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Thèse

pour le

Diplôme d'État de Docteur en Pharmacie

Mini revue sur les liens entre une exposition environnementale aux pesticides et l'obésité

--

Mini review on the links between exposure to pesticides and obesity

Exposome: example of complicity between an exposition and a pathology with pesticides and obesity.

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Plan

Liste des abréviations

ATP	Adenosine TriPhosphate
BMI	Body Mass Index
CAR	Constitutive Androstane Receptor
CFO	Crude Fish Oil
DDE	DichloroDiphenyldichloroEthylene
DDT	DichloroDiphenylTrichloroethane
DNA	DeoxyriboNucleic Acid
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organisation of the United Nations
HBC	Glyphosate-Based Herbicides
HDL	High Density Lipoprotein
HFC	Crude Salmon Oil group
HFR	Refined Salmon Oil group
LDL	Low Density Lipoprotein
MRL	Maximum Residue Limits
NIEHS	National Institute of Environmental Health Sciences
OPP	Organophosphate Pesticide
PCB	PolyChlorinated Biphenyl
POP	Persistent Organic Pollutant
PPAR	Peroxisome Proliferator-Activated Receptors
PPREs	Specifics Response Elements
PXR	Pregnane X Receptor
WHO	World Health Organization
WT	Wild males

INTRODUCTION EN FRANÇAIS

Depuis plusieurs années, les pesticides font l'objet d'une surveillance constante de la part des autorités de santé. En effet, depuis 2009, l'Union Européenne règlemente la commercialisation des pesticides. Les pesticides sont commercialisés sur la base d'études in vitro et in vivo au titre du règlement n°1107/2009 relatif à la mise sur le marché des produits phytosanitaires où chaque principe actif est évalué individuellement (**1**).

Un pesticide est défini comme un produit qui « prévient, détruit ou contrôle un organisme nuisible (« ravageur ») ou une maladie, ou qui protège les plantes ou les produits végétaux pendant leur production, leur stockage et leur transport. Ils comprennent entre autres : les herbicides, les fongicides, les insecticides, les acaricides, les nématicides, les molluscicides, les régulateurs de croissance, les répulsifs, les rodenticides et les biocides » (**2**). En raison de leur large champ d'action, ils sont de plus en plus utilisés dans des domaines variés (agriculture, médecine vétérinaire parfois même à l'intérieur des habitations, etc.), ce qui suscite des interrogations quant à leurs effets sur la santé humaine. En effet, malgré le durcissement de la règlementation, les populations sont de plus en plus exposées à ces composés qui se retrouvent partout, en mélange dans l'environnement, et il est encore difficile de mesurer tous leurs effets. Certains pesticides, comme les organochlorés sont interdits mais toujours présents dans l'environnement dû à leurs caractéristiques physico-chimiques (**3**).

Pour tenter de répondre à cette question, un certain nombre d'études épidémiologiques sont réalisées (**4**,**5**,**6**). Cependant, ces études peuvent présenter de nombreux biais. Parmi les difficultés rencontrées par les équipes de recherche figurent la complexité d'évaluer les effets des faibles doses, les effets des mélanges ainsi que les effets chroniques des expositions, parfois multigénérationnels. L'exemple du lien entre l'exposition aux pesticides et l'obésité illustre parfaitement cette problématique.

L'obésité est aujourd'hui un problème majeur de santé publique. L'OMS estime que 650 millions de personnes dans le monde souffrent d'obésité. L'obésité est définie comme un indice de masse corporelle (IMC) supérieur à 30 kg/m² (**7**). Les autorités sanitaires s'inquiètent également des répercussions que peut avoir cette maladie sur les populations (comorbidités, risque accru d'autres pathologies chroniques, espérance de vie réduite, etc.). De plus, les

causes d'obésité sont multifactorielles, parfois difficiles à contrôler et pour certaines encore mal comprises. De plus en plus de scientifiques s'interrogent donc sur un éventuel lien entre l'exposition aux pesticides et le développement de l'obésité.

Cette mini revue propose de s'intéresser au potentiel lien entre l'obésité et les pesticides en étudiant les différents effets des pesticides sur l'Homme. Elle traite également des mécanismes d'action qui pourraient être à l'origine du développement de l'obésité suite à l'exposition aux pesticides. Elle abordera également les difficultés et les interrogations actuelles sur le sujet notamment les effets cocktails et ceux d'une exposition fœtale.

INTRODUCTION

For several years now, pesticides have been under constant scrutiny by the health authorities. In fact, since 2009, the European Union has regulated the marketing of pesticides. Pesticides are placed on the market on the basis of in vitro and in vivo studies under regulation n°1107/2009 on the placing of plant protection products on the market where each active ingredient is evaluated individually (**1**).

A pesticide is defined like a product which "prevents, destroys, or controls a harmful organism ('pest') or disease, or protects plants or plant products during production, storage and transport. They include, amongst others: herbicides, fungicides, insecticides, acaricides, nematicides, molluscicides, growth regulators, repellents, rodenticides and biocides" (**2**). Because of their broad field of action, they are being used more and more in various fields (agriculture, veterinary medicine, even inside the home, etc.), which raises questions about their effects on human health. Indeed, despite the tightening of regulations, populations are increasingly exposed to these compounds which are found everywhere, mixed in the environment, and it is still difficult to measure all their effects. Certain pesticides, such as organochlorines, are banned but still present in the environment due to their physicochemical characteristics (**3**).

To overcome these difficulties, a number of epidemiological studies are being carried out (**4**,**5**,**6**). However, these studies are highly biased. The difficulties encountered by research teams include the complexity of assessing the effects of low doses, the effects of mixtures and the chronic effects of exposure, sometimes multigenerational. The example of the link between pesticides and obesity is a perfect illustration of this problem.

Obesity is now a major public health problem. The WHO estimates that 650 million people worldwide suffer from obesity. Obesity is defined as a body mass index (BMI) greater than or equal to 30 kg/m^2 (**7**). The health authorities are also concerned about the repercussions that this disease can have on populations (co-morbidities, increased risk of other chronic pathologies, reduced life expectancy, etc.). What's more, the causes of obesity are multifactorial, sometimes difficult to control and in some cases still poorly understood. More and more scientists are therefore looking into a possible link between exposure to pesticides and the development of obesity.

This mini review looks at the potential link between obesity and pesticides by studying the various effects of pesticides on humans. It also looks at the mechanisms of action that could be responsible for the development of obesity following exposure to pesticides. It will also address the difficulties and questions currently being asked on the subject like the cocktail effects and effects of foetal exposure.

METHODS

For the development of this mini review, a method of research by keywords was used. The keywords used were: obesity, pesticides, organochlorines, cocktails effects, endocrine disruptors, obesogens, physiological and endocrinological modifications, gene expression modifications.

The following search engines were selected: Pubmed, Google Scholar and Science Direct.

For more details, the keywords were used on their own and in association. All the references found during the search are listed in Appendix. Duplicates were then removed, and the selection began. In fact, only references deemed relevant to the subject were retained (verification of concordance with the subject, choice of pesticides studied…).

After reading the preselected references, only those meeting the predefined criteria were retained. Thus, this mini review will deal with pesticides frequently used at tolerated doses, but also with pesticides currently banned but which are still present in the soil and the environment due to their persistence.
The figure 1 represents a flow diagram corresponding to the 4 steps of the method applied to this synthesis.

