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Agrochemicals and obesity

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Abstract

Obesity has become a very large concern worldwide, reaching pandemic proportions over the past several decades. Lifestyle factors, such as excess caloric intake and decreased physical activity, together with genetic predispositions, are well-known factors related to obesity. There is accumulating evidence suggesting that exposure to some environmental chemicals during critical windows of development may contribute to the rapid increase in the incidence of obesity. Agrochemicals are a class of chemicals extensively used in agriculture, which have been widely detected in human. There is now considerable evidence linking human exposure to agrochemicals with obesity. This review summarizes human epidemiological evidence and experimental animal studies supporting the association between agrochemical exposure and obesity and outlines possible mechanistic underpinnings for this link.

Keywords

Obesogen; EDC; endocrine disrupting chemical; agrochemical; pesticide; fungicide; transgenerational; epigenetic; microbiome

1. Introduction

Agrochemicals constitute a diverse class of chemicals extensively used in agriculture for many different purposes. These include preventing harmful effects caused by pests, controlling infectious diseases induced by bacteria or fungi, and promoting crop growth. Agrochemicals are thought to play critical roles in increased agricultural productivity as well as the control of insect pests that are disease vectors.

Agrochemicals of concern are typically pesticides including insecticides, herbicides, fungicides and nematicides (Sparks, 2013). These agrochemicals can be further subdivided

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into organochlorines, organophosphorus, carbamates, pyrethroids and neonicotinoids, according to their chemical structures and modes of action (Xiao, Clark and Park, 2017). While bringing benefits to humans, agrochemicals have also become major contaminants that are widely detected in the environment as well as in humans (Tsatsakis, Tzatzarakis, Tutudaki et al., 2008). Many efforts have been made to reduce the harmful effects of agrochemicals on humans by designing lower toxicity chemicals and by controlling the time and location of applications. However, agrochemical exposure and consequent toxicity to humans and animals is inevitable (Sparks and Lorsbach, 2017). Numerous epidemiological studies together with experimental evidence in animal models indicated that agrochemicals may be harmful to human health in multiple ways (Cano-Sancho, Salmon and La Merrill, 2017,Androutsopoulos, Hernandez, Liesivuori et al., 2013). For example, agrochemicals may have carcinogenicity, neurotoxicity, immunotoxicity, reproductive toxicity, developmental toxicity and endocrine disrupting effects (Mostafalou and Abdollahi, 2017). In view of this, the toxicity of agrochemicals is of great concern around the world.

Currently, obesity has become a worldwide pandemic and public health problem (Hales, Fryar, Carroll et al., 2018). According to the World Health Organization, approximately 39% of adults worldwide are overweight (body mass index, BMI $\geqslant$ 25 kg/m^2) and 13% are obese (BMI $\geqslant$ 30) (World Health Organization, 2018). The obesity problem is also severe for children and adolescents (World Health Organization, 2014). Obesity is a complex and multifactorial condition that increases the risk of many other chronic diseases such as cardiovascular disease, diabetes mellitus type 2 (T2D), hypertension, stroke and even some kinds of cancers (Picon-Ruiz, Morata-Tarifa, Valle-Goffin et al., 2017). It was suggested that at least 2.8 million deaths worldwide could be attributed to the results of overweight or obesity each year (World Health Organization, 2015).

Obesity is generally considered to be the result of energy imbalance, i.e., when energy intake exceeds energy expenditure. However, in reality the origins of obesity are multifactorial and result from the combined effects of both genetic and environmental factors (Heindel and Blumberg, 2019). Currently, the full spectrum of potential factors associated with obesity remains unclear. Previous studies have shown that factors such as genetic susceptibility, increased energy intake and lack of physical activity could contribute to the development of obesity (Turcot, Lu, Highland et al., 2018). However, these factors cannot fully explain the current dramatically increased rates of obesity. Over the past several decades, there is considerable evidence that environmental pollutants may contribute to the rapid increase of obesity (Heindel and Blumberg, 2019). Endocrine-disrupting chemicals (EDCs) are natural or man-made substances that may interfere with the normal function of the endocrine system, including hormone biosynthesis, metabolism or action (Zoeller, Brown, Doan et al., 2012). There is growing evidence showing links between EDCs and obesity as well as other health problems such as metabolic issues, diabetes, reproductive disabilities and cardiovascular problems (Gore, Chappell, Fenton et al., 2015). Metabolism disrupting chemicals (MDCs) specifically refer to those EDCs having the ability to promote metabolic changes that can result in obesity, T2D or fatty liver in animals (Heindel, Blumberg, Cave et al., 2017). These EDCs or MDCs might be important factors leading to obesity. Identifying all of the important factors that contribute to obesity is, therefore, an important issue and could help to control and reduce the obesity epidemic and related diseases.

"Obesogens" are functionally defined as chemicals th at promote obesity after exposure, in vivo. Some natural chemicals (such as fructose), pharmaceutical chemicals (such as thiazolidinedione anti-diabetic drugs) or xenobiotic chemicals [such as tributyltin (TBT)] have found to be obesogens (Janesick and Blumberg, 2016). Obesogens might act directly on fat cells by increasing their number or increasing the storage of fat into the existing cells. These chemicals might also act indirectly by affecting mechanisms regulating appetite and satiety, by altering basal metabolic rate, altering energy balance to favor the storage of calories, or by altering gut microbiota to promote energy intake (Heindel and Blumberg, 2019). Some agrochemicals have been shown to act as obesogens by promoting adipogenesis and inducing obesity in experimental animals and are found at higher levels in obese humans. For example, dichlorodiphenyldichloroethylene (DDE) was classified as "presumed" to be obesogenic for humans by using a systematic review-based strategy to identify and integrate evidence from epidemiological, in vivo, and in vitro studies (Cano-Sancho et al., 2017). Others suggested that the evidence for DDE as an obesogen was "moderate" due to the consistency in prospective associations with childhood growth and obesity (Vrijheid, Casas, Gascon et al., 2016). Here we present a review of current studies linking agrochemical exposure and obesity, including studies from human and animals, and discuss possible mechanisms underlying these effects.

2. Human epidemiological studies relating agrochemicals and obesity

2.1 Association between agrochemicals and adult obesity

There is a growing body of epidemiological studies suggesting an association between agrochemicals and adult obesity (Table 1). Agrochemicals of concern include dichlorodiphenyltrichloroethane (DDT), DDE, hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCH) and malathion. For example, multiple prospective cohort studies identified a positive association between levels of DDT/DDE and obesity or overweight (Mendez, Garcia-Esteban, Guxens et al., 2011,Valvi, Mendez, Garcia-Esteban et al., 2014,Valvi, Mendez, Martinez et al., 2012,Lee, Lind, Jacobs et al., 2012). Pre-pregnancy levels of DDT were found to be moderately associated with gestational weight gain in a prospective cohort study of pregnant women (Jaacks, Boyd Barr, Sundaram et al., 2016). A positive correlation between β-HCH and BMI, waist circumference, percentage of fat mass, as well as total and subcutaneous abdominal adipose tissue has also been demonstrated in a cross-sectional study of 98 obese men and women (Dirinck, Jorens, Covaci et al., 2011). There was a positive correlation between malathion blood concentration and waist circumference among a group of farmers (Raafat, Abass and Salem, 2012). In addition to increased weight or elevated BMI, the levels of some obesity biomarkers (levels of total cholesterol and total serum lipids) were also positively associated with the concentrations of pesticides such as HCB, β-HCH and DDE (Dusanov, Ruzzin, Kiviranta et al., 2018,La Merrill, Lind, Salihovic et al., 2018,Bachelet, Truong, Verner et al., 2011,Langer, Ukropec, Kocan et al., 2014,Ibarluzea, Alvarez-Pedrerol, Guxens et al., 2011,Lee, Steffes, Sjodin et al., 2011), suggesting that these compounds can aggravate clinically relevant complications of obesity.

Although the use of DDT has been banned in many countries, some populations still bear significant levels of DDT and DDE due to the extremely long half-life of these chemicals in the environment and in the human body, bioaccumulation and via the continued use of DDT in some developing countries (United Nations Environment Programme, 2010,Bornman, Aneck-Hahn, de Jager et al., 2017). HCB and β-HCH were banned globally several decades ago, but persist in the environment. Malathion is a pesticide that is still widely used in agriculture, in residential landscaping, and in public health pest control programs. All these agrochemicals can be detected in humans currently. Information about the human exposure levels of these agrochemicals is listed in Table 1. The obesogenic effects of these pesticides in humans still needs to be considered.

