How advanced are we on the consequences of oral exposure to food contaminants on the occurrence of chronic non communicable diseases?

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Review

How advanced are we on the consequences of oral exposure to food contaminants on the occurrence of Chronic Non Communicable Diseases?

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Abstract: The development of an individual during fetal life and childhood is characterized by rapid growth as well as gradual maturation of organs and systems. Beyond the nutritional intake in essential nutrients, food contaminants can permanently influence the way organs mature and function. These processes are called "programming" and play an essential role in the occurrence of non-communicable chronic diseases throughout the lifespan. Populations as pregnant women, fetuses and young children are vulnerable and particularly sensitive to food contaminants which can induce epigenetic modifications transmissible to future generations. Among these contaminants, pesticides are found in most food matrices exposing humans to cocktails of molecules through variable concentrations and duration of exposure. The Maillard reaction products (MRPs) represent other food contaminants resulting from heat treatment of food. Modern diet, rich in fats and sugars, is also rich in neoformed pathogenic compounds, Advanced Glycation End products (AGEs), the levels of which depend on the heat treatment of foods and eating habits and whose effects on health are controversial. In this review, we have chosen to present the current knowledge on the impacts of selected pesticides and MRPs, on the risk of developing during life non-communicable chronic diseases such as IBD, metabolic disorders or allergies. A large review of literature was performed via Pubmed, and the most appropriate studies were summarised.

Keywords: Perinatal period; food contaminants; pesticides; neoformed compounds; allergies; obesity; metabolic dysfunction; gut inflammation; non-communicable chronic diseases

Terms used in order to perform the bibliographic analysis: mancozeb/glyphosate/organophosphorus/metabolic disorders; organophosphorus/metabolic disorders/obesity/metabolic syndrome; food allergy; food contaminants; food pollutants; atopic march; development of allergy; pesticides/allergy; pesticides/asthma; pesticides/atopic disease; organophosphorus/allergy; food contaminants/allergy; AGE/Maillard reaction products/IBD/allergy/inflammation/metabolic syndrome/obesity; pesticides/IBD; pesticides/crohn's disease; pesticides/ulcerative colitis; epigenetics/allergy; epigenetics/metabolic syndrome/obesity; epigenetics/IBD/inflammation.

1. Introduction

Development during fetal life and infancy is characterized by rapid growth as well as maturation of organs and systems. Food contributes to tissular growth thanks to the metabolism and absorption of nutrients. However, our diet also contains numerous environmental contaminants ranging from residues (pesticides, mycotoxins …) to neoformed compounds (HAP, Maillard Reaction Products …) that are said to be contributing to the appearance of non-communicable diseases. As thus, beyond the changes in food quality and quantity and the nutrients brought to the developing child, food contaminants may permanently influence the way these organs mature and function. These effects are termed as "programming" and play an important role in the occurrence of chronic non-communicable diseases through the lifespan and the early like period is a window of life particularly sensitive to food contaminants due to the maximal vulnerability of the individual. Some contaminants may alter the programmed expression of some genes, resulting in

effective remodeling of tissue structure and functionality. When this phenomenom concerns germinal cells, these epigenetic modifications can be transmitted to further generations, adding evidence that hereditable epigenetic modifications play a critical role in nutritional programming. Among food contaminants, pesticides residues constitute an ubiquitous groups of molecules in food matrices to which we are exposed to throughout life, in variable duration and concentrations. The consequences of exposure can be very variable and depend on the timing, length and dose of exposure, but also on the chemical class considered. Another category of food contaminants belongs to those generated through domestic or industrial process of food. Among them, Maillard Reaction Products (MRPs) are produced during heat treatment of food and represent a large family of molecules ranging from early to more complexed ones. They occur between sugars and proteins in foods when they are cooked at mildly to high temperature. This reaction not only produces flavoring compounds but also molecules potentially toxic to health and involved in aging. This non-enzymatic glycation, that also takes place naturally in the human body, may generate some glycotoxins known to alter our health status, the dietary Advanced Glycation End products (AGEs) whose levels are known to be modulated by the heat treatment of the food matrix or diet habits. Controversial effects of those AGEs on health are described in the literature in some studies and deserve to be discussed. In this work, we will focus and summarize the actual understanding and knowledge about the impacts of different classes of pesticides (organophosphates, glyphosate, mancozeb, diquat), and MRPs on the risks of developing later in life chronic non-communicable diseases (NCDs) such as metabolic disorders, inflammatory bowel disease (IBD), and allergies. According to the World Health Organization (WHO), NCDs, also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioural factors. The main types of NCDs are cardiovascular diseases (such as heart attacks and stroke), chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma), cancers, diabetes and associated metabolic diseases, chronic inflammatory bowel diseases (IBD such as Crohn's disease and ulcerative colitis) and allergies. NCDs kill 41 million people each year, equivalent to 71% of all deaths globally. More than 15 million people die from a NCD between the ages of 30 and 69 years every year and 85% of these "premature" deaths occur in low- and middle-income countries. Alcohol consumption, tobacco use and physical inactivity but also unhealthy diets all increase the risk of dying from a NCD. In this review, we have specifically focused on metabolic syndrome and obesity, IBD and allergies.

The objectives of our review were to focus on the consequences of perinatal exposure to food contaminants on the occurrence of chronic non-communicable diseases during life. However, when data related to the perinatal period were not available, we included results from adults as well as in cellular model studies.

2. Food contaminants and the occurrence of metabolic disorders

Childhood obesity is now globally considered as an epidemia. Within twenty years, it has established itself permanently in the pediatric field. Many diseases, previously considered to be exclusive of adulthood (e.g "idiopathic" arterial hypertension, dyslipidemia, type 2 diabetes…) have appeared in children and adolescents, with imaginable difficulties of immediate management and especially in the long term. These factors increase cardiovascular risks and can occur simultaneously in the individual, constituting a nosological entity which takes the name of metabolic syndrome. There is currently no unanimous consensus to define metabolic syndrome in children. The treatment of the metabolic syndrome is based, first of all, on the management of obesity and possibly on the treatment of comorbidities. The development of prevention and treatment strategies requires a global vision of the metabolic syndrome, interpreted as a continuum and not as a frozen entity. In adults, metabolic syndrome is characterized by a large waist circumference (due to excess abdominal fat), high blood pressure, resistance to the effects of insulin (insulin resistance) or diabetes, and levels of cholesterol and other abnormal blood lipids (dyslipidemia). In 2016, more than 1.9 billion adults, 18 years-old and older, were overweight. Of that total, over 650 million were obese. Globally, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. The prevalence of obesity tripled globally between 1975 and 2020 when an estimated 38.2 million children under 5 were overweight or obese. Once considered as a specific

problem of high-income countries, overweight and obesity are now on increasing in low- and middle-income countries, especially in urban areas (WHO, 2021). Beyond aspects of food quality and balance, the presence of food contaminants is increasingly suspected in the occurrence of metabolic pathologies. Pesticides residues are found in conventional crops and may be ingested by pregnant women and infants as early as food diversification if prepared domestically. Among the large panel of pesticides, we chose to focus on organophosphates and glyphosate because they are still widely used in intensive agriculture, can be found as residues in food and are said to be involved in the occurrence of chronic non-communicable diseases.

2.1. Pesticides residues and metabolic disorders

2.1.1. Organophosphates

Organophosphates (OPs) pesticides represent a major class of pest control products used for many years in agriculture to replace very toxic organochlorines. OPs are frequently used insecticides acting as cholinesterase activity inhibitors. In human, they are absorbed through the digestive tract, lungs and skin and may cause acute muscarinic manifestations and some nicotinic symptoms. By inhibiting plasma and erythrocyte cholinesterase, they prevent the breakdown of acetylcholine, which then accumulates in synapses but can irreversibly bind to cholinesterase. Due to their many very well-documented effects on the nervous system, their effects can therefore be multi-system and then alter metabolic function. In a cohort of 300 participants from Cameroon and Pakistan, Leonel Javeres et al (Leonel Javeres et al., 2021) measured the presence of malathion, parathion and chlorpyrifos residues in Cameroonian workers urine samples, and malathion and chlorpyrifos in Pakistani workers samples, respectively. Striking data obtained from the samples as an elevated body mass index (BMI), elevated insulin and blood glucose, dyslipidemia and hypertension appeared as hallmarks of OPs exposure, associated to liver and kidney dysfunctions. Such studies help us to conclude that the metabolic dysregulations associated to chronic exposure to OPs may provide precursors for establishment of metabolic syndrome and other chronic diseases.