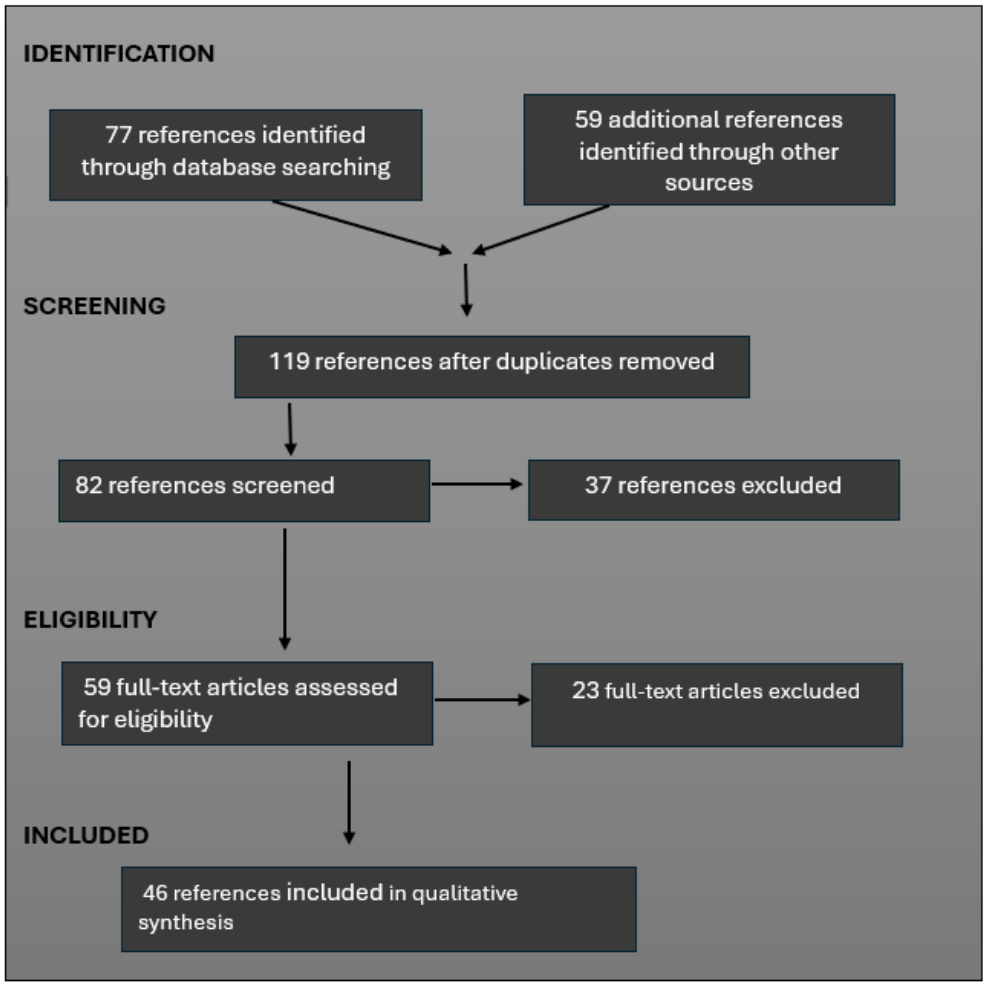

Figure 1. Flow diagram of bibliographic research method.

RESULTS

1. Summary of existing knowledge

1.1. Pesticides : exposure and general issues

Among the pollutants potentially responsible for obesity, pesticides are a new suspect.

Pesticides are found in people's food and environment (**8**). According to the WHO, the main source of exposure to pesticides remains food. However, indoor and outdoor air contamination is also a factor to consider. Often forgotten, drinking water accounts for a large proportion of exposure to pesticides (**9**). Its daily consumption makes it a key factor in increasing exposure to pesticides. It accounts for 10% of people's exposure to pesticides. The figure 2 represent different exposure routes of pesticides.

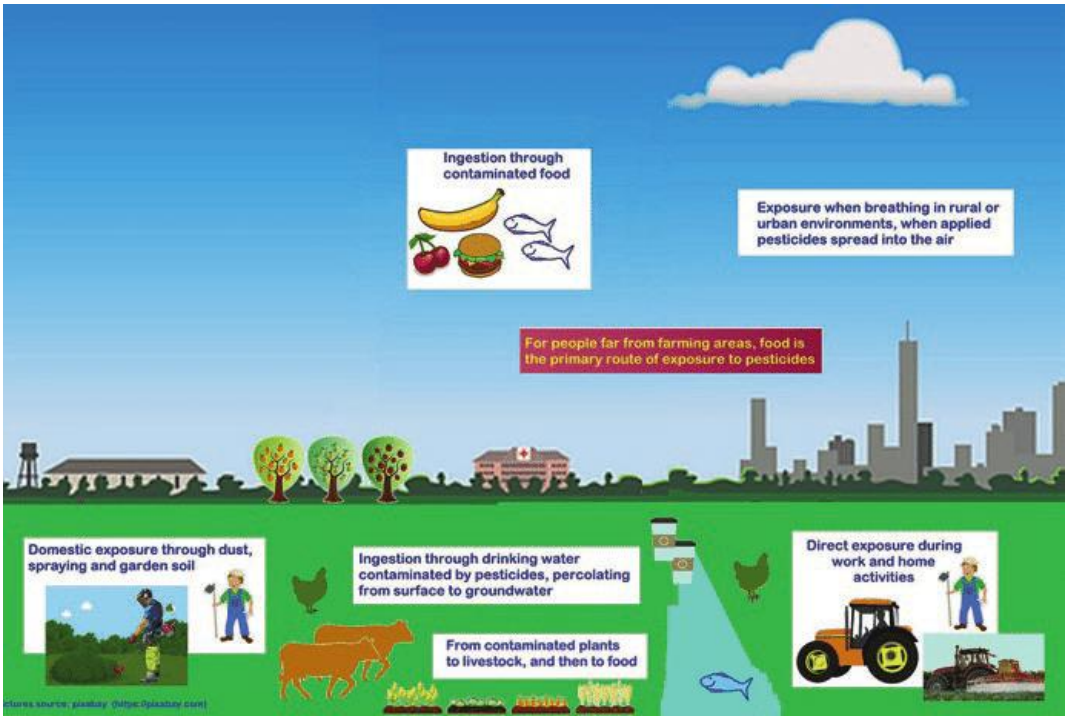

Figure 2. Different pathways of pesticides exposures (**10**)

As shown in the previous figure, pesticides are found in many areas (food, agriculture, domestic, air and soil). As their use has become more widespread over the last few years, exposure can occur in a variety of ways : by breathing them in urban areas but also in rural areas, by spraying them on crops or in the home itself (flea treatment for pets), and sometimes even on skin (mosquito repellents). Exposure can therefore sometimes be voluntary, as when they are used in family vegetable gardens. They can also be found on food to limit the destruction of crops by insects, for example. Sometimes, exposure is not voluntary and can occur through the meat we eat. Animals are often fed on products that have been treated with pesticides, whether deliberately or not. What's more, for a number of years now we've been seeing soil pollution caused by pesticides that are now banned. Because of their characteristics, these pesticides persist in soil and water, making exposure to them difficult to measure. The routes of exposure to pesticides are therefore multiple and difficult to control.

The currently recognized effects of pesticides on health come from observations reported among workers exposed to pesticides as well as documented cases of poisoning (**8**). Among the acute reactions to exposure to pesticides, we identify local signs such as skin and mucosal irritations, vomiting, allergic skin or eye reactions, respiratory discomfort or even coughing. The occupational exposure of agricultural workers to pesticides has been extensively studied to demonstrate the harmful effects of prolonged exposure to pesticides, revealing both acute and chronic effects (**4, 5**). Much of what we know today about the effects of pesticides comes from studies carried out on this population.

Chronic effects have been determined by epidemiological studies which have revealed a link between the risk of appearance of cancerous, neurological and reproductive disorders and exposure to pesticides in a professional environment in particular. These people were therefore in contact with probably high doses of pesticides; it is therefore difficult to estimate the risk for the general population due to variation in dose-response relationships. Moreover, it is important to raise the fact that some pesticides also have non-dose-dependent endocrine disrupting effects.