2.2 Non-monotonic dose-response relationships between agrochemicals and adult obesity

Some studies showing the potential relationship between pesticide exposure and serum lipids/obesity/BMI revealed that the effects followed non-monotonic dose-response relationships. This unconventional dose-response relationship is characterized by a curve whose slope changes direction within the range of tested doses (Lee et al., 2012). For example, Arrebola et al. found that HCB, DDE and β-HCH showed quadratic associations with BMI, and the quadratic models had a positive trend at low exposure levels, while the slope decreased or even became negative at higher exposure levels (Arrebola, Ocana-Riola, Arrebola-Moreno et al., 2014). Numerous studies investigating the effects of EDCs described the occurrence of non-monotonic dose-response relationships for EDCs with relatively high frequency (Zoeller and Vandenberg, 2015). The molecular mechanisms underlying non-monotonic dose-response relationships are complex and can arise from opposing effects induced by multiple receptors, receptor desensitization, negative feedback with increasing dose, or dose-dependent metabolism modulation (Zoeller and Vandenberg, 2015). Usual risk assessment approaches used by regulatory agencies are developed based on the fundamental principle that the toxicity of a chemical scales linearly in proportion to the exposure level. Therefore, non-monotonicity represents a challenge to fundamental concepts in toxicology and risk assessment (Dietrich, von Aulock, Marquardt et al., 2013). These non-monotonic dose-response relationships of agrochemicals suggest that mechanisms by which they induce obesity are complex. Lipophilic organochlorine pesticides such as DDE and HCB usually accumulate in adipose tissue to a major degree. Therefore, the circulating levels of these chemicals might be influenced by the degree of fat mass (Glynn, Granath, Aune et al., 2003), which can also make it difficult to study the relationships between chemicals and obesity in adults.

2.3 Agrochemicals and the development of early-onset obesity

Many environmental factors have been shown to play a prominent role in the development of early-onset obesity (La Merrill and Birnbaum, 2011). Building on Barker's fetal origins of disease model (Barker, 1995), Gluckman and Hanson proposed the Developmental Origins of Health and Disease (DOHaD) hypothesis, which holds that environmental disruptions during critical windows of development can lead to increased susceptibility to diseases, including obesity, later in life (Gluckman and Hanson, 2004). Compared with adults, the fetus and neonate are more sensitive to perturbation by environmental chemicals during

critical windows of development because protective mechanisms (such as DNA repair, immune system, xenobiotic metabolism, and the blood/brain barrier, among others) are not yet fully functional (Newbold, 2011). The higher metabolic rates of developing organisms may also result in increased toxicity compared to adults. Therefore, developmental exposures to xenobiotic toxicants are of particular concern.

Measuring the levels of agrochemicals in pregnant mothers and follow-up of the weight gain of the children over their lives may provide evidence for the obesogenic effect of these chemicals during development. Several reviews have reported moderate evidence linking prenatal agrochemical exposure to childhood obesity (La Merrill and Birnbaum, 2011,Tang-Peronard, Andersen, Jensen et al., 2011). Recently, the body of evidence for obesogenic effects of agrochemicals especially DDE after exposure during prenatal development has increased notably. There have been more than 10 prospective cohort studies showing that prenatal DDE exposure is significantly associated with increased birth weight, increased levels of some obesity markers, overweight risk or increased risk of childhood obesity ranging from 6 months to 9 years old (Mendez et al., 2011,Valvi et al., 2014,Valvi et al., 2012,Vafeiadi, Georgiou, Chalkiadaki et al., 2015,Agay-Shay, Martinez, Valvi et al., 2015,Verhulst, Nelen, Hond et al., 2009,Karmaus, Osuch, Eneli et al., 2009,Iszatt, Stigum, Verner et al., 2015,Heggeseth, Harley, Warner et al., 2015) (Table 2). Furthermore, DDE exposure might exacerbate the effects of other known contributing factors for obesity such as smoking (Verhulst et al., 2009). However, some other prospective cohort studies found no association between developmental exposure to DDE and infant or child obesity (Garced, Torres-Sanchez, Cebrian et al., 2012,Govarts, Nieuwenhuijsen, Schoeters et al., 2012,Hoyer, Ramlau-Hansen, Henriksen et al., 2014,Cupul-Uicab, Klebanoff, Brock et al., 2013,Warner, Aguilar Schall, Harley et al., 2013,Cupul-Uicab, Hernandez-Avila, Terrazas-Medina et al., 2010,Gladen, Klebanoff, Hediger et al., 2004).

A number of studies also showed associations between DDE or HCB and low birth weight and/or preterm birth (Govarts et al., 2012,Guo, Jin, Cheng et al., 2014,Lenters, Portengen, Rignell-Hydbom et al., 2016,de Cock, de Boer, Lamoree et al., 2014,Vafeiadi, Vrijheid, Fthenou et al., 2014). Both of these are established risk factors for subsequent rapid growth and long-term obesity (Stettler and Iotova, 2010). While more data are needed, these studies support the conclusion that developmental exposure to DDE and perhaps some other agrochemicals might lead to obesity in humans.

Relatively fewer studies have examined links between prenatal DDT and DDD, β-HCH or HCB exposure and potential of childhood obesity. Some prospective cohort studies (Valvi et al., 2014,Valvi et al., 2012,Vafeiadi et al., 2015,Agay-Shay et al., 2015,Heggeseth et al., 2015,Smink, Ribas-Fito, Garcia et al., 2008,Warner, Ye, Harley et al., 2017,Warner, Wesselink, Harley et al., 2014) or cross-sectional studies(Xu, Yin, Tang et al., 2017) showed positive associations with obesity (Table 2). However, a few other prospective cohort studies did not identify such significant associations (Cupul-Uicab et al., 2013,Warner et al., 2013,Delvaux, Van Cauwenberghe, Den Hond et al., 2014).

2.4 Gender-specific effects of agrochemicals

Sexually dimorphic responses are a common finding when examining EDC effects, including links to obesity (Gore et al., 2015). Currently, some prospective cohort studies (Valvi et al., 2012,Warner et al., 2017,Warner et al., 2014,Delvaux et al., 2014,Tang-Peronard, Heitmann, Andersen et al., 2014) or cross-sectional studies (Cabrera-Rodriguez, Luzardo, Almeida-Gonzalez et al., 2019) showed gender-specific effects of agrochemicals on childhood obesity (see Table 2). For example, Warner et al. showed a positive association between DDE and childhood obesity in boys but not in girls (Warner et al., 2017,Warner et al., 2014). However, some other studies showed the effects of DDE on childhood obesity existed in girls but not in boys (Delvaux et al., 2014,Tang-Peronard et al., 2014). The reason for this difference warrants further study. The mechanisms underlying gender-specific effects of agrochemicals also need to be studied in the future.

3. Animal studies and the relationship between agrochemicals and obesity

3.1 Studies showing the obesogenic effects of agrochemicals in adult experimental animals

Most of the animal studies relating chemical exposures to obesity demonstrated that the exposures led to weight gain and changes in adiposity, increased expression of obesity and adipogenesis-related biomarkers and affected hormones and adipokines involved in the regulation of food intake and energy expenditure (La Merrill, Karey, Moshier et al., 2014,Angle, Do, Ponzi et al., 2013). Exposures to the agrochemicals HCB, γ-HCH, parathion, chlorpyrifos (CPF), mancozeb and imidacloprid led to increased body weight in rodents (Howell, Meek, Kilic et al., 2014,Peris-Sampedro, Cabre, Basaure et al., 2015,Peris-Sampedro, Basaure, Reverte et al., 2015,Basaure, Guardia-Escote, Biosca-Brull et al., 2019,Meggs and Brewer, 2007,Lassiter, Ryde, Mackillop et al., 2008,Bhaskar and Mohanty, 2014) (Table 3). In addition, some obesity-related indicators such as decreased total energy expenditure, alterations in glucose and lipid metabolism were observed after exposure to DTT and DDE (La Merrill et al., 2014,Howell et al., 2014,Ishikawa, Graham, Stanhope et al., 2015,Howell, Mulligan, Meek et al., 2015), malathion (Kalender, Uzun, Durak et al., 2010) or CPF (Acker and Nogueira, 2012,Uchendu, Ambali, Ayo et al., 2018) (Table 3).