With both human studies and experimental models, an exposure to OPs was described to be associated with the inhibition of cholinesterase enzymatic activity and more especially to butyrylcholinesterase (BuChE). A link may exist between metabolic syndrome, diabetes and obesity and the modulation of this enzyme activity. Indeed, the study of Molina-Pintor et al (Molina-Pintor et al., 2020) aimed at evaluating the lipid parameters in urban sprayers and their association with BuChE activity. This group showed that the level of exposures to pesticides was correlated to variations in glucose, cholesterol, albumin, atherogenic index, creatinine, LDL, VLDL, triglycerides and total lipids in people suffering from overweight and obesity. Additionally, a positive correlation was identified between BuChE activity and lipid parameters, effects associated with the body mass index. In humans, the evaluation of the prenatal environment is not as easy to run as some animal studies might suggest for the evident reason that the many factors involved are difficult to analyze separately. Indeed, joint environmental factors can accelerate or accentuate physiological processes or on the contrary limit them. In the case of type 2 diabetes, there are not many and very clearly argued data on prenatal exposure to certain factors and the long-term effects associated with them. The study from Debost-Legrand and collaborators (Debost-Legrand et al., 2016) was aimed at evaluating the effects of prenatal exposure to persistent organic pollutants (POP) and OPs on fetal markers of glucose metabolism in a sample of newborns from the Pelagie mother-child cohort in Brittany (France). In order to identify and measure dialkylphosphate (DAP), a metabolite of OPs, maternal urine samples were collected at the beginning of pregnancy. Other molecules of interest were also assayed from cord blood samples: POPs, adiponectin and insulin serum levels. They identified lower adiponectin and insulin levels related to increased levels of dichlorodiphenyl dichloroethene (DDE) in girls but not boys, while the adiponectin levels were not dependent of other POP and DAP metabolites and insulin levels increased with DAP urinary levels. Those results were in agreement with a potential role of OPs and POP in the alterations of glucose metabolism observed at birth. In the Canadian study of Ranjbar and colleagues (Ranjbar et al., 2015), they determined whether detectable levels of OPs

metabolites influence the relationship between BMI and cardiometabolic health. Independent of BMI, individuals with detectable metabolites suffered from higher diastolic blood pressure, lower HDL and higher triglycerides levels. On the contrary, those with detectable DMTP had better LDL, HDL, and total cholesterol levels, independent of BMI. They concluded that cardiometabolic health outcome differs depending on the specific OPs metabolite being examined, with higher BMIs amplifying health risks.

Animal models of exposure to OPs, which are most often chronic models, underline the relevance of the informations obtained with regard to data in humans. Rats chronically exposed to monocrotophos (MCT) at 0.9 and 1.8 mg/kg bw/d for 180 days displayed increased fasting glucose, hyperinsulinemia and dyslipidemia (Nagaraju et al., 2020). Interestingly, tumor necrosis factor-alpha and leptin levels were elevated, while plasma adiponectin level was suppressed in treated rats. In association with these features, perirenal and epididymal weights of white adipose tissues were found increased. Corroborative changes were also observed in the expression profiles of proteins that are involved in lipogenesis and adipose tissue differentiation, demonstrating that a long-term exposure to OPs such as MCP has obvious consequences on the metabolism as evidenced by the association of adipogenic outcomes with insulin resistance, hyperinsulinemia, endocrine dysregulations, and dyslipidemia.

Chlorpyrifos (CPF) is a widely used OP pesticide which is frequently detected in fruits, vegetables, as in human fluids as blood and urine. Many studies presented below have suggested that CPF can induce metabolic disruption, such as type-2 diabetes mellitus and changed body weight. The main mechanisms are linked to oxidative damage, fatty acid synthesis, and lipid peroxidation. The reproductive hormone levels can also be affected by CPF exposure and finally result in metabolic disorder (Li et al., 2019). One main mechanism may be the disruption of the gut microbiota homeostasis which may induce low-grade inflammation leading to obesity-related diseases. Indeed, in normal conditions, the mucus layer exerts the heavy task of keeping microbiota bacteria away from the intestinal epithelium. In order to identify a potential link between insulin resistance/obesity and an interference of pesticides on mucus-bacterial interactions, Liang and colleagues (Liang et al., 2019a) determined how long-term exposure to CPF affected C57Bl/6 and CD-1 mice fed high- or normal-fat diets. In addition, to identify the effects of CPF-altered microbiota, antibiotic treatment and microbiota transplantation experiments were achieved. They showed that CPF altered the integrity of the intestinal epithelial barrier at the origin of a low-grade inflammation through the entry of bacterial lipopolysaccharide, the diet pattern influence being limited. Interestingly, the mice given CPF-altered microbiota gained more fat and lower insulin sensitivity, giving more attention to the role of OPs in the worldwide epidemic of inflammation-related diseases.

Since human data are not available, the results from animal models are of great help to predict the consequences on our health. During the neonatal period, rats were administered three different pesticides, chlorpyrifos, diazinon or parathion at doses devoid of any acute signs of toxicity (Slotkin, 2011). OPs exposure during a critical developmental window altered the trajectory of hepatic adenylyl cyclase/cyclic AMP signaling reaching a final hyperresponse to gluconeogenic stimuli. As a consequence, rats developed a metabolic dysfunction being very close to prediabetes. Interestingly, the association between OPs exposure and an obesogenic diet (high-fat diet) in adulthood intensified the metabolic deficiencies as observed by an excess weight gain compared to unexposed rats on the same diet. Surprisingly this study also revealed that the HFD had the ability to improve some of the central synaptic flaws caused by OPs. These studies suggest how common insecticides may contribute to the increased worldwide incidence of obesity and diabetes. Even if the administration of the OP pesticide diazinon has not been performed during the perinatal period or in young animals, the study of Salek-Maghsoudi and collaborators (Salek-Maghsoudi et al., 2019) is noteworthy regarding the results obtained. Vaspin is an adipocytokine recently identified as a modulator of obesity with insulin-sensitizing effects. Insulin-resistant rats were administered HFD and diazinon (DZN; 70 mg/kg) during 30 days. As other OPs, DZN significantly inhibited almost 50% of the plasma cholinesterase activity. A strong increase of MDA and reactive oxygen species (ROS) levels was observed in groups that received DZN and DZN + HFD, as also noticed for TNF-α. In all the treated groups, insulin levels significantly increased, accompanied by a severe fatty change in HFD + DZN-treated group. The highest increase in vaspin level was observed in HFD group followed by DZN-treated animals.

Consequently, in contrast to oxidative stress and inflammatory biomarkers, vaspin level would be a more reliable diagnostic factor when it comes to the insulin resistance. There is growing evidence of the role of the gut microbiome in human health. Many studies also show the role of environmental toxicants in altering the gut microbiome and its metabolic functions. By using a mouse model, metabolomics profiling revealed an altered metabolic profile after exposure to DZN. Such an exposure altered the gut microbiome community structure, functional metagenome and associated metabolic profiles in a sex-specific manner (Gao et al., 2017). Possible effects of different kinds of widely used pesticides on the gut microbiota in different experimental models is discussed and the authors analyzed their possible subsequent effects on the health of the host. Many studies indicated that the gut microbiota of animals played a strong role in pesticides-induced toxicity (Yuan et al., 2019).

2.1.2. Glyphosate

Glyphosate (N- (phosphonomethyl) glycine, C3H8NO5P) is the most widely used herbicide in the world. It is a systemic, ie non-selective, leaf absorbing, systemic total foliar herbicide. Exclusively produced by Monsanto from 1974 (under the Roundup® brand), it is also produced by other firms since its patent passed into the public domain (in 2000). The rate of degradation of glyphosate depends on the type of soil. It can persist, along with its degradation product, the aminomethylphosphonic acid (AMPA), for more than a year in soils with a high clay content but is leached much more quickly in sandy soils. Due to its widespread use, glyphosate or AMPA is now commonly found in rain, various water sources or in sediment. Treatments on crops close to harvest partly explain why glyphosate is found in food. Laboratory studies have shown that ingested glyphosate and AMPA are absorbed from 15 to 40% and at about 20% respectively.
Glyphosate is still the best-selling weedkiller in the world, sprayed every year on millions of hectares. Its use has increased by approximately 100 times in the world in 40 years (from 1974 to 2014). Globally, nearly 0.5 kg of glyphosate-based pesticide is reportedly sprayed per hectare (Vandenberg et al., 2017). Pigs are the most common food animal species across the globe for human consumption. It also represents a good model to investigate the consequences on human health due to its close physiological mechanisms. As thus, studying the effects of glyphosate on their health would be a good approach to evaluate its consequences on human health. In order to define the impact of glyphosate on microbiota and the consequences on their long-term health, Krause and collaborators applied glyphosate on cultivated intestinal microbiota resembling a worst-case scenario for an 8-9 week-old pig, i.e. the physiological weaning stage (Krause et al., 2020). As a consequence, the glyphosate formulation Roundup® LB plus did not affect the community taxonomy or the enzymatic repertoire. Significant impacts of Roundup® LB have not been observed by targeting metabolites as short chain fatty acids (SCFA), free amino acids and bile acids whereas other meta-metabolomics approaches did identify some effects on the functional level, providing evidence for metabolic effects of Roundup® LB plus upon those specific experimental conditions. Furthermore, through the help of the 16S sequencing analysis approach, the study of Lozano and collaborators (Lozano et al., 2018) identified variations of bacteria species after long-term exposure to three different doses of glyphosate and formulants in Sprague-Dawley rats. This study revealed an increase of Bacteroidetes and a decrease of Lactobacillaceae, and the presence of a high tolerant or resistant strain of *Escherichia coli* explained by the absence of a gene coding glyphosate target enzyme. As many other pesticides, glyphosate residues are largely detected in the environment and aquatic systems and alter its equilibrium. Exposure of juvenile common carp to glyphosate for 45 days was hepatotoxic. This was confirmed by serum liver damage biomarkers and hepatic histopathological analysis. Interestingly, oxidative stress was found an early event, followed by hepatic inflammatory response. Lipid metabolism disorder was a late event during glyphosate exposure, as evidenced by overproduced hepatic free fatty acids, enhanced lipogenesis-related gene expression levels, reduced lipolysis-related gene expression levels, and resultant hepatic lipid accumulation (Liu et al., 2021). The toxicity of glyphosate-based herbicide was also tested on goldfish (Carassius auratus) after long-term exposure. After harvesting specimens of blood, brain, kidney and liver tissues, NMR-based metabolomics analysis have been performed. The results revealed that a long-

