

# UC Irvine

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### Title

Agrochemicals and obesity

### Permalink

<https://escholarship.org/uc/item/8sz5m2sk>

### Authors

Ren, Xiao-Min

Kuo, Yun

Blumberg, Bruce

### Publication Date

2020-09-01

### DOI

10.1016/j.mce.2020.110926

Peer reviewed

Elsevier Editorial System(tm) for Molecular  
and Cellular Endocrinology

Manuscript Draft

Manuscript Number: MCE-D-19-00782R1

Title: Agrochemicals and Obesity

Article Type: VSI: Agrochemical and ED

Keywords: obesogen; EDC; endocrine disrupting chemical; agrochemical;  
pesticide; fungicide; transgenerational; epigenetic; microbiome

Corresponding Author: Professor Bruce Blumberg, PhD

Corresponding Author's Institution: University of California

First Author: Xiao-Min Ren

Order of Authors: Xiao-Min Ren; Yun Kuo; Bruce Blumberg, PhD

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.



Developmental and Cell Biology  
School of Biological Sciences

Bruce Blumberg, Ph.D  
Professor

2011 Biological Sciences 3  
Irvine, CA 92697-2300  
Phone: (949) 824-8573  
Fax: (949) 824-4709  
E-mail: [blumberg@uci.edu](mailto:blumberg@uci.edu)  
<http://blumberg-lab.bio.uci.edu>

6 June, 2020

Prof. Dr. Enrique H. Luque  
Prof. Dr. Monica Muñoz-de-Toro  
Guest Editors  
Molecular and Cellular Endocrinology  
Special Issue on Agrochemicals and Endocrine Disruption

Dear Enrique and Monica,

Attached please find the revised version of our manuscript for the special issue of MCE that you so kindly invited us to contribute. I apologize for the long delay in providing this revised version, but the revisions requested by the reviewers were extensive. We hope that the manuscript will now be acceptable for publication in Molecular and Cellular Endocrinology.

Best wishes,

A handwritten signature in black ink that reads "Bruce Blumberg".

Bruce Blumberg

## Response to Reviewers' Comments

Dear Enrique

Thank you very much for your email regarding our manuscript submitted to Molecular and Cellular Endocrinology (Ms. Ref. No.: MCE-D-19-00782). We appreciate the valuable and constructive comments by you and the reviewers. We have extensively revised the manuscript to address these points and provide detailed point-by-point responses below.

### Response to Reviewer 1

#### Major:

#### Question 1.

Before diving into the human epidemiology section, it might make sense to first address some of the broader issues that impact endocrine research, including studies of obesogens. For example, in the human epidemiology section, I think you should separate out the discussion of non-monotonicity. Can you also expand on this sentence: "Such non-monotonic effects are predictable and expected when considering how the endocrine system works." Although many readers of MCE understand these principles, readers from non-endocrine backgrounds may not. This sentence is also out of place in this section: "In contrast, non-monotonic dose-response curves are an anathema to the industry and regulatory toxicology communities (Dietrich, von Aulock, Marquardt et al., 2013)." I don't disagree, but many endocrinologists will not understand what point you are making. You also might pull out, and discuss separately from the epidemiology section, the issue of vulnerable periods. This is relevant to human and animal studies (although there are particular challenges in the human studies.)

#### Answer:

Although we wonder how many readers from outside the field of Endocrinology will be reading Molecular and Cellular Endocrinology, we adopted the reviewer's suggestion and added more introduction about EDCs, MDCs and obesogens before diving into the human epidemiology section in the revised manuscript.

*Lines 86-95:* "Endocrine-disrupting chemicals (EDCs) are natural or man-made substances that may interfere with the normal function of endocrine system, including hormone biosynthesis, metabolism or action (Zoeller, Brown, Doan et al., 2012). There is growing evidence showing the link 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."

*Lines 98-101:* "'Obesogens' are functionally defined as chemicals that 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).”

According to the reviewer’s suggestion, we have separated out the discussion about non-monotonicity and the issue of vulnerable periods in the human epidemiology section. We have separated the original human epidemiology section into four parts:

2. Human epidemiological studies relating agrochemicals and obesity
  - 2.1 Association between agrochemicals and adult obesity
  - 2.2 Non-monotonic dose-response relationships between agrochemicals and adult obesity
  - 2.3 Agrochemicals and the development of early-onset obesity
  - 2.4 Gender-specific effects of agrochemicals

We have included more explanation and introduction about the non-monotonic dose-response relationships between agrochemicals and adult obesity in the revised manuscript. We have revised these two sentences to make them clearer.

*lines 151-158:* “Some studies showing the potential relationship between pesticide exposure and serum lipids/obesity/BMI revealed that the effects were non-monotonic” **has been changed to** “Some studies showing the potential relationship between pesticide exposure and serum lipids/obesity/BMI revealed that the effects were non-monotonic dose-response relationships, an unconventional dose-response relationship 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  $\beta$ -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).”

*lines 158-164:* “Such non-monotonic effects are predictable and expected when considering how the endocrine system works.” **has been changed to** “Previously, numerous studies investigating the effects of EDCs described with relatively high frequency the occurrence of non-monotonic dose-response relationships for EDCs (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 (Lagarde, Beausoleil, Belcher et al., 2015).”

*line 164-170:* “In contrast, non-monotonic dose-response curves are an anathema to the industry and regulatory toxicology communities.” **has been changed to** “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. 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.”

**Question 2:**

In the animal section, it would help to better explain what is meant by a "second hit". (The principles behind "two hit" effects could be elaborated, even with just a sentence or two.)

**Answer:**

According to reviewer’s suggestion, we have introduced the principle of “two-hit” hypothesis and explained the meaning of “second hit” in the revised manuscript (*Page, line*).

*lines 255-262:* The “two-hit” hypothesis, first formulated by Knudson 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 adopted 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).

**Question 3:**

It would be great if the authors thought about some figures or tables to break up the text. I know these can be a lot of work, but they could be fairly simple organizational drawings.

**Answer:**

According to reviewer’s suggestion, we have added 4 tables to summarize the human studies, animal studies, and the possible mechanisms in the revised manuscript. The titles of these tables are listed below, and the tables included at the end of this file.

**Table 1.** Literature summarizing associations between agrochemicals and adult obesity.

**Table 2.** Literature summarizing association between agrochemicals and the development of early-onset obesity.

**Table 3.** Literature summary of animal studies linking agrochemicals and obesity.

**Table 4.** Possible mechanisms through which agrochemicals may lead to obesity and example chemicals providing evidence to support these mechanisms.

**Minor:**

**Question 4:**

"Numerous epidemiological studies together with experimental evidence in animal models indicated that agrochemicals may be harmful to human health in multiple ways

(Mostafalou and Abdollahi, 2017, Cano-Sancho, Salmon and La Merrill, 2017, Montgomery, Kamel, Saldana et al., 2008, Androutsopoulos, Hernandez, Liesivuori et al., 2013)." Can you give some brief examples, especially beyond the obesity outcomes you outline below?

**Answer:**

According to reviewer's suggestion, we have added a brief introduction about the toxicities related to agrochemicals in the revised manuscript.

*lines 63-66:* "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."

**Question 5:**

In addition to introducing EDCs in the intro section, can you also briefly explain the subset of chemicals that are MDCs (metabolism disrupting chemicals)?

**Answer:**

According to reviewer's suggestion, we have added a brief explanation of MDCs in the revised manuscript.

*Lines 92-97:* "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)."

**Question 6:**

"In addition to increased weight or elevated BMI, the levels of some obesity biomarkers (levels of total cholesterol and total serum lipids) were also positive associated with the concentrations of pesticides such as HCB,  $\beta$ -HCH and DDE" - please edit to "positively"

**Answer:**

We have changed the "positive" to "positively" in this sentence (*line 133*).

**Question 7:**

"Many environmental factors have been showed to play a prominent role in the development of early-onset obesity" please edit to "shown"

**Answer:**

We have changed the "showed" to "shown" in this sentence (*line 177*).

**Question 8:**

Section title "Animal studies about the relationship between agrochemicals and obesity" could be more descriptive, or remove "about" and replace with "and". Same with "Induce adipocyte differentiation" can you make this more descriptive? Or "Agrochemicals can induce adipocyte differentiation". Same with "Affect metabolic

homeostasis mediated by metabolic sensors, the PPARs", "Affect metabolic homeostasis by disturbing the thyroid hormone pathway", etc. - this phrasing is particularly awkward.

**Answer:**

According to reviewer's suggestion, we have revised some section titles to make them more descriptive in the revised manuscript.

*line 238:* "Animal studies about the relationship between agrochemicals and obesity" **has been changed to** "Animal studies and the relationship between agrochemicals and obesity"

*line 294:* "Promote the commitment phase of adipogenesis" **has been changed to** "Agrochemicals might promote the commitment phase of adipogenesis"

*line 352:* "Induce adipocyte differentiation" **has been changed to** "Agrochemicals might induce adipocyte differentiation"

*Line 408-409:* "Effects mediated by sex steroid hormone dysregulation" **has been changed to** "Agrochemicals might exert obesogenic effects mediated by sex steroid hormone dysregulation"

*Line 493-494:* "Affect metabolic homeostasis mediated by metabolic sensors, the PPARs" **has been changed to** "Agrochemicals might exert obesogenic effects by affecting metabolic homeostasis through PPARs"

*Line 563-564:* "Affect metabolic homeostasis by disturbing the thyroid hormone pathway" **has been changed to** "Agrochemicals might exert obesogenic effects by affecting metabolic homeostasis through disturbing the thyroid hormone pathway"

*Line 616:* "By affecting the gut microbiota" **has been changed to** "Agrochemicals might exert obesogenic effects by affecting the gut microbiota"

**Question 9:**

"One possibility is that obesogen exposure early in life the alters the fate of MSCs, leading to more white adipocytes in adulthood" edit to remove first "the"

**Answer:**

We have removed the first "the" in this sentence (*line 313-315*).

**Question 10:**

"Activation of PPAR<gamma>/RXR<alpha> heterodimers plays a key role in promoting adipocyte differentiation of 3T3-L1 adipocytes" remove the first "adipocyte"

**Answer:**

We have removed the first "adipocyte" in this sentence (*Line 371-372*).

**Question 11:**

"However, at the time of this writing no convincing evidence exists that precisely establishes the molecular mechanisms through which epigenetic transgenerational inheritance occurs." Please edit to make clear that you mean transgenerational inheritance of obesity.



**Answer:**

Sorry, we disagree with this statement by the reviewer. In fact, there is no convincing evidence that precisely establishes the molecular mechanisms underlying transgenerational inheritance. We have changed this sentence slightly to read: “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. *Lines 720-723*)”

**Response to reviewer 3**

The reviewer noted that we had published other reviews on this topic and stated that this one is similar to another recently published in Endocrinology. We reject this statement. There is deliberately very little overlap between the current manuscript and the Endocrinology MINIREVIEW noted by the reviewer. Moreover, we cite the current review in the minireview as the definitive source for agrochemicals and obesity. It should be noted that this is an INVITED rather than an unsolicited review. I get about 2-3 requests to write such reviews per week and in 2019/2020 agreed to write only 3. Each of these was written by a different person in the lab and has a very different focus.

**Question 1:**

Authors should consider including tables summarizing existing epidemiologic and animal evidence in support of various aspects of obese phenotypes, BMI, gestational weight gain, fat accumulation, WAT vs BAT, adipocyte differentiation, hyperplasia vs. hypertrophy etc. This would make it user friendly instead of our filtering through the series of findings reported.

**Answer:**

We added three tables summarizing existing epidemiologic and animal evidence in support of various aspects of obese phenotypes. The titles of these tables are listed as below, and the detail are listed in the end of this word file.

**Table 1.** Literature summarizing associations between agrochemicals and adult obesity.

**Table 2.** Literature summarizing association between agrochemicals and the development of early-onset obesity.

**Table 3.** Literature summary of animal studies linking agrochemicals and obesity.

**Question 2:**

In the human and animal studies section of this review, authors make a case for direct as well as developmental exposure effects on obesity. However, when they get to the mechanisms, they drop the developmental exposure until they talk about transgenerational effects of agrochemicals. Similar to what was done for human and animal studies, under each section they should address direct and developmental effects.

**Answer:**

According to reviewer's suggestion, we have addressed direct and/or developmental effects under each section of the mechanism.

*Line 297:* "Both direct and developmental exposure of chemicals might affect adipogenesis."

*Line 354-355:* "Usually, the process of adipocyte differentiation is influenced by direct chemical exposure."

*Line 425-426:* "Both direct and developmental exposure of chemicals might disrupt the regulation of sex hormone signaling."

*Line 510-511:* "Usually, the influence on metabolic homeostasis through PPARs is due to direct chemical exposure."

*Line 585-586:* "Usually, the influence on metabolic homeostasis through the thyroid signaling pathway is due to direct chemical exposure."

*Line 627:* "Usually, the gut microbiota is affected by the direct exposure of chemicals."

### **Question 3:**

Considerable time is spent on discussing the physiological process of adipocyte commitment and differentiation, an aspect well addressed in other reviews. This should be reduced, and reference made to other reviews.

#### **Answer:**

According to reviewer's suggestion, we have revised this part by reducing the introducing about the physiological process of adipocyte commitment and differentiation (*Page, line*).

*Lines 305-309:* "Multipotent mesenchymal stromal stem cells, also known as mesenchymal stem cells (MSCs) give rise to adipocytes (Rosen and MacDougald, 2006). MSCs can differentiate into adipocytes, chondrocytes and osteoblasts (among other cell types) in response to tissue-specific signals and are thought to renew these cells in adults (da Silva Meirelles, Chagastelles and Nardi, 2006). Like most differentiation events, adipogenesis involves determination and terminal differentiation. Determination occurs when MSCs commit irreversibly to the adipocyte lineage, lose their potential to differentiate into other types of cells and become preadipocytes (Park, Halperin and Tontonoz, 2008, Rosen and Spiegelman, 2014, Tontonoz and Spiegelman, 2008). Terminal differentiation occurs when preadipocytes undergo growth arrest and subsequent differentiate into mature fat cells (Park et al., 2008, Rosen and Spiegelman, 2014, Tontonoz and Spiegelman, 2008)." **has been changed to** "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)."

**Question 4:**

Changes associated with the agrochemical exposure are being discussed one by one without integrating them mechanistically.

**Answer:**

To integrate the results associated with the agrochemical exposure more mechanistically, we have separated the human epidemiology part and animal study part into several sections.

We have separated the original one human epidemiology section into four parts:

2. Human epidemiological studies relating agrochemicals and obesity
  - 2.1 Association between agrochemicals and adult obesity
  - 2.2 Non-monotonic dose-response relationships between agrochemicals and adult obesity
  - 2.3 Agrochemicals and the development of early-onset obesity
  - 2.4 Gender-specific effects of agrochemicals

We have separated the original one animal study section into two parts listed as bellow:

3. Animal studies and the relationship between agrochemicals and obesity
  - 3.1 Studies showing the obesogenic effects of agrochemicals in adult experimental animals
  - 3.2 Animal studies showing the development and transgenerational obesogenic effects of agrochemicals

**Question 5:**

While they make a case for sexual dimorphism, when discussing the mechanism, they fail to describe in which sex the observation comes from. They should consider adding a table with this information from different studies grouped by agrochemical and limit the text portion.

**Answer:**

To make the description about sexually dimorphic effects of agrochemicals on childhood obesity more clear, we revised this part and separated it into an individual section 2.4. We also added the information about sexually dimorphic responses in Table 2.

*Lines 225-236:* “**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 the gender-specific effects of agrochemicals on childhood obesity. The results about the reported gender-specific effects of agrochemicals are noted in 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.”

**Question 6:**

A figure consolidating the various mechanistic underpinnings and which chemicals provide evidence for which mechanism would be beneficial.

**Answer:**

Since there are many different kinds of agrochemicals providing evidence for a mechanism, we have provided a table consolidating the various mechanistic underpinnings and which chemicals provide evidence for the mechanism in the revised manuscript. The title of this table is listed as below, and the table provided at the end of this file.

**Table 4.** Possible mechanisms through which agrochemicals may lead to obesity and example chemicals providing evidence to support these mechanisms.

**Question 7:**

Several of their own reviews are listed for many statements. Reference to the most recent review would suffice.

**Answer:**

According to reviewer’s suggestion, we have deleted several of our reviews keeping only the most recent and/or important ones.

**Question 8:**

Providing a list of chemicals being reviewed and their exposure levels as detected in human, pointing to what is continuing to be used now vs those that are no longer being used but persist would put things in perspective in terms of thinking through interventions.

**Answer:**

According to reviewer’s suggestion, we have listed the names of the agrochemicals mentioned in the review in the Tables 1-4, and provided available information about the human exposure levels of these agrochemicals in Table 1. We have also provided information about the status of these agrochemicals in the revised manuscript.

*Lines 139-148:* “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  $\beta$ -HCH have been banned globally several decades ago, but they are persistent in the

environment. Malathion is a pesticide that is still widely used in agriculture, residential landscaping, and public health pest control programs. All of these agrochemicals can still be detected in human populations. Information about human exposure levels is provided in Table 1. The obesogenic effects of these pesticides in humans still needs to be considered.

**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)	$\beta$ -HCH	1.9-200 ng/g lipid	Belgium, $\geq$ 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; $\beta$ -HCH; HCB	Mean level: DDE: 110.0 ng/g lipid; $\beta$ -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.