However, studies are not limited to highly exposed populations. Some epidemiological studies also look at the effects of exposure on pregnant women and the repercussions on their children once they are born, such as the PELAGIE study (**11**). This study concluded that there was an increase in externalised and internalised behaviour in children whose mothers had been exposed to Per-and polyfluoroalkyl substances. These children showed signs of hyperactivity, generalised anxiety and major depression.

Other studies are also looking at the notion of children's exposome by monitoring them from birth to adulthood, such as the ELFE study (**12**), which is conducted in France on more than 18 000 children since 2011. The aim of this study is to monitor children over a 20-year period in order to study the influence of their environment on their behaviour and health. Among the areas being studied are pollutants, including pesticides. The final results of this study are not yet known, but they will certainly enable us to learn more about the window of vulnerability and the long-term effects of pesticides.

Certain pesticides are classified in the list of endocrine disruptors such as DDT for example (**13**). An endocrine disruptor is thus defined as any chemical substance of natural or artificial origin foreign to the body which can interfere with the physiological functioning of the endocrine system and thus induce deleterious effects on the body of an individual or their descendants.

It is also important to consider the effects of mixing these products. As well as having effects when used separately, they can also reveal their deleterious effects when they act in synergy. The massive use of pesticides (both in agriculture and in the home) increases the risk of cocktail effects, which are still difficult to measure and control.

Indeed, given their persistence, pesticides remain present in soil and water for years after their use has ceased. Pesticides are dispersed in the air or soil. It is well known that they have a very poor solubility in water, but that they have a strong affinity for fat, leading to their accumulation in adipose tissue.

Despite the ban on the use of certain pesticides in the Stockholm Convention (continually revised), people are still exposed to them because of their long half-life and bioaccumulation due to the limited detoxification capacity of the liver.

In fact, some pesticides are classified like Persistent Organic Pollutant (**14**). Like defined by the Stockholm Convention on Persistent Organic Pollutants (POPs), "POPs are organic chemical substances, that is, they are carbon-based. They possess a particular combination of physical and chemical properties such that, once released into the environment, they remain intact for exceptionally long periods of time (many years). They become widely distributed throughout the environment as a result of natural processes involving soil, water and, most notably, air. They accumulate in the living organisms including humans and are found at higher concentrations at higher levels in the food chain and are toxic to both humans and wildlife" (**14**).

So even though certain pesticides considered toxic have now been banned (**3**), they can still be found in high concentrations in the environment (particularly in soil and water). These pesticides are therefore highly persistent and continue to pose problems despite being banned (like lindane or DDT for examples).

Lindane, for example, is an organochlorine insecticide used in human and veterinary medicine since 1930s. Its use has been banned across the world since 2009 because of its harmful effects on the liver, kidneys, nervous system and immune system (**15**). Like many pesticides, it is also suspected of being an endocrine disrupter. However, despite its ban over 15 years ago, it is still present in environment in low concentrations, continuing to exert is effects alone or in mixture with other pesticides (**16**).

Organochlorine pesticides (such as DDT and Lindane) persist in soil, water and sediment and continue to have harmful effects on human health. Despite the ban on DDT, it continues to pollute the environment because of its stability and difficult degradation. Some of its metabolites also have harmful effects on ecosystems. It is assumed that DDT could persist in the environment for around fifty years after its use (**3**). Many studies have been conducted to examine the persistence of DDT and its metabolites in the environment long after it use was banned. This is particularly the case of the meta-analysis carried out by Dechasa Adare Mengistu and his team. This study concludes that DDT metabolites are still present in fruits and meat today. Even if the concentrations recorded are below the maximum recommended levels, these metabolites represent a risk to human health given their persistence and the difficulty of predicting their harmful effects in synergy with other pesticides. The presence of these metabolites in low doses in the food chain raises questions about the dangers even at low doses of regulated products (**17**).

The wide range of organochlorine pesticides was among the most widely used substances in agriculture and have properties similar to those POPs. In addition, because of their lipophilic properties, organochlorines and POPs accumulate in the fatty tissue of living organisms. This bioaccumulation in adipose tissue also explains the body's difficulty in breaking them down (**3**).

1.2. Obesity

The World Health Organization (WHO) (**7**) defines obesity as « an abnormal or excessive fat accumulation that can be detrimental to health ». It is a chronic progressive disease presenting in different clinical forms (**18**). According to the WHO, an adult is considered obese when his body mass index (BMI) is greater than or equal to 30 kg/m² (**7**). There are 3 forms of obesity: moderate obesity (30-34,9 kg/m²), severe obesity (35-39,9 kg/m²) and massive obesity (more than 40 kg/m²). Morbid obesity also manifests itself through an accumulation of body fat, difficulties in carrying out daily activities, respiratory problems and the onset of other chronic illnesses such as premature osteoarthritis, metabolic diseases, high blood pressure, etc.

Worldwide (**7**), more than 650 million people suffer from obesity. For more than 20 years, the number of people suffering from obesity has almost tripled. Obesity, once considered as a health problem affecting high-income countries, is now on the rise in low and middle-income countries, especially in urban areas.
The prevalence among children and adolescents is also clearly increasing.

Currently in the world (**7**), we have more obese people than underweight people (except in certain regions of Sub-Saharan Africa and Asia).

A major increase in BMI and consequently obesity represents a major risk factor for other chronic pathologies (**7**). Thus, an obese person will be more exposed to the risk of developing cardiovascular diseases, diabetes, musculoskeletal disorders or even cancers.

The main cause of obesity is an energy imbalance between calories consumed and calories expended (**7**, **19**).

This imbalance is notably due to dietary changes and an increased sedentary lifestyle (**20**) of the population, thus making it more vulnerable to weight gain. Indeed, the increase in portion size, greater energy density or even excessive reliance on industrial foods are risk factors for developing obesity. In parallel with these dietary changes which lead to an increase in caloric intake, there is a reduction in their expenditure linked in particular to a lack of physical activity, the development of the use of cars and public transports rather than walking or even the bike.

A genetic predisposition to weight gain induces different susceptibility to obesity (**19**).

It is also important to note the role of environment (**20**) in the development of obesity. Indeed, it seems that a lack of sleep, working at night or even irregular meals disrupts the body's biological clock, thus inducing a risk of overweight and therefore obesity. Some medications, viruses, stress or even exposure to certain pollutants are also risk factors in obesity.

With health authorities increasingly pointing the finger at pesticides for their probable harmful effects on human health, the question of their involvement in the rise in obesity is being raised.

2. Link between pesticides and obesity

2.1. Massive use of pesticides – The cases of Atrazine and Flufenacet

The National Institute of Environmental Health Sciences (NIEHS) and the European Union agree that chronic exposure to certain chemical compounds is responsible for an increase in the incidence of obesity (**21**).

The metabolism of pesticides and endocrine disruptors is a fundamental factor in understanding their effects on the physiology of living organisms. In humans, endocrine disruptors are theoretically metabolised by the liver. This process involves their oxidation by cytochrome P450 detoxification enzymes, followed by glucuroconjugation or sulfoconjugation, leading to their renal or enteral elimination.

However, given the limited capacity for hepatic detoxification and the long half-life of these products, they will be bioaccumulated for several years in adipose tissue. This phenomenon is explained by their lipophilic nature. This is particularly the case for organochlorine pesticides, which were frequently used in agriculture (**21**).

As we mentioned earlier, it is still difficult to make a link between exposures doses and pathologies.

Many questions are now being asked about massive industrialisation and the link to health, in particularly in view of the use of Atrazine in the United States and the development of obesity, which seems to be correlated.

In fact, according to Soo Lim and his team (**6**), industrialisation and, consequently, the increased use of pesticides are linked to the development of the obesity epidemic.