The “two-hit” hypothesis, first formulated by Knudso n in 1971, suggested that most tumor suppressor genes require both alleles to be inactivated to result in a cancer (Knudson, 1971). Now, this “two-hit” hypothesis has been adopt ed to explain the multifactorial nature of obesity, which may result from the combined effects of both genetic and environmental factors. A subject who is genetically-prone to obesity has the “first hit” (genetic susceptibility or epigenetic predisposition) intrinsically. Obesogenic factors such as chemical exposures, high energy diet, low physical activity, alcohol and smoking that act as “second hit” trigger gain weight and result in obesity (Heindel et al., 2017). The obesogenic effects of some agrochemicals were only observed upon co-treatment with high-fat diet (HFD) or were exacerbated by HFD, indicating that a second hit was needed to elicit obesity. It was reported that low doses of orally administrated permethrin (Xiao, Sun, Kim et al., 2018) or imidacloprid (Sun, Xiao, Kim et al., 2016,Sun, Qi, Xiao et al., 2017) potentiated weight gain

in male mice only when a HFD was provided. HFD-fed rats exposed to CPF exhibited a pro-obesity phenotype compared with controls (Fang, Li, Zhang et al., 2018). Chronic administration of atrazine increased body weight without changing food intake or physical activity levels, and feeding a HFD further exacerbated obesity (Lim, Ahn, Song et al., 2009).

3.2 Animal studies showing the development and transgenerational obesogenic effects of agrochemicals

Obesogenic effects of agrochemical exposure during development have been reported (Table 3). Li et al. showed that prenatal triflumizole exposure increased white adipose depot weight in vivo (Li, Pham, Janesick et al., 2012). Sexually dimorphic responses have also been reported in most animal studies. For example, perinatal exposure (gestational day 11.5 through postnatal day 5) to DDT caused a transient increase in body fat mass in young female, but not in male mice (La Merrill et al., 2014). In contrast, developmental exposure to CPF led to weight gain in male, but not female rats (Lassiter and Brimijoin, 2008).

Transgenerational obesogenic effects of agrochemicals have been reported. Two studies established links between DDT exposure in pregnant F0 rat dams and increased obesity rates in subsequent generations. Male and female offspring from the F3 generation and male offspring from the F4 generation in the DDT lineage had an increased prevalence of obesity compared with controls (King, McBirney, Beck et al., 2019,Skinner, Manikkam, Tracey et al., 2013). Two other studies showed that parental exposure to glyphosate or vinclozolin was linked to increased obesity rates in the F2 and F3 offspring (Kubsad, Nilsson, King et al., 2019,Nilsson, King, McBirney et al., 2018). Overall, current data support the notion that exposure to multiple types of agrochemicals can play a role in obesity. More evidence from in vivo studies will be required to further establish the links between agrochemicals and obesity.

4. Potential mechanisms through which agrochemicals induce obesity

4.1 Agrochemicals might promote the commitment phase of adipogenesis

Although the mechanisms through which environmental chemicals induce obesity are not fully understood, affecting adipogenesis is an important mechanism (Heindel et al., 2017). Both direct and developmental exposure of chemicals might affect adipogenesis. Chemical exposure may lead to increased numbers of white adipocytes by modulating the differentiation of progenitor cells or by altering the birth/death rate of adipocytes to affect overall numbers of white adipocytes. Increased lipid storage in existing adipocytes is thought to be another major reason. Generally speaking, early developmental changes lead to increased adipocyte numbers, yet gain weight later in life during adulthood probably derives from increased fat content of existing white adipocytes (Spalding, Arner, Westermark et al., 2008).

Adipogenesis occurs in cells derived from the embryonic mesoderm. Multipotent mesenchymal stromal stem cells, also known as mesenchymal stem cells (MSCs) give rise to adipocytes, which involves determination (MSCs commit irreversibly to the adipocyte lineage) and terminal differentiation (preadipocytes differentiate into mature fat cells)

(Rosen and MacDougald, 2006). The current consensus is that white adipocyte numbers are set by the end of childhood and that any factors that increase adipocyte numbers in early life lead to a life-long increase in white adipocyte number (Spalding et al., 2008). While it is controversial whether having more white adipocytes leads to obesity, obese people definitely have more white adipocytes than do those of normal weight (Spalding et al., 2008). One possibility is that obesogen exposure early in life alters the fate of MSCs, leading to more white adipocytes in adulthood (Janesick and Blumberg, 2011,Chamorro-Garcia, Sahu, Abbey et al., 2013). The inference is that obese individuals may have a pool of MSCs that is intrinsically biased toward the adipocyte lineage (Kirchner, Kieu, Chow et al., 2010). Therefore, early life events, including obesogen exposure, that alter the fate of MSCs could predispose the exposed individual to increased numbers of white adipocytes and consequently obesity, particularly in combination with a Western Dietary pattern (Janesick and Blumberg, 2016).

Several studies suggested that agrochemicals might influence MSC fate. Chlorpyrifos and carbofuran were found to inhibit the osteogenic differentiation capacity of human MSCs, although the potential of MSCs to differentiate into adipocytes was not tested (Hoogduijn, Rakonczay and Genever, 2006). Another study showed that DDT could enhance both adipogenic and osteogenic differentiation of human MSCs via an estrogen receptor (ER) mediated pathway (Strong, Shi, Strong et al., 2015). Janesick et al. found that zoxamide, spirodiclofen, fludioxonil and quinoxyfen all induced adipogenesis in mouse MSCs (Janesick, Dimastrogiovanni, Vanek et al., 2016). Increased adipogenic potential of MSCs could correspondingly increase the steady state number of adipocytes in the adult, which might favor the development of obesity over time (Chamorro-Garcia et al., 2013).

In vitro and in vivo studies have demonstrated that TBT promotes adipocyte differentiation and obesity by activating peroxisome-proliferator activated receptor γ (PPARγ) and its heterodimeric partner, retinoid X receptor α (RXRα). TBT can bind to and activate both receptors, but it appears to mediate its effects on adipocyte differentiation via PPARγ (Kirchner et al., 2010,Li, Ycaza and Blumberg, 2011). In contrast, activation of RXR is required to commit mouse MSCs to the adipocyte lineage (Shoucri, Martinez, Abreo et al., 2017). TBT and chemicals that activate RXR (rexinoids) commit MSCs to the adipocyte lineage by inhibiting the expression and function of enzymes that deposit repressive histone 3 lysine 27 trimethyl ($H3K27^{me3}$) marks. Exposure of MSCs to TBT or rexinoids led to genome-wide decreases in $H3K27^{me3}$ at the promoters of genes required for adipogenic commitment. Currently, there is a relative paucity of data regarding how other agrochemicals might influence MSC fate. Triflumizole was found to induce adipogenic differentiation in human and mouse MSCs through a PPARγ-dependent mechanism and to promote fat accumulation, in vivo (Li et al., 2012). Taken together, the current data suggest that exposure to agrochemicals might promote adipogenesis by increasing commitment of MSCs to the adipocyte lineage. Therefore, assessing the capability of an agrochemical to induce adipogenic commitment of MSCs together with its ability to promote terminal adipocyte differentiation, and the mechanisms through which these processes occur will be valuable in identifying additional agrochemical obesogens.

4.2 Agrochemicals might induce adipocyte differentiation

After MSCs are committed to the adipocyte lineage, these preadipocytes can be induced to differentiate into mature adipocytes. Usually, the process of adipocyte differentiation is influenced by direct chemical exposure. In contrast to the relative paucity of data regarding the effect of agrochemicals on the commitment of MSCs to preadipocytes, there is much known about the effects of these chemicals on adipocyte differentiation. Murine pre-adipocyte cell lines such as 3T3-L1 cells are commonly used as an in vitro cell model to test the capacity of chemicals to induce adipogenesis. Such experiments have provided strong support for the notion that agrochemicals could promote adipocyte differentiation. Treatment with DDT and DDE resulted in increased lipid accumulation accompanied by up-regulation of multiple key regulator of adipocyte differentiation, such as CCAAT/enhancer-binding protein α and PPARγ (Kim, Sun, Yue et al., 2016). Using the 3T3-L1 cell model, other studies have identified agrochemicals including quizalofop-p-ethyl (QpE) (Biserni, Mesnage, Ferro et al., 2019), diazinon (Smith, Yu and Yin, 2018), pyraclostrobin (Luz, Kassotis, Stapleton et al., 2018), DDE (Mangum, Howell and Chambers, 2015), imidacloprid (Park, Kim, Kim et al., 2013), fipronil (Sun, Qi, Yang et al., 2016), permethrin (Xiao, Qi, Clark et al., 2017), zoxamide, spirodiclofen quinoxyfen, tebupirimfos, forchlorfenuron, flusilazole, acetamaprid and pymoetrozine (Janesick et al., 2016) as having the ability to promote adipocyte differentiation.

Activation of PPARγ/RXRα heterodimers plays a key role in promoting differentiation of 3T3-L1 adipocytes by regulating the expression of genes involved in lipid droplet formation, glucose uptake, and fatty acid synthesis (Janesick and Blumberg, 2011,Tontonoz and Spiegelman, 2008). QpE might promote adipogenesis by activating PPARγ as demonstrated by RNAseq analysis of cells and PPARγ reporter gene assay (Biserni et al., 2019). Triflumizole was found to induce adipogenic differentiation in 3T3-L1 cells through a PPARγ-dependent mechanism (Li et al., 2012). Zoxamide, triflumizole, spirodiclofen, and quinoxyfen induced adipogenesis in 3T3-L1 cells through PPARγ/RXRα heterodimers by activating PPARγ, while fludioxonil activated RXRα (Janesick et al., 2016).