<b>References</b>	<b>Names</b>	<b>The age of the children</b>	<b>Population (number of subjects)</b>	<b>Outcomes (Whether showed gender-specific effects)</b>
(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)	<i>o,p'</i> -DDD; <i>p,p'</i> -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; $\beta$ -HCH; DDE	7 years old	Spain (N=657)	Increased BMI and overweight risk.
(Heggeseth et al. 2015)	<i>o,p'</i> -DDT; <i>p,p'</i> -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 and 14 months old	Spain (N=1285)	Increased growth and overweight.
(Warner et al. 2014)	<i>o,p'</i> -DDT; <i>p,p'</i> -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)	Glyphosate	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)	Permethrin	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; deltamethrin	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)	Vinclozolin	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)	Imidacloprid	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)	Imidacloprid	Male C57BL/6J mice	0.06, 0.6, or 6 mg/kg/day; 12 weeks.	Increased high fat diet-induced body

			weeks.	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)	Mancozeb; Imidacloprid	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	F3 generation developed obesity.

			gestation.	
(Li et al. 2012)	TFZ	CD1 mice	0.1, 1.0, or 10.0 $\mu$ M; During breeding and throughout pregnancy.	Increased adipose depot weight.
(Acker and Nogueira 2012)	Chlorpyrifos	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.
(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)	Parathion	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 through which agrochemicals may lead to obesity and example chemicals providing evidence to support these mechanisms.

<b>Possible mechanisms</b>	<b>Agrochemicals provide evidence for the mechanism</b>
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, tebuirimfos, forchlorfenuron, flusilazole, acetamiprid, pymetrozine, 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, flucyclohexuron, 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, oxychlorodane, trans-nonachlor, chlorpyrifos, carbendazim,
Epigenetic programming and transgenerational effects	DDT, glyphosate, vinclozolin



1 **Agrochemicals and obesity**

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5 **Xiao-Min Ren<sup>1,2</sup>, Yun Kuo<sup>2</sup> and Bruce Blumberg<sup>2,3,4</sup>**

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8 **<sup>1</sup>Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences,**  
9 **Beijing, China**

10

11 **<sup>2</sup>Department of Developmental and Cell Biology, University of California, Irvine, CA**  
12 **92697-2300**

13

14 **<sup>3</sup>Department of Pharmaceutical Sciences, University of California, Irvine, CA**

15

16 **<sup>4</sup>Department of Biomedical Engineering, University of California, Irvine, CA**

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19 **Correspondence to Bruce Blumberg, [Blumberg@uci.edu](mailto:Blumberg@uci.edu)**

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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.



34	<b>Keywords</b>
35	Obesogen
36	EDC
37	endocrine disrupting chemical
38	agrochemical
39	pesticide
40	fungicide
41	transgenerational
42	epigenetic
43	microbiome
44	

## 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 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 Lorschach, 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  $\geq 25$  kg/m<sup>2</sup>) and 13% are obese (BMI  $\geq 30$ ) (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

95 all of the important factors that contribute to obesity is, therefore, an important issue and  
96 could help to control and reduce the obesity epidemic and related diseases.

97 “Obesogens” are functionally defined as chemicals that promote obesity after exposure,  
98 in vivo. Some natural chemicals (such as fructose), pharmaceutical chemicals (such as  
99 thiazolidinedione anti-diabetic drugs) or xenobiotic chemicals [such as tributyltin (TBT)]  
100 have found to be obesogens (Janesick and Blumberg, 2016). Obesogens might act directly on  
101 fat cells by increasing their number or increasing the storage of fat into the existing cells.  
102 These chemicals might also act indirectly by affecting mechanisms regulating appetite and  
103 satiety, by altering basal metabolic rate, altering energy balance to favor the storage of  
104 calories, or by altering gut microbiota to promote energy intake (Heindel and Blumberg,  
105 2019). Some agrochemicals have been shown to act as obesogens by promoting adipogenesis  
106 and inducing obesity in experimental animals and are found at higher levels in obese humans.  
107 For example, dichlorodiphenyldichloroethylene (DDE) was classified as “presumed” to be  
108 obesogenic for humans by using a systematic review-based strategy to identify and integrate  
109 evidence from epidemiological, in vivo, and in vitro studies (Cano-Sancho et al., 2017).  
110 Others suggested that the evidence for DDE as an obesogen was “moderate” due to the  
111 consistency in prospective associations with childhood growth and obesity (Vrijheid, Casas,  
112 Gascon et al., 2016). Here we present a review of current studies linking agrochemical  
113 exposure and obesity, including studies from human and animals, and discuss possible  
114 mechanisms underlying these effects.

## 115 **2. Human epidemiological studies relating agrochemicals and obesity**

### 116 **2.1 Association between agrochemicals and adult obesity**

117 There is a growing body of epidemiological studies suggesting an association between  
118 agrochemicals and adult obesity (Table 1). Agrochemicals of concern include  
119 dichlorodiphenyltrichloroethane (DDT), DDE, hexachlorobenzene (HCB),  $\beta$ -  
120 hexachlorocyclohexane ( $\beta$ -HCH) and malathion. For example, multiple prospective cohort  
121 studies identified a positive association between levels of DDT/DDE and obesity or  
122 overweight (Mendez, Garcia-Esteban, Guxens et al., 2011, Valvi, Mendez, Garcia-Esteban et  
123 al., 2014, Valvi, Mendez, Martinez et al., 2012, Lee, Lind, Jacobs et al., 2012). Pre-pregnancy  
124 levels of DDT were found to be moderately associated with gestational weight gain in a  
125 prospective cohort study of pregnant women (Jaacks, Boyd Barr, Sundaram et al., 2016). A  
126 positive correlation between  $\beta$ -HCH and BMI, waist circumference, percentage of fat mass,  
127 as well as total and subcutaneous abdominal adipose tissue has also been demonstrated in a  
128 cross-sectional study of 98 obese men and women (Dirinck, Jorens, Covaci et al., 2011).  
129 There was a positive correlation between malathion blood concentration and waist  
130 circumference among a group of farmers (Raafat, Abass and Salem, 2012). In addition to  
131 increased weight or elevated BMI, the levels of some obesity biomarkers (levels of total  
132 cholesterol and total serum lipids) were also positively associated with the concentrations of  
133 pesticides such as HCB,  $\beta$ -HCH and DDE (Dusanov, Ruzzin, Kiviranta et al., 2018, La  
134 Merrill, Lind, Salihovic et al., 2018, Bachelet, Truong, Verner et al., 2011, Langer, Ukropec,  
135 Kocan et al., 2014, Ibarluzea, Alvarez-Pedrerol, Guxens et al., 2011, Lee, Steffes, Sjodin et al.,  
136 2011), suggesting that these compounds can aggravate clinically relevant complications of  
137 obesity.

138 Although the use of DDT has been banned in many countries, some populations still  
139 bear significant levels of DDT and DDE due to the extremely long half-life of these  
140 chemicals in the environment and in the human body, bioaccumulation and via the continued  
141 use of DDT in some developing countries (United Nations Environment Programme,  
142 2010, Bornman, Aneck-Hahn, de Jager et al., 2017). HCB and  $\beta$ -HCH were banned globally  
143 several decades ago, but persist in the environment. Malathion is a pesticide that is still  
144

145 widely used in agriculture, in residential landscaping, and in public health pest control  
146 programs. All these agrochemicals can be detected in humans currently. Information about  
147 the human exposure levels of these agrochemicals is listed in Table 1. The obesogenic effects  
148 of these pesticides in humans still needs to be considered.

## 149 **2.2 Non-monotonic dose-response relationships between agrochemicals and adult** 151 **obesity**

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

## 175 **2.3 Agrochemicals and the development of early-onset obesity**

176 Many environmental factors have been shown to play a prominent role in the  
177 development of early-onset obesity (La Merrill and Birnbaum, 2011). Building on Barker's  
178 fetal origins of disease model (Barker, 1995), Gluckman and Hanson proposed the  
179 Developmental Origins of Health and Disease (DOHaD) hypothesis, which holds that  
180 environmental disruptions during critical windows of development can lead to increased  
181 susceptibility to diseases, including obesity, later in life (Gluckman and Hanson, 2004).  
182 Compared with adults, the fetus and neonate are more sensitive to perturbation by  
183 environmental chemicals during critical windows of development because protective  
184 mechanisms (such as DNA repair, immune system, xenobiotic metabolism, and the  
185 blood/brain barrier, among others) are not yet fully functional (Newbold, 2011). The higher  
186 metabolic rates of developing organisms may also result in increased toxicity compared to  
187 adults. Therefore, developmental exposures to xenobiotic toxicants are of particular concern.

189 Measuring the levels of agrochemicals in pregnant mothers and follow-up of the weight  
190 gain of the children over their lives may provide evidence for the obesogenic effect of these  
191 chemicals during development. Several reviews have reported moderate evidence linking  
192 prenatal agrochemical exposure to childhood obesity (La Merrill and Birnbaum, 2011, Tang-  
193 Peronard, Andersen, Jensen et al., 2011). Recently, the body of evidence for obesogenic  
194 effects of agrochemicals especially DDE after exposure during prenatal development has

195 increased notably. There have been more than 10 prospective cohort studies showing that  
196 prenatal DDE exposure is significantly associated with increased birth weight, increased  
197 levels of some obesity markers, overweight risk or increased risk of childhood obesity  
198 ranging from 6 months to 9 years old (Mendez et al., 2011, Valvi et al., 2014, Valvi et al.,  
199 2012, Vafeiadi, Georgiou, Chalkiadaki et al., 2015, Agay-Shay, Martinez, Valvi et al.,  
200 2015, Verhulst, Nelen, Hond et al., 2009, Karmaus, Osuch, Eneli et al., 2009, Iszatt, Stigum,  
201 Verner et al., 2015, Heggeseth, Harley, Warner et al., 2015) (Table 2). Furthermore, DDE  
202 exposure might exacerbate the effects of other known contributing factors for obesity such as  
203 smoking (Verhulst et al., 2009). However, some other prospective cohort studies found no  
204 association between developmental exposure to DDE and infant or child obesity (Garced,  
205 Torres-Sanchez, Cebrian et al., 2012, Govarts, Nieuwenhuijsen, Schoeters et al., 2012, Hoyer,  
206 Ramlau-Hansen, Henriksen et al., 2014, Cupul-Uicab, Klebanoff, Brock et al., 2013, Warner,  
207 Aguilar Schall, Harley et al., 2013, Cupul-Uicab, Hernandez-Avila, Terrazas-Medina et al.,  
208 2010, Gladen, Klebanoff, Hediger et al., 2004).

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

216 Relatively fewer studies have examined links between prenatal DDT and DDD,  $\beta$ -HCH  
217 or HCB exposure and potential of childhood obesity. Some prospective cohort studies (Valvi  
218 et al., 2014, Valvi et al., 2012, Vafeiadi et al., 2015, Agay-Shay et al., 2015, Heggeseth et al.,  
219 2015, Smink, Ribas-Fito, Garcia et al., 2008, Warner, Ye, Harley et al., 2017, Warner,  
220 Wesselink, Harley et al., 2014) or cross-sectional studies (Xu, Yin, Tang et al., 2017) showed  
221 positive associations with obesity (Table 2). However, a few other prospective cohort studies  
222 did not identify such significant associations (Cupul-Uicab et al., 2013, Warner et al.,  
223 2013, Delvaux, Van Cauwenberghe, Den Hond et al., 2014).

224

## 225 **2.4 Gender-specific effects of agrochemicals**

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

237

## 238 **3. Animal studies and the relationship between agrochemicals and obesity**

### 239 **3.1 Studies showing the obesogenic effects of agrochemicals in adult experimental** 240 **animals**

241 Most of the animal studies relating chemical exposures to obesity demonstrated that the  
242 exposures led to weight gain and changes in adiposity, increased expression of obesity and  
243 adipogenesis-related biomarkers and affected hormones and adipokines involved in the  
244 regulation of food intake and energy expenditure (La Merrill, Karey, Moshier et al.,

245 2014,Angle, Do, Ponzi et al., 2013). Exposures to the agrochemicals HCB,  $\gamma$ -HCH, parathion,  
246 chlorpyrifos (CPF), mancozeb and imidacloprid led to increased body weight in rodents  
247 (Howell, Meek, Kilic et al., 2014,Peris-Sampedro, Cabre, Basaure et al., 2015,Peris-  
248 Sampedro, Basaure, Reverte et al., 2015,Basaure, Guardia-Escote, Biosca-Brull et al.,  
249 2019,Meggs and Brewer, 2007,Lassiter, Ryde, Mackillop et al., 2008,Bhaskar and Mohanty,  
250 2014) (Table 3). In addition, some obesity-related indicators such as decreased total energy  
251 expenditure, alterations in glucose and lipid metabolism were observed after exposure to  
252 DDT and DDE (La Merrill et al., 2014,Howell et al., 2014,Ishikawa, Graham, Stanhope et al.,  
253 2015,Howell, Mulligan, Meek et al., 2015), malathion (Kalender, Uzun, Durak et al., 2010)  
254 or CPF (Acker and Nogueira, 2012,Uchendu, Ambali, Ayo et al., 2018) (Table 3).

255 The “two-hit” hypothesis, first formulated by Knudson in 1971, suggested that most  
256 tumor suppressor genes require both alleles to be inactivated to result in a cancer (Knudson,  
257 1971). Now, this “two-hit” hypothesis has been adopted to explain the multifactorial nature  
258 of obesity, which may result from the combined effects of both genetic and environmental  
259 factors. A subject who is genetically-prone to obesity has the “first hit” (genetic susceptibility  
260 or epigenetic predisposition) intrinsically. Obesogenic factors such as chemical exposures,  
261 high energy diet, low physical activity, alcohol and smoking that act as “second hit” trigger  
262 gain weight and result in obesity (Heindel et al., 2017). The obesogenic effects of some  
263 agrochemicals were only observed upon co-treatment with high-fat diet (HFD) or were  
264 exacerbated by HFD, indicating that a second hit was needed to elicit obesity. It was reported  
265 that low doses of orally administrated permethrin (Xiao, Sun, Kim et al., 2018) or  
266 imidacloprid (Sun, Xiao, Kim et al., 2016,Sun, Qi, Xiao et al., 2017) potentiated weight gain  
267 in male mice only when a HFD was provided. HFD-fed rats exposed to CPF exhibited a pro-  
268 obesity phenotype compared with controls (Fang, Li, Zhang et al., 2018). Chronic  
269 administration of atrazine increased body weight without changing food intake or physical  
270 activity levels, and feeding a HFD further exacerbated obesity (Lim, Ahn, Song et al., 2009).

271

### 272 **3.2 Animal studies showing the development and transgenerational obesogenic** 273 **effects of agrochemicals**

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

281 Transgenerational obesogenic effects of agrochemicals have been reported. Two studies  
282 established links between DDT exposure in pregnant F0 rat dams and increased obesity rates  
283 in subsequent generations. Male and female offspring from the F3 generation and male  
284 offspring from the F4 generation in the DDT lineage had an increased prevalence of obesity  
285 compared with controls (King, McBirney, Beck et al., 2019,Skinner, Manikkam, Tracey et al.,  
286 2013). Two other studies showed that parental exposure to glyphosate or vinclozolin was  
287 linked to increased obesity rates in the F2 and F3 offspring (Kubsad, Nilsson, King et al.,  
288 2019,Nilsson, King, McBirney et al., 2018). Overall, current data support the notion that  
289 exposure to multiple types of agrochemicals can play a role in obesity. More evidence from  
290 in vivo studies will be required to further establish the links between agrochemicals and  
291 obesity.

292

## 293 **4. Potential mechanisms through which agrochemicals induce obesity**



#### 294 **4.1 Agrochemicals might promote the commitment phase of adipogenesis**

295 Although the mechanisms through which environmental chemicals induce obesity are  
296 not fully understood, affecting adipogenesis is an important mechanism (Heindel et al., 2017).  
297 Both direct and developmental exposure of chemicals might affect adipogenesis. Chemical  
298 exposure may lead to increased numbers of white adipocytes by modulating the  
299 differentiation of progenitor cells or by altering the birth/death rate of adipocytes to affect  
300 overall numbers of white adipocytes. Increased lipid storage in existing adipocytes is thought  
301 to be another major reason. Generally speaking, early developmental changes lead to  
302 increased adipocyte numbers, yet gain weight later in life during adulthood probably derives  
303 from increased fat content of existing white adipocytes (Spalding, Arner, Westermark et al.,  
304 2008).

305 Adipogenesis occurs in cells derived from the embryonic mesoderm. Multipotent  
306 mesenchymal stromal stem cells, also known as mesenchymal stem cells (MSCs) give rise to  
307 adipocytes, which involves determination (MSCs commit irreversibly to the adipocyte  
308 lineage) and terminal differentiation (preadipocytes differentiate into mature fat cells) (Rosen  
309 and MacDougald, 2006). The current consensus is that white adipocyte numbers are set by  
310 the end of childhood and that any factors that increase adipocyte numbers in early life lead to  
311 a life-long increase in white adipocyte number (Spalding et al., 2008). While it is  
312 controversial whether having more white adipocytes leads to obesity, obese people definitely  
313 have more white adipocytes than do those of normal weight (Spalding et al., 2008). One  
314 possibility is that obesogen exposure early in life alters the fate of MSCs, leading to more  
315 white adipocytes in adulthood (Janesick and Blumberg, 2011, Chamorro-Garcia, Sahu, Abbey  
316 et al., 2013). The inference is that obese individuals may have a pool of MSCs that is  
317 intrinsically biased toward the adipocyte lineage (Kirchner, Kieu, Chow et al., 2010).  
318 Therefore, early life events, including obesogen exposure, that alter the fate of MSCs could  
319 predispose the exposed individual to increased numbers of white adipocytes and  
320 consequently obesity, particularly in combination with a Western Dietary pattern (Janesick  
321 and Blumberg, 2016).