They speculate that the intensive use of Atrazine (a synthetic herbicide) could be associated with the increase in the number of cases of obesity in the United States. They indicate that chronic exposure to low doses of this herbicide could lead to weight gain, particularly when combined weigh a high-fat diet (**6**). To support their claim, they conducted a study in rats comparing rats on a high-fat diet with mice on a balanced conventional diet (with double testing with and without exposure to Atrazine). The aim was to demonstrate an effect of Atrazine on weight gain and the development of obesity (**6**). The research showed an increase in visceral fat in rats on high-fat diet and an increase in the quantity of lipids in the muscles and liver in rats on a balanced diet (**6**). They observed that Atrazine caused impaired glucose tolerance and insulin resistance in rats, regardless of the diet adopted. In addition, exposure to this herbicide reduces energy metabolism (**6**).

To go beyond simple exposure, they then observed the effects of Atrazine as a function of the frequency and quantity of exposure. They found that acute exposure to high doses of Atrazine induced toxicity, leading to weight loss. Chronic exposure to low doses, on the other hand, caused slight mitochondrial damage mimicking the characteristics of insulin resistance, leading to weight gain (**6**).

The mitochondrial alterations induced by Atrazine are thought to be responsible for a drop in membrane potential and a reduction in intracellular ATP (Adenosine TriPhosphate) content (**6**).

The increase in lipid content in the muscles observed in rats fed a conventional diet but exposed to this herbicide would therefore lead to mitochondrial damage. This would lead to problems in the insulin signalling pathway, resulting in insulin resistance and the accumulation of fat that can lead to obesity (**6**).

As a reminder, Atrazine is still used in the United States, particularly in the corn consumed in American fast-food restaurants, but also in soaking water (hence the presence of its metabolites in rivers and groundwaters). This raises the question of more widespread pollution via international waters (**6**).

More recently, the Europeans authorities examined the case of Flufenacet. Flufenacet is a herbicide in the per- and polyfluoroalkyl family, better known as PFAS. This pesticide is widely used in European countries, particularly in France, for winter crops (especially wheat, barley and rye).

Flufenacet (**22**) has been the subject of studies into its effects and toxicity on both living organisms and the ecosystem. Indeed, its widespread use also raises many questions about the future of our ecosystem. It is also considered to be an endocrine disruptor, having revealed long-term toxicity effects on the liver and thyroid in murine tests. What's more, as an endocrine disrupter, it is suspected of increasing the risk of obesity and diabetes. So what about its effects on humans and its persistence in soil and water?

In the light of the information gathered and the studies conducted, the European Food Safety Authority (EFSA) decided to ban the use of this herbicide after finding excessive concentrations in tap water (**22**).

The example of the Flufenacet ban raises questions about the little-known effects of the pesticides we use every day, whether for agricultural, domestic or veterinary purposes. And what about persistence in soil and water? About cocktails and chronic effects? About health effects? About their possible link to obesity? All these questions arise in relation to pesticides that are still in use, as well as those that have been banned but have long been dispersed.

2.2. Mechanisms of action in relation to obesity

2.2.1. Interactions with nuclear factors

a) CAR/PXR

According to different research (**23**,**24**), persistent organic pollutants (including a large number of pesticides like organochlorine pesticides) are capable of binding to xenobiotic receptors as well as to the receptors of certain steroid hormones and modifying the expression of different genes.

The main receptors of POPs and organochlorine pesticides bind to the Pregnane-X-Receptor (PXR) and the Constitutive Androstane Receptor (CAR).

The Pregnane X receptor (PXR) is a xenobiotic nuclear receptor that regulates the expression of genes for drug-metabolising enzymes and drug transporters to detoxify and eliminate xenobiotics and endotoxins from the body (**25**).

Recent studies have suggested an important role for PXR in obesity. Indeed, according to the mouse study of Krisstonia Spruiell and her team, ablation of PXR in murine animals would protect against obesity (**26**). The study compared wild-type mice with mice with humanised PXR receptors. The study concluded that mice fed a high-fat diet with humanised PXR receptors showed moderate obesity, but above all elevated glucose, insulin and leptin levels, as well as glucose intolerance. These findings raise the question of the involvement of PXR receptors in the development of both type 2 diabetes and obesity.

Other studies suggest new avenues for the action of PXR receptors (**26**). For example, activation of PXR receptors by their ligand could modify the expression of genes involved in lipid homeostasis, thereby altering patients' plasma lipid levels. PXR is also thought to reduce energy metabolism by regulating glucogenesis. Finally, the PXR receptor is also thought to be sensitive to bile acids, regulating the toxicity of the cholesterol metabolite. These data therefore raise questions about the impact of PXR in obesity, given that it is highly expressed in the liver (a major organ involved in metabolism, lipogenesis and lipid secretion) (**26**). By binding to PXRs, organochlorine pesticides interfere with traditional signalling pathways and are thought to cause a change in gene expression that can induce the effects mentioned above and thus lead to the development of obesity (**26**).

The constitutive androstane receptor (CAR) is a nuclear receptor that acts as a xeno-sensor involved in regulating responses to xenobiotics (**27**). Recent studies have shown that this receptor plays a role in controlling energy metabolism. In particular, it has been suggested that activation of the CAR could reduce obesity because of the nutrient stress it generates. It is also thought to interact with the peroxisome proliferator-activated receptor (PPAR) and its coactivator, both of which are known to regulate adaptive responses to starvation. According to other studies, the CAR plays an inhibitory role in lipogenesis and cholesterol secretion.

It has been shown that some pesticides act as CAR agonists and others as CAR antagonists. In view of what is known about the effects of receptor activation of inhibition, it is essential to question the role of pesticide interaction with the constitutive androstane receptor. By binding to CARs in a antagonistic manner, organochlorine pesticides limit their regulatory effects on energy metabolism, leading to a reduction in the inhibition of lipogenesis and therefore favouring the development of obesity (**28**).

These receptors PXR and CAR (**23**, **24**), also called "xeno-sensors", are involved in the activation of the body's detoxification system and in particular play a role in the xenobiotic metabolization chain. By binding to these different receptors, pesticides can also induce oxidative stress leading to the production of reactive oxygen species with directly interfere with the DNA and cause mutations. These mutations can in particular lead to cancers or to increase in the production of a cholesterol agonist.

b) PPAR

Peroxisome proliferator-activated receptors (PPAR) are made up of three nuclear receptors isoforms (gamma, alpha and delta) encoded by different genes (**29**). They are ligand-regulated transcription factors. The ligand controls gene expression by binding to specific response elements (PPREs) within the promoters. PPAR interact by binding to retinoid X receptors as heterodimers. This agonist binding allows them to interact with cofactors to increase the rate of transcription initiation.

These PPAR receptors play an important role in lipid metabolism and glucose homeostasis. They act as lipid sensors and regulators of lipid metabolism. In particular, fatty acids have been identified as natural ligands for PPAR receptors (**29**).

As PPAR plays a fundamental role in adipogenesis and adipocyte gene expression, a study vas carried out to determine the link between PPAR gamma mRNA expression and the development of obesity (**30**). Researchers found that PPAR gamma was more highly expressed in the serum of obese patients, whether or not they had diabetes. They found a positive correlation between body mass index and PPAR gamma expression in these patients. This study therefore suggests a regulatory role for the PPAR receptor in the deposition of fat in adipose tissue. In fact, it could be responsible for the increase in adipose tissue mass in the adipose tissue of obese patients (**30**). Consequently, pesticides (like carbamates) that interact with these receptors could potentially be at the origin of an increase in PPAR gamma expression and therefore obesity (**31**).

c) ER

The main effects of POPs and pesticides on DNA are therefore transcriptional but not only. Indeed, some products (like organochlorine pesticides or bisphenol A, recognized endocrine disruptor) are suspected of mimicking the effects of oestradiol on glucose homeostasis in pancreatic cells.

