., Richardson, R.J., Goodman, M., 2015. A review of epidemiologic studies of low-level exposures to organophosphorus insecticides in non-occupational populations. Crit. Rev. Toxicol. 45, 531–641. https://doi.org/10.3109/10408444.2015.1043976.
Réquilé, M., Gonzàlez Alvarez, D.O., Delanaud, S., Rhazi, L., Bach, V., Depeint, F., Khorsi-Cauet, H., 2018. Use of a combination of in vitro models to investigate the impact of chlorpyrifos and inulin on the intestinal microbiota and the permeability of the intestinal mucosa. Environ. Sci. Pollut. Res. Int. 25, 22529–22540. https://doi.org/10.1007/s11356-018-2332-4.
Reygner, J., Joly Condette, C., Bruneau, A., Delanaud, S., Rhazi, L., Depeint, F., Abdennebi-Najar, L., Bach, V., Mayeur, C., Khorsi-Cauet, H., 2016a. Changes in composition and function of human intestinal microbiota exposed to chlorpyrifos in oil as assessed by the SHIME® model. Int. J. Environ. Res. Public Health 13. https://doi.org/10.3390/ijerph13111088.
Reygner, J., Lichtenberger, L., Elmhiri, G., Dou, S., Bahi-Jaber, N., Rhazi, L., Depeint, F., Bach, V., Khorsi-Cauet, H., Abdennebi-Najar, L., 2016b. Inulin supplementation lowered the metabolic defects of prolonged exposure to chlorpyrifos from gestation to young adult stage in offspring rats. PLoS One 11, e0164614. https://doi.org/10.1371/journal.pone.0164614.
Roberfroid, M., Gibson, G.R., Hoyles, L., McCartney, A.L., Rastall, R., Rowland, I., Wolvers, D., Watzl, B., Szajewska, H., Stahl, B., Guarner, F., Respondek, F., Whelan, K., Coxam, V., Davicco, M.-J., Léotoing, L., Wittrant, Y., Delzenne, N.M., Cani, P.D., Neyrinck, A.M., Meheust, A., 2010. Prebiotic effects: metabolic and health benefits. Br. J. Nutr. 104 (Suppl), S1–S63. https://doi.org/10.1017/S0007114510003363.
Rodríguez-Fandiño, O., Hernández-Ruiz, J., Schmulson, M., 2010. From cytokines to toll-like receptors and beyond - current knowledge and future research needs in irritable bowel syndrome. J. Neurogastroenterol. Motil. 16, 363–373. https://doi.org/10.5056/jnm.2010.16.4.363.
Rohlman, D.S., Anger, W.K., Lein, P.J., 2011. Correlating neurobehavioral performance with biomarkers of organophosphorous pesticide exposure. Neurotoxicology 32, 268–276. https://doi.org/10.1016/j.neuro.2010.12.008.
Roman, P., Abalo, R., Marco, E.M., Cardona, D., 2018a. Probiotics in digestive, emotional, and pain-related disorders. Behav. Pharmacol. 29, 1. https://doi.org/10.1097/FBP.0000000000000385.
Roman, P., Rueda-Ruzafa, L., Cardona, D., Cortes-Rodríguez, A., 2018b. Gut–brain axis in the executive function of austism spectrum disorder. Behav. Pharmacol. 29, 654–663. https://doi.org/10.1097/FBP.0000000000000428.
Ross, S.M., McManus, I.C., Harrison, V., Mason, O., 2013. Neurobehavioral problems following low-level exposure to organophosphate pesticides: a systematic and meta-analytic review. Crit. Rev. Toxicol. 43, 21–44. https://doi.org/10.3109/10408444.2012.738645.
Sánchez-Santed, F., Colomina, M.T., Herrero Hernández, E., 2016. Organophosphate pesticide exposure and neurodegeneration. Cortex 74, 417–426. https://doi.org/10.1016/j.cortex.2015.10.003.
Sapbamrer, R., Hongsibsong, S., 2019. Effects of prenatal and postnatal exposure to organophosphate pesticides on child neurodevelopment in different age groups: a systematic review. Environ. Sci. Pollut. Res. https://doi.org/10.1007/s11356-019-05126-w.
Savin, Z., Kivity, S., Yonath, H., Yehuda, S., 2018. Smoking and the intestinal microbiome. Arch. Microbiol. 200, 677–684. https://doi.org/10.1007/s00203-018-1506-2.
Sender, R., Fuchs, S., Milo, R., 2016. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell 164, 337–340. https://doi.org/10.1016/j.cell.2016.01.013.
Sharon, G., Garg, N., Debelius, J., Knight, R., Dorrestein, P.C., Mazmanian, S.K., 2014. Specialized metabolites from the microbiome in health and disease. Cell Metab. 20, 719–730. https://doi.org/10.1016/j.cmet.2014.10.016.
Shreiner, A.B., Kao, J.Y., Young, V.B., 2015. The gut microbiome in health and in disease. Curr. Opin. Gastroenterol. 31, 69–75. https://doi.org/10.1097/MOG.0000000000000139.
Singh, A.K., Jiang, Y., 2003. Lipopolysaccharide (LPS) induced activation of the immune system in control rats and rats chronically exposed to a low level of the organothiophosphate insecticide, acephate. Toxicol. Ind. Health 19, 93–108. https://doi.org/10.1191/0748233703th181oa.
Slotkin, T.A., 2011. Does early-life exposure to organophosphate insecticides lead to prediabetes and obesity? Reprod. Toxicol. 31, 297–301. https://doi.org/10.1016/j.reprotox.2010.07.012.
Taverniti, V., Guglielmetti, S., 2011. The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept). Genes Nutr. 6, 261–274. https://doi.org/10.1007/s12263-011-0218-x.