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

332 In vitro and in vivo studies have demonstrated that TBT promotes adipocyte  
333 differentiation and obesity by activating peroxisome-proliferator activated receptor  $\gamma$  (PPAR $\gamma$ )  
334 and its heterodimeric partner, retinoid X receptor  $\alpha$  (RXR $\alpha$ ). TBT can bind to and activate  
335 both receptors, but it appears to mediate its effects on adipocyte differentiation via PPAR $\gamma$   
336 (Kirchner et al., 2010, Li, Ycaza and Blumberg, 2011). In contrast, activation of RXR is  
337 required to commit mouse MSCs to the adipocyte lineage (Shoucri, Martinez, Abreo et al.,  
338 2017). TBT and chemicals that activate RXR (rexinoids) commit MSCs to the adipocyte  
339 lineage by inhibiting the expression and function of enzymes that deposit repressive histone 3  
340 lysine 27 trimethyl (H3K27<sup>me3</sup>) marks. Exposure of MSCs to TBT or rexinoids led to  
341 genome-wide decreases in H3K27<sup>me3</sup> at the promoters of genes required for adipogenic  
342 commitment. Currently, there is a relative paucity of data regarding how other agrochemicals  
343 might influence MSC fate. Triflumizole was found to induce adipogenic differentiation in

344 human and mouse MSCs through a PPAR $\gamma$ -dependent mechanism and to promote fat  
345 accumulation, in vivo (Li et al., 2012). Taken together, the current data suggest that exposure  
346 to agrochemicals might promote adipogenesis by increasing commitment of MSCs to the  
347 adipocyte lineage. Therefore, assessing the capability of an agrochemical to induce  
348 adipogenic commitment of MSCs together with its ability to promote terminal adipocyte  
349 differentiation, and the mechanisms through which these processes occur will be valuable in  
350 identifying additional agrochemical obesogens.

351

#### 352 **4.2 Agrochemicals might induce adipocyte differentiation**

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

371 Activation of PPAR $\gamma$ /RXR $\alpha$  heterodimers plays a key role in promoting differentiation  
372 of 3T3-L1 adipocytes by regulating the expression of genes involved in lipid droplet  
373 formation, glucose uptake, and fatty acid synthesis (Janesick and Blumberg, 2011, Tontonoz  
374 and Spiegelman, 2008). QpE might promote adipogenesis by activating PPAR $\gamma$  as  
375 demonstrated by RNAseq analysis of cells and PPAR $\gamma$  reporter gene assay (Biserni et al.,  
376 2019). Triflumizole was found to induce adipogenic differentiation in 3T3-L1 cells through a  
377 PPAR $\gamma$ -dependent mechanism (Li et al., 2012). Zoxamide, triflumizole, spiroticlofen, and  
378 quinoxifen induced adipogenesis in 3T3-L1 cells through PPAR $\gamma$ /RXR $\alpha$  heterodimers by  
379 activating PPAR $\gamma$ , while fludioxonil activated RXR $\alpha$  (Janesick et al., 2016).

380 However, the adipogenic effects of other agrochemicals on 3T3-L1 cells appear to be  
381 independent of PPAR $\gamma$  activation. For example, flusilazole, forchlorfenuron, acetamiprid and  
382 pymetrozine induced adipogenesis in 3T3-L1 cells, but did not activate PPAR $\gamma$  or RXR $\alpha$   
383 (Janesick et al., 2016). Pyraclostrobin was found to induce mitochondrial dysfunction which  
384 in-turn inhibited lipid homeostasis, resulting in triglyceride accumulation (Luz et al., 2018).  
385 Permethrin might potentiate adipogenesis in 3T3-L1 adipocytes via altering intracellular  
386 calcium levels and through endoplasmic reticulum stress-mediated mechanisms (Xiao et al.,  
387 2017), although, it also activates PPAR $\alpha$  (Fujino, Watanabe, Sanoh et al., 2019). The related  
388 chemical, deltamethrin may also activate an endoplasmic reticulum stress-mediated pathway  
389 in 3T3-L1 adipocytes (Yuan, Lin, Xu et al., 2019). An AMP-activated protein kinase  
390 AMPK $\alpha$ -mediated pathway was found to play a role in the induction of adipogenesis in 3T3-  
391 L1 preadipocytes by agrochemicals such as DDT and DDE (Kim et al., 2016), imidacloprid  
392 (Sun et al., 2017), deltamethrin (Yuan et al., 2019, Shen, Hsieh, Yue et al., 2017), and fipronil  
393 (Sun et al., 2016). Endrin and tolylfluanid promoted adipogenesis in 3T3-L1 cells via



394 glucocorticoid receptor activation (Sargis, Johnson, Choudhury et al., 2010). In contrast,  
395 another study showed that endrin inhibited adipogenesis in 3T3-L1 cells (Moreno-Aliaga and  
396 Matsumura, 1999).

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

407

### 408 **4.3 Agrochemicals might exert obesogenic effects mediated by sex steroid hormone** 409 **dysregulation**

410 Sex steroid hormones such as estrogens and androgens appear to play important roles in  
411 adipose tissue development during early development or in adulthood (Cooke and Naaz,  
412 2004). Estrogens play a pivotal role in regulating energy homeostasis, especially in female  
413 mammals, either by acting directly on the brain or through activation of ERs in adipocytes  
414 (Mauvais-Jarvis, Clegg and Hevener, 2013). Imbalances in the sex steroid levels can lead to  
415 dyslipidemias and obesity. For example, weight gain was observed following androgen  
416 deprivation therapy for prostate cancer (Braunstein, Chen, Loffredo et al., 2014) or polycystic  
417 ovary syndrome (Stanley and Misra, 2008). Obesogenic effects have been observed for  
418 xenoestrogenic compounds such as diethylstilbestrol (DES) (Newbold, Padilla-Banks, Snyder  
419 et al., 2007) and bisphenol A (BPA) (Rubin, Murray, Damassa et al., 2001), suggesting that  
420 dysregulated signaling through sex steroid receptors can produce pro-adipogenic effects. This  
421 might also influence the sexually dimorphic effects of some chemicals on the incidence and  
422 health consequences of obesity observed in humans (Palmer and Clegg, 2015). Therefore,  
423 chemicals that can disrupt the regulation of estrogen and androgen signaling by changing  
424 hormone levels or by directly interacting with the cognate nuclear receptors may contribute to  
425 disturbances in the regulation of adipose tissue formation and maintenance. Both direct and  
426 developmental exposure of chemicals might disrupt the regulation of sex hormone signaling.

427 Many *in vivo* experimental animal studies examined estrogenic or anti-androgenic  
428 effects of agrochemicals. By using the rat uterotrophic (estrogen) and Hershberger (anti-  
429 androgen) assays, it was found that the insecticide permethrin might have estrogenic effects  
430 on female rats, but anti-androgenic effects on male rats (Kim, Lee, Lim et al., 2005). *In vivo*  
431 anti-androgenic effects have also been reported in response to agrochemicals including  
432 linuron (Wolf, Lambright, Mann et al., 1999, Lambright, Ostby, Bobseine et al., 2000),  
433 prochloraz (Vinggaard, Christiansen, Laier et al., 2005), procymidone (Ostby, Kelce,  
434 Lambright et al., 1999), tebuconazole (Taxvig, Hass, Axelstad et al., 2007), vinclozolin  
435 (Anway, Memon, Uzumcu et al., 2006, Uzumcu, Suzuki and Skinner, 2004)), DDE (Wolf et  
436 al., 1999), endosulfan (Sinha, Adhikari and D, 2001), dimethoate (Verma and Mohanty, 2009)  
437 and deltamethrin (Andrade, Araujo, Santana et al., 2002). After reviewing the animal and  
438 epidemiologic data from previous studies, Li et al. suggested that chlorpyrifos induces  
439 metabolic disruption by altering levels of reproductive hormones (Li, Ren, Li et al., 2019).

440 Mechanistic studies suggested that agrochemicals might exert estrogenic or anti-  
441 androgenic effect by affecting sex hormone status or by acting directly on estrogen receptors  
442 (ERs) and/or androgen receptor (AR). Several agrochemicals were documented to affect sex  
443 hormone levels through interference with hormone synthesis or breakdown. For example,

444 testicular apoptosis was found in adult rats following exposure to a single dose of  
445 methoxychlor (Vaithinathan, Saradha and Mathur, 2010). DDE inhibited the action of 5 $\alpha$ -  
446 reductase, the major enzyme that converts testosterone to dihydro-testosterone (Lo, King,  
447 Allera et al., 2007). DDE stimulated aromatase activity in ovarian granulosa cells (Younglai,  
448 Holloway, Lim et al., 2004). An analysis of the hepatic transcriptome of mice treated with  
449 DDE revealed altered mRNA levels of genes encoding enzymes involved in testosterone  
450 catabolism and excretion, resulting in impaired testosterone metabolism (Morales-Prieto,  
451 Ruiz-Laguna, Sheehan et al., 2018). Numerous agrochemicals, including DDT, can affect the  
452 expression levels and/or activity of multiple cytochrome P450 enzymes (P450) (Abass and  
453 Pelkonen, 2013,Blizard, Sueyoshi, Negishi et al., 2001), which are involved in the  
454 metabolism of steroid hormones and many xenobiotic chemicals.

455 Many studies have investigated the activity of agrochemicals on ER and AR using  
456 reporter gene assays. DDE was demonstrated to be a potent AR antagonist (Kelce, Stone,  
457 Laws et al., 1995). Kjeldsen et al. (Kjeldsen, Ghisari and Bonfeld-Jorgensen, 2013)  
458 investigated the effects of five agrochemicals (terbuthylazine, propiconazole, prothioconazole,  
459 cypermethrin and malathion) on ER and AR transactivation using luciferase reporter gene  
460 assays. The results showed that these five pesticides weakly activated ER and that three  
461 pesticides (bitertanol, propiconazole and mancozeb) antagonized AR activity in a  
462 concentration-dependent manner. Kojima et al, (Kojima, Katsura, Takeuchi et al., 2004)  
463 screened 200 agrochemicals and reported that 66 were anti-androgenic, whereas only 29 were  
464 estrogenic. Numerous in vitro studies based on reporter gene assays demonstrated estrogenic  
465 and anti-androgenic effect of agrochemicals (Kitamura, Suzuki, Ohta et al., 2003,Andersen,  
466 Vinggaard, Rasmussen et al., 2002,Bauer, Bitsch, Brunn et al., 2002,Okubo, Yokoyama,  
467 Kano et al., 2004,Orton, Lutz, Kloas et al., 2009,Vinggaard, Niemela, Wedebye et al.,  
468 2008,Sun, Xu, Xu et al., 2007,Zhang, Zhu, Zheng et al., 2008,Robitaille, Rivest and  
469 Sanderson, 2015,Xu, Liu, Ren et al., 2008,Li, Li, Ma et al., 2008,Martin, Dix, Judson et al.,  
470 2010,Knudsen, Houck, Sipes et al., 2011). In addition to the canonical ERs, binding of DDT  
471 and DDE to the seven-transmembrane estrogen receptor, GPR30, which activates alternative  
472 estrogen signaling was demonstrated (Thomas and Dong, 2006). Molecular dynamic  
473 simulations showed that estrogen-related receptor  $\gamma$ , which might affect estrogen signaling  
474 indirectly, could also be a potential target of DDT and DDE (Zhuang, Zhang, Wen et al.,  
475 2012). Estrogenic or anti-androgenic effects of agrochemicals might involve more than one  
476 mechanism; thus, their effects might be mediated through multiple cellular pathways.

477 Typically, humans are only rarely exposed to a single agrochemical. Rather they are  
478 simultaneously exposed to multiple xenobiotic chemicals, including agrochemicals and  
479 supposedly inert carriers. It is probable that these different agrochemicals may act in  
480 combination through additive, synergistic, or antagonistic mechanisms, which may influence  
481 the doses of such ligands required to induce adipogenesis. Notably, additive and synergistic  
482 anti-androgenic activities of agrochemical mixtures have been observed (Kjeldsen et al.,  
483 2013,Ma, Chen, Yang et al., 2019,Orton, Rosivatz, Scholze et al., 2012,Kolle, Melching-  
484 Kollmuss, Krennrich et al., 2011,Birkhoj, Nellesmann, Jarfelt et al., 2004). Christen et al.,  
485 studied additive and synergistic anti-androgenic activities of binary mixtures of five anti-  
486 androgenic fungicides and found that about half of the tested mixtures produced additive  
487 effects and half synergistic effects (Christen, Crettaz and Fent, 2014). These observed  
488 additive and synergistic effects emphasize the importance of considering the combined  
489 actions of these chemicals. Although the underlying molecular mechanisms remain to be  
490 fully understood, these studies suggested the agrochemicals might induce obesity by  
491 disturbing normal sex hormone signaling.

492

#### 493 **4.4 Agrochemicals might exert obesogenic effects by affecting metabolic homeostasis** 494 **through PPARs**

495       Obesogens might induce obesity by perturbing metabolic homeostasis resulting in  
496 unbalanced energy expenditure. Many nuclear receptors respond to specific hormones such as  
497 thyroid hormone, mineralocorticoids, glucocorticoids, retinoic acid, sex steroids and  
498 lipophilic endogenous substances. These are involved in various physiological and  
499 pathological processes in the regulation of metabolic homeostasis (Mangelsdorf, Thummel,  
500 Beato et al., 1995). Among these, the PPAR subfamily, comprising PPAR $\alpha$ , PPAR $\beta/\delta$ ) and  
501 PPAR $\gamma$  are key players in adipogenesis and lipid metabolism (Feige, Gelman, Michalik et al.,  
502 2006). After forming heterodimers with RXR, PPARs regulate the transcription of genes  
503 involved in the regulation of adipogenesis (adipocyte proliferation and differentiation),  
504 intracellular lipid metabolism and storage, glucose homeostasis and insulin responsiveness  
505 (Wang, 2010). The three PPAR subtypes act as ligand sensors for a variety of lipophilic  
506 hormones, dietary fatty acids and their metabolites to regulate lipid homeostasis (Bensinger  
507 and Tontonoz, 2008). They work together to control almost every aspect of fatty acid  
508 metabolism. Many pharmaceutical drugs and environmental chemicals target PPARs,  
509 enabling them to affect PPAR signaling pathways involved in regulating metabolic balance  
510 (Lau, Abbott, Corton et al., 2010). Usually, chemical influences on metabolic homeostasis  
511 acting through PPARs are due to direct chemical exposure.

512       Several in vivo studies revealed changes in the expression levels of genes encoding  
513 PPARs and PPAR-regulated genes after agrochemical exposure. The herbicide dicamba (2-  
514 methoxy-3,6-dichlorobenzoic acid) caused a significant increase in peroxisomal beta-  
515 oxidation activity and changed the expression of a variety of PPAR regulated enzymes in rat  
516 livers, suggesting that dicamba acts as a peroxisome proliferator in rats (Espandiari, Thomas,  
517 Glauert et al., 1995). The herbicide diclofop was also shown to be a rodent peroxisome  
518 proliferator (Palut, Ludwicki, Kostka et al., 2001). Atrazine induced a near-significant  
519 increase in PPAR $\beta$  mRNA in *Xenopus laevis* tadpoles (Zaya, Amini, Whitaker et al., 2011),  
520 and diclofop-methyl and pyrethrins changed the expression of PPAR $\alpha$ -inducible cytochrome  
521 P450 genes in mice (Takeuchi, Matsuda, Kobayashi et al., 2006). 2,4-dichlorophenoxyacetic  
522 acid increased expression of PPAR $\delta$  in HepG2 cells (Sun, Shao, Liu et al., 2018). DDT  
523 enhanced expression of PPAR $\gamma$  mRNA in human MSCs (Strong et al., 2015). Therefore,  
524 expression of PPAR genes themselves may be potential agrochemical targets.

525       Results of in vitro reporter gene assays and in silico ligand binding simulations  
526 suggested that agrochemicals could function as agonistic ligands for one or more of the  
527 PPARs. Using an in vitro reporter gene assay based on CV-1 cells, Takeuchi et al. screened  
528 the ability of 200 agrochemicals to activate mouse PPAR $\alpha$  and they found three chemicals  
529 (diclofop-methyl, pyrethrins and imazalil) had PPAR $\alpha$  agonistic activity, yet none of the  
530 tested agrochemicals showed PPAR $\gamma$  agonistic activity (Takeuchi et al., 2006). Using a  
531 reporter gene assay based on COS-1 cells it was found that none of eight tested pyrethroids  
532 activated PPAR $\alpha$  but that a metabolite of cis-/trans-permethrin as well as a metabolite of  
533 phenothrin (3-phenoxybenzoic acid) activated rat PPAR $\alpha$  (Fujino et al., 2019). Five chitin  
534 synthesis inhibitors activated PPAR $\gamma$ -mediated reporter gene activity with the rank order of  
535 diflubenzuron > chlorfluazuron > flucycloxuron > noviflumuron > flufenoxuron (Ning, Ku,  
536 Gao et al., 2018). Other agrochemicals such as quizalofop-p-ethyl (Biserni et al., 2019)  
537 spirodiclofen, zoxamide (Janesick et al., 2016) and triflumizole (Li et al., 2012) were found  
538 to have PPAR $\gamma$  agonistic activity. An in silico study modeling the binding of pesticides in the  
539 PPAR $\gamma$  ligand-binding pocket suggested that the pesticide dithiocarbamate and the fungicide  
540 mancozeb might bind to this receptor (Bhaskar and Mohanty, 2014). The PPAR $\gamma$  ligand-  
541 binding pocket is rather large and can bind multiple compounds as the same time (Balaguer,

542 Delfosse, Grimaldi et al., 2017). Therefore, it is not surprising that many agrochemicals with  
543 dissimilar structures could be PPARs ligands.