term exposure to glyphosate caused disorders of blood biochemical indexes and renal tissue injury in goldfish. Further studies provided additional data on the toxicity of glyphosate with metabolomics approaches giving rise to an identification of oxidative stress and several markers of cell metabolism dysfunction. Associated to these parameters, metabolomics analysis combined with correlation network analysis uncovered significant perturbations in oxidative stress, energy, amino acids and nucleosides metabolisms in glyphosate dosed fish, providing new clues to the toxicity of glyphosate (Li et al., 2017) . In a recent study published in the journal Microbiome (Suppa et al., 2020), Suppa and colleagues used a biology approach system to the biomedical and ecological model species Daphnia to evaluate and quantify the impact of glyphosate and of its commercial formula Roundup®, on microbiota changes. As an important result, the functionality and composition of the microbiota is altered by the weed killer chronic exposure by interference from carbon or fat metabolism. They also identified conserved pathways which are potential targets for Roundup® in other species, including collagen degradation involved in the repair of wounds and tissue remodeling, liver metabolism and inflammation pathways. Then, by using the interesting model species Daphnia, occupying a central position in the food web of aquatic ecosystems, the authors provided significant findings that chronic exposure to concentrations of glyphosate at the approved regulatory threshold for drinking water causes alteration of key metabolic functions via indirect effects on the microbiota. This fact raises a potential environmental threat and triggers public health concerns. For many years, scientists and different industry-paid studies have provided evidence that the weedkiller has no adverse effects on humans or animals. However, a growing body of evidence suggests that dysbiosis of the gut microbiota induced by environmental pollutants, particularly pesticides, may play a role in the occurrence of metabolic disorders. Then based on all these data, the potential side effects of glyphosate on the intestinal microbiota of various animals, from honeybees to livestock and humans, are currently under investigation.

Reference	**Size human population/animal model/cells/exposure**	**Samples/markers analyzed**
Pesticides residues and metabolic disorders		
Leonel-Javeres et al, 2021	Human cohort 300 participants, evaluation of the possible metabolic dysregulations as a consequence of chronic OPPs exposure	Blood samples, BMI, insulin, blood glucose
Molina-Pintor et al, 2020	Analytical cross sectional study, 208 urban sprayers, evaluation of lipid parameters in urban sprayers and their association with BuChE activity	BuChE activity, lipid and metabolic parameters
Debost-Legrand et al, 2016	Pelagie cohort of 3421 pregnant women in Brittany (2002-2006), 601 births, 579 urine and 394 cord blood samples	Urine, blood, PCB congeners, DDE, POPs, insulin, adiponectin
Ranjbar et al, 2015	Cross-sectional study, 2227 adults from NHANES datasets, determine whether detectable levels of OP metabolites influence the relationship between BMI and cardiometabolic health	Urine samples, DAP metabolites, blood pressure, lipid and metabolic parameters
Nagaraju et al, 2020	Wistar rats, chronic exposure to MCP (0.9 and 1.8 mg/kg bw/180 d)	Blood, perirenal and epididymal white adipose tissues, metabolic and enzymatic markers
Li et al, 2019	Review, studies showing that CFP causes metabolic disruption and changes RH levels	

Liang et al, 2019	C57Bl/6 and CD-1 male mice (n=8/gp), 5 mg/kg bw oral CPF for 4 mo	Blood, epididymal adipose tissue, colon, liver, food intake, microbiota, biochemical markers
Slotkin et al, 2011	Review, studies showing how common insecticides may contribute to the increased worldwide incidence of obesity and diabetes.	
Salek-Maghsoudi et al, 2019	Insulin-resistant rats/HFD, diazinon 70 mg/kg bw	Blood, liver, ChE activity, metabolic markers, inflammatory and oxidative stress markers
Gao et al, 2017	Mice treated wih diazinon	Gut microbiome, metagenome, metabolic profiles
Yuan et al, 2019	Review, effects of different kinds of widely used pesticides on the gut microbiota in different experimental models	
Vandenberg et al, 2017	Review (humans), informations on glyphosate-based herbicides use, exposures, mechanisms of action, toxicity and epidemiology	
Krause et al, 2020	Pigs (n=2) exposed to 228 mg glyphosate (max dietary burden of 2.85 mg/kg bw/d)=worst case scenario	Microbiota, enzymatic activities
Lozano et al, 2018	Sprague-Dawley rats (n=3 each dose, 3 males and 3 females/gp, 0.1 ppb, 400 and 5000 ppm in tap water)	Microbiota analysis
Liu et al, 2021	Juvenile common carp, sub-chronic exposure to 0.5 and 50 mg/l glyphosate for 45 d	Plasma, liver, hepatic biomarkers, inflammatory and oxidative markers, lipid markers
Li et al, 2017	Goldfish, glyphosate 0.2 mmol/l, 90 d	Plasma, brain, kidney, liver, metabolic markers in liver, oxidative stress markers, energy metabolism
Suppa et al, 2020	Daphnia magna, chronic exposure to ecologically relevant concentrations	Fitness-linked life history traits, genome-wide transcription, microbiota

Table 1: References related to pesticides residues and metabolic disorders. Different parameters are indicated as the size of human cohorts, the animal model or cells used, the type of exposure, and the samples and markers analyzed.

2.2. Maillard Reaction Products and metabolic disorders

During the last century, in many western countries, the food system has gone through major transition to get commercially efficient highly processed and readily available food products. To maintain food quality and safety, food preparation has been using additives and successive processes among which sometimes intensive thermic treatment. Heat treatment of food generates multiple chemical reactions inside the food matrix. One, the non-enzymatic glycation or the Maillard reaction, is responsible for the appearance and development of taste and aroma of food as well as the browning of the food matrix. Maillard reactions products represent a large family of molecules ranging from the early ones (Amadori products) to the most complexed ones: the melanoidins resulting from the rearrangement of

intermediary products, the Advanced Glycation End products (AGEs). As thus, modern western diet may not only be rich in fat, sugar and salt but also in neoformed pathogenic compounds known as dietary AGEs whose levels are known to be modulated by the heat treatment of the food matrix or by diet habits (Krajčovičová-Kudláčková et al., 2002). Baby and infant diet do not escape this process either through infant formula or baby food preparation. Furthermore, the Maillard reaction is also an endogenous reaction which tends to increase while ageing. While an increase of circulating AGEs is clearly associated to chronic inflammatory diseases ranging from nephropathy to metabolic syndrome, there is no few evidences on the contribution of food born AGEs on those effects. The most common AGEs markers measured in food are pentosidine, carboxy-methyllysine (CML), hydroxymethylfurfural (HMF) or acrylamide (AA). They are partially absorbed into circulation (Somoza et al., 2006; Uribarri et al., 2005). Acrylamide is a ubiquitous chemical contaminant present in carbohydrate/asparagin rich food. Its glycation of hemoglobin is positively correlated to obesity. It may bond to DNA which results in genotoxic and carcinogenic properties. As thus, AA has been classified as a probable human carcinogen by the International Agency for Research on Cancer (IARC, 1994). Presence of AA in HFD increases body weight, fat mass and organ weight in mice (Lee and Pyo, 2019). According to the authors, the upregulation of adipogenesis by AA is due to the regulation of the MAPKs and the AMPK-ACC pathways. While the toxic effects of acrylamide are widely acknowledged, the consequences of other AGEs are still under investigation since, depending on the context their fate on health may be different. At last, melanoidins the most complex molecules formed through the Maillard Reaction taking place during food processing and preservation may have interesting effects on health. These molecules are generally anionic coloured compounds that have been suggested to have antioxidant, anti-inflammatory and prebiotics properties (Morales et al., 2012). Administration of melanoidins from black garlic to C57Bl/6J mice under High Fat Diet (HFD) limited their weight gain and reversed glucose tolerance. This was associated with alleviation of dyslipidemia, reduction of hepatic lipid accumulation and steatosis but also reduction of serum LPS levels and modulation of the gut microbiota (Wu et al., 2020). Furthermore, the administration of aged black garlic to Sprague Dawley male rats receiving a high sucrose/high fat diet was evaluated for its benefits in the context of obesity and diabetes. The study confirmed that animals had a lower caloric intake associated to a lower body weight gain, and that serum concentrations of triglycerides, low density lipoprotein cholesterol (LDL-c), insulin and leptin were reduced while they observed higher high density lipoprotein cholesterol (HDL-c) and adiponectin serum concentrations than in non-treated rats (Amor et al., 2019). These metabolic changes were correlated to an increase in the expression of gene coding for proopiomelanocortin (POMC) and a decrease in leptin receptor (ObR) mRNA levels in the hypothalamus and an overexpression of β3-adrenergic receptor (β3-ADR) in the visceral adipose tissue. However, while investigations on the consequences of MRPs on health have been running for many years now, there are very few studies related to the role of dietary MRPs on pregnant women and baby's health during infancy and later in life. Nonetheless, it has been stated that prenatal exposure of female rats to a diet rich in MRPs resulted in altered metabolic status of dams and of insulin resistance and oxidative stress in the offspring (Gurecká et al., 2015). Those results were corroborated by similar results in human. Infants of mothers showing elevated circulating AGEs, i.e. glycotoxins, had higher plasma insulin and lower adiponectin levels than infants from mothers with low AGEs levels (Mericq et al., 2010). These levels were close to those found in individuals suffering from diabetes or chronic liver disease. Authors concluded that excess AGEs transferred via placenta or fed to infants could promote the appearance of chronic diseases such as diabetes at a later

time. These data shall be taken seriously since several studies have evidenced that significant amounts of some AGEs such as AA and CML were present in infant canned food and infant powdered milk (Charissou et al., 2007; Ghiasi et al., 2021). As for AA, the perinatal oral exposure may represent a strong hazard to health since it is quickly absorbed via the oral route and due to its hydrosolubility. A Norwegian study recently evidenced that prenatal AA exposure was negatively associated to fetal growth but was positively correlated to a moderate increase in weight growth velocity during early childhood (Kadawathagedara et al., 2018). Moreover, this presence of high levels of AGEs in infant milk and infant formula feeding has been demonstrated to be at the origin of a decreased insulin sensitivity (Birlouez-Aragon et al., 2004). This phenomenon not only concern the offspring but also the descending generations of an individual. Indeed, the consumption by C57BL6 mice of isocaloric diets containing AGEs (synthetic methyl-glyoxal-derivatives) during four generations was found to increase adiposity, insulin resistance and diabetes with marked deficiency of AGER-1 and SIRT-1 (anti AGER-1) and sirtuin 1 in white adipose tissue, liver and skeletal muscle (Cai et al., 2012). Authors concluded in a strong contribution of AGEs exposure at a perinatal stage on the development of chronic non-communicable diseases later in life.