The action on oestrogens would also be an important source of concern regarding the action of POPs. Indeed, the hormones reduce the apoptosis of pancreatic beta cells and increase the synthesis and release of glucose-dependent insulin while improving tissue sensitivity to insulin at the peripheral level and reducing lipogenesis and the accumulation of triglycerides in adipose tissue (**32**).

Estrogenic actions are proven for POPs and organochlorines. It has been demonstrated that through oestrogen signalling pathways, they induce an increase in abdominal adiposity as well as an increase in serum concentrations of inflammatory markers. This therefore assumes a correlation between obesity levels and serum levels of POPs (**33**,**34**).

2.2.2. Insulin resistance and modification of lipid homeostasis

Jérome Ruzzin and his team (**35**) looked at the effects of persistent organic pollutants (including organochlorines pesticides and PCBs) on rats. They fed rats a high-fat diet based on

salmon oil. They differentiated between 2 groups: one fed on crude salmon oil (the HFC group) and the other fed on refined salmon oil (the HFR group). The aim was to demonstrate whether or not there was a link between the rat's obesity and the presence of POPs in their diet.

After 28 days of experimentation, they observed weight gain in the HFR rats that could be explained by the high-fat diet. For the HFC group, the main observations were an increase in adipose tissue and profound deregulation of homeostasis. They then found that POPs induced robust down-regulation of the insulin-induced gene 1 and the Lpin 1 gene. These two genes are the main regulators of lipogenesis and the synthesis of triglycerides and cholesterol (**35**). POPs therefore significantly affect the expression of critical genes involved in regulating lipid homeostasis.

The other observation made by this team was insulin resistance in rats that had consumed crude salmon oil. In the adipose tissue of these rats, they observed an alteration in the capacity of insulin to stimulate glucose uptake (**35**). The reduction in insulin-stimulated glucose uptake in adipocytes was observed in rats treated with a mixture of organochlorines as well as in rats treated with DDT. These pesticides were the most widely used in the world (**35**).

This study leads to two conclusions. The first is that exposure to pesticides can cause insulin resistance and alter lipid and glucose metabolism. Pesticides would therefore potentially contribute to an increase in insulin resistance and associated disorders (**35**).
The second conclusion reached by the research team was that the presence of beneficial n-3 polyunsaturated fatty acids in crude fish oil (CFO) could not counteract the deleterious metabolic effects induced by exposure to POPs (**35**).

Also, as explained above, significant exposure to pesticides such as Atrazine causes mitochondrial damage. This would lead to a drop in membrane potential and a reduction in intracellular ATP content. As a result, mitochondrial damage leads to insulin resistance and fat accumulation by interfering with insulin signalling pathways, which can lead to the development of obesity (**6**).

These results also seem to be confirmed in the study conducted by Ali Arab and Sara Mostafalou. Their research concluded that pesticides like organochlorines or PCBs induce an increase in insulin resistance via different pathways, depending on their composition. The main targets are pancreatic beta cells, the hypothalamus and the intestinal microbiota. Their actions at these different sites would all lead to an increase in insulin resistance (via cascades mediated by inflammatory cytokines or by release of adipokines, etc.) (**36**).

Despite restrictions on the production of organochlorine pesticides since the 1970s, their worldwide production and use are poorly controlled. Furthermore, these compounds tend to bioaccumulate and are transported over long distances. Among the mixtures of pesticides tested in vitro in this study, organochlorine pollutants could be the most powerful disruptors of insulin action (**35**).

2.2.3. Microbiota

After studying the different effects of pesticides on the body's homeostasis, researchers looked at their effects on the intestinal microbiota (**37**). Indeed, the intestine is the main place of absorption of nutrients but also of drugs and toxicants. In fact, they suspect that pesticides affect toxico-dynamics, which could lead to an increase in individual exposure to obesogenic and diabetogenic pollutants.

To develop their idea, they transferred the intestinal microbiota of obese mice to normal mice (with a conventional diet and a weight considered normal). They observed greater weight and body fat gain than in the mice that had received the microbiota of mice considered to be lean, even though both groups were fed the same diet (**37**).

As the intestine play a role in regulating fat storage and levels of satiety factors such as glucagon and leptin, it could be the target of the new obesogens (**37**).

A high-fat diet is thought to alter intestinal permeability via endotoxin. Endotoxemia would then cause inflammation and metabolic changes that would have a strong influence on the risk of obesity (**37**).

Other studies also suggest a link between intestinal microbiota and metabolic health. For example, researchers have established that exposure to Chlorpyrifos increases glucose tolerance and insulin sensitivity in exposed rats. Another analysis tends to demonstrate a link between changes in the structure and composition of the intestinal microbiota and the metabolic profile of rats and the use of Endosulfan (**36**).

The effects of organophosphate pesticides (OPPs) on intestinal microbiota have also been studied. OPPs are one of the classes of pesticides most frequently used worldwide because of their biodegradable properties (**38**). Exposure of mice to OPPs is thought to lead to glucose intolerance. This effect is explained by the modification of esterase and acetate activity during the degradation of OPPs by the intestinal microbiota of the mice. This modification would be at the origin of gluconeogenesis, linked to the metabolization of organophosphate into acetic acid (substrate of gluconeogenesis), and resistance to glucose (**38**).

2.3. Current issues and difficulties

2.3.1. Cocktails effects

After studying the effects of individual pesticides particularly when they are launched on the market, researchers set out to learn more about the effects of mixtures. As we saw earlier, pesticides bioaccumulate significantly (in soil, water, adipose tissue, etc.). Their lifespan is therefore extended and their effects increased tenfold. Understanding the effects of mixtures is a major challenge if we are to learn more about the chronic effects of pesticides. To this end, the research team studies the action of a mixture of six pesticides frequently used in France (particularly in apple orchards), named boscalid, captan, chlorpyrifos, thiofanate, thiacloprid and ziram, on a group of mice. The dose used were controlled so as to correspond

to the tolerable daily doses of each pesticide. The pesticides were included in the mice's pellets for their daily diet (**39**).

The mice in this experiment were males and females deficient in either androstane receptors (WT) or constitutive androstane receptors (car -/-, CAR -/-). They were fed a diet enriched or not with pesticides for 52 weeks to mimic 30 years' exposure in humans, and various parameters were assessed (**39**).

At the end of the weeks of experimentation, the research team was able to make a number of observations. The wild males (WT) exposed to the pesticide mixture showed greater body weight gain, increased adiposity as well as characteristics of hepatic steatosis and glucose intolerance (**39**).

The CAR-/- females showed a higher body weight gain and mortality rate than the other females (**39**).

Indeed, after 52 weeks, exposed male WT mice had gained 2 times more weight than unexposed mice. In the exposed female, there were few significant differences in body mass. They did, however, have more water than those fed the control diet (**39**).

Exposed male and female WT mice had higher blood glucose levels than control mice. Between exposed male and female WT mice, it was the females that had significantly higher fasting blood glucose levels. However, this difference in blood sugar levels between males and females was also observed in the control group (**39**).

The researchers found no difference in insulin levels between the mice exposed to the pesticides and those fed the control diet (**39**).

By examining the liver histology of the mice, the researchers discovered hepatocellular vacuolation located mainly in the centrilobular zone in the livers of the male mice exposed to the pesticides. These signs suggest emergent steatosis (**39**).

In addition, male WT mice exposed to pesticides had higher triglycerides than unexposed mice. There was no difference in total cholesterol, HDL or LDL between exposed and unexposed male mice (**39**).

The harmful effects of pesticides mixtures are all the more difficult to predict because they vary according to the products they contain, and the doses used. Pesticides may act synergistically, antagonistically or not react together, depending on their class and the dose used. Some pesticides used on their own does not appear to present any danger, but when combined with another pesticide can be harmful to humans. This is particularly true of the rare organochlorines still used in developing countries such as India (**40**).