Terry, A.V., 2012. Functional consequences of repeated organophosphate exposure: potential non-cholinergic mechanisms. Pharmacol. Ther. 134 (3), 355–365. https://doi.org/10.1016/j.pharmthera.2012.03.001.

Thursby, E., Juge, N., 2017. Introduction to the human gut microbiota. Biochem. J. 474, 1823–1836. https://doi.org/10.1042/BCJ20160510.

Trinder, M., McDowell, T.W., Daisley, B.A., Ali, S.N., Leong, H.S., Sumarah, M.W., Reid, G., 2016. Probiotic Lactobacillus rhamnosus reduces organophosphate pesticide absorption and toxicity to Drosophila melanogaster. Appl. Environ. Microbiol. 82, 6204–6213. https://doi.org/10.1128/AEM.01510-16.

van de Wouw, M., Boehme, M., Lyte, J.M., Wiley, N., Strain, C., O'Sullivan, O., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2018. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain–gut axis alterations. J. Physiol. 1–39. https://doi.org/10.1113/JP276431.

Velmurugan, G., Ramprasath, T., Swaminathan, K., Mithieux, G., Rajendhran, J., Dhivakar, M., Parthasarathy, A., Babu, D.D.V., Thumburaj, L.J., Freddy, A.J., Dinakaran, V., Puhari, S.S.M., Rekha, B., Christy, Y.J., Anusha, S., Divya, G., Suganya, K., Meganathan, B., Kalyanaraman, N., Vasudevan, V., Kamaraj, R., Karthik, M., Jeyakumar, B., Abhishek, A., Paul, E., Pushpanathan, M., Rajmohan, R.K., Velayutham, K., Lyon, A.R., Ramasamy, S., 2017. Gut microbial degradation of organophosphate insecticides-induces glucose intolerance via gluconeogenesis. Genome Biol. 18, 8. https://doi.org/10.1186/s13059-016-1134-6.

Vismaya, Rajini, P.S., 2014. Oral exposure to the organophosphorus insecticide, Monocrotophos induces intestinal dysfunction in rats. Food Chem. Toxicol. 71, 236–243. https://doi.org/10.1016/j.fct.2014.05.030.

Vyas, U., Ranganathan, N., 2012. Probiotics, prebiotics, and synbiotics: gut and beyond. Gastroenterol. Res. Pract. 2012, 1–16. https://doi.org/10.1155/2012/872716.

Wallace, T.C., Guarner, F., Madsen, K., Cabana, M.D., Gibson, G., Hentges, E., Sanders, M.E., 2011. Human gut microbiota and its relationship to health and disease. Nutr. Rev. 69, 392–403. https://doi.org/10.1111/j.1753-4887.2011.00402.x.

WHO, 2001. In: Report of the Joint FAO/ WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. Córdoba, Argentina, 1-4 October 2001. Food and Agriculture Organization of the United Nations.

Xia, X., Zheng, D., Zhong, H., Qin, B., Gurr, G.M., Vasseur, L., Lin, H., Bai, J., He, W., You, M., 2013. DNA sequencing reveals the midgut microbiota of diamondback moth, Plutella xylostella (L.) and a possible relationship with insecticide resistance. PLoS One 8, e68852. https://doi.org/10.1371/journal.pone.0068852.

Zaja-Milatovic, S., Gupta, R.C., Aschner, M., Milatovic, D., 2009. Protection of DFP-induced oxidative damage and neurodegeneration by antioxidants and NMDA receptor antagonist. Toxicol. Appl. Pharmacol. 240, 124–131. https://doi.org/10.1016/j.taap.2009.07.006.

Zhao, Y., Zhang, Y., Wang, G., Han, R., Xie, X., 2016. Effects of chlorpyrifos on the gut microbiome and urine metabolome in mouse (Mus musculus). Chemosphere 153, 287–293. https://doi.org/10.1016/j.chemosphere.2016.03.055.