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

562

#### 563 **4.5 Agrochemicals might exert obesogenic effects by affecting metabolic homeostasis** 564 **through disturbing the thyroid hormone pathway**

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

587 A broad range of human and animal studies documented that agrochemicals could  
588 interfere with the normal function of the thyroid endocrine system (Requena, Lopez-Villen,  
589 Hernandez et al., 2019). An association between the use of organochlorine pesticides and risk  
590 of hypothyroidism and hyperthyroidism has been established among women in Iowa and  
591 North Carolina enrolled in the Agricultural Health Study in 1993-1997 (Goldner, Sandler, Yu



592 et al., 2010). Animal studies indicated that in utero exposure to pesticides such as DDT, DDE  
593 and chlorpyrifos-methyl may affect thyroid hormone status in offspring (Luo, Pu, Tian et al.,  
594 2017, Jeong, Kim, Kang et al., 2006). Mechanistic studies also supported the disruptive  
595 effects of agrochemicals on thyroid function. The hypothalamus–pituitary–thyroid (HPT) axis  
596 determines systemic thyroid hormone levels (Ortiga-Carvalho, Chiamolera, Pazos-Moura et  
597 al., 2016). Acetochlor was found to alter the mRNA expression of HPT axis-related genes  
598 and changed circulating thyroid hormone levels in zebrafish larvae (Yang, Hu, Li et al.,  
599 2016, Xu, Sun, Niu et al., 2019). Most activity of T3 is mediated by its nuclear receptors,  
600 thyroid hormone receptor alpha (TR $\alpha$ ) and beta (TR $\beta$ ) which require heterodimerization with  
601 RXRs to bind DNA and regulate the expression of target genes (Yen, 2001). A GH3-  
602 luciferase reporter gene assay was used to investigate the activities of 21 pesticides towards  
603 TRs. Among the tested pesticides, 5 had agonistic effects (procymidone, imidacloprid, atrazine,  
604 fluroxypyr, mancozeb), whereas 11 pesticides (butachlor, beta-cypermethrin, fenobucarb,  
605 cyhalothrin, theta-cypermethrin, bifenthrin, carbaryl, pymetrozine, pendimethalin, metolcarb, and  
606 acetochlor) inhibited luciferase activity induced by T3 to varying degrees, demonstrating their  
607 antagonistic activities (Xiang, Han, Yao et al., 2017). Xiang et al. also found that 13  
608 pesticides bound directly to TR as measured by surface plasmon resonance (SPR) biosensors  
609 (Xiang et al., 2017). Co-exposure of mice to the dithiocarbamate fungicide, mancozeb and  
610 the neonicotinoid insecticide, imidacloprid during lactation decreased plasma T3 levels and  
611 molecular dynamics simulations predicted that both of these chemicals might compete with  
612 T3 for binding to TRs (Bhaskar and Mohanty, 2014). Taken together, these studies  
613 established strong links between agrochemicals and disruption of thyroid signaling; however,  
614 possible obesogenic effects through this mechanism require further investigation.

615

#### 616 **4.6 Agrochemicals might exert obesogenic effects by affecting the gut microbiota**

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

634 Emerging evidence supports the involvement of the gut microbiota in agrochemical-  
635 induced obesity. In a human cross-sectional study, levels of Methanobacteriales in the gut  
636 were associated with higher body weight and waist circumference and it was already known  
637 that these bacteria are linked to obesity (Lee, Lee, Lee et al., 2011). Serum organochlorine  
638 pesticides (cis-nonachlor, oxychlorodane and trans-nonachlor) levels were also positively  
639 correlated with levels of Methanobacteriales. This supports a possible link among  
640 organochlorine pesticide levels, gut Methanobacteriales levels, and obesity in the general  
641 population. Some animal studies also established potentially causal links among

642 agrochemical levels, composition of the gut microbiota and obesity. Chlorpyrifos disrupted  
643 gut microbial homeostasis and increased lipopolysaccharide entry into the body leading to  
644 low-grade systemic inflammation (Liang, Zhan, Liu et al., 2019). Mice given this  
645 chlorpyrifos-altered microbiota gained more white adipose tissue and had lower insulin  
646 sensitivity, supporting a link between the microbiota and obesity-related diseases (Liang et al.,  
647 2019). Chlorpyrifos exposure also significantly altered the composition of bacteria previously  
648 associated with obese and diabetic phenotypes in gut microbiome of rats (Fang et al., 2018).  
649 Chlorpyrifos exposure caused hepatic lipid metabolism disorders that were associated with  
650 gut oxidative stress and microbiota dysbiosis in zebrafish (Wang, Shen, Zhou et al., 2019).  
651 Carbendazim induced gut microbiota dysbiosis and disturbed lipid metabolism, which  
652 promoted the intestinal absorption of excess triglycerides and caused multiple tissue  
653 inflammatory responses in mice (Jin, Zeng, Wang et al., 2018). Taken together, these studies  
654 showed that altering the composition of the gut microbiota is a possible mechanism through  
655 which agrochemicals can promote obesity. It will be important to establish a mechanistic  
656 understanding of how perturbation of gut microbiota by agrochemicals ultimately leads to  
657 obesity in humans as well as to evaluate agrochemicals in widespread use for these effects.  
658

#### 659 **4.7 Epigenetic programming and transgenerational effects of agrochemicals**

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

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

684 Environmental factor-induced transgenerational inheritance of pathologies and  
685 phenotypic variations have been found in different species (Nilsson et al., 2018). Many  
686 studies showed that EDC exposure can result in increased disease susceptibility later in life  
687 and in subsequent generations (Anway and Skinner, 2006, Uzumcu, Zama and Oruc,  
688 2012, Skinner, Manikkam and Guerrero-Bosagna, 2011, Rissman and Adli, 2014, Ho, Johnson,  
689 Tarapore et al., 2012, Skinner and Anway, 2005, Guerrero-Bosagna, Weeks and Skinner,  
690 2014). A number of studies revealed that pesticides such as vinclozolin (Nilsson et al.,  
691 2018, Beck, Sadler-Riggleman and Skinner, 2017, Anway, Cupp, Uzumcu et al., 2005),

692 permethrin, methoxychlor (Manikkam, Haque, Guerrero-Bosagna et al., 2014), DDT  
693 (Skinner, Ben Maamar, Sadler-Riggelman et al., 2018, Ben Maamar, Nilsson, Sadler-  
694 Riggelman et al., 2019), atrazine (McBirney, King, Pappalardo et al., 2017, Hao, Gely-Pernot,  
695 Kerverrec et al., 2016) and the insect repellent diethyltoluamide (Manikkam, Tracey,  
696 Guerrero-Bosagna et al., 2012) promoted transgenerational inheritance of disease  
697 susceptibility and sperm epimutations. Transgenerational disease pathologies related to  
698 pesticide exposure included effects on the testis (King et al., 2019, Skinner et al., 2013, Anway,  
699 Leathers and Skinner, 2006), prostate (King et al., 2019, Anway et al., 2006), ovaries (King et  
700 al., 2019, Skinner et al., 2013, Manikkam et al., 2014, Manikkam et al., 2012), kidneys (King et  
701 al., 2019, Skinner et al., 2013, Manikkam et al., 2014, Anway et al., 2006), immune system  
702 (Anway et al., 2006), behavior (McBirney et al., 2017) and tumor development (Anway et al.,  
703 2006).

704 Exposure to obesogenic chemicals during critical periods of development might alter  
705 epigenetic programming processes that predispose a stem cell or progenitor cell toward a  
706 particular lineage such as the adipocyte. Epigenetic changes caused by exposures to EDCs  
707 such as TBT and DES may lead to obesity in subsequent generations (Chamorro-Garcia,  
708 Diaz-Castillo, Shoucri et al., 2017, Chamorro-Garcia and Blumberg, 2014, Stel and Legler,  
709 2015, van Dijk, Tellam, Morrison et al., 2015). Skinner and colleagues showed that ancestral  
710 exposures of F0 rat dams to DDT led to a striking increase in the incidence of obesity in both  
711 F3 males and females (King et al., 2019, Skinner et al., 2013). In a similarly designed  
712 transgenerational experiment, they found that F0 exposure to glyphosate led to increased  
713 obesity rates in subsequent generations (Kubsad et al., 2019). Exposure to vinclozolin  
714 induced epigenetic transgenerational inheritance of increased obesity rates in F3 generation  
715 female rats (Nilsson et al., 2018). However, the molecular mechanisms underlying how these  
716 chemicals induce epigenetic changes and how these changes are transmitted to future  
717 generations to produce obesity and other adverse outcomes remains unclear. Many different  
718 mechanisms have been proposed for how epigenetic changes can affect subsequent disease  
719 outcomes including modulating methyl donor availability and altering the expression of  
720 enzymes that act as epigenetic readers, writers and erasers (Walker, 2016). However, at the  
721 time of this writing no convincing evidence exists that precisely establishes the molecular  
722 mechanisms through which epigenetic transgenerational inheritance of any phenotype,  
723 including obesity occurs.

724

## 725 **5. Conclusions and future directions**

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

738 There are many possible modes of action for how agrochemicals can promote obesity as  
739 discussed above. What is missing is a systematic effort to understand which of the many  
740 agrochemicals in current use can lead to adverse health outcomes, including obesity and  
741 through which molecular pathways they act to exert these effects. Current practice in

742 toxicological research is becoming focused on “adverse outcome pathways” and “molecular  
743 initiating events”. These are useful paradigms for simple systems, but it is abundantly clear  
744 that agrochemicals can act through multiple pathways. These cellular signaling pathways  
745 interact with each other in complex ways. It is likely that individual chemicals act at multiple  
746 levels on metabolic homeostasis. Moreover, humans are typically exposed to poorly defined  
747 mixtures of chemicals that may interact in combinatorial ways that can be additive or  
748 inhibitory. Typical agrochemicals are also applied as mixtures that include so-called “inert  
749 ingredients” that may not be inert and whose composition and levels are not required to be  
750 reported. Much remains undiscovered about the possible molecular mechanisms for  
751 agrochemicals and their relationship with the obesity epidemic.

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



758 **Acknowledgements**

759 Supported by grants from the NIH (ES023316) to BB, by the EU Horizon 2020 research and  
760 innovation program under grant agreement GOLIATH [825489], and by a grant from China  
761 Scholarship Council to XR.

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**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	Increased BMI.

			(N= 1055)	
(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.

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**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)	<i>o,p'</i> -DDD; <i>p,p'</i> -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; $\beta$ -HCH; DDE	7 years old	Spain (N=657)	Increased BMI and overweight risk.
(Heggeseth et al. 2015)	<i>o,p'</i> -DDT; <i>p,p'</i> -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 and 14 months old	Spain (N=1285)	Increased growth and overweight.
(Warner et al. 2014)	<i>o,p'</i> -DDT; <i>p,p'</i> -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)	<b>DDE</b>	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.

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**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)	Glyphosate	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)	Permethrin	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; deltamethrin	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)	Vinclozolin	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)	Imidacloprid	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)	Imidacloprid	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)	Mancozeb; Imidacloprid	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)	Chlorpyrifos	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.
(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)	Parathion	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.

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



1590 **Table 4.** Possible mechanisms through which agrochemicals may lead to obesity and example  
 1591 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, tebuirimfos, forchlorfenuron, flusilazole, acetamiprid, pymetrozine, 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, oxylchlorane, trans-nonachlor, chlorpyrifos, carbendazim,
Epigenetic programming and transgenerational effects	DDT, glyphosate, vinclozolin

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1 Agrochemicals and obesity

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5 | Xiao-Min Ren<sup>1,2</sup>, **Yun Kuo**<sup>2</sup> and Bruce Blumberg<sup>2,3,4</sup>

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8 | <sup>1</sup>Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences,  
9 Beijing, China

10

11 <sup>2</sup>Department of Developmental and Cell Biology, University of California, Irvine, CA  
12 92697-2300

13

14 <sup>3</sup>Department of Pharmaceutical Sciences, University of California, Irvine, CA

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16 <sup>4</sup>Department of Biomedical Engineering, University of California, Irvine, CA

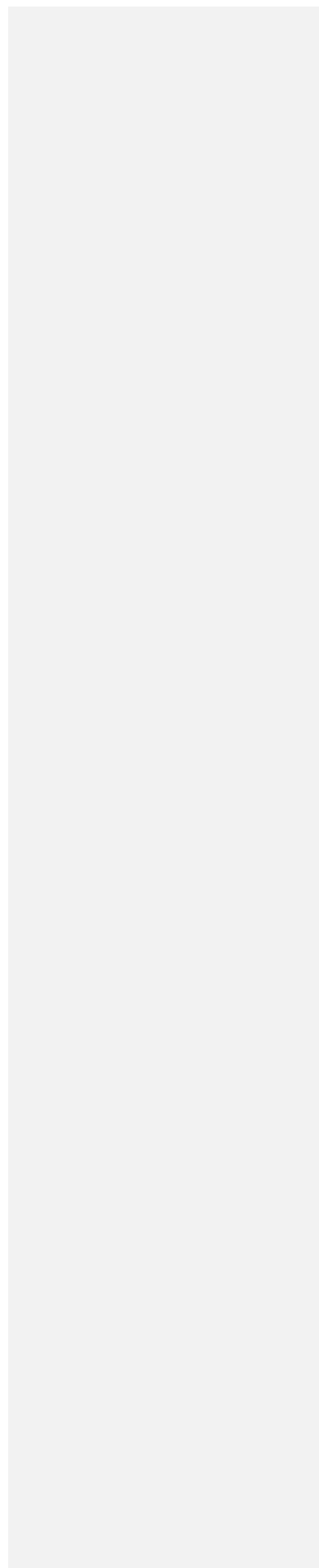
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19 | Correspondence to Bruce Blumberg, [Blumberg@uci.edu](mailto:Blumberg@uci.edu)

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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.

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**Keywords**

Obesogen  
EDC  
endocrine disrupting chemical  
agrochemical  
pesticide  
fungicide  
transgenerational  
epigenetic  
microbiome

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## 48 1. Introduction

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

54 Agrochemicals ~~of concern are typically of particular interest for obesity are usually refer~~  
55 ~~to the~~ pesticides including insecticides, herbicides, fungicides and nematicides (Sparks, 2013).  
56 These agrochemicals can be further subdivided into organochlorines, organophosphorus,  
57 carbamates, pyrethroids and neonicotinoids, according to their chemical structures and modes  
58 of action (Xiao, Clark and Park, 2017). While bringing benefits to humans, agrochemicals  
59 have also become major contaminants that are widely detected in the environment as well as  
60 in humans (Tsatsakis, Tzatzarakis, Tutudaki et al., 2008). Many efforts have been made to  
61 reduce the harmful effects of agrochemicals on humans by designing lower toxicity  
62 chemicals and by controlling the time and location of applications. ~~H;~~ however, agrochemical  
63 exposure and consequent toxicity to humans and animals is inevitable (Sparks and Lorschach,  
64 2017). Numerous epidemiological studies together with experimental evidence in animal  
65 models indicated that agrochemicals may be harmful to human health in multiple ways  
66 (Cano-Sancho, Salmon and La Merrill, 2017, Androutsopoulos, Hernandez, Liesivuori et al.,  
67 2013). For example, agrochemicals may have carcinogenicity, neurotoxicity,  
68 immunotoxicity, reproductive toxicity, developmental toxicity and endocrine disrupting  
69 effects (Mostafalou and Abdollahi, 2017) (Mostafalou and Abdollahi, 2017). In view of this,  
70 the toxicity of agrochemicals is of great concern around the world.

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

81 Obesity is generally considered to be the result of energy imbalance, i.e., when energy  
82 intake exceeds energy expenditure. However, in reality the origins of obesity are  
83 multifactorial and result from the combined effects of both genetic and environmental factors  
84 (Heindel and Blumberg, 2019). Currently, the full spectrum of potential factors associated  
85 with obesity remains unclear. Previous studies have shown that factors such as genetic  
86 susceptibility, ~~epigenetic predisposition,~~ increased energy intake and lack of physical activity  
87 could contribute to the development of obesity (Turcot, Lu, Highland et al., 2018). However,  
88 these factors cannot fully explain the current dramatically increased rates of obesity. Over the  
89 past several decades, there is considerable evidence that environmental pollutants ~~especially~~  
90 ~~endocrine disrupting chemicals (EDCs)~~ may contribute to the rapid increase of obesity  
91 (Heindel and Blumberg, 2019). Endocrine-disrupting chemicals (EDCs) are a kind of natural  
92 or man-made substances that may interfere with the normal function of the endocrine system,  
93 including hormone biosynthesis, metabolism or action (Zoeller, Brown, Doan et al., 2012).  
94 There is growing evidence showing ~~the~~ links between EDCs and obesity as well as other  
95 health problems such as metabolic issues, diabetes, reproductive disabilities and  
96 cardiovascular problems (Gore, Chappell, Fenton et al., 2015).- Metabolism disrupting  
97 chemicals (MDCs) specifically refer to those EDCs having the ability to promote metabolic

98 [changes that can result in obesity, T2D or fatty liver in animals](#) (Heindel, Blumberg, Cave et  
99 al., 2017). [These EDCs or MDCs might be important factors leading to obesity.](#) Identifying  
100 all of the important factors that contribute to obesity is, therefore, an important issue and  
101 could help to control and reduce the obesity epidemic and related diseases.