The studies concerning the products of the Maillard reaction and their impact on health are not very extensive in the literature, which has led us to keep all the data found in humans as in animals. Indeed, *in vitro* treatment of 3T3-L1 preadipocytes with CML resulted in lipid accumulation in the cells. This was associated to the increased expression of miR-103 and miR-143, two miRNA known to be correlated with impaired glucose homeostasis and increased lipid accumulation (Holik et al., 2016). Furthermore, in the same study, the authors demonstrated that short term treatment of mature 3T3-L1 adipocytes with CML decreased basal uptake of glucose by the cells.

Reference	**Size human population/animal model/cells/exposure**	**Samples/markers analyzed**
Maillard Reaction Products and metabolic disorders		
Krajčovičová-Kudláčková et al., 2002	Humans, 2 population groups (n=19 each, vegetarians vs omnivorous)	BMI, CML levels, food intakes
Somoza et al., 2006	Adult male Wistar rats (n=6/group), MRPs administered to rats 10 d	Feces, urine, liver, kidney samples
Uribarri et al., 2005	Review; generation of AGEs during the cooking of food, the gastrointestinal absorption of these compounds, and their biological effects in vitro and in vivo	
Lee and Pyo, 2019	HFD fed C57BL/6J mice, 3T3 L1 preadipocytes exposed to acrylamide	Adipogenic transcription factors for adipocyte differentiation, adipocyte lipid droplets
Morales et al., 2012	Review; physiological relevance of dietary melanoidins	
Wu et al., 2020	HFD-fed C57BL/6J mice, administered low (50 mg/kg/d), medium (100 mg/kg/d) and high (200 mg/kg/d) doses of melanoidins, 12 weeks	Weight, plasma LPS levels, adipose tissue, liver, lipids metabolism

Amor et al., 2019	male Sprague–Dawley rats fed either a standard chow (controls; n = 12) or a high-fat/sucrose diet (HFD; n = 24)+black garlic extract, 16 weeks, effects on the vascular and metabolic alterations	Blood, brown and white adipose tissues, hypothalamus, lipid metabolism
Gurecká et al., 2015	Female Wistar rats (n=9) fed a diet rich in MRP, offspring submitted to Coca-Cola	Circulating markers of inflammation, oxidative stress, glucose and lipid metabolism
Mericq et al., 2010	Humans, CML and methylglyoxal derivatives tested in sera of healthy mothers in labor (n=60), their infants (12-mo old), and infant foods	Fasting glucose, insulin, leptin, and adiponectin levels
Charissou et al., 2007	Monitoring of three indicators of the MR reaction CML by GC/MS in model cookies	GC/MS
Ghiasi et al., 2021	Identification of CML levels in infant powder formulas	ME-GC–MS method based on CCD developed for the optimal determination of acrylamide
Kadawathagedara et al., 2018	Norwegian Mother and Child Cohort Study (MoBa), 51,952 mother-child pairs, study of the association between prenatal acrylamide exposure and child postnatal growth up to 8 years	Weight, height, logistic regression models
Birlouez-Aragon et al., 2004	Six parameters for protein modification measured for 41 commercially available infant formulas samples	Amino acids by HPLC, AGEs (CML and OMA) by ELISA, monitoring AGEs by FAST index
Cai et al., 2012	C57BL6 mice fed isocaloric diets with or without AGEs, 3T3-L1 preadipocytes	WAT, skeletal muscle, liver, insulin resistance, adiposity parameters
Holik et al., 2016	3T3-L1 preadipocytes treated with 5, 50, or 500 μM CML, effects on adipogenesis	Parameters associated with adipogenesis and glucose homeostasis, miRNA levels

Table 2: References related to Maillard Reaction Products and metabolic disorders. Different parameters are indicated as the size of human cohorts, the animal model or cells used, the type of exposure, and the samples and markers analyzed.

2.3. Epigenetic dysregulation by food contaminants and metabolic disorders

DNA methylation is one of the most studied epigenetic modification. It occurs when DNA methyltransferases (DNMTs) transfer, in a reversible way, methyl groups from S-adenine methionine to the fifth carbon of a cytosine residue that is followed by a guanosine (CpG site), to form 5-methylcytosine (5 mC) (Jin and Liu, 2018). In clusters known as CpG islands, the frequency of CpG is higher than expected. Those islands are generally located in the promoter region of genes and the methylation degree regulates the ability of transcription factors to bind to the promoter and consequently activates or depresses gene expression. Exposure to different food contaminants are linked to metabolic function disorders.These perturbations may mainly be explained by gene expression dysregulations which are sometimes not easy to correlate with food contaminants exposure. Based on many studies, the main hypothesis is that food contaminants can directly act on the deposit of epigenetic marks i.e. on the one hand, methylation of the nucleotide C from a CpG island, and on other hand epigenetic marks corresponding to posttranslational histone modification on the N-terminal tail of histone proteins associated with DNA in the nucleosome. By acting on epigenetic marks, food

contaminants could affect gene accessibility by altering the ability for RNA polymerase and/or transcription factors to access to the promoter or the response elements they normally bind to (Shock et al., 2021).

In a study including analysis of a hundred samples of blood and saliva from different patients, it has been shown that OPs exposure was linked to differential methylation patterns for many genes (Paul et al., 2018) inducing genes dysregulation, particularly genes involved in acetylcholine receptor pathways, a common pathway found dysregulated after OPs exposure. These observations can be linked to an *in vitro* study using Human hematopoietic K562 cells exposed to common pesticides including OPs. In this study, authors demonstrated that cells displayed gene dysregulation associated to alterations of the methylation process at the promoter CpG island sites (Zhang et al., 2012). These alterations would be linked to a modification of the access to the promoter which, as a consequence,would generate a dysregulation of the gene or genes concerned. Metabolic disorders, as described earlier, are frequently associated with insulin resistance and diabetes. These pathological states are frequently correlated to epigenetic perturbations whose perinatal origins are more and more often suggested. For example, it has been observed that insulin resistance was associated with dysregulation of specific miRNA expression, miRNA being small non coding RNA involved in gene regulation by inducing mRNA degradation or inhibition of translation (Cirillo et al., 2019). Expression of these miRNA are known to be particularly sensitive to diet as shown for example in a study from Slattery and colleagues, where miRNA expression from colorectal tissue is highly correlated with level of carbohydrate intake (Slattery et al., 2016) . Sometimes the miRNA-induced modification of mRNA expression could be associated with a specific food ingestion (Holik et al., 2016), but in many cases, it still remains to evaluate possible correlations between a specific miRNA expression and a particular exposure. This will participate in the detection of a potential influence of a food contaminant on the appearance of, for example, insulin resistance and diabetes especially during the perinatal stage.

Reference	**Size human population/animal model/cells/exposure**	**Samples/markers analyzed**
Epigenetic dysregulation and metabolic disorders		
Shock et al, 2021	Review	
Paul et al, 2018	Humans, 580 blood sample (342 Parkinson's disease (PD) patients *vs* controls), 259 saliva samples (128 PD *vs* 131 controls)	Blood, saliva, genome-wide DNA methylation analysis
Zhang et al, 2012	K562 Human hematopoietic cell line, exposure to OPs pesticides	Genome-wide DNA methylation analysis
Cirillo et al, 2019	Review, animal models, humans	Colon mucosa
Slattery et al, 2016	Humans, 1447 samples	
Holik et al, 2016	3T3-L1 preadipocytes, exposure to 5.5 and 500 μM CML	Glucose homeostasis, lipid accumulation

Table 3: References related to Epigenetic dysregulation and metabolic disorders. Different parameters are indicated as the size of human cohorts, the animal model or cells used, the type of exposure, and the samples and markers analyzed.