The difficulty of predicting toxic doses is therefore immense, given the harmful effects of persistent pesticides in environment and the cocktails effects that can result.

2.3.2. Foetal exposure and window of vulnerability

As explained above, the effects of pesticides are not limited to the immediate effects or after long exposure. Like medications or toxicants, it is important to ask the question of the effects on the descendants of those exposed. Thus, various studies have been conducted on pregnant women to assess the effect of pesticides on the fœtus (**41**).

Foetuses and newborns are exposed to pesticides via the cord blood/placenta and through breast milk. Given the immaturity of their bodies, they are therefore potentially more vulnerable to endocrine disruptors than adults (**42**).

The obesogenic effects in foetuses and newborns could be explained by inappropriate activation of receptors and epigenetic changes that interfere with adipocyte differentiation and lipid metabolism, predisposing to obesity. Particularly at this young age, when children are more vulnerable to external factors (**42**).

These studies have demonstrated a positive association between concentrations of organochlorine pesticides in the mother's plasma or cord blood and the child's weight growth for several years after birth (**41**).

To reach this conclusion, the researchers examined whether there was a link between prenatal concentrations of various organochlorine pesticides and overweight at the age of 6 and a half. They also investigated whether the child's sex or fat intake could influence these associations (**42**).

For this study, 344 children were monitored from before birth to the age of 6 and a half. Organochlorine concentrations in cord blood were measured. The children's diet was then assessed using a food frequency questionnaire (**42**).

In this study, the pesticides assessed were synthetic organochlorine compounds (PCBs, HBCs, and DDT/its metabolite DDE). These products are banned from production and use under the Stockholm Agreement. However, given the poor degradation and bioaccumulation of the compounds, people are still exposed to them via the food chain. It is therefore important to examine their various effects (**42**).

The results of this study suggest that prenatal exposure to organochlorine pesticides is associated with overweight children at the age of 6 and a half, as well as a variable susceptibility depending on the child's diet and sex. Researchers have demonstrated differences in effects depending on the pesticide used. Exposure to PCBs and DDE had a greater effect on overweight in girls than in boys. On the other hand, the effects of DDT on weight gain were only observed in boys (**42**).

The results of this study tend to show that there is a window of vulnerability. At certain points of their lives, people are likely to be more or less vulnerable to a product. This notion is also demonstrated in the study by Yifan Xu and his team (**43**). This study highlights the sensitivity of newborn babies while they are still in the placenta. Exposure to pesticides by the mother during pregnancy is thought to be the cause of disorders in the foetus. Indeed, researchers have noticed that children whose mothers were exposed to varying concentrations of organochlorines developed more behavioural disorders such as autism or hyperactivity (**43**).

The routes of exposure to pesticides are numerous and omnipresent in our daily lives. It is therefore necessary to attempt to measure the association between a wide array of early-life exposures and childhood obesity, using an exposome-wide approach. This is the approach used by Martine Vrijheid and her team in their study (**44**).

They studied the effects of different exposures on pregnant women and also measured the effects on their children once they were older. This study did not show any significant results, as exposure varied greatly depending on the child being monitored. As the organochlorine pesticides studied are highly lipophilic, they are stored in fatty tissue. As the quantity of adipose tissue varies from one individual to another, it is necessary to determine the amount of adipose tissue present in each child (**44**).

However, it was noted that there was a balance between the storage of POPs in adipose tissue and their circulation in the blood, which could be disrupted during phases of increased or decrease exposure, but also during weight gain or loss. Studies have shown that weight loss leads to an increase in the concentration of POPs in serum, and consequently in their deleterious effects (**44**).

Nevertheless, it remains difficult to assess the link between POPs (especially pesticides) and increased BMI without taking into account the complex toxico kinetics, age, amount of adipose tissue, dose and duration of exposure… Many factors come into play in this issue, and are not easily quantifiable and reproductible… (**44**)

DISCUSSION AND PERSPECTIVES

The WHO (**45**), in collaboration with the FAO (Food and Agriculture Organisation of the United Nations), is responsible for assessing the risks of pesticides to human health and for drawing up recommendations for appropriate protective measures.

The risks associated with pesticide residues in food are assessed by a group of independent international scientific experts. Once the studies have been completed, the risk is assessed, and limits are set to ensure a risk-free dietary intake. To do this, the group ensures that the quantity of pesticide residues to which the population is exposed through the consumption of food does not have harmful effects on health.

The acceptable daily intakes defined by this group of experts enable governments and risk managers at international level to set maximum residue limits (MRLs) for pesticides contained in food.

The WHO and FAO have jointly drawn up the International Code of Conduct on Pesticide Management to guide the various authorities, governments and private companies in the management of pesticides throughout their life cycle. In particular, it sets out best practice for managing pesticides from production to disposal (**46**).

To prevent overweight and obesity, it is advisable to monitor children's body mass index. As weight and height are already monitored on a regular basis, it is recommended that

BMI be added to this. Curves for recording BMI values throughout childhood are available in health record books (**46**).

As explained above, pesticides are endocrine disruptors. They therefore have an effect on the adrenal glands and thyroid gland, as well as on various hormones such as oestrogen. They interact with their receptors to modify signalling pathways, leading to changes in DNA transcription. As a result, the organism is no longer able to interact properly with its environment. These modifications could therefore be at the root of obesity through their toxic effect on the body.

Indeed, studies carried out on mouse models have shown that exposure to pesticides (alone or in mixtures) resulted in insulin resistance and a reduction in the expression of genes involved in lipid metabolism, factors that favour the development of obesity.

However, the effects of these pesticides may vary according to the sex and age of population exposed. A theory of foetal programming has been proposed, assuming that there is a window of vulnerability to endocrine disruptors such as pesticides.

The results of the various studies also raise the question of tolerable daily doses. These doses were established for each pesticide taken separately, indicating that at this dose their effect was not harmful, but what about their combination? The study on cocktail effects assumed that a mixture of several pesticides had toxic effects even though they did not exceed the tolerable daily doses.

Nonetheless, these studies have some limitations. It is difficult to quantify the exposure of each individual to pesticides. It is also difficult to estimate the chronicity of exposure. Pesticides have been used many years, particularly with the intensification of industrialisation. The sources of exposure are also varied. Consequently, the exact quantification of exposure to each pesticide, not to mention cocktail effects, remains complicated in the human population. There is also the question of transposing murine results to human models.

Another difficulty arises from the fact that obesity does not depend solely on uncontrollable external factors. It also comes from the way we eat, move, live with our environment, etc. Obesity also comes from ultra-transformation in many areas (notably food).

Research into obesogenic effects of pesticides therefore remains a major area for further study. However, the various results of these numerous studies suggest that pesticides play a major role in the development of obesity and could therefore be new obesogens.

CONCLUSION

To conclude, the various studies mentioned in this mini review tend to show a link between exposure to pesticides and the development of obesity. However, it is still early to say that pesticides are the new obesogens. This is a subject that deserves to be explored in greater depth, with more closely supervised analyses, in particular by monitoring quantitative and qualitative exposure to different pesticides.

DISCUSSION EN FRANCAIS

Cette mini revue a pour but de traiter d'un sujet de préoccupation actuel. En effet, elle propose d'étudier le lien entre l'utilisation croissante des pesticides et le développement de l'obésité à travers les populations mondiales. Ainsi, à travers les différentes études analysées, il est possible de soulever un certain nombre d'effets néfastes produits par l'utilisation de divers pesticides.