102 “Obesogens” are functionally defined as chemicals ~~(natural, pharmaceutical, or~~  
103 ~~xenobiotic)~~ that promote obesity after exposure, [in vivo](#). [Some natural chemicals \(such as](#)  
104 [fructose\), pharmaceutical chemicals \(such as thiazolidinedione anti-diabetic drugs\) or](#)  
105 [xenobiotic chemicals \[such as tributyltin \(TBT\)\] have found to be obesogens.](#) (Janesick and  
106 Blumberg, 2016). Obesogens might act directly on fat cells by increasing their number or  
107 increasing the storage of fat into the existing cells. These chemicals might also act indirectly  
108 by affecting mechanisms regulating ~~the~~ appetite and satiety, by altering basal metabolic rate,  
109 ~~by~~ altering energy balance to favor the storage of calories, or ~~by~~ altering gut microbiota to  
110 promote energy intake (Heindel and Blumberg, 2019). Some agrochemicals have been shown  
111 to act as obesogens by promoting adipogenesis and inducing obesity in experimental animals  
112 and are found at higher levels in obese humans. For example,  
113 dichlorodiphenyldichloroethylene (DDE) was classified as “presumed” to be obesogenic for  
114 humans by using a systematic review-based strategy to identify and integrate evidence from  
115 epidemiological, in vivo, and in vitro studies (Cano-Sancho et al., 2017). Others suggested  
116 that the evidence for DDE as an obesogen was “moderate” due to the consistency in  
117 prospective associations with childhood growth and obesity (Vrijheid, Casas, Gascon et al.,  
118 2016). [The annual cost of exposure to DDE in the EU from type 2 diabetes and obesity was](#)  
119 [estimated to be more than €860 million despite its parent chemical, DDT being banned many](#)  
120 [years ago \(Legler, Fletcher, Govarts et al., 2015\).](#) Here we present a review of current studies  
121 linking agrochemical exposure and obesity, including studies from human and animals, and  
122 discuss possible mechanisms underlying these effects.  
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## 2. Human epidemiological studies relating agrochemicals and obesity

### [2.1 Association between agrochemicals and adult obesity](#)

127 There is a growing body of epidemiological studies suggesting an association between  
128 agrochemicals and adult obesity [\(Table 1\)](#). Agrochemicals of concern include  
129 ~~dichlorodiphenyltrichloroethane (dichlorodiphenyltrichloroethane (DDT)DDT) and its major,~~  
130 ~~in vivo metabolite, dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), as~~  
131 ~~well as β-hexachlorocyclohexane (β-HCH) and malathion. These are the most frequently~~  
132 ~~found to be related to obesity in humans (Tang Peronard, Andersen, Jensen et al., 2011, Liu~~  
133 ~~and Peterson, 2015, La Merrill and Birnbaum, 2014). For example, In addition, agrochemicals~~  
134 ~~such as malathion (Raafat, Abass and Salem, 2012), allethrin and prallethrin (Narendra,~~  
135 ~~Kavitha, Helah Kiranmai et al., 2008) have also been associated with obesity. Obesity is~~  
136 ~~typically assessed based on weight gain and BMI as the endpoints in epidemiological studies.~~  
137 ~~m~~Multiple prospective cohort studies identified a positive association between levels of ~~some~~  
138 ~~agrochemicals such as DDT, DDE~~ and obesity or overweight (Mendez, Garcia-Esteban,  
139 Guxens et al., 2011, Valvi, Mendez, Garcia-Esteban et al., 2014, Valvi, Mendez, Martinez et  
140 al., 2012, Lee, Lind, Jacobs et al., 2012). Pre-pregnancy levels of DDT were found to be  
141 moderately associated with gestational weight gain in a prospective cohort study of pregnant  
142 women (Jaacks, Boyd Barr, Sundaram et al., 2016), ~~and levels of DDE were linked with rapid~~  
143 ~~weight gain and overweight in infancy based on prospective cohort studies (Valvi et al.,~~  
144 ~~2014, Mendez et al., 2011, Valvi et al., 2012).~~ In a cross-sectional study of workers  
145 occupationally exposed to β-HCH, a positive relationship was reported between the  
146 percentage of body fat and levels of β-HCH (Jung, Becher, Edler et al., 1997). A positive  
147 correlation between β-HCH and BMI, waist circumference, percentage of fat mass, as well as

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148 total and subcutaneous abdominal adipose tissue has also been demonstrated in a cross-  
149 sectional study of 98 obese men and women (Dirinck, Jorens, Covaci et al., 2011). There was  
150 a positive correlation between malathion blood concentration and waist circumference among  
151 a group of farmers (Raafat, Abass and Salem, 2012). In addition to increased weight or  
152 elevated BMI, the levels of some obesity biomarkers (levels of total cholesterol and total  
153 serum lipids) were also positively associated with the concentrations of pesticides such as  
154 HCB,  $\beta$ -HCH ~~and and~~ DDE (Dusanov, Ruzzin, Kiviranta et al., 2018, La Merrill, Lind,  
155 Salihovic et al., 2018, Bachelet, Truong, Verner et al., 2011, Langer, Ukropec, Kocan et al.,  
156 2014, Ibarluzea, Alvarez-Pedrerol, Guxens et al., 2011, Lee, Steffes, Sjodin et al., 2011),  
157 suggesting that these compounds can aggravate clinically relevant complications of obesity.

158 Although the use of DDT has been banned in many countries, some populations still  
159 bear significant levels of DDT and DDE due to the extremely long half-life of these  
160 chemicals in the environment and in the human body, bioaccumulation and via the continued  
161 use of DDT in some developing countries (United Nations Environment Programme,  
162 2010, Bornman, Aneck-Hahn, de Jager et al., 2017). HCB and  $\beta$ -HCH have been  
163 globally several decades ago, but they are persistent in the environment. Malathion is a  
164 pesticide that is still widely used in agriculture, in residential landscaping, and in public  
165 health pest control programs. All these agrochemicals can be detected in humans  
166 currently now. The information about and the human exposure levels of these agrochemicals  
167 are listed in Table 1. Therefore, the ~~the~~ obesogenic effects of these pesticides in humans still  
168 needs to be considered.

## 171 2.2 Non-monotonic dose-response relationships between agrochemicals and adult 172 obesity

173 Some studies showing the potential relationship between pesticide exposure and serum  
174 lipids/obesity/BMI revealed that the effects ~~were followed~~ non-monotonic dose-response  
175 relationships. This is an unconventional dose-response relationship is characterized by a curve  
176 whose slope changes direction within the range of tested doses (Lee et al., 2012). For  
177 example, Arrebola et al. found that HCB, DDE and  $\beta$ -HCH showed quadratic associations  
178 with BMI, and the quadratic models had a positive trend at low exposure levels, while the  
179 slope decreased or even became negative at higher exposure levels (Arrebola, Ocana-Riola,  
180 Arrebola-Moreno et al., 2014). Previously, numerous studies investigating the effects of  
181 EDCs described with relative high frequency the occurrence of non-monotonic dose-response  
182 relationships for this kind of chemicals EDCs with relatively high frequency (Zoeller and  
183 Vandenberg, 2015) This is consistent with previous studies which found that some chemicals  
184 (such as BPA) exhibited a non-linear relationship between dose and effect based on both in  
185 vitro and in vivo studies (Vandenberg et al., 2012, Zoeller and Vandenberg, 2015, Angle, Do,  
186 Ponzi et al., 2013). Such non-monotonic effects are predictable and expected when  
187 considering how the endocrine system works (Vandenberg et al., 2012, Zoeller and  
188 Vandenberg, 2015, Vandenberg, Colborn, Hayes et al., 2013). The molecular mechanisms  
189 underlying non-monotonic dose-response relationships are complex and can arise from  
190 opposing effects induced by multiple receptors, receptor desensitization, negative feedback  
191 with increasing dose, or dose-dependent metabolism modulation ~~The molecular mechanisms~~  
192 for non-monotonic dose-response relationships might be complex, which can arise from  
193 opposing effects induced by multiple receptors, receptor desensitization, negative feedback  
194 with increasing dose, or dose-dependent metabolism modulation (Zoeller and Vandenberg,  
195 2015). In contrast, non-monotonic dose-response curves are an anathema to the industry and  
196 regulatory toxicology communities Usually, the environmental risk assessment approaches  
197 used by regulatory agencies are developed based on the fundamental principle that the



198 ~~toxicity of a chemical scales linearly in is-proportional~~ to the exposure level. Therefore,  
199 ~~n~~Non-monotonicity represents a challenge to fundamental concepts in toxicology and risk  
200 assessment (Dietrich, von Aulock, Marquardt et al., 2013). These ~~current non-monotonic~~  
201 ~~dose-response relationships results of agrochemicals suggested-suggest that the complex of~~  
202 ~~mechanisms by which they induce-of these chemicals in inducing-~~ obesity are complex.  
203 ~~Besides, Usually, the H~~lipophilic organochlorine pesticides such as DDE and HCB usually  
204 accumulate in adipose tissue to a major degree. Therefore, the circulating levels of these  
205 chemicals might be influenced by the degree of fat mass (Glynn, Granath, Aune et al., 2003),  
206 ~~which can also makeing~~ it difficult to study the relationships between ~~chemicals and them~~  
207 ~~and~~ obesity in adults.

### 209 2.3 Agrochemicals and the development of early-onset obesity

210 ~~and levels of DDE were linked with rapid weight gain and overweight in~~  
211 ~~infancy based on prospective cohort studies (Mendez et al., 2011, Valvi et~~  
212 ~~al., 2014, Valvi et al., 2012).~~

213 Many environmental factors have been ~~showed-shown~~ to play a prominent role in the  
214 development of early-onset obesity (La Merrill and Birnbaum, 2011). Building on Barker's  
215 fetal origins of disease model (Barker, 1995), Gluckman and Hanson proposed the  
216 Developmental Origins of Health and Disease (DOHaD) hypothesis, which holds that  
217 environmental disruptions during critical windows of development can lead to increased  
218 susceptibility to diseases, including obesity, later in life (Gluckman and Hanson, 2004).  
219 Compared with adults, the fetus and neonate are more sensitive to perturbation by  
220 environmental chemicals during critical windows of development because protective  
221 mechanisms (such as DNA repair, immune system, xenobiotic metabolism, and the  
222 blood/brain barrier, among others) are not yet ~~maximally-fully~~ functional ~~(Janesick and~~  
223 ~~Blumberg, 2011)~~. (Newbold, 2011). The higher metabolic rates of developing organisms may  
224 also result in increased toxicity compared to adults. Therefore, developmental exposures to  
225 xenobiotic toxicants are of particular concern.

226 Measuring the levels of agrochemicals in pregnant mothers and follow-up of the weight  
227 gain of the children over their lives may provide evidence for the obesogenic effect of these  
228 chemicals during development. Several reviews have reported moderate evidence linking  
229 prenatal agrochemicals exposure to childhood obesity (La Merrill and Birnbaum, 2011, Tang-  
230 Peronard, Andersen, Jensen et al., 2011). Recently, the body of evidence for obesogenic  
231 effects of agrochemicals especially DDE after exposure during prenatal development has  
232 increased notably. There have been more than 10 prospective cohort studies ~~showed-showing~~  
233 that prenatal DDE exposure is significantly associated with increased birth weight, increased  
234 levels of some obesity markers, overweight risk or increased risk of childhood obesity  
235 ranging from 6 months to 9 years old (Mendez et al., 2011, Valvi et al., 2014, Valvi et al.,  
236 2012, Vafeiadi, Georgiou, Chalkiadaki et al., 2015, Agay-Shay, Martinez, Valvi et al.,  
237 2015, Verhulst, Nelen, Hond et al., 2009, Karmaus, Osuch, Eneli et al., 2009, Iszatt, Stigum,  
238 Verner et al., 2015, Heggeseth, Harley, Warner et al., 2015) ~~.(Valvi et al., 2012, Iszatt et al.,~~  
239 ~~2015, Heggeseth et al., 2015)(Table 2)~~. Furthermore, ~~DDE exposure might exacerbate the~~  
240 ~~effects of when combined with~~ other known contributing factors for obesity such as smoking,  
241 ~~DDE exposure might exacerbate~~ (Verhulst et al., 2009). However, some other prospective  
242 cohort studies found no association between developmental exposure to DDE and infant or  
243 child obesity (Garced, Torres-Sanchez, Cebrian et al., 2012, Govarts, Nieuwenhuijsen,  
244 Schoeters et al., 2012, Hoyer, Ramlau-Hansen, Henriksen et al., 2014, Cupul-Uicab, Klebanoff,  
245 Brock et al., 2013, Warner, Aguilar Schall, Harley et al., 2013, Cupul-Uicab, Hernandez-Avila,  
246 Terrazas-Medina et al., 2010, Gladen, Klebanoff, Hediger et al., 2004).

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247 Some prospective cohort studies (Valvi et al., 2012, Delvaux, Van Cauwenberghe, Den  
248 Hond et al., 2014, Tang-Peronard, Heitmann, Andersen et al., 2014, Warner, Wesselink,  
249 Harley et al., 2014, Warner, Ye, Harley et al., 2017) or cross-sectional studies (Cabrera-  
250 Rodriguez, Luzardo, Almeida-Gonzalez et al., 2019) revealed gender-specific effects of DDE  
251 on childhood obesity.

252 Sexually dimorphic responses are a common finding when examining EDC effects,  
253 including links to obesity (Gore, Chappell, Fenton et al., 2015). A number of studies also  
254 showed associations between DDE or HCB and low birth weight and/or preterm birth  
255 (Govarts et al., 2012, Guo, Jin, Cheng et al., 2014, Lenters, Portengen, Rignell-Hydbom et al.,  
256 2016, de Cock, de Boer, Lamoree et al., 2014, Vafeiadi, Vrijheid, Fthenou et al., 2014). Both  
257 of these are established risk factors for subsequent rapid growth and long-term obesity  
258 (Stettler and Iotova, 2010). While more data are needed, these studies support the conclusion  
259 that developmental exposure to DDE and perhaps some other agrochemicals might lead to  
260 obesity in humans.

261 Relatively fewer studies have examined links between prenatal DDT and DDD,  $\beta$ -HCH  
262 or HCB exposure and potential of childhood obesity. Some prospective cohort studies (Valvi  
263 et al., 2014, Valvi et al., 2012, Vafeiadi et al., 2015, Agay-Shay et al., 2015, Heggeseth et al.,  
264 2015, Smink, Ribas-Fito, Garcia et al., 2008, Warner, Ye, Harley et al., 2017, Warner,  
265 Wesselink, Harley et al., 2014) or cross-sectional studies (Xu, Yin, Tang et al., 2017) showed  
266 positive associations with obesity (Table 2). However, a few other prospective cohort studies  
267 did not identify such significant associations (Cupul-Uicab et al., 2013, Warner et al.,  
268 2013, Delvaux, Van Cauwenberghe, Den Hond et al., 2014).

#### 269 **2.4 Gender-specific effects of agrochemicals**

271 Sexually dimorphic responses are a common finding when examining EDC effects,  
272 including links to obesity (Gore et al., 2015). Currently, some prospective cohort studies  
273 (Valvi et al., 2012, Warner et al., 2017, Warner et al., 2014, Delvaux et al., 2014, Tang-  
274 Peronard, Heitmann, Andersen et al., 2014) or cross-sectional studies (Cabrera-Rodriguez,  
275 Luzardo, Almeida-Gonzalez et al., 2019) showed the gender-specific effects of  
276 agrochemicals on childhood obesity (see ~~The results about the reported gender-specific~~  
277 ~~effects of agrochemicals are noted in~~ Table 2). For example, Warner et al. showed a positive  
278 association between DDE and childhood obesity in boys but not in girls (Warner et al.,  
279 2017, Warner et al., 2014). However, some other studies showed the effects of DDE on  
280 childhood obesity existed in girls but not in boys (Delvaux et al., 2014, Tang-Peronard et al.,  
281 2014). The reason for this difference ~~warrants~~ further study. The mechanisms  
282 underlying gender-specific effects of agrochemicals also need to be studied in the future.

283 Although the use of DDT has been banned in many countries, some populations still  
284 bear significant levels of DDT and DDE due to the extremely long half-life of these  
285 chemicals in the environment and in the human body, bioaccumulation and via the continued  
286 use of DDT in some developing countries (Valvi et al., 2014, United Nations Environment  
287 Programme, 2010, Rogan and Chen, 2005, Bornman, Aneck Hahn, de Jager et al., 2017).  
288 Therefore, despite the ban on DDT in much (but not all) of the world, and the slow decrease  
289 in its levels in human tissues and in the environment, the obesogenic effects of such legacy  
290 pesticides in humans needs to be considered.