However, the adipogenic effects of other agrochemicals on 3T3-L1 cells appear to be independent of PPARγ activation. For example, flusilazole, forchlorfenuron, acetamiprid and pymetrozine induced adipogenesis in 3T3-L1 cells, but did not activate PPARγ or RXRα (Janesick et al., 2016). Pyraclostrobin was found to induce mitochondrial dysfunction which in-turn inhibited lipid homeostasis, resulting in triglyceride accumulation (Luz et al., 2018). Permethrin might potentiate adipogenesis in 3T3-L1 adipocytes via altering intracellular calcium levels and through endoplasmic reticulum stress-mediated mechanisms (Xiao et al., 2017), although, it also activates PPARα (Fujino, Watanabe, Sanoh et al., 2019). The related chemical, deltamethrin may also activate an endoplasmic reticulum stress-mediated pathway in 3T3-L1 adipocytes (Yuan, Lin, Xu et al., 2019). An AMP-activated protein kinase AMPKα-mediated pathway was found to play a role in the induction of adipogenesis in 3T3-L1 preadipocytes by agrochemicals such as DDT and DDE (Kim et al., 2016), imidacloprid (Sun et al., 2017), deltamethrin (Yuan et al., 2019,Shen, Hsieh, Yue et al., 2017), and fipronil (Sun et al., 2016). Endrin and tolylfluanid promoted adipogenesis in 3T3-L1 cells via glucocorticoid receptor activation (Sargis, Johnson,

Choudhury et al., 2010). In contrast, another study showed that endrin inhibited adipogenesis in 3T3-L1 cells (Moreno-Aliaga and Matsumura, 1999).

By using a human adipose-derived stromal cell-based adipogenesis assay, Foley et al. found that some agrochemicals including triphenyltin hydroxide, lactofen, triflumizole, halosulfuron-methyl, cyfluthrin, flufenacet, isoxaflutole, piperonyl-butoxide, pyraclostrobin, and tebufenozide could induce lipid accumulation in these cells. By combining the results of gene transcription, protein expression, loss-of-function PPARγ siRNA assay and adipokine secretion, it was suggested that these chemicals might have moderate-to-strong activity for human adipogenesis (Foley, Doheny, Black et al., 2017). Considering the wide exposure of the humans and wildlife to agrochemicals, it will be of great interest to determine which pathways are causally associated with the adipogenic effects elicited by these chemicals and whether they also occur, in vivo.

4.3 Agrochemicals might exert obesogenic effects mediated by sex steroid hormone dysregulation

Sex steroid hormones such as estrogens and androgens appear to play important roles in adipose tissue development during early development or in adulthood (Cooke and Naaz, 2004). Estrogens play a pivotal role in regulating energy homeostasis, especially in female mammals, either by acting directly on the brain or through activation of ERs in adipocytes (Mauvais-Jarvis, Clegg and Hevener, 2013). Imbalances in the sex steroid levels can lead to dyslipidemias and obesity. For example, weight gain was observed following androgen deprivation therapy for prostate cancer (Braunstein, Chen, Loffredo et al., 2014) or polycystic ovary syndrome (Stanley and Misra, 2008). Obesogenic effects have been observed for xenoestrogenic compounds such as diethylstilbestrol (DES) (Newbold, Padilla-Banks, Snyder et al., 2007) and bisphenol A (BPA) (Rubin, Murray, Damassa et al., 2001), suggesting that dysregulated signaling through sex steroid receptors can produce pro-adipogenic effects. This might also influence the sexually dimorphic effects of some chemicals on the incidence and health consequences of obesity observed in humans (Palmer and Clegg, 2015). Therefore, chemicals that can disrupt the regulation of estrogen and androgen signaling by changing hormone levels or by directly interacting with the cognate nuclear receptors may contribute to disturbances in the regulation of adipose tissue formation and maintenance. Both direct and developmental exposure of chemicals might disrupt the regulation of sex hormone signaling.

Many in vivo experimental animal studies examined estrogenic or anti-androgenic effects of agrochemicals. By using the rat uterotrophic (estrogen) and Hershberger (anti-androgen) assays, it was found that the insecticide permethrin might have estrogenic effects on female rats, but anti-androgenic effects on male rats (Kim, Lee, Lim et al., 2005). In vivo anti-androgenic effects have also been reported in response to agrochemicals including linuron (Wolf, Lambright, Mann et al., 1999,Lambright, Ostby, Bobseine et al., 2000), prochloraz (Vinggaard, Christiansen, Laier et al., 2005), procymidone (Ostby, Kelce, Lambright et al., 1999), tebuconazole (Taxvig, Hass, Axelstad et al., 2007), vinclozolin (Anway, Memon, Uzumcu et al., 2006,Uzumcu, Suzuki and Skinner, 2004)), DDE (Wolf et al., 1999), endosulfan (Sinha, Adhikari and D, 2001), dimethoate (Verma and Mohanty, 2009) and

deltamethrin (Andrade, Araujo, Santana et al., 2002). After reviewing the animal and epidemiologic data from previous studies, Li et al. suggested that chlorpyrifos induces metabolic disruption by altering levels of reproductive hormones (Li, Ren, Li et al., 2019).

Mechanistic studies suggested that agrochemicals might exert estrogenic or anti-androgenic effect by affecting sex hormone status or by acting directly on estrogen receptors (ERs) and/or androgen receptor (AR). Several agrochemicals were documented to affect sex hormone levels through interference with hormone synthesis or breakdown. For example, testicular apoptosis was found in adult rats following exposure to a single dose of methoxychlor (Vaithinathan, Saradha and Mathur, 2010). DDE inhibited the action of 5α-reductase, the major enzyme that converts testosterone to dihydro-testosterone (Lo, King, Allera et al., 2007). DDE stimulated aromatase activity in ovarian granulosa cells (Younglai, Holloway, Lim et al., 2004). An analysis of the hepatic transcriptome of mice treated with DDE revealed altered mRNA levels of genes encoding enzymes involved in testosterone catabolism and excretion, resulting in impaired testosterone metabolism (Morales-Prieto, Ruiz-Laguna, Sheehan et al., 2018). Numerous agrochemicals, including DDT, can affect the expression levels and/or activity of multiple cytochrome P450 enzymes (P450) (Abass and Pelkonen, 2013,Blizard, Sueyoshi, Negishi et al., 2001), which are involved in the metabolism of steroid hormones and many xenobiotic chemicals.

Many studies have investigated the activity of agrochemicals on ER and AR using reporter gene assays. DDE was demonstrated to be a potent AR antagonist (Kelce, Stone, Laws et al., 1995). Kjeldsen et al. (Kjeldsen, Ghisari and Bonefeld-Jorgensen, 2013) investigated the effects of five agrochemicals (terbuthylazine, propiconazole, prothioconazole, cypermethrin and malathion) on ER and AR transactivation using luciferase reporter gene assays. The results showed that these five pesticides weakly activated ER and that three pesticides (bitertanol, propiconazole and mancozeb) antagonized AR activity in a concentration-dependent manner. Kojima et al, (Kojima, Katsura, Takeuchi et al., 2004) screened 200 agrochemicals and reported that 66 were anti-androgenic, whereas only 29 were estrogenic. Numerous in vitro studies based on reporter gene assays demonstrated estrogenic and anti-androgenic effect of agrochemicals (Kitamura, Suzuki, Ohta et al., 2003,Andersen, Vinggaard, Rasmussen et al., 2002,Bauer, Bitsch, Brunn et al., 2002,Okubo, Yokoyama, Kano et al., 2004,Orton, Lutz, Kloas et al., 2009,Vinggaard, Niemela, Wedebye et al., 2008,Sun, Xu, Xu et al., 2007,Zhang, Zhu, Zheng et al., 2008,Robitaille, Rivest and Sanderson, 2015,Xu, Liu, Ren et al., 2008,Li, Li, Ma et al., 2008,Martin, Dix, Judson et al., 2010,Knudsen, Houck, Sipes et al., 2011). In addition to the canonical ERs, binding of DDT and DDE to the seven-transmembrane estrogen receptor, GPR30, which activates alternative estrogen signaling was demonstrated (Thomas and Dong, 2006). Molecular dynamic simulations showed that estrogen-related receptor γ, which might affect estrogen signaling indirectly, could also be a potential target of DDT and DDE (Zhuang, Zhang, Wen et al., 2012). Estrogenic or anti-androgenic effects of agrochemicals might involve more than one mechanism; thus, their effects might be mediated through multiple cellular pathways.