3. Food contaminants and the occurrence of Inflammatory Bowel Disease (IBD)

Chronic inflammatory bowel disease (or IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). Both are characterized by inflammation of the lining of part of the digestive tract, due to dysregulation of the intestinal immune system. This uncontrolled inflammation is responsible for tissue damage and the chronicity of the disease. Its origin seems to result from the complex combination of environmental factors, associated with the genetic susceptibility of the patient and the particular reactivity of his immune system. IBD progresses by inflammatory outbreaks, of extremely

variable duration and frequency depending on the patient, which alternate with phases of remission. They are distinguished by the location and nature of the inflammation in the digestive tract, the complications, the risk factors, the symptoms, or the responses to treatment. In Crohn's disease, the inflammation can affect all segments of the digestive tract (from the mouth to the anus), but is most often localized in the intestine and frequently affects the terminal ileum, with or without colonic involvement. In ulcerative colitis, the inflammation always affects the lower part of the rectum and goes up more or less in the colon. The intestine is never touched. IBD is most often diagnosed between the ages of 20 and 30. However, they can occur at any age and 15% of cases involve children. Their frequency varies considerably from country to country, with the most significant incidences being found in industrialized countries, particularly in Northwestern Europe and the United States. In general, the incidence increases with the level of socio-economic development of countries, so that it increases strongly in Asia, the Middle East, South Africa and India. IBD currently affects 10 million people worldwide, 3 million in Europe and 250,000 in France with 8,000 new cases diagnosed each year, representing 1 case diagnosed every hour of which 20% are children. The peak of diagnosis is now between 15 and 35 years and the most worrying is the fact that these diseases have doubled in 13-19 year olds. IBD in children and adolescents is often responsible for slowing growth. Several susceptibility genes but also environmental factors are suspected, as well as modifications of the intestinal flora.

3.1. Pesticides residues and IBD

Everyone is exposed during his lifetime to a wide variety of pesticides residues. The large-scale pesticides use began during world war two and continues to increase even today. Thus, pesticides residues are found in our diet, in the air, in soil, in water and expose human beings every day in all aspects of their life. As diet appears the main source of exposure, the digestive tract and especially the gut is the first physiological barrier in direct contact with pesticides. Pregnancy and childhood are crucial and sensitive periods of exposure. Pesticides exposure *in utero* is potentially involved in the development of pathologies later in life since most of pesticides can easily cross the placental barrier and as a consequence impact newborn health. As already mentioned CPF is an organophosphate insecticide used worldwide to treat fruit and vegetable crops. Although domestic use of CPF was banned in the United States (US-EPA, 2002) and the European Union (EU, 2007), it remains one of the most commonly used insecticides in agriculture worldwide (Harishankar et al., 2013). Residues are often detected in food and drinking water and this molecule has been found able to cross the placental barrier (AKHTAR et al., 2006; Bolles et al., 1999). According to European Food Safety Authority (EFSA), CPF is one of the pesticides exceeding most frequently the acute reference dose (ARfD) in food products ("The 2016 European Union report on pesticide residues in food," 2018). In France, adult average exposure is estimated between 0.01 and 0.14 mg/kg body weight per day. In 2011, French children exposure was assessed between 0.01 and 0.15 mg/kg body weight per day (Nougadère et al., 2020); ANSES, 2011. Second French Total Diet Study (TDS 2) Report 2 Pesticide residues, additives, acrylamide and polycyclic aromatic hydrocarbons. Expert Report. June 2011. Scientific Publication. 350 pp.). Since the studies related to the consequences of pesticides residues on gut homeostatis are not numerous, we considered all the pesticide molecules for which data exist in the literature. Our laboratory has been working for many years on the impacts of CPF on the digestive tract. By the use of a combination of two *in vitro* models (the SHIME® and Caco2/TC7 cells), it has been revealed that CPF can inhibit the expression of intestinal tight junctions and induce a pro-inflammatory signal by increasing the secretion of interleukin-8 (IL-8) (Réquilé et al., 2018). In the rat model, a perinatal exposure to CPF can induce histological changes in the small intestine and colon segments as identified by a decrease of the height and width of ileum villi, crypt depth in the colon, epithelial thickness in both the ileum and colon (Joly Condette et al., 2015). This study revealed a developmental impact of the pesticide administered during the perinatal period as the circular and longitudinal muscles were also thinner. The intestinal epithelial integrity was also explored by the study of intestinal permeability through the use of the reliable fluorescent marker, the fluorescein isothiocyanate dextran (FITC-dextran 4 KDa) administered via the oral route. In CPF-exposed animals, the epithelial

passage of FITC-dextran was faster and higher. In addition, the mRNA expression of tight junction proteins such as ZO-1 and claudin 4 was lower in the ileum and colon. Finally, CPF increased bacterial translocation to spleen and liver, supporting a higher intestinal permeability (Joly Condette et al., 2014). In mice exposed to CPF from 4 to 12 weeks,an increase of pro-inflammatory cytokines concentration such as tumor necrosis factor (TNF-α), monocyte chemoattractant protein 1 (MCP1) and interleukin-1 beta (IL-1β) was observed in both blood, ileum, and colon (Liang et al., 2019b). Lipocalin-2, a fecal inflammatory marker, was increased after CPF exposure which, in turn, upregulated a marker of neutrophils infiltration, myeloperoxidase (MPO) activity, in the colon. Those data are in agreement with a potential proinflammatory role of CPF. As shown in rats, in mice exposed to CPF authors observed a higher intestinal epithelial permeability, characterized by a decrease in the mRNA expression of tight junction proteins (occludin, claudin 1, and ZO-1) in ileum and colon. In the study of Huang et al (Huang et al., 2020) where mice were submitted to a DSS-induced colitis and concomitantly to a diet enriched with CPF at different doses, the authors identified a higher level of circulating neutrophils and multiple alterations in T-cell subsets in colitic mice. Meanwhile, the colon weights were higher and injuries more severe in CPF-exposed groups. Such an interesting study provided evidence that CPF was able to alter the development of the colonic inflammatory process by suppressing T-cell populations and Treg polarization. Nonetheless, the absence of a group dedicated to CPF exposure alone, did not provide information on the ability of CPF by itself to induce inflammation. The studies on CPF effects in rats carried out in our laboratory have also failed to prove a pro-inflammatory effect of CPF administered alone.

Phosalone, another organophosphate insecticide, is extensively used as a pesticide in agriculture and as a domestic insect killer (O'Malley and McCurdy, 1990). Male Wistar rats exposure for 1 month resulted in colon histological lesions such as lymphocytes infiltration, increased MPO activity and high oxidative stress measured by lipid peroxidation (Ghasemi-Niri et al., 2016). Finally, expression levels of TNF-α, IL-1β and nuclear factor-kappa B (NF-κB) raised after such an exposure.

As already mentioned above, glyphosate (GLY), chemically known as isopropylamine salt of N-phosphonomethyl glycine, is a broad-spectrum herbicide commercialized in 1974 with a high efficiency in weed control (Benbrook, 2016). Glyphosate residues have been found in food, drinking water and even in the blood and urine of people (Solomon, 2016). Early life exposure of piglets to GLY increase the activity of CAT, MDA, and SOD in the duodenum but not in the jejunum (Qiu et al., 2020). The mRNA expression of IL-6 and NF-κB is also increased in the duodenum and jejunum. Concerning intestinal permeability, GLY decreases the mRNA expression of ZO-1 in the jejunum and claudin-1 in the duodenum. Studies on such animals could be of great interest to understand the incidence of pesticide residues on infant and toddlers. However, most of animal studies are realized on rodents. In 8-week-old male rats exposed to GLY for 35 days, authors observed a decrease in villus height and in the ratio of villus height to crypt depth in the duodenum, the jejunum and the ileum (Tang et al., 2020). MDA content increases in the ileum whereas GSH-Px decreases after GLY exposure. At the level of gene expression related to inflammation, the mRNA expression of TNF-α, mitogen-activated protein kinase 3 (MAPK3), Caspase-3 and NF-κB is enhanced in the duodenum. Similar results were observed in the jejunum where the expression levels of IL-1 β was also increased, as in the ileum for the expression levels of TNF-α, NF-κB and Caspase-3. In non-mammal species, acute exposure to GLY in chicken embryos results in histological changes in the digestive tract. Villus height, width and area significantly decrease as crypt depth and width and muscle thickness (Fathi et al., 2020). The mRNA expression of interferon gamma (IFN-γ) in the small intestine significantly increases after GLY exposure. The activities of GSH-Px, total superoxide dismutase (T-SOD), and MDA raise.

Another pesticide residue, Diquat, an extensively used desiccant, nonselective herbicide, is known to alter intestinal homeostasis. Young piglets exposed to diquat develop an intestinal permeability defect, an excess level of inflammatory cytokines and a decrease in antioxidant enzymes (Wang et al., 2019). Diquat can reduce total antioxidant capacity (T-AOC), SOD, and GSH-Px activities and increases MDA contents in intestinal mucosa. Similarly, diquat decreases the mRNA levels of copper and zinc superoxide dismutase (Cu/Zn-SOD), manganese-containing superoxide dismutase (Mn-SOD), glutathione peroxidase 1 (GPX-1), and glutathione peroxidase 4 (GPX-4) in the intestinal mucosa of pigs.

Furthermore, diquat elevates the abundance of TNF-α, IFN-γ, IL-6, and IL-1β. Additionally, the increase in intestinal permeability is reflected by elevated diamine oxidase activity and D-lactate concentration in serum, higher flux of FITC-dextran, and lower transepithelial electrical resistance in the intestine. Other studies using piglets showed that diquat can induce histological lesions such as reduction in jejunal and ileal villi height and width and crypt depth in the duodenum, jejunum, and ileum, and a rise in colon MPO activity (Yuan et al., 2017; Zheng et al., 2017). 3-weeks exposure of Wistar rats to diquat results in higher MPO activity in the stomach and the intestine as well as mucosal mast cell number and histamine levels (Anton et al., 2002, 2000). Diquat can also induce NF-κB activation and cyclooxygenase-2 (COX-2) dependent proinflammatory prostanoïds synthesis. Regardless of the animal species used in the studies, the results are consistent with the proinflammatory and prooxidant effects of Diquat.