En effet, les pesticides étant des molécules lipophiles, ils ont tendance à stagner dans les sols mais également au sein même du corps humain dans les tissus adipeux. De fait, ils peuvent continuer d'exercer leur effet encore longtemps après l'arrêt de leur utilisation. Il semblerait que les pesticides fréquemment utilisés dans le monde, aient une affinité particulière avec divers récepteurs comme CAR, PXR ou encore PPAR et ER. En conséquence, par la liaison à ces différents récepteurs nucléaires ou hormonaux, ils exercent des effets sur la résistance à l'insuline ou encore sur la voie de dégradation des lipides entrainant ainsi un risque plus important d'obésité. Une hypothèse a aussi été soulevée sur son incidence sur le fonctionnement du microbiote intestinal humain.

Les règlementations développées par les autorités de santé et phytosanitaires ne cessent d'évoluer suite aux différentes études réalisées. Ainsi, certains pesticides ont déjà été interdit à l'utilisation pour leurs effets néfastes relevés sur la santé humaine mais aussi sur l'environnement. Cependant, il reste encore difficile de quantifier les pesticides toujours présents dans l'environnement. En effet, malgré leur interdiction, ces pesticides ont une rémanence importante qu'il est difficile de mesurer. De fait, il est également important de prendre en compte les effets des pesticides en cocktail. Les règlementations définissent les doses maximales utilisables par pesticide sans prendre en compte les éventuels effets cocktails qui pourraient être d'autant plus néfastes alors même que ces pesticides sont utilisés aux doses minimales tolérées. Se pose également la question des effets transgénérationnels. Des études ont montré que la concentration en pesticides organochlorés dans le sang du cordon au cours de la grossesse était corrélée au développement de l'obésité de l'enfant dans ses premières années de vie.

Cependant, il est encore difficile d'affirmer que l'utilisation grandissante des pesticides est liée à l'augmentation des cas d'obésité dans le monde. En effet, les quantités de pesticides auxquelles sont exposées les populations sont difficilement quantifiables du fait de leur rémanence, des différents effets cocktails mais aussi des différentes voies d'exposition difficilement maitrisables. Il est également important de prendre en compte certains paramètres physiologiques comme l'âge ou encore le sexe de l'individu étudié. Il est aussi primordial de prendre en compte l'alimentation et tous les facteurs propres au style de vie de chaque individu (sédentarité, activité physique, classe sociale…). C'est ce que tentent de faire de plus en plus les études en prenant en compte l'exposome (**44**). De même, il reste difficile de transposer les résultats des études murines aux humains.

L'étude des pesticides et de leurs effets sur la santé humaine est un vaste domaine de recherche. Il reste encore beaucoup de paramètres à prendre en compte pour déterminer leur réel rôle dans le développement de l'obésité. Cependant, les différentes études proposées ici tendent à suggérer un rôle non négligeable de ceux-ci.

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Table des matières

Table des illustrations

Annexe - Excel spreadsheet of references

Search engine	Key words used	Authors/ Organization	Title	Web link
GOOGLE	*Obesity definition*	World Health Organization	Obesity and overwaight	https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
		National Heart, Lung, and Blood Institute	What are overweight and obesity ?	https://www.nhlbi.nih.gov/health/overweight-and-obesity
		Jonathan Q. Purnell	Definitions, Classification, and Epidemiology of Obesity	https://www.ncbi.nlm.nih.gov/books/NBK279167/
	Pesticides definition	National Cancer Institute	Pesticide	https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pesticide
		National Institute of Environmental Health Sciences	Pesticides	https://www.niehs.nih.gov/health/topics/agents/pesticides
		Eurostat	Pesticide	https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Glossary:Pesticide
		Volkan Yumuk, Constantine Tsigos, Martin Fried et all.	European Guidelines for Obesity Management in Adults	https://pmc.ncbi.nlm.nih.gov/articles/PMC5644856/
		Alexandra Lee, Michelle Cardel, William T Donahoo	Social and Environement al Factors Influencing Obesity	https://www.ncbi.nlm.nih.gov/books/NBK278977/

	Pesticides routes	United States Environmental Protection Agency	Exposure Assessment Tools by Chemical Classes - Pesticides	https://www.epa.gov/expobox/exposure-assessment-tools-chemical-classes-pesticides
		Muyesaier Tudi, Hairong Li, Hongying Li et all.	Exposure Routes and Health Risks Associated with Pesticides Application	https://pmc.ncbi.nlm.nih.gov/articles/PMC9231402/
	Pesticides use's recommendations	European Commission	Pesticides	https://food.ec.europa.eu/plants/pesticides_en
		World Health Organization	Recommendations on pesticides management	https://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/Recommendations08_01.pdf
		Food and Agriculture Organization of the United Nations	Pest and Pesticides Management	https://www.fao.org/pest-and-pesticide-management/pesticide-risk-reduction/code-conduct/en/
		Christos A Damalas, Ilias G Eleftherohorinos	Pesticide Exposure, Safety Issues, and Risk Assessment Indicators	https://pmc.ncbi.nlm.nih.gov/articles/PMC3108117/
	Health effects of pesticides	European Environement Agency	How pesticides impact human health and ecosystems in Europe	https://www.eea.europa.eu/publications/how-pesticides-impact-human-health

		Md Faruque Ahmad, Fakhruddin Ali Ahmad, Abdulrahman A. Alsayegh et all.	Pesticides impacts on human health and the environment with their mechanisms of action and possible countermeasures	https://www.sciencedirect.com/science/article/pii/S2405844024051594
		World Health Organization	Pesticide residues in food	https://www.who.int/news-room/fact-sheets/detail/pesticide-residues-in-food
		The Institute for Functional Medicine	Exposure to pesticides, herbicides & insecticides : Health Effects	https://www.ifm.org/articles/pesticides-and-human-health-effects
		Wei Zhou, Mengmeng Li, Varenyam Achal	A comprehensive review on environmental and human health impacts of chemical pesticide usage	https://www.sciencedirect.com/science/article/pii/S2405665024001112
	Endocrine disruptors	National Institute of Environmental Health Sciences	Endocrine disruptors	https://www.niehs.nih.gov/health/topics/agents/endocrine
PUBMED	***Obesity + pesticides***	Yuqing Zhang, Tianyu Dong,	Association between	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/30557812/

		Weiyue Hu et all.	exposure to a mixture of phenols, pesticides, and phthalates and obesity : Comparison of three statistical models	
		Philippa D Darbre	Endocrine Disruptors and Obesity	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/28205155/
		Rosiane Aparecida Miranda, Beatriz Souza Silva, Egberto Gaspar de Moura et all.	Pesticides as endocrine disruptors : programming for obesity and diabetes	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/36301509/
		Bingnan He, Yinhua Ni, Yuanxiang Jin et all.	Pesticides-induced energy metabolic disorders	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/32388131/
		Robert M Gutgesell, Evangelia E Tsakiridis, Shanza Jamshed et all.	Impact of pesticide exposure on adipose tissue development and function	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/32726435/
		Viviana Ramirez, Patricia Gonzales-	Effect of exposure to endocrine disrupting	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/36007653/

		Palacios, Miguel A Baca et all.	chemicals in obesity and neurodevelopment : The genetic and microbiota link	
		Duk-Hee Lee, Miquel Porta, David R Jacobs Jr et all.	Chlorinated persistent organic pollutants, obesity, and type 2 diabetes	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/24483949/
	Obesity + organochlorines	**Rosiane Aparecida Miranda, Beatriz Souza Silva, Egberto Gaspar de Moura et all.**	**Pesticides as endocrine disruptors : programming for obesity and diabetes**	**https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/36301509/**
		Michele La Merrill, Linda S Birnbaum	Chilhood obesity and environmental chemicals	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/21259261/
		Carolina Martins Ribeiro, Bruna Teles Soares Beserra, Nadyellem Graciano Silva et all.	Exposure to endocrine-disrupting chemicals ans anthropometric measures of obesity : a systematic review and meta-analysis	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/32565448/