Typically, humans are only rarely exposed to a single agrochemical. Rather they are simultaneously exposed to multiple xenobiotic chemicals, including agrochemicals and supposedly inert carriers. It is probable that these different agrochemicals may act in

combination through additive, synergistic, or antagonistic mechanisms, which may influence the doses of such ligands required to induce adipogenesis. Notably, additive and synergistic anti-androgenic activities of agrochemical mixtures have been observed (Kjeldsen et al., 2013,Ma, Chen, Yang et al., 2019,Orton, Rosivatz, Scholze et al., 2012,Kolle, Melching-Kollmuss, Krennrich et al., 2011,Birkhoj, Nellemann, Jarfelt et al., 2004). Christen et al., studied additive and synergistic anti-androgenic activities of binary mixtures of five anti-androgenic fungicides and found that about half of the tested mixtures produced additive effects and half synergistic effects (Christen, Crettaz and Fent, 2014). These observed additive and synergistic effects emphasize the importance of considering the combined actions of these chemicals. Although the underlying molecular mechanisms remain to be fully understood, these studies suggested the agrochemicals might induce obesity by disturbing normal sex hormone signaling.

4.4 Agrochemicals might exert obesogenic effects by affecting metabolic homeostasis through PPARs

Obesogens might induce obesity by perturbing metabolic homeostasis resulting in unbalanced energy expenditure. Many nuclear receptors respond to specific hormones such as thyroid hormone, mineralocorticoids, glucocorticoids, retinoic acid, sex steroids and lipophilic endogenous substances. These are involved in various physiological and pathological processes in the regulation of metabolic homeostasis (Mangelsdorf, Thummel, Beato et al., 1995). Among these, the PPAR subfamily, comprising PPARα, PPARβ/δ) and PPARγ are key players in adipogenesis and lipid metabolism (Feige, Gelman, Michalik et al., 2006). After forming heterodimers with RXR, PPARs regulate the transcription of genes involved in the regulation of adipogenesis (adipocyte proliferation and differentiation), intracellular lipid metabolism and storage, glucose homeostasis and insulin responsiveness (Wang, 2010). The three PPAR subtypes act as ligand sensors for a variety of lipophilic hormones, dietary fatty acids and their metabolites to regulate lipid homeostasis (Bensinger and Tontonoz, 2008). They work together to control almost every aspect of fatty acid metabolism. Many pharmaceutical drugs and environmental chemicals target PPARs, enabling them to affect PPAR signaling pathways involved in regulating metabolic balance (Lau, Abbott, Corton et al., 2010). Usually, chemical influences on metabolic homeostasis acting through PPARs are due to direct chemical exposure.

Several in vivo studies revealed changes in the expression levels of genes encoding PPARs and PPAR-regulated genes after agrochemical exposure. The herbicide dicamba (2-methoxy-3,6-dichlorobenzoic acid) caused a significant increase in peroxisomal beta-oxidation activity and changed the expression of a variety of PPAR regulated enzymes in rat livers, suggesting that dicamba acts as a peroxisome proliferator in rats (Espandiari, Thomas, Glauert et al., 1995). The herbicide diclofop was also shown to be a rodent peroxisome proliferator (Palut, Ludwicki, Kostka et al., 2001). Atrazine induced a near-significant increase in PPARβ mRNA in *Xenopus laevis* tadpoles (Zaya, Amini, Whitaker et al., 2011), and diclofop-methyl and pyrethrins changed the expression of PPARα-inducible cytochrome P450 genes in mice (Takeuchi, Matsuda, Kobayashi et al., 2006). 2,4-dichlorophenoxyacetic acid increased expression of PPARδ in HepG2 cells (Sun, Shao, Liu et al., 2018). DDT enhanced expression of PPARγ mRNA in human MSCs (Strong et al.,

2015). Therefore, expression of PPAR genes themselves may be potential agrochemical targets.

Results of in vitro reporter gene assays and in silico ligand binding simulations suggested that agrochemicals could function as agonistic ligands for one or more of the PPARs. Using an in vitro reporter gene assay based on CV-1 cells, Takeuchi et al. screened the ability of 200 agrochemicals to activate mouse PPARα and they found three chemicals (diclofop-methyl, pyrethrins and imazalil) had PPARα agonistic activity, yet none of the tested agrochemicals showed PPARγ agonistic activity (Takeuchi et al., 2006). Using a reporter gene assay based on COS-1 cells it was found that none of eight tested pyrethroids activated PPARα but that a metabolite of cis-/trans-permethrin as well as a metabolite of phenothrin (3-phenoxybenzoic acid) activated rat PPARα (Fujino et al., 2019). Five chitin synthesis inhibitors activated PPARγ-mediated reporter gene activity with the rank order of diflubenzuron > chlorfluazuron > flucycloxuron > noviflumuron > flufenoxuron (Ning, Ku, Gao et al., 2018). Other agrochemicals such as quizalofop-p-ethyl (Biserni et al., 2019) spirodiclofen, zoxamide (Janesick et al., 2016) and triflumizole (Li et al., 2012) were found to have PPARγ agonistic activity. An in silico study modeling the binding of pesticides in the PPARγ ligand-binding pocket suggested that the pesticide dithiocarbamate and the fungicide mancozeb might bind to this receptor (Bhaskar and Mohanty, 2014). The PPARγ ligand-binding pocket is rather large and can bind multiple compounds as the same time (Balaguer, Delfosse, Grimaldi et al., 2017). Therefore, it is not surprising that many agrochemicals with dissimilar structures could be PPARs ligands.

The PPARs have different tissue distributions and biological functions. PPARα is expressed predominantly in liver, kidney, heart, and muscle, and plays a major role in fatty acid oxidation. Activation of PPARα leads to peroxisome proliferation in rodents and stimulates β-oxidation of fatty acids (Ferre, 2004). PPARδ is ubiquitously expressed and can also promote fatty acid oxidation (Barish, Narkar and Evans, 2006). Consequently, xenobiotics that target PPARα and δ typically act as hypolipodemic agents. In contrast, PPARγ is primarily expressed in adipose tissue and is considered to be the master regulator of adipogenesis (Tontonoz and Spiegelman, 2008). A large body of work has clearly established that PPARγ plays key roles in diverse aspects of adipocyte biology including lipid biosynthesis and lipid storage (Evans, Barish and Wang, 2004). Activation of PPARγ is essential for the differentiation of resident preadipocytes and the conversion of mesenchymal progenitors to preadipocytes in white adipose tissues (Takada, Kouzmenko and Kato, 2009). Pharmaceutical drugs such as anti-diabetic thiazolidinediones as well as environmental chemicals such as the organotin compounds TBT and triphenyltin (TPT) (Grun, Watanabe, Zamanian et al., 2006,Kanayama, Kobayashi, Mamiya et al., 2005) act as obesogens by stimulating adipogenesis in a PPARγ-dependent manner. Since many agrochemicals have already been found to bind and activate PPARγ, it will be worthwhile to test all widely used agrochemicals for their ability to target PPARγ and act as bona fide obesogens, in vivo.

4.5 Agrochemicals might exert obesogenic effects by affecting metabolic homeostasis through disturbing the thyroid hormone pathway

Another mechanism through which obesogens could interfere with metabolic homeostasis is by altering the expression of hormones that regulate overall energy expenditure. Obesogens might change the balance between energy storage and consumption thereby leading to obesity. Thyroid hormone (triiodothyronine, T3) exerts widespread effects on carbohydrate, lipid and protein metabolism and is tightly associated with the basal metabolic rate (Mendoza and Hollenberg, 2017). It is essential to maintain thyroid function and thyroid hormone action within normal physiological limits to correctly regulate basal metabolic rate and thermogenesis. Increased activity of the thyroid pathway could accelerate metabolism leading to weight loss, whereas decreased thyroid activity could produce weight gain (Rotondi, Leporati, La Manna et al., 2009,Reinehr, 2010). Environmental chemicals might disrupt thyroid hormone signaling at many different levels, including the central regulatory system in the hypothalamus and pituitary, thyroid hormone biosynthesis and release from the thyroid gland, activity of deiodinases, transport in the blood, metabolism, and thyroid hormone action on nuclear receptors in target cells (Preau, Fini, Morvan-Dubois et al., 2015). There is considerable evidence from animal and human studies establishing relationships between EDC exposures and thyroid disruption. Most of these considered polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), perfluoroalkyl substances (PFASs), phthalates, BPA, and perchlorate (Zoeller, 2010). Many of these chemicals have also been shown to promote a propensity for obesity and metabolic syndrome. Thus, disrupting the thyroid signaling pathway is a plausible mechanism through which obesogens might contribute to obesity. Usually, influences on metabolic homeostasis through the thyroid signaling pathway are due to direct chemical exposure.