Mancozeb (MCZ) is a fungicide universally used in agriculture which belongs to the thiocarbamate family. It is a structural analogue of thioamide that can interfere with the production of thyroid hormone by inhibition of thyroperoxydase leading to a decrease in thyroxine (T4) in rats (Axelstad et al., 2011). Adult male Sprague-Dawley rats whose body weights ranged from 120 to 150 g were exposed to MCZ for 7 weeks. They developed colon histological lesions identified by epithelial desquamation, congestion and infiltration of inflammatory cells (especially lymphocytes and macrophages) in the lamina propria and submucosa, data in agreement with a potential proinflammatory role of MCZ (Yahia et al., 2019).

All those data illustrate the increased risks to which infants may be exposed to during the maturation of his gut to corrupt the programming of his intestinal homeostasis that may contribute to the genesis of pediatric or adult IBD.

Reference	**Size human population/animal model/cells/exposure**	**Samples/markers analyzed**
Pesticides residues and IBD		
Harishankar et al, 2013	Humans, *in vitro*	Human intestinal bacteria
Akhtar et al,	Wistar rats, exposure to 9.6, 12 and 15 mg/kg/d CPF during 20 d gestation	Uteri, liver, fetuses, brain, amniotic fluid, placenta
Bolles et al, 1999	Food items samples from market basket study in USA	CPF residues quantification in samples
Nougadère et al, 2020	Food items samples, 5484 food products total, 309 food composite samples	516 pesticides and metabolites analyzed
Réquilé et al, 2018	Caco-2/TC7 cell line; SHIME human microbiota ecosystem	Epithelial permeability, genes expression
Joly-Condette et al, 2015	Female rats exposed to 1 or 5 mg/kg/d CPF, offsprings studied at d21 and d60	Blood, ileum and colon samples, microbiota, histological analysis
Joly-Condette et al, 2014	Wistar rats exposed to CPF (n=7) or not (n=6); d21 pups (n=12-17), d60 pups (n=13-14)	Blood, ileum, colon, histological analysis
Liang et al, 2019	C57Bl/6 and CD-1 male mice (n=8/gp), 5 mg/kg bw oral CPF for 4 mo	Blood, epididymal adipose tissue, colon, liver, food intake, microbiota, biochemical markers
Huang et al, 2020	C57 Bl/6 mice submitted to colitis (n=10/gp), exposure to CPF at 1, 2.5 and 5 mg/kg/d	Blood, spleen, colon, immunological identification, histopathology
O'Malley and McCurdy, 1990	Migrant field workers (n=30) exposed to phosalone for several days	Gastrointestinal symptoms, constitutional bradycardia

Ghasemi-Niri, 2016	Male Wistar rats (n=6/gp) exposed to phosalone 6 to 40 mg/kg for 1 mo	Blood, colon, oxidative stress in colon cells
Benbrook et al, 2016	Data collection on glyphosate applications	
Solomon, 2016	Estimation of the population exposure to glyphosate 0.088 mg/kg bw/d below the Rfd and ADI	
Qiu et al, 2020	Female weaned piglets (n=7/gp) exposed to glyphosate at 0, 10, 20 and 40 mg/kg for 35 d	Intestine samples, oxidative stress
Tang et al, 2020	Rats exposed to glyphosate at 0, 5, 50 and 500 mg/kg bw for 35 d	Small intestine, inflammatory and oxidative stress markers, microbiota
Fathi et al, 2020	Chick embryos, exposure to 10 mg glyphosate/kg egg mass	Liver, intestine, oxidative stress
Wang et al, 2019	ICR mice exposed to TPHP at 0, 10, 100 and 1000 μg/kg bw, GD6 to LD21	Blood, liver, fat, fecal pellets, microbiota, glucose homeostasis, lipid metabolism
Yuan et al, 2017	Weaned piglets exposed to Diquat at 8 mg/kg bw for 21 d	Bood, intestine, inflammatory and oxidative stress markers
Anton et al, 2000, 2002	Rats exposed to oral Diquat at low dose O.1 mg/kg/d for 21 d	Blood, stomach, intestine, inflammatory and oxidative stress markers
Axelstad et al, 2011	Wistar rats exposed to 0, 50, 100 and 150 mg mancozeb/kg bw from GD7 to PND16	Blood, thyroid, reproductive organs, hormone levels, histopathology
Yahia et al, 2019	Sprague-Dawley rats (n=10/gp) exposed to oral mancozeb for 7 weeks	Colon, liver, stomach, histopathology

Table 4: References related to Pesticides residues and IBD. Different parameters are indicated as the size of human cohorts, the animal model or cells used, the type of exposure, and the samples and markers analyzed.

3.2. Maillard Reaction Products and IBD

The large body of literature published in the recent years confirmed that the presence of silent inflammation also called low grade inflammation, particularly in the early stages of life may lead to the development of many diseases later in life (Marcason, 2010). Among the food factors responsible for this low grade inflammation, AGEs are generated through endogenous reactions and glycation of cellular proteins is known to alter cell and tissue function leading to molecular aging and chronic disease development (Brás et al., 2019; Chaudhuri et al., 2018). There were recently considered as exogenous boosters of inflammation (Garay-Sevilla et al., 2021). For example, CML is a lipoxidation product involved in hepatic steatosis (for review see (Greenhill, 2011)). Furthermore, *in vitro* glycation of bovine or human serum albumin induced the production of VEGF, TNFα and IL-8 in human monocytes and macrophages (Pertyńska-Marczewska et al., 2004). These AGEs are able to bind endogenous multiligand receptors of the superfamily of immunoglobins called RAGE. Activation of the RAGE-CML axis is playing a key role in obesity associated inflammation and insulin resistance. This is caused by CML dysregulating the secretion of inflammatory adipokines in the adipocytes through a RAGE-dependent pathway (Gaens et al., 2014). Furthermore, due to the presence of RAGE at the surface of neutrophils, their rapid activation by AGEs induces a rapid calcium dependent activation of human neutrophils, associated with aberrant signal processing and altered neutrophil response (Collison et al., 2002). The ability of RAGE to stimulate cell proliferation, tumor growth, invasion and metastasis via p44/p42, p38 and JNK/MAPK signaling pathways is well known (Taguchi et al., 2000). Stimulation of Caco2 epithelial cells *in vitro* by CML bound BSA is responsible for RAGE activation leading to the p44/p42 MAPK signaling pathway. However, the proinflammatory role of dietary MRPs has been by far

less documented and their fate on the induction or modulation of gut inflammation is still debatable depending on the conditions of administrations, the type of MRP and the origin of the food matrix. Ingestion during 5 to 10 weeks of rodent chow by adult mice increased the accumulation of dietary AGEs in several mice organs: liver, plasma, kidneys, increased the concentration of inflammatory markers in the plasma and altered the gut microbiota composition characterized mainly by enrichment with *Dubosiella* spp, whose metabolic activities are still not clearly determined (van Dongen et al., 2021). Furthermore, feeding juvenile mice with acrylamide during 21 days resulted in a reduction of goblet cells and of MUC2 mucins forming a two layered mucus system in the colon, thus increasing the risk of developing intestinal inflammation and tumors (Koledin et al., 2016). By contrast, repeated administration of CML (21 days) in adult mice then submitted to an experimental colitis alleviated gut microbiota dysbiosis (ALJahdali et al., 2017). Administration of 5-hydroxymethylfurfural (5-HMF) on RAW264.7 cells stimulated by LPS to explore its underlying anti-inflammatory mechanisms significantly reduced the production of pro-inflammatory cytokines (TNFα, IL-6 and IL-1β) and of pro-inflammatory enzymes (iNOS, COX2) but also ROS content (Kong et al., 2019). The authors also determined the anti-oxidant and anti-inflammatory properties of these AGEs were related to the inhibition of MAPK, Akt/mTOR and NF-κB signaling pathways. Moreover, there seems to be a consensus on the protective effects of melanoidins, terminal MRPs on the gut. Due to their chemical composition, melanoidins contribute to the color and the organoleptic properties of food and may behave as prebiotics. The first works were published more than ten years ago, when Ames and collaborators stated that melanoidins could modify the gut microbiota *in vitro* (Ames et al., 1999). Melanoidins from different food were submitted to *in vitro* digestion and fermentation processes to evaluate their bioactivity. Digestion increased their antioxidant capacity but not fermentation (Pérez-Burillo et al., 2020). Some of these melanoidins were fermented into mainly acetate and lactate and to a lower extent into butyrate ad propionate. From those results, the authors suggested that melanoidins could behave as prebiotic compounds since the production of acetate/lactate results from *Bifidobacterium* fermentation and since they observed an increased abundance of *Faecalibacterium* in the *in vitro* batch. Indeed, both the genus of microorganisms are known to be beneficial for human health. In correlation with this work, Diaz-Morales and colleagues evaluated the effects of melanoidins from different bakery products on an epithelial intestinal (Caco2) and an endothelial (HUVEC) cell lines. None of the melanoidins tested had toxic effects on the cells and melanoidins from biscuits were the ones with the highest antioxidant capacity (Diaz-Morales et al., 2021). They also evidenced that incubation of HUVEC cells with biscuit melanoidins slightly decreased their viability and this was softened by gastrointestinal digestion. On our side, we also confirmed that bread crust melanoidins did not induce any gut inflammation in adult rats but we were unable to clearly evidence their impact on the gut microbiota (Helou et al., 2017). While this is acknowledged that dietary melanoidins escape digestion and reach the colon where they become substrates for the gut microbiota (Wang et al., 2011), the production of SCFA from melanoidins by the microbiota is still under investigation. Before reaching the colon and being fermented, melanoidins pass through the stomach and may be able to bind to ureases, mucin-targeted adhesins playing an important role in infection and colonization of the host by *Helicobacter pylori*. Indeed, administration of melanoidins to mice and human resulted in the limitation of *H pylori* colonization (Hiramoto et al., 2004). If confirmed, the use of dietary melanoidins could be an interesting alternative to antibiotic-based therapy to prevent *H pylori* gastric colonization. At last, while most of the works presented here on the consequences of MRPs on gut homeostasis were related to bakery products that may be consumed by infants and pregnant women, the literature lacks of studies evaluating the consequences of these molecules on human health. This is rather based on the effects observed in adult that the agri-food industries are adapting their processes to limit the presence of MRPs in infant food and infant milk formulas. CML is considered as a potential hazard to human health and its presence in infant milk formulas is higher than in breast milk and this is even worsen in the presence of hydrolyzed milk formulas (for review see (Baskara et al., 2017)). The presence of some lipids in milk such as linoleic acid, oleic acid or glycerol trioleate can stimulate the production of the hydroxyl radical promoting CML formation from intermediates such as ε-fructose-lysine and glyoxal. By contrast, glycerol is a scavenger of hydroxyl radical and prevents from CML formation in milk (Han et al., 2013). Another study evidenced that sulfites are good inhibitors of CML in a modelized Maillard