### 291 **3. Animal studies about and the relationship between agrochemicals and obesity**

#### 292 **3.1 Studies showing the obesogenic effects of agrochemicals in adult experimental** 293 **animals**

294 Most of the animal studies relating chemical exposures to obesity demonstrated that the  
295 exposures ~~induced~~ ~~led to~~ weight gain and changes in adiposity, increased ~~the~~ expression of  
296

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297 obesity and adipogenesis-related biomarkers and affected hormones and adipokines involved  
298 in the regulation of food intake and energy expenditure (La Merrill, Karey, Moshier et al.,  
299 2014, Angle, Do, Ponzi et al., 2013). Exposures to the agrochemicals HCB,  $\gamma\gamma$ -HCH,  
300 parathion, chlorpyrifos (CPF), mancozeb and imidacloprid led to increased body weight in  
301 rodents (Howell, Meek, Kilic et al., 2014, Peris-Sampedro, Cabre, Basaure et al., 2015, Peris-  
302 Sampedro, Basaure, Reverte et al., 2015, Basaure, Guardia-Escote, Biosca-Brull et al.,  
303 2019, Meggs and Brewer, 2007, Lassiter, Ryde, Mackillop et al., 2008, Bhaskar and Mohanty,  
304 2014) (Table 3). ~~Li et al. showed that prenatal triflumizole exposure elicited adipogenic~~  
305 ~~differentiation in mouse 3T3 L1 preadipocytes, in multipotent mesenchymal stromal stem~~  
306 ~~cells (also known as mesenchymal stem cells, MSCs) and increased white adipose depot~~  
307 ~~weight, in vivo (Li, Pham, Janesick et al., 2012). Sexually dimorphic responses have also~~  
308 ~~been reported in most animal studies. For example, perinatal exposure (gestational day 11.5~~  
309 ~~through postnatal day 5) to DDT caused a transient increase in body fat mass in young female,~~  
310 ~~but not in male mice (La Merrill et al., 2014). In contrast, developmental exposure to CPF led~~  
311 ~~to weight gain in male, but not female rats (Lassiter and Brimijoin, 2008).~~ In addition to,  
312 ~~some~~ obesity-related indicators such as decreased total energy expenditure, alterations in  
313 glucose and lipid metabolism ~~have been~~ were observed after exposure to DDT and DDE (La  
314 Merrill et al., 2014, Howell et al., 2014, Ishikawa, Graham, Stanhope et al., 2015, Howell,  
315 Mulligan, Meek et al., 2015), malathion; (Kalender, Uzun, Durak et al., 2010) ~~die~~ ~~chlorvos~~  
316 ~~(Oguteu, Suludere and Kalender, 2008)~~ or CPF (Acker and Nogueira, 2012, Uchendu, Ambali,  
317 Ayo et al., 2018) (Table 3).

318 The “two-hit” hypothesis, first formulated by Knudson in 1971, suggests that most  
319 tumor suppressor genes require both alleles to be inactivated to result in a phenotypic  
320 change cancer (Knudson, 1971). Now, this “two-hit” hypothesis has been is likely to be  
321 applied adopted to explain the multifactorial nature of obesity, which may results from the  
322 combined effects of both genetic and environmental factors. A subject who is who has  
323 genetically-prone to obesity has the “first hit” (genetic susceptibility or epigenetic  
324 predisposition) intrinsically. As the external factors, some oObesogenic factors such as  
325 chemical exposures, high energy diet, low physical activity, alcohol and smoking that act as  
326 “second hit” trigger gain weight and result in obesity (Heindel et al., 2017). The obesogenic  
327 effects of some agrochemicals were only observed upon co-treatment with high-fat diet (HFD)  
328 or were exacerbated by HFD, indicating that a second hit was needed to elicit obesity. It was  
329 reported that low doses of orally administrated permethrin (Xiao, Sun, Kim et al., 2018) or  
330 imidacloprid (Sun, Xiao, Kim et al., 2016, Sun, Qi, Xiao et al., 2017) potentiated weight gain  
331 in male mice only when a HFD was provided. HFD-fed rats exposed to CPF exhibited a pro-  
332 obesity phenotype compared with controls (Fang, Li, Zhang et al., 2018). Chronic  
333 administration of atrazine increased body weight without changing food intake or physical  
334 activity levels, and feeding a HFD further exacerbated obesity (Lim, Ahn, Song et al., 2009).

### 335 336 3.2 Animal studies showing the development and transgenerational obesogenic 337 effects of agrochemicals

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

346 Transgenerational obesogenic effects of agrochemicals have been reported. Two studies  
347 established links between DDT exposure in pregnant F0 rat dams and increased obesity rates  
348 in subsequent generations. Male and female offspring from the F3 generation and male  
349 offspring from the F4 generation in the DDT lineage had an increased prevalence of obesity  
350 compared with controls (King, McBirney, Beck et al., 2019, Skinner, Manikkam, Tracey et al.,  
351 2013). Two other studies showed that parental exposure to glyphosate or vinclozolin was  
352 linked to increased obesity rates in the F2 and F3 offspring (Kubsad, Nilsson, King et al.,  
353 2019, Nilsson, King, McBirney et al., 2018). Overall, current data support the notion that  
354 exposure to multiple types of agrochemicals can play a role in obesity. More evidence from  
355 in vivo studies will be required to further establish the links between agrochemicals and  
356 obesity.

## 359 4. Potential mechanisms through which 360 agrochemicals induce obesity

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### 362 4.1 Agrochemicals might promote the commitment phase of adipogenesis

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

374 Adipogenesis occurs in cells derived from the embryonic mesoderm. Multipotent  
375 mesenchymal stromal stem cells, also known as mesenchymal stem cells (MSCs) give rise to  
376 adipocytes, which involves determination (MSCs commit irreversibly to the adipocyte  
377 lineage) and terminal differentiation (preadipocytes differentiate into mature fat cells) (Rosen  
378 and MacDougald, 2006). ~~MSCs can differentiate into adipocytes, chondrocytes and~~  
379 ~~osteoblasts (among other cell types) in response to tissue specific signals and are thought to~~  
380 ~~renew these cells in adults (da Silva Meirelles, Chagastelles and Nardi, 2006). Like most~~  
381 ~~differentiation events, adipogenesis involves determination and terminal differentiation.~~  
382 ~~Determination occurs when MSCs commit irreversibly to the adipocyte lineage, lose their~~  
383 ~~potential to differentiate into other types of cells and become preadipocytes (Park, Halperin~~  
384 ~~and Tontonoz, 2008, Rosen and Spiegelman, 2014, Tontonoz and Spiegelman, 2008).~~  
385 ~~Terminal differentiation occurs when preadipocytes undergo growth arrest and subsequent~~  
386 ~~differentiate into mature fat cells (Park et al., 2008, Rosen and Spiegelman, 2014, Tontonoz~~  
387 ~~and Spiegelman, 2008).~~ The current consensus is that white adipocyte numbers are set by the  
388 end of childhood and that any factors that increase adipocyte numbers in early life lead to a  
389 life-long increase in white adipocyte number (Spalding et al., 2008). While it is controversial  
390 whether having more white adipocytes leads to obesity, obese people definitely have more  
391 white adipocytes than do those of normal weight (Spalding et al., 2008). One possibility is  
392 that obesogen exposure early in life ~~the~~ alters the fate of MSCs, leading to more white

393 adipocytes in adulthood (Janesick and Blumberg, 2011, Chamorro-Garcia, Sahu, Abbey et al.,  
394 2013). The inference is that obese individuals may have a pool of MSCs that is intrinsically  
395 biased toward the adipocyte lineage (Kirchner, Kieu, Chow et al., 2010). Therefore, early life  
396 events, including obesogen exposure, that alter the fate of MSCs could predispose the  
397 exposed individual to increased numbers of white adipocytes and consequently obesity,  
398 particularly in combination with a Western Dietary pattern (Janesick and Blumberg, 2016).

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

409 In vitro and in vivo studies have demonstrated that ~~tributyltin (TBT)~~ promotes adipocyte  
410 differentiation and obesity by activating peroxisome-proliferator activated receptor  $\gamma$  (PPAR $\gamma$ )  
411 and its heterodimeric partner, retinoid X receptor  $\alpha$  (RXR $\alpha$ ). TBT can bind to and activate  
412 both receptors, but it appears to mediate its effects on adipocyte differentiation via PPAR $\gamma$   
413 (Kirchner et al., 2010, Li, Ycaza and Blumberg, 2011). In contrast, activation of RXR is  
414 required to commit mouse MSCs to the adipocyte lineage (Shoucri, Martinez, Abreo et al.,  
415 2017). TBT and chemicals that activate RXR (retinoids) commit MSCs to the adipocyte  
416 lineage by inhibiting the expression and function of enzymes that deposit repressive histone 3  
417 lysine 27 trimethyl (H3K27<sup>me3</sup>) marks. Exposure of MSCs to TBT or retinoids led to  
418 genome-wide decreases in H3K27<sup>me3</sup> at the promoters of genes required for adipogenic  
419 commitment. Currently, there is a relative paucity of data regarding how other agrochemicals  
420 might influence MSC fate. Triflumizole was found to induce adipogenic differentiation in  
421 human and mouse MSCs through a PPAR $\gamma$ -dependent mechanism and to promote fat  
422 accumulation, in vivo (Li et al., 2012). Taken together, the current data suggest that exposure  
423 to agrochemicals might promote ~~adipogenesis~~ **adipogenesis** by increasing commitment of  
424 MSCs to the adipocyte lineage. Therefore, assessing the capability of an agrochemical to  
425 induce adipogenic commitment of MSCs together with its ability to promote terminal  
426 adipocyte differentiation, and the mechanisms through which these processes occur will be  
427 valuable in identifying additional agrochemical obesogens.

#### 430 4.2 Agrochemicals might induce adipocyte differentiation

431  
432 After MSCs are committed to the adipocyte lineage, these preadipocytes can be induced  
433 to differentiate into mature adipocytes. ~~Usually, the process of adipocyte differentiation is~~  
434 ~~influenced by the direct chemical exposure of chemicals.~~ In contrast to the relative paucity of  
435 data regarding the effect of agrochemicals on the commitment of MSCs to preadipocytes,  
436 there is much known about the effects of these chemicals on ~~the process of~~ adipocyte  
437 differentiation. Murine pre-adipocyte cell lines such as 3T3-L1 cells are commonly used as  
438 an in vitro cell model to test the capacity of chemicals to induce adipogenesis. Such  
439 experiments have provided strong support for the notion that agrochemicals could promote  
440 ~~the process of~~ adipocyte differentiation. Treatment ~~of with~~ DDT and DDE resulted in  
441 increased lipid accumulation accompanied by up-regulation of multiple key regulator of  
442 adipocyte differentiation, such as CCAAT/enhancer-binding protein  $\alpha$  and PPAR $\gamma$  (Kim, Sun,



443 Yue et al., 2016). Using the 3T3-L1 cell model, other studies have identified agrochemicals  
444 | ~~including~~ quinalofop-p-ethyl (QpE) (Biserni, Mesnage, Ferro et al., 2019), diazinon  
445 (Smith, Yu and Yin, 2018), pyraclostrobin (Luz, Kassotis, Stapleton et al., 2018), DDE  
446 (Mangum, Howell and Chambers, 2015), imidacloprid (Park, Kim, Kim et al., 2013), fipronil  
447 (Sun, Qi, Yang et al., 2016), permethrin (Xiao, Qi, Clark et al., 2017), zoxamide,  
448 spirodiclofen, quinoxifen, tebuirimfos, forchlorfenuron, flusilazole, acetamiprid and  
449 pymetrozine (Janesick et al., 2016) as having the ability to promote adipocyte differentiation.

450 | Activation of PPAR $\gamma$ /RXR $\alpha$  heterodimers plays a key role in promoting adipocyte  
451 differentiation of 3T3-L1 adipocytes by regulating the expression of genes involved in lipid  
452 droplet formation, glucose uptake, and fatty acid synthesis (Janesick and Blumberg,  
453 2011, Tontonoz and Spiegelman, 2008). QpE might promote adipogenesis by activating  
454 PPAR $\gamma$  as demonstrated by RNAseq analysis of cells and PPAR $\gamma$  reporter gene assay (Biserni  
455 et al., 2019). Triflumizole was found to induce adipogenic differentiation in 3T3-L1 cells  
456 through a PPAR $\gamma$ -dependent mechanism (Li et al., 2012). Zoxamide, triflumizole,  
457 spirodiclofen, and quinoxifen induced adipogenesis in 3T3-L1 cells through PPAR $\gamma$ /RXR $\alpha$   
458 heterodimers by activating PPAR $\gamma$ , while fludioxonil activated RXR $\alpha$  (Janesick et al., 2016).

459 | However, the adipogenic effects of other agrochemicals on 3T3-L1 cells appears to be  
460 independent of PPAR $\gamma$  activation. For example, flusilazole, forchlorfenuron, acetamiprid and  
461 pymetrozine induced adipogenesis in 3T3-L1 cells, but did not activate PPAR $\gamma$  or RXR $\alpha$   
462 (Janesick et al., 2016). Pyraclostrobin was found to induce mitochondrial dysfunction which  
463 in-turn inhibited lipid homeostasis, resulting in triglyceride accumulation (Luz et al., 2018).  
464 Permethrin might potentiate adipogenesis in 3T3-L1 adipocytes via altering intracellular  
465 calcium levels and through endoplasmic reticulum stress-mediated mechanisms (Xiao et al.,  
466 2017), although, it also activates PPAR $\alpha$  (Fujino, Watanabe, Sanoh et al., 2019). The related  
467 chemical, deltamethrin may also activate an endoplasmic reticulum stress-mediated pathway  
468 in 3T3-L1 adipocytes (Yuan, Lin, Xu et al., 2019). An AMP-activated protein kinase  
469 AMPK $\alpha$ -mediated pathway was found to play a role in the induction of adipogenesis in 3T3-  
470 | L1 preadipocytes by agrochemicals such as DDT and DDE<sub>7</sub> (Kim et al., 2016), imidacloprid  
471 (Sun et al., 2017), deltamethrin (Yuan et al., 2019, Shen, Hsieh, Yue et al., 2017), and fipronil  
472 (Sun et al., 2016). Endrin and tolylfluanid promoted adipogenesis in 3T3-L1 cells via  
473 glucocorticoid receptor activation (Sargis, Johnson, Choudhury et al., 2010). In contrast,  
474 another study showed that endrin inhibited adipogenesis in 3T3-L1 cells (Moreno-Aliaga and  
475 Matsumura, 1999).

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

486 |

487 |

#### 488 | **4.3 Agrochemicals might exert obesogenic effects** Effects mediated by sex steroid 489 | **hormone dysregulation**

490 | Sex steroid hormones such as estrogens and androgens appear to play important roles in  
491 | adipose tissue development during early development or ~~at-in~~ adulthood (Cooke and Naaz,  
492 | 2004). Estrogens play a pivotal role in regulating energy homeostasis, especially in female

493 mammals, either by acting directly on the brain or through activation of ERs in adipocytes  
494 (Mauvais-Jarvis, Clegg and Hevener, 2013). Imbalances in the sex steroid levels can lead to  
495 dyslipidemias and obesity. For example, weight gain was observed following androgen  
496 deprivation therapy for prostate cancer (Braunstein, Chen, Loffredo et al., 2014) or polycystic  
497 ovary syndrome (Stanley and Misra, 2008). Obesogenic effects have been observed for  
498 xenoestrogenic compounds such as diethylstilbestrol (DES) (Newbold, Padilla-Banks, Snyder  
499 et al., 2007) and bisphenol A (BPA) (Rubin, Murray, Damassa et al., 2001), suggesting that  
500 dysregulated signaling through sex steroid receptors can produce pro-adipogenic effects. This  
501 might also influence the sexually dimorphic effects of some chemicals on the incidence and  
502 health consequences of obesity observed in humans (Palmer and Clegg, 2015). Therefore,  
503 chemicals that can disrupt the regulation of estrogen and androgen signaling, ~~either~~ by  
504 changing hormone levels or by directly interacting with the cognate nuclear receptors may  
505 contribute to disturbances in the regulation of adipose tissue formation and maintenance.  
506 [Both direct and developmental exposure of chemicals might disrupt the regulation of sex  
507 hormones signaling.](#)

508 Many in vivo experimental animal studies examined estrogenic or anti-androgenic  
509 effects of agrochemicals. By using the rat uterotrophic (estrogen) and Hershberger (anti-  
510 androgen) assays, it was found that the insecticide permethrin might have estrogenic effects  
511 on female rats, but anti-androgenic effects on male rats (Kim, Lee, Lim et al., 2005). In vivo  
512 anti-androgenic effects have also been reported in response to agrochemicals including  
513 linuron (Wolf, Lambright, Mann et al., 1999, Lambright, Ostby, Bobseine et al., 2000),  
514 prochloraz (Vinggaard, Christiansen, Laier et al., 2005), procymidone (Ostby, Kelce,  
515 Lambright et al., 1999), tebuconazole (Taxvig, Hass, Axelstad et al., 2007), vinclozolin  
516 (Anway, Memon, Uzumcu et al., 2006, Uzumcu, Suzuki and Skinner, 2004), DDE (Wolf et  
517 al., 1999), endosulfan (Sinha, Adhikari and D, 2001), dimethoate (Verma and Mohanty, 2009)  
518 and deltamethrin (Andrade, Araujo, Santana et al., 2002). After reviewing the animal and  
519 epidemiologic data from previous studies, Li et al. suggested that chlorpyrifos induces  
520 metabolic disruption by altering levels of reproductive hormones (Li, Ren, Li et al., 2019).