A broad range of human and animal studies documented that agrochemicals could interfere with the normal function of the thyroid endocrine system (Requena, Lopez-Villen, Hernandez et al., 2019). An association between the use of organochlorine pesticides and risk of hypothyroidism and hyperthyroidism has been established among women in Iowa and North Carolina enrolled in the Agricultural Health Study in 1993–1997 (Goldner, Sandler, Yu et al., 2010). Animal studies indicated that in utero exposure to pesticides such as DDT, DDE and chlorpyrifos-methyl may affect thyroid hormone status in offspring (Luo, Pu, Tian et al., 2017,Jeong, Kim, Kang et al., 2006). Mechanistic studies also supported the disruptive effects of agrochemicals on thyroid function. The hypothalamus–pituitary–thyroid (HPT) axis determines systemic thyroid hormone levels (Ortiga-Carvalho, Chiamolera, Pazos-Moura et al., 2016). Acetochlor was found to alter the mRNA expression of HPT axis-related genes and changed circulating thyroid hormone levels in zebrafish larvae (Yang, Hu, Li et al., 2016,Xu, Sun, Niu et al., 2019). Most activity of T3 is mediated by its nuclear receptors, thyroid hormone receptor alpha (TRα) and beta (TRβ) which require heterodimerization with RXRs to bind DNA and regulate the expression of target genes (Yen, 2001). A GH3-luciferase reporter gene assay was used to investigate the activities of 21 pesticides towards TRs. Among the tested pesticides, 5 had agonistic effects (procymidone, imidacloprid, atrazine, fluroxypyr, mancozeb), whereas 11 pesticides (butachlor, beta-cypermethrin, fenobucarb, cyhalothrin, theta-cypermethrin, bifenthrin, carbaryl, pymetrozine, pendimethalin, metolcarb, and acetochlor) inhibited luciferase

activity induced by T3 to varying degrees, demonstrating their antagonistic activities (Xiang, Han, Yao et al., 2017). Xiang et al. also found that 13 pesticides bound directly to TR as measured by surface plasmon resonance (SPR) biosensors (Xiang et al., 2017). Co-exposure of mice to the dithiocarbamate fungicide, mancozeb and the neonicotinoid insecticide, imidacloprid during lactation decreased plasma T3 levels and molecular dynamics simulations predicted that both of these chemicals might compete with T3 for binding to TRs (Bhaskar and Mohanty, 2014). Taken together, these studies established strong links between agrochemicals and disruption of thyroid signaling; however, possible obesogenic effects through this mechanism require further investigation.

4.6 Agrochemicals might exert obesogenic effects by affecting the gut microbiota

The human gut is the natural host for a large diverse and dynamic microbial community comprising bacteria and fungi, which together constitute the gut microbiota. The potential role of the gut microbiota in the development of obesity and obesity-related metabolic disorders has attracted considerable attention in the last several decades (Turnbaugh, Backhed, Fulton et al., 2008,Turnbaugh, Hamady, Yatsunenko et al., 2009,Zhao, 2013,Snedeker and Hay, 2012). Mechanistic studies indicated that the gut microbiota play a vital role in the development of obesity as they can influence energy utilization from the diet and produce microbiota-derived metabolites that regulate host metabolism and appetite (Turnbaugh and Gordon, 2009,Chen and Devaraj, 2018). The composition of the gut microbiota is highly dynamic and can be altered rapidly and substantially by diet and other environmental factors. Usually, the gut microbiota is affected by direct chemical exposure. Consumption of contaminated foods represents the major sources of human exposure to agrochemicals and this can lead to direct interactions between agrochemicals and the gut microbiota. Numerous studies showed that agrochemicals could affect the composition and function of gut microbiota and played an important role in agrochemical-induced toxicity (Joly Condette, Khorsi-Cauet, Morliere et al., 2014,Yuan, Pan, Jin et al., 2019,Mao, Manservisi, Panzacchi et al., 2018).

Emerging evidence supports the involvement of the gut microbiota in agrochemical-induced obesity. In a human cross-sectional study, levels of Methanobacteriales in the gut were associated with higher body weight and waist circumference and it was already known that these bacteria are linked to obesity (Lee, Lee, Lee et al., 2011). Serum organochlorine pesticides (cis-nonachlor, oxychlordane and trans-nonachlor) levels were also positively correlated with levels of Methanobacteriales. This supports a possible link among organochlorine pesticide levels, gut Methanobacteriales levels, and obesity in the general population. Some animal studies also established potentially causal links among agrochemical levels, composition of the gut microbiota and obesity. Chlorpyrifos disrupted gut microbial homeostasis and increased lipopolysaccharide entry into the body leading to low-grade systemic inflammation (Liang, Zhan, Liu et al., 2019). Mice given this chlorpyrifos-altered microbiota gained more white adipose tissue and had lower insulin sensitivity, supporting a link between the microbiota and obesity-related diseases (Liang et al., 2019). Chlorpyrifos exposure also significantly altered the composition of bacteria previously associated with obese and diabetic phenotypes in gut microbiome of rats (Fang et al., 2018). Chlorpyrifos exposure caused hepatic lipid metabolism disorders that were

associated with gut oxidative stress and microbiota dysbiosis in zebrafish (Wang, Shen, Zhou et al., 2019). Carbendazim induced gut microbiota dysbiosis and disturbed lipid metabolism, which promoted the intestinal absorption of excess triglycerides and caused multiple tissue inflammatory responses in mice (Jin, Zeng, Wang et al., 2018). Taken together, these studies showed that altering the composition of the gut microbiota is a possible mechanism through which agrochemicals can promote obesity. It will be important to establish a mechanistic understanding of how perturbation of gut microbiota by agrochemicals ultimately leads to obesity in humans as well as to evaluate agrochemicals in widespread use for these effects.

4.7 Epigenetic programming and transgenerational effects of agrochemicals

Previous studies have demonstrated that genetic differences such as single polynucleotide polymorphisms in a variety of genes may explain why some people are more likely to become obese (Locke, Kahali, Berndt et al., 2015). However, it is inconceivable that the rapid increase in the rate of obesity over the past decades in the U.S. and other countries is due to changes in human genetics. Moreover, it was estimated that the possible spectrum of genetic changes might explain only 20% of the incidence of obesity (Locke et al., 2015). This means that environmental and lifestyle factors must play key roles in the obesity pandemic. Epigenetic modification refers to heritable changes that modulate how the genome is expressed, but that do not involve altering the underlying DNA sequence. Epigenetic changes are natural occurrences but these can also be influenced by dietary and environmental factors (Skinner, 2015). Epigenetic modifications include methylation of cytosine residues on DNA, post-translational modification of histones, histone retention, chromatin remodeling and altered non-coding RNA expression (Whitelaw and Whitelaw, 2008). Epigenetic processes can affect patterns of gene expression by directly influencing DNA accessibility and/or by regulating chromatin compaction (Nilsson, Sadler-Riggleman and Skinner, 2018).

Epigenetic modifications acting on somatic tissues typically only influence the physiology of the exposed individual, changing the risk of disease development later in life. This might partly explain the developmental origins of disease (Burdge, Hanson, Slater-Jefferies et al., 2007). However, in some cases environmental factors alter the epigenetic programming of germ cells (sperm or egg) and phenotypes can appear in future generations without further direct exposure. This can lead to epigenetic transgenerational inheritance (Skinner, 2011). Therefore, epigenetic changes might be a plausible explanation for the pandemic of obesity and related diseases that cannot be fully accounted for by genetic variations and lifestyle factors.

Environmental factor-induced transgenerational inheritance of pathologies and phenotypic variations have been found in different species (Nilsson et al., 2018). Many studies showed that EDC exposure can result in increased disease susceptibility later in life and in subsequent generations (Anway and Skinner, 2006,Uzumcu, Zama and Oruc, 2012,Skinner, Manikkam and Guerrero-Bosagna, 2011,Rissman and Adli, 2014,Ho, Johnson, Tarapore et al., 2012,Skinner and Anway, 2005,Guerrero-Bosagna, Weeks and Skinner, 2014). A number of studies revealed that pesticides such as vinclozolin (Nilsson et al., 2018,Beck,

Sadler-Riggleman and Skinner, 2017,Anway, Cupp, Uzumcu et al., 2005), permethrin, methoxychlor (Manikkam, Haque, Guerrero-Bosagna et al., 2014), DDT (Skinner, Ben Maamar, Sadler-Riggleman et al., 2018,Ben Maamar, Nilsson, Sadler-Riggleman et al., 2019), atrazine (McBirney, King, Pappalardo et al., 2017,Hao, Gely-Pernot, Kervarrec et al., 2016) and the insect repellant diethyltoluamide (Manikkam, Tracey, Guerrero-Bosagna et al., 2012) promoted transgenerational inheritance of disease susceptibility and sperm epimutations. Transgenerational disease pathologies related to pesticide exposure included effects on the testis (King et al., 2019,Skinner et al., 2013,Anway, Leathers and Skinner, 2006), prostate (King et al., 2019,Anway et al., 2006), ovaries (King et al., 2019,Skinner et al., 2013,Manikkam et al., 2014,Manikkam et al., 2012), kidneys (King et al., 2019,Skinner et al., 2013,Manikkam et al., 2014,Anway et al., 2006), immune system (Anway et al., 2006), behavior (McBirney et al., 2017) and tumor development (Anway et al., 2006).