Reaction in milk (Xu et al., 2013). Furthermore, for many years, whey-dominant infant formulas have been developed since they more closely resemble to the content of human milk. However, according to Prosser and colleagues, CML content is far more important than in other formulas (Prosser et al., 2019). The authors concluded their work in indicating that addition of whey proteins either intact or as hydrolysates significantly increases the risk of having more CML in infant formulas which may be harmful for babies. In light with all these results, new techniques of milk formulas preparations were tested. Mild pasteurization of whey proteins limiting the formation of AGEs was described as promoting a better intestinal maturation, less intestinal macroscopic lesions and infiltration of inflammatory cells in preterm and near-term piglets (Navis et al., 2020b, 2020a). Although this work is one of the first ones on the topics to our knowledge, it seems to confirm that limitation of AGEs content in infant formulas could be good for gut maturation and a better health. Gut inflammation is linked with epigenetic changes in the different cells composing the mucosa. For example in the case of IBD, it has been shown that cells from mucosa present global genome methylation pattern modifications (Cooke et al., 2012). These modifications can be understood by the observation in adipose tissue of obeses patients of expression modifications of enzymes involved in methylation of DNA called DNA methyltransferases (DNMT) (Crujeiras et al., 2018). IBD patients also present histone acetylation pattern modifications (Tsaprouni et al., 2011) Changes in miRNA expression is also observed associated with gut inflammation (Tili et al., 2017). Expression of these miRNA by blocking proteins translation are strongly suspected to be responsible from symptoms and/or establishment of the inflammation.

Reference	**Size human population/animal model/cells/exposure**	**Samples/markers analyzed**
Maillard Reaction Products and IBD		
Marcason, 2010	Review	
Chaudhuri et al, 2018	Review, use of invertebrate models, notably Drosophila melanogaster and Caenorhabditis elegans to explore AGE-related pathways	
Brás et al, 2019	Review	
Garay-Sevilla et al, 2021	Review focused on specific components of the diet associated with inflammation, specifically advanced glycation end products (AGEs)	
Greenhill, 2011	Review	
Pertyńska-Marczewska et al., 2004	THP-1 cells and human monocyte-derived macrophages, AGE-modified albumin incubation for 24h	VEGF, TNFα, IL-8 and tissue factor production
Gaens et al, 2014	Humans, obese mouse model, preadipocytes in culture	Adipose tissue, measures of CML and RAGE levels, adipokines production
Collison et al., 2002	Human neutrophils exposed to AGEs	Transendothelial migration, ROS production
Taguchi et al., 2000	Study of growth and metastases of both implanted tumours and tumours developing spontaneously in susceptible mice	p44/p42, p38 and SAP/JNK MAP kinases activity
van Dongen et al., 2021	Young healthy C57BL/6 mice submitted to standard chow (n = 10) or a baked chow high AGE-diet (n = 10) (~1.8–6.9 fold increased protein-bound Nε-(carboxymethyl)lysine (CML), Nε-(1-	Plasma, kidney, liver, AGEs accumulation, inflammatory markers, microbiota composition

	carboxyethyl)lysine (CEL), and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1)) for 10 weeks or a switch diet with baked chow for 5 weeks followed by 5 weeks of standard chow (n = 10).	
Koledin et al., 2016	Male Wistar rats gavaged with AA (0, 25, 50 mg/kg/d) for 5 d a week for 21 days	Colon goblet cell mucin secretion, IHC staining for MUC2
(ALJahdali et al., 2017	Mice (n=75) into 5 groups, consumption of melanoidins from barley malts	Sampling of feces at days 0, 1, 2, 3, 7, 14, and 21, gut microbiota composition, SCFA production
Kong et al., 2019	Anti-inflammatory activity of 5-HMF (31.5 to 126.0 μg/mL) and its underlying mechanisms in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells	NO, PGE2, TNF-α, IL-1β and IL-6 production
Ames et al., 1999	*In vitro* models	Digestibility of melanoidins, effect of melanoidins on colonic bacteria in the gastrointestinal tract
Pérez-Burillo et al., 2020	*In vitro* digestion and fermentation process (gut microbes) submitted to melanoidins from different sources	Quantification of individual phenolic compounds
Diaz-Morales et al., 2021	Isolation and characterization of melanoidins from baked products	Extraction yield, spectrophotometric characteristics, colorimetric properties, antioxidant capacity, and cytotoxicity of melanoidins
Helou et al., 2017	Rats fed with pellets supplemented with 13% bread crust, bread crumb, a fiber-free bread crust model, 4 weeks	Evaluation of CML and melanoidins, microbiota analysis
Wang et al., 2011	Review, comprehensive look at what is known to date about melanoidin structure, the formation mechanism for these compounds, and the biological properties related to the beneficial health effects of melanoidins	
Hiramoto et al., 2004	Humans, mice infected with H.pylori fed melanoidins (10 weeks)	Inhibitory activity of melanoidins, on urease-gastric mucin adhesion, anticolonization effect of melanoidin I in mice and humans
Baskara et al., 2017	Review, AGEs and allergy	
Han et al, 2013	Diet sampling	Diet-derived CML and its key intermediates, epsilon-fructoselysine and glyoxal determined with HPLC-MS in model system containing lipid compounds

Xu et al., 2013	Analytical method for quantification of CML, lysine, and reducing sugars (glucose, lactose, and galactose)	High performance anion-exchange chromatography with pulsed amperometric electrochemical detection
Prosser et al., 2019	Formulas manufactured from cow or goat milk tested for CML levels	ELISA kit
Navis et al., 2020b, 2020a	Preterm and near-term piglets model hypersensitive to enteral nutrition submitted to mildly pasteurized whey protein concentrate compared to the extensively heated	Histological analysis of GI tract, qPCR
Cooke et al., 2012	Rectal biopsies from UC and CD patients; impact of differences in methylation patterns in the intestine with regard to IBD susceptibility and activity	Genome-wide methylation profiling using the HumanMethylation27 BeadChip microarray
Crujeiras et al., 2018	Visceral adipose tissue from morbidly obese patients; 2 independent cohorts (n=60 and 40)	Global human methylome ; Infinium Human Methylation 450 BeadChip array
Tsaprouni et al., 2011	Human biopsies from CD patients, animal models of inflammation	Expression of acetylated histones (H) 3 and 4 in inflamed mucosa
Tili et al., 2017	Review; micro RNA in gut pathologies	

Table 5: References related to Maillard Reaction Products and IBD. Different parameters are indicated as the size of human cohorts, the animal model or cells used, the type of exposure, and the samples and markers analyzed.

3.3. Epigenetic dysregulation and IBD

All these observations point clearly that gut inflammation is linked with epigenetic dysregulations. More researches are needed to establish precisely which are the epigenetic marks or the non coding RNA affected by gut inflammation. This mapping will then make it possible to find out the origin of these modifications, and from this, it will be possible to make links between food contaminants exposure and molecular changes and the window of life particularly vulnerable to all these changes.

4. Food contaminants and the occurrence of allergies

Allergies are abnormal Th2 immune reaction towards food, pollen, dust or animal proteins called allergens. The mechanisms of the allergic reaction are now well known for many years but the etiology of the allergy remains unclear. Allergies alter the quality of life due to food eviction or preventive seasonal treatment in the case of respiratory allergy. Nowadays, allergies are considered as an « epidemic wave » and became a major public health concern of the twenty first century. Food allergies, which is one of the allergic manifestations among skin and respiratory allergy, affect 6-8% of children under one-year-old, 3-4% of adolescents and 2-5% of adults (Iweala et al., 2018). However, there is evidence that some food and skin allergies in infancy may evolve into respiratory allergies in childhood (Yang et al., 2020). The incidence and prevalence of allergies have substantially increased in last decades. Several hypotheses have been proposed to explain this increase and many studies showed that the development of allergies is impacted by several factors such as the maternal nutrition during gestation (Miles and Calder, 2015), the mode of delivery (Bager et al., 2003; Negele et al., 2004; Neu and Rushing, 2012), breastfeeding (Bouchaud et al., 2016; Silva et al., 2014), the age of introduction of food diversification (Koplin et al., 2010; Palmer and Prescott, 2016) and the genetic background (Hong et al., 2011; Toit et al., 2008). Another hypothesis of the allergy prevalence increase is the presence of food contaminants, such as

pesticide residues or neoformed compounds. However, even if the presence of pesticides residues or neoformed compounds has increased in recent years in food, no causal link has really been demonstrated to date.