		Nikos Stratakis, Sarah Rock, Michele A La Merril et all.	Prenatal exposure to persistent organic pollutants and childhood obesity : A systematic review and meta-analysis of human studies	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/34766696/
		Elin V Magnusdottir, Tanja Thorsteinsson, Sigridur Thorsteinsdottir et all.	Persistent organochlorines, sedentary occupation, obesity and human male subfertility	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/15567884/
	Pesticides + endocrines disruptors	**Rosiane Aparecida Miranda, Beatriz Souza Silva, Egberto Gaspar de Moura et all.**	**Pesticides as endocrine disruptors : programming for obesity and diabetes**	**https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/36301509/**
		Haotang Zhao, Honghao Qian, Jianwei Cui et all.	Endocrine toxicity of atrazine and its underlying mechanisms	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/38815618/
		Shi-Yu Qi, Xue-Ling Xu, Wen-Zhi Ma et all.	Effects of organochlorine pesticide residues in	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/35757428/

			maternal body on infants	
		R McKinlay, J A Plant, J N B Bell et all.	Endocrine disrupting pesticides : implications for risk	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/17881056/
	Pesticides + obesogens	Bayram Yilmaz, Hakan Tereci, Suleuman Sandal et all.	Endocrine disrupting chemicals : exposure, effects on human health, mechanism of action, models for testing and strategies for prevention	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/31792807/
		Yuqing Zhang, Tianyu Dong, Weiyue Hu et all.	**Association between exposure to a mixture of phenols, pesticides, and phthalates and obesity : Comparison of three statistical models**	**https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/30557812/**
		Mallory D Griffin, Sean R Pereira,	Mechanisms of action, chemical characteristics,	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/32903358/

		Megan K DeBari et all.	and model systems of obesogens	
		Nitazi Emre Kursunoglu, Banu Pinar Sarer Yurekli	Endocrine disruptors chemicals as obesogen and diabetogen : Clinical and mechanistic evidence	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/36387809/
		Annalise N Vonderembse, Sarah E Elmore, Kyle B Jackson et all.	Developmental exposure to DDT or DDE alters sympathetic innervation of brown adipose in adult female mice	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/33794904/
	Pesticides + gene expression modifications	M Collotta, P A Bertazzi, V Bollati	Epigenetics and pesticides	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/23380243/
		Rahul Mittal, Nathanael Camick, Joana R N Lemos et all.	Gene-environment interaction in the pathophysiology of type 1 diabetes	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/38344660/
		Maria Florencia Rossetti, Guillermina Canesini,	Epigenetic changes associated with exposure to glyphosate-	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/34093442/

		Virginia Lorenz et all.	based herbicides in mammals	
		Michel B Vandegehuchte, Colin R Janssen	Epigenetics and its implications for ecotoxicology	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/21424724/
	Pesticides and health issues	**Christos A Damalas, Ilias G Eleftherohorinos**	**Pesticide Exposure, Safety Issues, and Risk Assessment Indicators**	**https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/21655127/**
		Gustavo Dos Santos Souza, Luciana Cristina Alves da Costa, Alana Coelho Maciel et all.	Presence of pesticides in atmosphere and risk to human health : a discussion for the Environmental Surveillance	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/29069183/
		Kushik Jaga, Chandrabhan Dharmani	Sources of exposure to and public health implications of organophosphate pesticides	https://pubmed-ncbi-nlm-nih-gov.buadistant.univ-angers.fr/14653904/
	Persistent organic pollutants	Diogo Pestana, Gil Faria, Carla Sa et al.	Persistent organic pollutant levels in human visceral	https://pubmed.ncbi.nlm.nih.gov/24949816/

			and subcutaneous adipose tissue in obese individuals - depot differences and dysmetabolism implications	
GOOGLE SCHOLAR	***Obesity + pesticides***	**Rosiane Aparecida Miranda, Beatriz Souza Silva, Egberto Gaspar de Moura et all.**	**Pesticdes as endocrine disruptors : programming for obesity and diabetes**	**https://link-springer-com.buadistant.univ-angers.fr/article/10.1007/s12020-022-03229-y**
		Magdalena Czajka, Magdalena Matysiak-Kucharek, Barbara Jodlowska-Jedrych et all.	Organophosphorus pesticides can influence the development of obesity and type 2 diabetes with concomitant metabolic changes	https://www-sciencedirect-com.buadistant.univ-angers.fr/science/article/pii/S0013935119304827
		Helena Pinos, Beatriz Carrillo, Ana Merchan et all.	Relationship between prenatal or postnatal exposure to pesticides and obesity : A	https://www.mdpi.com/1660-4601/18/13/7170

			systematic review	
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		with obesity and diabetes	

DAUBAIRE Morgane

Mini revue sur les liens entre une exposition environnementale aux pesticides et l'obésité

RÉSUMÉ

Malgré la fréquente utilisation des pesticides, il est encore difficile de prédire les risques d'une exposition chronique à faibles doses et en mélange de ces produits pourtant réglementés. En effet, du fait de leur caractéristique lipophile entrainant leur rémanence dans les sols et les eaux ainsi que dans le tissu adipeux, il est difficile de mesurer l'exposition réelle aux pesticides. L'objectif de cette mini-revue est donc de tenter de déterminer s'il existe un lien entre cette exposition chronique aux pesticides et le développement de maladies comme l'obésité. Ainsi, au travers de différentes études, il a été démontré que l'usage intensif de pesticides était corrélé à une augmentation des cas d'obésité dans les régions concernées. Les effets des pesticides ont notamment été soulevés sur les récepteurs nucléaires PXR, CAR, PPAR ou encore ER de par leurs actions de perturbateurs endocriniens. Les pesticides sont également impliqués dans une augmentation de la résistance à l'insuline ainsi qu'une modification de l'homéostasie lipidique. Il est également important de prendre en compte les possibles effets des mélanges et effets transgénérationnels de l'exposition chronique aux pesticides. Il a notamment été démontré que les enfants dont les mères ont été exposés aux pesticides pendant la grossesse, avaient plus de risques de développer certaines maladies comme l'obésité, laissant ainsi suspecter d'une fenêtre de vulnérabilité. Ce domaine de recherche est donc encore vaste et les biais encore nombreux (difficile mesure des doses d'exposition, effets cocktails, variations inter-individuelles, multiples voies d'exposition, etc.).

Mots-clés : exposome, pesticides, obésité, perturbateurs endocriniens, polluants organiques persistants, effets cocktails, effets chroniques

Mini review on the links between exposure to pesticides and obesity

ABSTRACT

Despite the frequent use of pesticides, it is still difficult to predict the risks of chronic exposure to low doses and mixtures of these regulated products. In fact, because of their lipophilic nature, which means that they persist in soil and water as well as in fatty tissue, it is difficult to measure actual exposure to pesticides. The aim of this mini review is therefore to attempt to determine whether there is a link between chronic exposure to pesticides and the development of illnesses such as obesity in the regions concerned. Various studies have shown that the intensive use of pesticides is correlated with and increase in obesity. The effects of pesticides on the nuclear receptors PXR, CAR, PPAR and ER have also been highlighted as endocrine disruptors. Pesticides have also been implicated in increased insulin resistance and altered lipid homeostasis. It is also important to take into account the possible effects of mixtures and the transgenerational effects of chronic exposure to pesticides. In particular, it has been shown that children whose mothers were exposed to pesticides during pregnancy were more likely to develop certain illnesses, such as obesity, suggesting a window of vulnerability. This area of research is still vast, and there are still many biases (difficult to measure exposure doses, cocktails effects, inter-individual variations, multiple exposure routes, etc.).

Keywords : exposome, pesticides, obesity, endocrine disruptors, persistent organic pollutants, cocktails effects, chronic effects