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

536 Many studies have investigated the activity of agrochemicals on ER and AR using  
537 reporter gene assays. DDE was demonstrated to be a potent AR antagonist (Kelce, Stone,  
538 Laws et al., 1995). Kjeldsen et al. (Kjeldsen, Ghisari and Bonefeld-Jorgensen, 2013)  
539 investigated the effects of five agrochemicals (terbuthylazine, propiconazole, prothioconazole,  
540 cypermethrin and malathion) on ER and AR transactivation using luciferase reporter gene  
541 assays. The results showed that these five pesticides weakly activated ER and that three  
542 pesticides (bitertanol, propiconazole and mancozeb) antagonized AR activity in a

543 concentration-dependent manner. Kojima et al, (Kojima, Katsura, Takeuchi et al., 2004)  
544 screened 200 agrochemicals and reported that 66 were anti-androgenic, whereas only 29 were  
545 estrogenic. Numerous in vitro studies based on reporter gene assays demonstrated estrogenic  
546 and anti-androgenic effect of agrochemicals (Kitamura, Suzuki, Ohta et al., 2003, Andersen,  
547 Vinggaard, Rasmussen et al., 2002, Bauer, Bitsch, Brunn et al., 2002, Okubo, Yokoyama,  
548 Kano et al., 2004, Orton, Lutz, Kloas et al., 2009, Vinggaard, Niemela, Wedebye et al.,  
549 2008, Sun, Xu, Xu et al., 2007, Zhang, Zhu, Zheng et al., 2008, Robitaille, Rivest and  
550 Sanderson, 2015, Xu, Liu, Ren et al., 2008, Li, Li, Ma et al., 2008, Martin, Dix, Judson et al.,  
551 2010, Knudsen, Houck, Sipes et al., 2011). ~~(Sun et al., 2007, Zhang et al., 2008, Robitaille et~~  
552 ~~al., 2015, Xu et al., 2008, Li et al., 2008, Martin et al., 2010, Knudsen et al., 2011).~~ In addition  
553 to the canonical ERs, binding of DDT and DDE to the seven-transmembrane estrogen  
554 receptor, GPR30, which activates alternative estrogen signaling was demonstrated (Thomas  
555 and Dong, 2006). Molecular dynamic simulations showed that estrogen-related receptor  $\gamma$ ,  
556 which might affect estrogen signaling indirectly, could also be a potential target of DDT and  
557 DDE (Zhuang, Zhang, Wen et al., 2012). Estrogenic or anti-androgenic effects of  
558 agrochemicals might involve more than one mechanism; thus, their effects might be mediated  
559 through multiple cellular pathways.

560 Typically, humans are only rarely exposed to a single agrochemical. Rather they are  
561 simultaneously exposed to multiple xenobiotic chemicals, including agrochemicals and  
562 supposedly inert carriers. It is probable that these different agrochemicals may act in  
563 combination through additive, synergistic, or antagonistic mechanisms, which may influence  
564 the doses of such ligands required to induce adipogenesis. Notably, additive and synergistic  
565 anti-androgenic activities of agrochemical mixtures have been observed (Kjeldsen et al.,  
566 2013, Ma, Chen, Yang et al., 2019, Orton, Rosivatz, Scholze et al., 2012, Kolle, Melching-  
567 Kollmuss, Krennrich et al., 2011, Birkhoj, Nellemann, Jarfelt et al., 2004). Christen et al.,  
568 studied additive and synergistic anti-androgenic activities of binary mixtures of five anti-  
569 androgenic fungicides and found that about half of the tested mixtures produced additive  
570 effects and half synergistic effects (Christen, Crettaz and Fent, 2014). These observed  
571 additive and synergistic effects emphasize the importance of considering the combined  
572 actions of these chemicals. Although the underlying molecular mechanisms remain to be  
573 fully understood, these studies suggested the agrochemicals might induce obesity by  
574 disturbing normal sex hormone signaling.

#### 575 576 577 **4.4 Agrochemicals might exert obesogenic effects by ~~Affect~~-affecting metabolic** 578 **homeostasis mediated by ~~through~~-metabolic sensors, the PPARs**

579 Obesogens might induce obesity by perturbing metabolic homeostasis resulting in  
580 unbalanced energy expenditure. Many nuclear receptors respond to specific hormones such as  
581 thyroid hormone, mineralocorticoids, glucocorticoids, retinoic acid, sex steroids and  
582 lipophilic endogenous substances. These are involved in various physiological and  
583 pathological processes in the regulation of metabolic homeostasis. (Mangelsdorf, Thummel,  
584 Beato et al., 1995). Among these, the ~~peroxisome proliferator-activated receptor (PPAR)~~  
585 subfamily, comprising PPAR $\alpha$ , PPAR $\beta/\delta$  and PPAR $\gamma$  are key players in adipogenesis and  
586 lipid metabolism (Feige, Gelman, Michalik et al., 2006). After forming heterodimers with  
587 ~~retinoid X receptors (RXR)~~, PPARs regulate the transcription of genes involved in the  
588 regulation of adipogenesis (adipocyte proliferation and differentiation), intracellular lipid  
589 metabolism and storage, glucose homeostasis and insulin responsiveness (Wang, 2010). The  
590 three PPAR subtypes act as ligand sensors for a variety of lipophilic hormones, dietary fatty  
591 acids and their metabolites to regulate lipid homeostasis (Bensinger and Tontonoz, 2008).  
592 They work together to control almost every aspect of fatty acid metabolism. Many



593 pharmaceutical drugs and environmental chemicals target PPARs, enabling them to affect  
594 PPAR signaling pathways involved in regulating metabolic balance (Lau, Abbott, Corton et  
595 al., 2010). Usually, the chemical influences on metabolic homeostasis acting through PPARs  
596 are due to the direct chemical exposure of chemicals.

597 Several in vivo studies revealed changes in the expression levels of genes encoding  
598 PPARs and PPAR-regulated genes after agrochemical exposure. The herbicide dicamba (2-  
599 methoxy-3,6-dichlorobenzoic acid) caused a significant increase in peroxisomal beta-  
600 oxidation activity and changed the expression of a variety of PPAR regulated enzymes in rat  
601 livers, suggesting that dicamba acts as a peroxisome proliferator in rats (Espandiari, Thomas,  
602 Glauert et al., 1995). The herbicide diclofop was also shown to be a rodent peroxisome  
603 proliferator (Palut, Ludwicki, Kostka et al., 2001). Atrazine induced a near-significant  
604 increase in PPAR $\beta$  mRNA in *Xenopus laevis* tadpoles (Zaya, Amini, Whitaker et al., 2011),  
605 and diclofop-methyl and pyrethrins changed the expression of PPAR $\alpha$ -inducible cytochrome  
606 P450 genes in mice (Takeuchi, Matsuda, Kobayashi et al., 2006). 2,4-dichlorophenoxyacetic  
607 acid increased expression of PPAR $\delta$  in HepG2 cells (Sun, Shao, Liu et al., 2018). DDT  
608 enhanced expression of PPAR $\gamma$  mRNA in human MSCs (Strong et al., 2015). Therefore,  
609 expression of PPAR genes themselves may be potential agrochemical targets.

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

629 The PPARs have different tissue distributions and biological functions. PPAR $\alpha$  is  
630 expressed predominantly in liver, kidney, heart, and muscle, and plays a major role in fatty  
631 acid oxidation. Activation of PPAR $\alpha$  leads to peroxisome proliferation in rodents and  
632 stimulates  $\beta$ -oxidation of fatty acids (Ferre, 2004). PPAR $\delta$  is ubiquitously expressed and can  
633 also promote fatty acid oxidation (Barish, Narkar and Evans, 2006). Consequently,  
634 xenobiotics that target PPAR $\alpha$  and  $\delta$  typically act as hypolipidemic agents. In contrast,  
635 PPAR $\gamma$  is primarily expressed in adipose tissue and is considered to be the master regulator  
636 of adipogenesis (Tontonoz and Spiegelman, 2008). A large body of work has clearly  
637 established that PPAR $\gamma$  plays key roles in diverse aspects of adipocyte biology including lipid  
638 biosynthesis and lipid storage (Evans, Barish and Wang, 2004). Activation of PPAR $\gamma$  is  
639 essential for the differentiation of resident preadipocytes and the conversion of mesenchymal  
640 progenitors to preadipocytes in white adipose tissues (Takada, Kouzmenko and Kato, 2009).  
641 Pharmaceutical drugs such as anti-diabetic thiazolidinediones as well as environmental  
642 chemicals such as the organotin compounds ~~tributyltin (TBT)~~ and triphenyltin (TPT) (Grun,

643 Watanabe, Zamanian et al., 2006, Kanayama, Kobayashi, Mamiya et al., 2005) act as  
644 | obesogens by stimulating adipogenesis in a PPAR $\gamma$ -dependent manner. Since many  
645 agrochemicals have already been found to bind and activate PPAR $\gamma$ , it will be worthwhile to  
646 test all widely used agrochemicals for their ability to target PPAR $\gamma$  and act as bona fide  
647 | obesogens, in vivo.

648  
649

#### 650 4.5 Agrochemicals might exert obesogenic effects by affecting metabolic homeostasis 651 through disturbing the thyroid hormone pathway~~Affect metabolic homeostasis by~~ 652 ~~disturbing the thyroid hormone pathway~~

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

677 A broad range of human and animal studies documented that agrochemicals could  
678 interfere with the normal function of the thyroid endocrine system (Requena, Lopez-Villen,  
679 Hernandez et al., 2019). An association between the use of organochlorine pesticides and risk  
680 of hypothyroidism and hyperthyroidism has been established among women in Iowa and  
681 North Carolina enrolled in the Agricultural Health Study in 1993-1997 (Goldner, Sandler, Yu  
682 et al., 2010). Animal studies indicated that in utero exposure to pesticides such as DDT, DDE  
683 and chlorpyrifos-methyl may affect thyroid hormone status in offspring (Luo, Pu, Tian et al.,  
684 2017, Jeong, Kim, Kang et al., 2006). Mechanistic studies also supported the disruptive  
685 effects of agrochemicals on thyroid function. The hypothalamus-pituitary-thyroid (HPT) axis  
686 determines systemic thyroid hormone levels (Ortiga-Carvalho, Chiamolera, Pazos-Moura et  
687 al., 2016). Acetochlor was found to alter the mRNA expression of HPT axis-related genes  
688 | and changed circulating thyroid hormone levels in zebrafish larvae (Yang, Hu, Li et al.,  
689 2016, Xu, Sun, Niu et al., 2019). Most activity of T3 is mediated by its nuclear receptors,  
690 thyroid hormone receptor alpha (TR $\alpha$ ) and beta (TR $\beta$ ) which require heterodimerization with  
691 RXRs to bind DNA and regulate the expression of target genes (Yen, 2001). A GH3-  
692 luciferase reporter gene assay was used to investigate the activities of 21 pesticides towards

693 TRs. Among the tested 5 of 21 pesticides, 5 of them (procymidone, imidacloprid, atrazine,  
694 fluroxypyr, mancozeb) had agonistic effects; (procymidone, imidacloprid, atrazine, fluroxypyr,  
695 mancozeb), whereas 11 pesticides (butachlor, beta-cypermethrin, fenobucarb, cyhalothrin, theta-  
696 cypermethrin, bifenthrin, carbaryl, pymetrozine, pendimethalin, metolcarb, and acetochlor)  
697 inhibited luciferase activity induced by T3 to varying degrees, demonstrating their  
698 antagonistic ~~activity-activities~~ (Xiang, Han, Yao et al., 2017). Xiang et al. also found that 13  
699 pesticides ~~bound-were-shown-to-bind~~ directly to TR as measured by surface plasmon  
700 resonance (SPR) biosensors (Xiang et al., 2017). Co-exposure of mice to the dithiocarbamate  
701 fungicide, mancozeb and the neonicotinoid insecticide, imidacloprid during lactation  
702 decreased plasma T3 levels and molecular dynamics simulations predicted that both of these  
703 chemicals might compete with T3 for binding to TRs (Bhaskar and Mohanty, 2014). Taken  
704 together, these studies established strong links between agrochemicals and disruption of  
705 thyroid signaling; however, possible obesogenic effects through this mechanism require  
706 further investigation.

#### 708 **4.6 Agrochemicals might exert obesogenic effects by By-affecting the gut microbiota**

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

726 Emerging evidence supports the involvement of the gut microbiota in agrochemical-  
727 induced obesity. In a human cross-sectional study, levels of Methanobacteriales in the gut  
728 were associated with higher body weight and waist circumference and it was already known  
729 that these bacteria are linked to obesity ~~(Lee, Lee, Lee et al., 2011)~~. (Lee, Lee, Lee et al.,  
730 2011). Serum organochlorine pesticides (cis-nonachlor, oxychlorane and trans-nonachlor)  
731 levels were also positively correlated with levels of Methanobacteriales. This supports a  
732 possible link among organochlorine pesticide levels, gut Methanobacteriales levels, and  
733 obesity in the general population. Some animal studies also established potentially causal  
734 links among agrochemical levels, composition of the gut microbiota and obesity.  
735 Chlorpyrifos disrupted gut microbial homeostasis and increased lipopolysaccharide entry into  
736 the body leading to low-grade systemic inflammation (Liang, Zhan, Liu et al., 2019). Mice  
737 given this chlorpyrifos-altered microbiota gained more white adipose tissue and had lower  
738 insulin sensitivity, supporting a link between the microbiota and obesity-related diseases  
739 (Liang et al., 2019). Chlorpyrifos exposure also significantly altered the composition of  
740 bacteria previously associated with obese and diabetic phenotypes in gut microbiome of rats  
741 (Fang et al., 2018). Chlorpyrifos exposure caused hepatic lipid metabolism disorders that  
742 were associated with gut oxidative stress and microbiota dysbiosis in zebrafish (Wang, Shen,

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

751  
752

#### 753 **4.7 Epigenetic programming and transgenerational effects of agrochemicals**

754 Previous studies have demonstrated that genetic differences such as single  
755 polynucleotide polymorphisms in a variety of genes may explain why some people are more  
756 likely to become obese (Locke, Kahali, Berndt et al., 2015). However, it is inconceivable that  
757 the rapid increase in the rate of obesity over the past decades in the U.S. and other countries  
758 is due to ~~the~~ changes in human genetics. Moreover, it was estimated that the possible  
759 spectrum of genetic changes might explain only 20% of the incidence of obesity (Locke et al.,  
760 2015). This means that environmental and lifestyle factors ~~may-must~~ play key roles in the  
761 obesity pandemic. Epigenetic modification refers to heritable changes that modulate how the  
762 genome is expressed, but that do not involve altering the underlying DNA sequence.  
763 Epigenetic changes are natural occurrences but these can also be influenced by dietary and  
764 environmental factors (Skinner, 2015). Epigenetic modifications include methylation of  
765 cytosine residues on DNA, post-translational modification of histones, histone retention,  
766 chromatin remodeling and altered non-coding RNA expression (Whitelaw and Whitelaw,  
767 2008). Epigenetic processes can affect patterns of gene expression by directly influencing  
768 DNA accessibility and/or by regulating chromatin compaction (Nilsson, Sadler-Riggelman  
769 and Skinner, 2018).

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

779 Environmental factor-induced transgenerational inheritance of pathologies and  
780 phenotypic variations have been found in different species (Nilsson et al., 2018). Many  
781 studies showed that EDC exposure can result in increased disease susceptibility later in life  
782 and in subsequent generations (Anway and Skinner, 2006, Uzumcu, Zama and Oruc,  
783 2012, Skinner, Manikkam and Guerrero-Bosagna, 2011, Rissman and Adli, 2014, Ho, Johnson,  
784 Tarapore et al., 2012, Skinner and Anway, 2005, Guerrero-Bosagna, Weeks and Skinner,  
785 2014). A number of studies revealed that pesticides such as vinclozolin (Nilsson et al.,  
786 2018, Beck, Sadler-Riggelman and Skinner, 2017, Anway, Cupp, Uzumcu et al., 2005),  
787 permethrin, methoxychlor (Manikkam, Haque, Guerrero-Bosagna et al., 2014), DDT  
788 (Skinner, Ben Maamar, Sadler-Riggelman et al., 2018, Ben Maamar, Nilsson, Sadler-  
789 Riggelman et al., 2019), atrazine (McBirney, King, Pappalardo et al., 2017, Hao, Gely-Pernot,  
790 Kervarrec et al., 2016) and the insect repellent diethyltoluamide (Manikkam, Tracey,  
791 Guerrero-Bosagna et al., 2012) promoted transgenerational inheritance of disease  
792 susceptibility and sperm epimutations. Transgenerational disease pathologies related to

793 pesticide exposure included effects on the testis (King et al., 2019, Skinner et al., 2013, Anway,  
794 Leathers and Skinner, 2006), prostate (King et al., 2019, Anway et al., 2006), ovaries (King et  
795 al., 2019, Skinner et al., 2013, Manikkam et al., 2014, Manikkam et al., 2012), kidneys (King et  
796 al., 2019, Skinner et al., 2013, Manikkam et al., 2014, Anway et al., 2006), immune system  
797 (Anway et al., 2006), behavior (McBirney et al., 2017) and tumor development (Anway et al.,  
798 2006).