Exposure to obesogenic chemicals during critical periods of development might alter epigenetic programming processes that predispose a stem cell or progenitor cell toward a particular lineage such as the adipocyte. Epigenetic changes caused by exposures to EDCs such as TBT and DES may lead to obesity in subsequent generations (Chamorro-Garcia, Diaz-Castillo, Shoucri et al., 2017,Chamorro-Garcia and Blumberg, 2014,Stel and Legler, 2015,van Dijk, Tellam, Morrison et al., 2015). Skinner and colleagues showed that ancestral exposures of F0 rat dams to DDT led to a striking increase in the incidence of obesity in both F3 males and females (King et al., 2019,Skinner et al., 2013). In a similarly designed transgenerational experiment, they found that F0 exposure to glyphosate led to increased obesity rates in subsequent generations (Kubsad et al., 2019). Exposure to vinclozolin induced epigenetic transgenerational inheritance of increased obesity rates in F3 generation female rats (Nilsson et al., 2018). However, the molecular mechanisms underlying how these chemicals induce epigenetic changes and how these changes are transmitted to future generations to produce obesity and other adverse outcomes remains unclear. Many different mechanisms have been proposed for how epigenetic changes can affect subsequent disease outcomes including modulating methyl donor availability and altering the expression of enzymes that act as epigenetic readers, writers and erasers (Walker, 2016). However, at the time of this writing no convincing evidence exists that precisely establishes the molecular mechanisms through which epigenetic transgenerational inheritance of any phenotype, including obesity occurs.

5. Conclusions and future directions

There is compelling evidence to suggest that widespread exposure to agrochemicals is an important factor contributing to the human obesity pandemic. For example, DDE has been found to be a probable human obesogen based on multiple studies in vitro and in vivo using animal models and on longitudinal studies in humans, with a significant annual cost to the European Union (Legler, Fletcher, Govarts et al., 2015). DDE is thought to work as an anti-androgen and there are many other agrochemicals that exhibit anti-androgenic effects in vitro and in vivo (Orton et al., 2012,Orton, Rosivatz, Scholze et al., 2011). Therefore, it will be very important to establish the molecular mechanisms through which DDT/DDE act to influence obesity and to conduct the same sorts of cell-based, animal-based and longitudinal cohort studies in humans with other agrochemicals. We need to understand both the effects

of perinatal exposure to obesogenic agrochemicals as well as the effects of exposures during other times across the life course.

There are many possible modes of action for how agrochemicals can promote obesity as discussed above. What is missing is a systematic effort to understand which of the many agrochemicals in current use can lead to adverse health outcomes, including obesity and through which molecular pathways they act to exert these effects. Current practice in toxicological research is becoming focused on “adverse outcome pathways” and “molecular initiating events”. These are useful paradigms for s imple systems, but it is abundantly clear that agrochemicals can act through multiple pathways. These cellular signaling pathways interact with each other in complex ways. It is likely that individual chemicals act at multiple levels on metabolic homeostasis. Moreover, humans are typically exposed to poorly defined mixtures of chemicals that may interact in combinatorial ways that can be additive or inhibitory. Typical agrochemicals are also applied as mixtures that include so-called “inert ingredients” that may not be inert and whose composi tion and levels are not required to be reported. Much remains undiscovered about the possible molecular mechanisms for agrochemicals and their relationship with the obesity epidemic.

Epigenetic changes may underlie the transgenerational effects of early life obesogen exposure; however, we know very little about the operational molecular mechanisms and even less about how the effects are transmitted across generations. The contributions of the gut microbiome to human health and disease are becoming widely appreciated, yet the effects of agrochemicals on the microbiome are only very poorly understood. Many more epidemiological and molecular studies will be required to clarify these issues.

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Highlights

1. Positive associations exist between agrochemical exposures and adult obesity.
2. Prenatal exposure to agrochemicals could lead to childhood obesity.
3. Numerous possible mechanisms underlie the obesogenic effects of agrochemicals.
4. Nuclear receptors likely mediate many obesogenic effects of agrochemicals.
5. Epigenetics and the gut microbiome likely play key roles in the obesogenic effect of agrochemicals.

Table 1.

Literature summarizing associations between agrochemicals and adult obesity.

References	Names	Exposure levels (serum level)	Population (number of subjects)	Outcomes
(Dusanov et al. 2018)	HCB; β-HCH; p,p'-DDT; DDE	HCB: 66.8–101.2 pg/mL; β-HCH: 22.9–47.6 pg/mL; p,p'-DDT: 11.3–20 pg/mL; DDE: 315–679 pg/mL;	Norway, adult, (N=431)	Increased odds of metabolic syndrome.
(La Merrill et al. 2018)	DDE	170–570 ng/g lipid	Sweden, 70 years old (N = 988)	Increased BMI.
(Jaacks et al. 2016)	p,p'-DDT	Mean level: 0.0158 ng/mL	USA, pregnant women, 18–40 years old (N=218)	Gestational weight gain.
(Arrebola et al. 2014)	HCB; DDE; β-HCH	Mean level: HCB: 32.81 ng/g lipid; β-HCH: 19.60ng/g lipid; DDE: 183.99ng/g lipid;	Spain, adults (N=298)	Increased BMI and levels of total cholesterol, HDL, LDL, and total serum lipids.
(Langer et al. 2014)	DDE; HCB	DDE: 54–22382 ng/g lipid; HCB: 22–17928 ng/g lipid	Slovakia, adults, (N=2053)	Increased BMI and increased levels of cholesterol and triglyceride.
(Raafat et al. 2012)	Malathion	Mean level: 0.0746 mg/L	Egypt, 39±12 years old (N=98)	Increased waist circumference.
(Lee et al. 2012)	DDE	Mean level: 2654 ng/g lipid	Sweden, 70 years old (N=970)	Increased odds ratios of abdominal obesity.
(Lee et al. 2012)	DDE	11–23271 pg/mL	Sweden, 70 years old people (N=970)	Increased existence or development of abdominal obesity.
(Dirinck et al. 2011)	β-HCH	1.9–200 ng/g lipid	Belgium, ≥18 years (N=145)	Increased BMI, waist, fat mass percentage, and total and subcutaneous abdominal adipose tissue.
(Bachelet et al. 2011)	DDE	Mean level: 85 ng/g lipid	French, women (N= 1055)	Increased BMI.
(Ibarluzea et al. 2011)	DDE; β-HCH; HCB	Mean level: DDE: 110.0 ng/g lipid; β-HCH: 19.1 ng/g lipid; HCB: 33.5 ng/g lipid	Spain, pregnant women (N=1259)	Increased BMI.
(Lee et al. 2011)	HCB; DDE;	Not supplied	USA, adults, (N=5115)	Increased BMI, triglycerides, HOMA-IR, lower HDL-cholesterol and triglycerides.

Table 2.

Literature summarizing associations between agrochemicals and the development of early-onset obesity.