799 Exposure to obesogenic chemicals during critical periods of development might alter  
800 epigenetic programming processes that predispose a stem cell or progenitor cell toward a  
801 particular lineage such as the adipocyte. Epigenetic changes caused by exposures to EDCs  
802 such as TBT and DES may lead to obesity in subsequent generations (Chamorro-Garcia,  
803 Diaz-Castillo, Shoucri et al., 2017, Chamorro-Garcia and Blumberg, 2014, Stel and Legler,  
804 2015, van Dijk, Tellam, Morrison et al., 2015). Skinner and colleagues showed that ancestral  
805 exposures of F0 rat dams to DDT led to a striking increase in the incidence of obesity in both  
806 F3 males and females (King et al., 2019, Skinner et al., 2013). In a similarly designed  
807 transgenerational experiment, they found that F0 exposure to glyphosate led to increased  
808 obesity rates in subsequent generations (Kubsad et al., 2019). Exposure to vinclozolin  
809 induced epigenetic transgenerational inheritance of increased obesity rates in F3 generation  
810 female rats (Nilsson et al., 2018). However, the molecular mechanisms underlying how these  
811 chemicals induce epigenetic changes and how these changes are transmitted to future  
812 generations to produce obesity and other adverse outcomes remains unclear. Many different  
813 mechanisms have been proposed for how epigenetic changes can affect subsequent disease  
814 outcomes including modulating methyl donor availability and altering the expression of  
815 enzymes that act as epigenetic readers, writers and erasers (Walker, 2016). However, at the  
816 time of this writing no convincing evidence exists that precisely establishes the molecular  
817 mechanisms through which epigenetic transgenerational inheritance [of any phenotype,](#)  
818 [including obesity](#) occurs.

819  
820

## 821 **5. Conclusions and future directions**

822 There is compelling evidence to suggest that [widespread exposure to](#) agrochemicals [are](#)  
823 [is](#) an important factor contributing to the [human](#) obesity pandemic [in the human population.](#)  
824 For example, DDE has been found to be a probable human obesogen based on multiple  
825 studies in vitro and in vivo using animal models and on longitudinal studies in humans, with  
826 a significant annual cost to the European Union (Legler, Fletcher, Govarts et al., 2015). DDE  
827 is thought to work as an anti-androgen and there are many other agrochemicals that exhibit  
828 anti-androgenic effects in vitro and in vivo (Orton et al., 2012, Orton, Rosivatz, Scholze et al.,  
829 2011). Therefore, it will be very important to establish the molecular mechanisms through  
830 which DDT/DDE act to influence obesity and to conduct the same sorts of cell-based,  
831 animal-based and longitudinal cohort studies in humans with other agrochemicals. We need  
832 to understand both the effects of perinatal exposure to obesogenic agrochemicals as well as  
833 the effects of exposures during other times across the life course.

834 There are many possible modes of action for how agrochemicals can promote obesity as  
835 discussed above. What is missing is a systematic effort to understand which of the many  
836 agrochemicals in current use can lead to adverse health outcomes, including obesity and  
837 through which molecular pathways they act to exert these effects. Current practice in  
838 toxicological research is becoming focused on “adverse outcome pathways” and “molecular  
839 initiating events”. These are useful paradigms for simple systems, but it is abundantly clear  
840 that agrochemicals can act through multiple pathways. These cellular signaling pathways  
841 interact with each other in complex ways. It is likely that individual chemicals act at multiple  
842 levels on metabolic homeostasis. Moreover, humans are typically exposed to poorly defined

843 mixtures of chemicals that may interact in combinatorial ways that can be additive or  
844 inhibitory. Typical agrochemicals are also applied as mixtures that include so-called “inert  
845 ingredients” that may not be inert and whose composition and levels are not required to be  
846 reported. Much remains undiscovered about the possible molecular mechanisms for  
847 agrochemicals and their relationship with the obesity epidemic.

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



854 **Acknowledgements**

855 Supported by grants from the NIH (ES023316) to BB, by the EU Horizon 2020 research and  
856 innovation program under grant agreement GOLIATH [825489], and by ~~the~~a grant from  
857 China Scholarship Council- to XR.  
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**Table 1. Literature summarizing Summary of the literatures about the associations between agrochemicals and adult obesity.**

<u>References</u>	<u>Names</u>	<u>Exposure levels (serum level)</u>	<u>Population (number of subjects)</u>	<u>Outcomes</u>
<u>(Dusanov et al. 2018)</u>	<u>HCB;</u> <u>β-HCH;</u> <u>p,p'-DDT;</u> <u>DDE</u>	<u>HCB:</u> <u>66.8-101.2 pg/mL;</u> <u>β-HCH:</u> <u>22.9-47.6 pg/mL;</u> <u>p,p'-DDT:</u> <u>11.3-20 pg/mL;</u> <u>DDE:</u> <u>315-679 pg/mL;</u>	<u>Norway, adult,</u> <u>(N=431)</u>	<u>Increased odds of metabolic syndrome.</u>
<u>(La Merrill et al. 2018)</u>	<u>DDE</u>	<u>170-570</u> <u>ng/g lipid</u>	<u>Sweden, 70 years</u> <u>old (N = 988)</u>	<u>Increased BMI.</u>
<u>(Jaacks et al. 2016)</u>	<u>p,p'-DDT</u>	<u>Mean level:</u> <u>0.0158 ng/mL</u>	<u>USA, pregnant</u> <u>women, 18-40 years</u> <u>old (N=218)</u>	<u>Gestational- weight- gain.</u>
<u>(Arrebola et al. 2014)</u>	<u>HCB;</u> <u>DDE;</u> <u>β-HCH</u>	<u>Mean level:</u> <u>HCB: 32.81 ng/g</u> <u>lipid;</u> <u>β-HCH: 19.60ng/g</u> <u>lipid;</u> <u>DDE: 183.99ng/g</u> <u>lipid;</u>	<u>Spain, adults</u> <u>(N=298)</u>	<u>Increased BMI and levels of</u> <u>total cholesterol, HDL, LDL,</u> <u>and total- serum- lipids.</u>

<a href="#">(Langer et al. 2014)</a>	<a href="#">DDE;</a> <a href="#">HCB</a>	<a href="#">DDE:</a> 54-22382 ng/g lipid; <a href="#">HCB:</a> 22-17928 ng/g lipid	<a href="#">Slovakia, adults,</a> (N=2053)	<a href="#">Increased BMI and increased levels of cholesterol and triglyceride.</a>
<a href="#">(Raafat et al. 2012)</a>	<a href="#">Malathion</a>	<a href="#">Mean level:</a> 0.0746 mg/L	<a href="#">Egypt, 39±12 years old</a> (N=98)	<a href="#">Increased waist circumference.</a>
<a href="#">(Lee et al. 2012)</a>	<a href="#">DDE</a>	<a href="#">Mean level:</a> 2654 ng/g-lipid	<a href="#">Sweden, 70 years old</a> (N=970)	<a href="#">Increased odds ratios of abdominal-obesity.</a>
<a href="#">(Lee et al. 2012)</a>	<a href="#">DDE</a>	11-23271 pg/mL	<a href="#">Sweden, 70 years old people</a> (N=970)	<a href="#">Increased existence or development of abdominal obesity.</a>
<a href="#">(Dirinck et al. 2011)</a>	<a href="#">-β-HCH</a>	1.9-200 ng/g lipid	<a href="#">Belgium, ≥18 years</a> (N=145)	<a href="#">Increased BMI, waist, fat mass percentage, and total and subcutaneous abdominal adipose tissue.</a>
<a href="#">(Bachelet et al. 2011)</a>	<a href="#">-DDE</a>	<a href="#">Mean level:</a> 85 ng/g lipid	<a href="#">French, women</a>  (N= 1055)	<a href="#">Increased BMI.</a>
<a href="#">(Ibarluzea et al. 2011)</a>	<a href="#">DDE;</a> <a href="#">β-HCH;</a> <a href="#">HCB</a>	<a href="#">Mean level:</a> <a href="#">DDE:</a> 110.0 ng/g lipid; <a href="#">β-HCH:</a> 19.1 ng/g lipid; <a href="#">HCB:</a> 33.5 ng/g lipid	<a href="#">Spain,</a>  <a href="#">pregnant women</a>  (N=1259)	<a href="#">Increased BMI.</a>
<a href="#">(Lee et al. 2011)</a>	<a href="#">HCB;</a> <a href="#">DDE;</a>	Not supplied	<a href="#">USA, adults,</a> (N=5115)	<a href="#">Increased BMI, triglycerides, HOMA-IR, lower HDL-cholesterol and triglycerides.</a>

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Table 2. Literature summarizing Summary of the literatures about the associations between agrochemicals and the development of early-onset obesity.

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<u>References</u>	<u>Names</u>	<u>The age of the children</u>	<u>Population (number of subjects)</u>	<u>Outcomes (Whether showed gender-specific effects)</u>
<u>(Cabrera-Rodriguez et al. 2019)</u>	<u>DDE</u>	<u>Infants</u>	<u>Spain (N=447)</u>	<u>Increased neonatal birth weight, with a special emphasis on girls. (Showed gender-specific effects)</u>
<u>(Warner et al. 2017)</u>	<u>DDT; DDE</u>	<u>12 years old</u>	<u>USA (N=240)</u>	<u>Increased BMI for boys but not girls. (Showed gender-specific effects)</u>
<u>(Xu et al. 2017)</u>	<u>o,p'-DDD; p,p'-DDT</u>	<u>Infants</u>	<u>Chinese (N=120)</u>	<u>Increased neonatal- birth- weight.</u>
<u>(Vafeiadi et al. 2015)</u>	<u>DDE; HCB</u>	<u>4 years old</u>	<u>Greece (N = 689).</u>	<u>Increased BMI,- obesity, abdominal-obesity.-</u>

<a href="#">(Agay-Shay et al. 2015)</a>	<a href="#">HCB;</a> <a href="#">β-HCH;</a> <a href="#">DDE</a>	<a href="#">7- years old</a>	<a href="#">Spain</a> <a href="#">(N=657)</a>	<a href="#">Increased BMI and overweight risk.</a>
<a href="#">(Heggeseth et al. 2015)</a>	<a href="#">- o,p'-</a> <a href="#">DDT;</a> <a href="#">p,p'-DDT;</a> <a href="#">DDE</a>	<a href="#">2-9 years old</a>	<a href="#">USA</a> <a href="#">(N=415)</a>	<a href="#">Increased BMI among boys but not girls.-</a> <a href="#">(Showed gender-specific effects)</a>
<a href="#">(Iszatt et al. 2015)</a>	<a href="#">DDE</a>	<a href="#">2 years old</a>	<a href="#">Norway</a> <a href="#">(N=1864)</a>	<a href="#">Increased- growth.</a>
<a href="#">(Valvi et al. 2014)</a>	<a href="#">DDE;</a> <a href="#">HCB</a>	<a href="#">6 and 14 months old</a>	<a href="#">Spain</a> <a href="#">(N=1285)</a>	<a href="#">Increased- growth and overweight.-</a>
<a href="#">(Warner et al. 2014)</a>	<a href="#">o,p'-DDT;</a> <a href="#">p,p'-DDT;</a> <a href="#">DDE</a>	<a href="#">9 years old</a>	<a href="#">USA</a> <a href="#">(N=261)</a>	<a href="#">Increased BMI and waist circumference in boys but not in girls.</a> <a href="#">(Showed gender-specific effects)</a>
<a href="#">(Delvaux et al. 2014)</a>	<a href="#">DDE</a>	<a href="#">7 to 9 years old</a>	<a href="#">Belgium</a> <a href="#">(N=114)</a>	<a href="#">- Increased- waist circumference and waist/height ratio in girls but not in boys.</a> <a href="#">(Showed gender-specific effects)</a>
<a href="#">(Tang-Peronard et al. 2014)</a>	<a href="#">DDE</a>	<a href="#">5- and- 7- years- old</a>	<a href="#">Denmark-</a> <a href="#">(N=656)</a>	<a href="#">Increased waist circumference in girls with overweight mothers but not in boys.</a> <a href="#">(Showed gender-specific effects)</a>
<a href="#">(Valvi et al. 2012)</a>	<a href="#">DDE;</a> <a href="#">DDT;</a>	<a href="#">6.5 years old</a>	<a href="#">Spain</a> <a href="#">(N=344)</a>	<a href="#">Increased overweight in boys but not in girls.</a> <a href="#">(Showed gender-specific effects)</a>
<a href="#">(Mendez et al. 2011)</a>	<a href="#">DDE</a>	<a href="#">6 and 14 months old</a>	<a href="#">Spain</a> <a href="#">(N=657)</a>	<a href="#">Increased- weight and BMI.-</a>
<a href="#">(Verhulst et al. 2009)</a>	<a href="#">DDE</a>	<a href="#">1-3- years- old</a>	<a href="#">Belgium</a> <a href="#">(N=138)</a>	<a href="#">Increased BMI.</a>
<a href="#">(Karmaus et al. 2009)</a>	<a href="#">DDE</a>	<a href="#">20-50 years old</a>	<a href="#">USA</a> <a href="#">(N=259)</a>	<a href="#">Increased weight- and BMI.-</a>
<a href="#">(Smink et al. 2008)</a>	<a href="#">HCB</a>	<a href="#">6 years old</a>	<a href="#">Spain</a> <a href="#">(N=482)</a>	<a href="#">Increase in weight and BMI.-</a>

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**Table 3. Literature sSummary of the literatures of the animal studies about the relationship between-linking agrochemicals and obesity.**

<u>Reference</u>	<u>Names</u>	<u>Animal used</u>	<u>Dose and exposure time</u>	<u>Outcomes (Whether showed gender-specific effects)</u>
<a href="#">(King et al. 2019)</a>	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.
<a href="#">(Kubsad et al. 2019)</a>	Glyphosate	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.
<a href="#">(Basaure et al. 2019)</a>	CPF	Male apoE4-mice	2 mg/kg/day; 15 days.	Increased body weight.
<a href="#">(Xiao et al. 2018)</a>	Permethrin	Male C57BL/6J mice	50, 500, and 5000 µg/kg/day; 12 weeks.	Increased body weight, fat mass, and increased TG and TC.
<a href="#">(Uchendu et al. 2018)</a>	CPF; deltamethrin	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.
<a href="#">(Fang et al. 2018)</a>	CPF	Male Wistar rats	0.3 or 3.0 mg/kg/day; 9 weeks.	Increased bodyweight.
<a href="#">(Nilsson et al. 2018)</a>	Vinclozolin	Sprague Dawley rats	100 mg/kg/day; F0 females were	F3 generation rats showed transgenerational

			administered on days 8 to 14 of gestation.	increased obesity rate in females. (Showed gender-specific effects)
(Sun et al. 2017)	Imidacloprid	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)	Imidacloprid	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)	Mancozeb; Imidacloprid	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)	Chlorpyrifos	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.
(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.	Parathion	Sprague Dawley	0.1 or 0.2 mg/kg/day;	Increased body weight

<a href="#">2008</a> )		<a href="#">neonatal rats</a>	<a href="#">postnatal days 1-4.</a>	<a href="#">and impaired fat metabolism. Females showed greater sensitivity. (Showed gender-specific effects)</a>
<a href="#">(Lassiter and Brimijoin 2008)</a>	<a href="#">CPF</a>	<a href="#">Long-Evans rats</a>	<a href="#">2.5 mg/kg/day; From gestational day 7 through the end of lactation on postnatal day 21.</a>	<a href="#">Increased body weight in males. (Showed gender-specific effects)</a>
<a href="#">(Meggs and Brewer 2007)</a>	<a href="#">CPF</a>	<a href="#">Female Long-Evans rats</a>	<a href="#">5 mg/kg/day; 4 months.</a>	<a href="#">Increased body weight.</a>

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

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**Table 4. The possible mechanisms through which agrochemicals may lead to obesity and example chemicals providing evidence to support these mechanisms.:**

<u>Possible mechanisms</u>	<u>Agrochemicals provide evidence for the mechanism</u>
<u>Promote the commitment phase of adipogenesis</u>	<u>DDT, chlorpyrifos, carbofuran, zoxamide, spirodiclofen, fludioxonil and quinoxyfen, triflumizole</u>
<u>Induce adipocyte differentiation</u>	<u>DDT, DDE, quizalofop-p-ethyl, diazinon, pyraclostrobin, imidacloprid, fipronil, permethrin, zoxamide, spirodiclofen, quinoxyfen, tebuirimfos, forchlorfenuron, flusilazole, acetamiprid, pymetrozine, triflumizole, quinoxyfen, fludioxonil, deltamethrin, endrin, tolylfuanid, triphenyltin hydroxide, lactofen, halosulfuron-methyl, cyfluthrin, flufenacet, isoxaflutole,</u>



	<a href="#">piperonyl-butoxide, tebufenozide</a>
<a href="#">Mediated by sex steroid hormone dysregulation</a>	<a href="#">Permethrin, linuron, prochloraz, procymidone, tebuconazole, vinclozolin, DDE, endosulfan, dimethoate, deltamethrin, chlorpyrifos, methoxychlor, DDT, terbuthylazine, propiconazole, prothioconazole, cypermethrin, malathion</a>
<a href="#">Affecting metabolic homeostasis through PPARs</a>	<a href="#">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</a>
<a href="#">Affecting metabolic homeostasis through disturbing the thyroid hormone pathway</a>	<a href="#">DDT, DDE, chlorpyrifos-methyl, acetochlor, procymidone, imidacloprid, atrazine, fluroxyppy, mancozeb, butachlor, beta-cypermethrin, fenobucarb, cyhalothrin, theta-cypermethrin, bifenthrin, carbaryl, pymetrozine, pendimethalin, metolcarb,</a>
<a href="#">Affecting the gut microbiota</a>	<a href="#">Cis-nonachlor, oxylchlordane, trans-nonachlor, chlorpyrifos, carbendazim,</a>
<a href="#">Epigenetic programming and transgenerational effects</a>	<a href="#">DDT, glyphosate, vinclozolin</a>

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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.