References	Names	The age of the children	Population (number of subjects)	Outcomes (Whether showed gender-specific effects)
(Cabrera-Rodriguez et al. 2019)	DDE	Infants	Spain (N=447)	Increased neonatal birth weight, with a special emphasis on girls. (Showed gender-specific effects)
(Warner et al. 2017)	DDT; DDE	12 years old	USA (N=240)	Increased BMI for boys but not girls. (Showed gender-specific effects)
(Xu et al. 2017)	o,p'-DDD; p,p'-DDT	Infants	Chinese (N=120)	Increased neonatal birth weight.
(Vafeiadi et al. 2015)	DDE; HCB	4 years old	Greece (N = 689).	Increased BMI, obesity, abdominal obesity.
(Agay-Shay et al. 2015)	HCB; β-HCH; DDE	7 years old	Spain (N=657)	Increased BMI and overweight risk.
(Heggeseth et al. 2015)	*o,p*'-DDT; *p,p*'-DDT; DDE	2–9 years old	USA (N=415)	Increased BMI among boys but not girls. (Showed gender-specific effects)
(Iszatt et al. 2015)	DDE	2 years old	Norway (N=1864)	Increased growth.
(Valvi et al. 2014)	DDE; HCB	6 and14 months old	Spain (N=1285)	Increased and overweight.
(Warner et al. 2014)	*o,p′*-DDT; *p,p′*-DDT; DDE	9 years old	USA (N=261)	Increased BMI and waist circumference in boys but not in girls. (Showed gender-specific effects)
(Delvaux et al. 2014)	**DDE**	7 to 9 years old	Belgium (N=114)	Increased waist circumference and waist/height ratio in girls but not in boys. (Showed gender-specific effects)
(Tang-Peronard et al. 2014)	DDE	5 and 7 years old	Denmark (N=656)	Increased waist circumference in girls with overweight mothers but not in boys. (Showed gender-specific effects)
(Valvi et al. 2012)	DDE; DDT;	6.5 years old	Spain (N=344)	Increased overweight in boys but not in girls. (Showed gender-specific effects)
(Mendez et al. 2011)	DDE	6 and 14 months old	Spain (N=657)	Increased weight and BMI.
(Verhulst et al. 2009)	DDE	1–3 years old	Belgium (N=138)	Increased BMI.
(Karmaus et al. 2009)	DDE	20–50 years old	USA (N=259)	Increased weight and BMI.
(Smink et al. 2008)	HCB	6 years old	Spain (N=482)	Increase in weight and BMI.

Table 3.

Literature summary of animal studies linking agrochemicals and obesity.

Reference	Names	Animal used	Dose and exposure time	Outcomes (Whether showed gender-specific effects)
(King et al. 2019)	DDT	Sprague Dawley rats	25 mg/kg/day; F0 females were administered on days 8 to 14 of gestation.	The F3 generation had significant increases in the incidence of obesity.
(Kubsad et al. 2019)	Glyphos ate	Sprague Dawley rats	25 mg/kg/day; F0 females were administered on days 8 to 14 of gestation.	The transgenerational pathologies of obesity was observed.
(Basaure et al. 2019)	CPF	Male apoE4-mice	2 mg/kg/day; 15 days.	Increased body weight.
(Xiao et al. 2018)	Permeth rin	Male C57BL/6J mice	50, 500, and 5000 μg/kg/day; 12 weeks.	Increased body weight, fat mass, and increased TG and TC.
(Uchendu et al. 2018)	CPF; deltamet hrin	Male Wistar rats	CPF: 4.75 mg/kg/day; deltamethrin: 6.25 mg/kg/day; 120 days.	Increased levels of TG, TC, LDL, and VLDL, and decreased HDL level.
(Fang et al. 2018)	CPF	Male Wistar rats	0.3 or 3.0 mg/kg/day; 9 weeks.	Increased bodyweight.
(Nilsson et al. 2018)	Vinclozo lin	Sprague Dawley rats	100 mg/kg/day; F0 females were administered on days 8 to 14 of gestation.	F3 generation rats showed transgenerational increased obesity rate in females. (Showed gender-specific effects)
(Sun et al. 2017)	Imidaclo prid	Female C57BL/6J mice	0.06, 0.6, or 6 mg/kg/day; 12 weeks.	Increased high fat diet-induced body weight gain and adiposity.
(Sun et al. 2016)	Imidaclo prid	Male C57BL/6J mice	0.06, 0.6, or 6 mg/kg/day; 12 weeks.	Increased high fat diet-induced body weight gain and adiposity.
(Peris-Sampedro et al. 2015a)	CPF	Male apoE 3 mice	2mg/kg/day; 13 weeks.	Increased body weight.
(Peris-Sampedro et al. 2015b)	CPF	apoE 3 mice	2 mg/kg /day; 8 weeks.	Increased body weight.
(Ishikawa et al. 2015)	DDT	Obese Sprague Dawley rats	5.60 μg /kg/day; 4 weeks.	Increased postprandial non-esterified fatty acids and decreased body temperature.
(La Merrill et al. 2014)	DDT	C57BL/6J mice	1.7 mg/kg/day; From gestational day 11.5 to postnatal day 5.	Reduced core body temperature, impaired cold tolerance, decreased energy expenditure, and produced a transient early-life increase in body fat in female offspring. (Showed gender-specific effects)
(Howell et al. 2014)	DDE	Male C57BL/6H mice	0.4 mg/kg/day or 2.0 mg/kg/day; 5 days.	Hyperglycemic effect.
(Bhaskar and Mohanty 2014)	Mancoz eb; Imidaclo prid	Swiss albino mice	imidacloprid: 131 mg/kg/day; mancozeb: 8000 mg/kg/day. Lactating mothers were exposed to the pesticides from PND1 to natural weaning (PND 28).	Increased body weight.
(Skinner et al. 2013)	DDT	Sprague Dawley rats	50 or 25 mg/kg/day; F0 females were administered on days 8 to 14 of gestation.	F3 generation developed obesity.
(Li et al. 2012)	TFZ	CD1 mice	0.1, 1.0, or 10.0 μM; During breeding and throughout pregnancy.	Increased adipose depot weight.
(Acker and Nogueira 2012)	Chlorpyr ifos	Male Wistar rats	50 mg /kg; A single dose.	Increased TC, LDL levels and caused hyperglycemia and hyperlipidemia.
(Kalender et al. 2010)	Malathion	Male Wistar rats	27 mg/kg/day; 4 weeks.	Increased TC.

Reference	Names	Animal used	Dose and exposure time	Outcomes (Whether showed gender-specific effects)
(Lim et al. 2009)	Atrazine	Male Sprague Dawley rats	30 or 300 mg/kg/day; 5 months.	Increased body weight and intra-abdominal fat, but decreased basal metabolic rate.
(Lassiter et al. 2008)	Parathio n	Sprague Dawley neonatal rats	0.1 or 0.2 mg/kg/day; postnatal days 1–4.	Increased body weight and impaired fat metabolism. Females showed greater sensitivity. (Showed gender-specific effects)
(Lassiter and Brimijoin 2008)	CPF	Long–Evans rats	2.5 mg/kg/day; From gestational day 7 through the end of lactation on postnatal day 21.	Increased body weight in males. (Showed gender-specific effects)
(Meggs and Brewer 2007)	CPF	Female Long-Evans rats	5 mg/kg/day; 4 months.	Increased body weight.

Note: apolipoprotein E (apoE), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein-cholesterol (LDL), very low-density lipoprotein-cholesterol (VLDL),

Table 4.

Possible mechanisms though which agrochemicals may lead to obesity and example chemicals providing evidence to support these mechanisms.

Possible mechanisms	**Agrochemicals provide evidence for the mechanism**
Promote the commitment phase of adipogenesis	DDT, chlorpyrifos, carbofuran, zoxamide, spirodiclofen, fludioxonil and quinoxyfen, triflumizole
Induce adipocyte differentiation	DDT, DDE, quizalofop-p-ethyl, diazinon, pyraclostrobin, imidacloprid, fipronil, permethrin, zoxamide, spirodiclofen, quinoxyfen, tebupirimfos, forchlorfenuron, flusilazole, acetamiprid, pymoetrozine, triflumizole, quinoxyfen, fludioxonil, deltamethrin, endrin, tolylfluanid, triphenyltin hydroxide, lactofen, halosulfuron-methyl, cyfluthrin, flufenacet, isoxaflutole, piperonyl-butoxide, tebufenozide
Mediated by sex steroid hormone dysregulation	Permethrin, linuron, prochloraz, procymidone, tebuconazole, vinclozolin, DDE, endosulfan, dimethoate, deltamethrin, chlorpyrifos, methoxychlor, DDT, terbuthylazine, propiconazole, prothioconazole, cypermethrin, malathion
Affecting metabolic homeostasis through PPARs	Dicamba, diclofop, diclofop-methyl, pyrethrins, 2,4-dichlorophenoxyacetic acid, DDT, diclofop-methyl, pyrethrins, imazalil, diflubenzuron, chlorfluazuron, flucycloxuron, noviflumuron, flufenoxuron, quizalofop-p-ethyl, spirodiclofen, zoxamide, triflumizole, dithiocarbamate, mancozeb
Affecting metabolic homeostasis through disturbing the thyroid hormone pathway	DDT, DDE, chlorpyrifos-methyl, acetochlor, procymidone, imidacloprid, atrazine, fluroxypyr, mancozeb, butachlor, beta-cypermethrin, fenobucarb, cyhalothrin, theta-cypermethrin, bifenthrin, carbaryl, pymetrozine, pendimethalin, metolcarb,
Affecting the gut microbiota	Cis-nonachlor, oxychlordane, trans-nonachlor, chlorpyrifos, carbendazim,
Epigenetic programming and transgenerational effects	DDT, glyphosate, vinclozolin