4.1. Pesticide residues and allergies

The data relating to pesticides and the occurrence of the allergy are not very extensive and led us to retain the studies dealing with the impacts of organophosphates and sometimes organochlorines. A relationship between some pesticides use and the severity of allergies' symptoms (Amaral, 2014) or allergen sensitization (Dantzer et al., 2021; Falak et al., 2012; Jerschow et al., 2012) has been shown. OPs pesticides are known to play roles in the modulation of immune responses. Several studies between 2004 and 2014 show a modulation of immune systems in fish and mice models. In 2015, Díaz-Resendiz et al. list, in a review article, sixteen articles which show that some OP (Chlorpyrifos, Diazinon, Malathion, Phosalone and Metrifonate) can target constituents of fish immune system and cause the alteration of neuro-immune communication. Among the described effects we found either a decrease in lymphocyte proliferation and phagocytic function or a modulation of antibodies secretion and contents of complement C3 (Díaz-Resendiz et al., 2015). The alteration of the neuro-immune crosstalk could lead to a modulation of the allergic reaction induced by the variation of cytokines levels in the lung or the intestine among others (Kabata and Artis, 2019). Earlier, Fukuyama et al. shown an increase in the allergic potential of environmental chemical allergens in lymph node by a prior exposure to either OP or organochlorine (OC) in an *in vivo* model. In this study, the authors have exposed 4-weeks-old mice to parathion (OP) from 0 to 1.2 mg/kg or methoxychlor (OC) from 0 to 300 mg/kg. About one month after the last oral administration, two different environmental chemicals known as allergens (2,4-D-butyl and eugenol) has been applied on the mice ear for three consecutive days in order to sensitize them. After *ex vivo* restimulation of auricular lymph node cells from pesticides pre-treated mice, the number of surface antigen expression of T cells has increased significantly as well as the levels of pro-inflammatory cytokines compared to those from non-pre-treated mice (Fukuyama et al., 2010).

As early as 1977, Rycroft expected that OP pesticides were irritant molecules and could be involved in the development of allergic contact dermatitis (RYCROFT, 1977). Since then, other studies have confirmed these claims (Sato et al., 1998; Sharma and Kaur, 1990) and others have shown effects on asthma symptoms (from non-allergic origin) (Hernández et al., 2011) and development of food allergies (Gallo et al., 2020). Recently, a large-scale survey from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) was used by Dantzer et al. to highlight a relationship between pesticides exposure and the development of allergies. In this survey, several variables are available including urinary OP metabolites (dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate, diethylphosphate, diethylthiophosphate, and diethyldithiophosphate), allergy history and allergen-specific IgE. The cross study of them shows lower odds of food sensitization and hay fever and an increased odds of eczema for individuals who had urinary levels of OP pesticides metabolites detected (Dantzer et al., 2021). However, a decade earlier, Jerschow et al. bring out an association between elevated urinary levels of dichlorophenols and the presence of sensitization to foods in US population from the same survey (Jerschow et al., 2012). This suggests that depending on the studied pesticides family, the mechanisms need to be investigated to understand how they can be a risk factor for the development of allergies.

While most studies focus on the modulation of the allergic reaction, Falak et al. hypothesize in a review that the growing use of some OPs over the last decades might explain the increase in the food allergy incidence due to altered allergens levels or altered proteins allergenicity in pesticides-treated plants. Pesticides treatments could cause a state of stress during plant development leading to a modulation of allergen expression responsible for increase in allergic reactions. Other leads have been suggested, such as the modulation of the phosphorylation of signaling molecules by organic phosphate residues, the increase in the production of polyamine responsible for pseudo-allergic reactions or epigenetic modifications in plants (Falak et al., 2012).

Lastly, even if some studies show the impact of pesticides on allergic reactions, including food, skin or respiratory manifestations, the lack of evidence and knowledge about these concepts outlined before in human concerning studies during the last decade must be considered. In addition, in recent years, there has been a particular desire on the part of

the population to move towards products with proven traceability and, where possible, organic origin (Barański et al., 2017; Vigar et al., 2019). However, it should be borne in mind that industrial baby food is governed by very strict specifications and where the presence of pesticides residues is controlled compared to a home-cooked preparation using either organic or non-organic products.

Reference	Size human population/animal model/cells/exposure	Samples/markers analyzed
Food contaminants and allergies		
Iweala et al., 2018	Review; updated summary of the natural history of major childhood and adult food allergies	
Yang et al., 2020	Humans, 59 patients suffering from P.aeruginosa bacteremia and disease	Multivariate analysis
Miles and Calder, 2015	Review; identification of essential nutrients that may have important roles in foetal development	
Bager et al., 2003	Humans, cohort study with 9722 singleton women, link between modes of delivery and increased risk of allergic rhinitis or asthma	Information on mode of delivery (spontaneous delivery, cesarean section, vacuum extraction, or other complicated mode of delivery, gestational age, birth weight, and length at birth
Negele et al., 2004	Humans, prospective multicenter birth cohort study, 2500 infants, association between cesarean delivery and atopic diseases	Evaluation of specific IgE production
Neu and Rushing, 2012	Review; whether the increase in Cesarean delivery incidence is also causally related with the occurrence of allergies and autoimmune diseases	
Bouchaud et al., 2016	Balb/c mice, study on the preventive effects of prebiotics in mothers during pregnancy and breastfeeding on food allergy development in offspring	Immunological, physiological, and microbial parameters
Silva et al., 2014	Systematic review; ways to prevent the development of food allergy in children and adults	
Koplin et al., 2010	Humans, 2589 infants, population-based cross-sectional study (HealthNuts), investigation on the associations between diet and egg allergy adjusted for possible confounding factors	Egg allergy parameters
Palmer and Prescott, 2016	Humans, Discussion about the benefits to introduce food allergens during infancy	
Hong et al., 2011	Humans, prospective US birth cohort (970 children), breast feeding history, genotyping of 18 genes involved in innate immunity or T_H1/T_H2 balance	Logistic regression models were used to test the effects of breast-feeding and gene–breast-feeding interactions
Toit et al., 2008	Humans, Jewish schoolchildren (5171 in the UK and 5615 in Israel)	Clinically validated questionnaire for the determination of peanut allergy

Amaral, 2014	Humans, opinion article, epidemiological studies on pesticides and asthma	
Dantzer et al., 2021	Humans, cross-sectional survey (data from the 2005-2006 NHANES) of the noninstitutionalized US population	urinary OP metabolites, allergy history, allergen-specific IgE
Falak et al., 2012	Humans, review on some evidence regarding possible mechanisms on pesticide-induced allergenicity of plant proteins	
Jerschow et al., 2012	Humans, 2,211 persons 6 years and older in the National Health and Nutrition Examination Survey 2005-2006, test of the association between exposure to environmental pesticides represented by dichlorophenols and allergic sensitization	Urine, allergen-specific serum IgE levels, logistic regression models
Díaz-Resendiz et al., 2015	Fish, review about the effect of organophosphorus pesticides on the immune system and in immunotoxicology	
Kabata and Artis, 2019	Review, recent findings regarding neuro-immune crosstalk regulating inflammation	
Fukuyama et al., 2010	4-week-old mice, oral parathion (0, 0.4, 1.2 mg/kg) or methoxychlor (0, 100, 300 mg/kg), 4 weeks, local lymph node assay with 2,4-D-butyl (0%, 2.5%, 5%, and 10%) and eugenol (0%, 5%, 10%, and 25%)	Auricular lymph nodes, surface antigen expression of T cells and local cytokine production
Rycroft, 1977	Humans, review, OPs and contact dermatitis	
Sato et al., 1998	Male Wistar rats (10-11 weeks-old), effects of several pesticides on histamine release from mast cells of rats that had been sensitized passively by anti-dinitrophenol (DNP) monoclonal IgE antibodies	AchE activity, PCA reaction, histamine release, TBARS and TNFα concentrations
Sharma and Kaur, 1990	Humans, 30 farmers with contact dermatitis, 20 controls patch tested with locally used pesticides	Allergic reactions
Hernández et al., 2011	Humans, review on the concept that either acute or chronic low-level inhalation of pesticides may trigger asthma attacks, exacerbate asthma or increase the risk of developing asthma	
Gallo et al., 2020	Humans, review, relationships between food and diseases	
Barański et al., 2017	Humans, commentary about consumption of organic and conventional food and health impacts	
Vigar et al., 2019	Humans, systematic review of organic vs conventional food consumption and benefits for human health	

Table 6: References related to food contaminants and allergies. Different parameters are indicated as the size of human cohorts, the animal model or cells used, the type of exposure, and the samples and markers analyzed.

4.2. Maillard Reaction Products and allergies

Neoformed compounds are generated by reactions during food transformation. As already described above in the review's part related to metabolic and inflammatory diseases, the Maillard reaction induced by heat treatment of food is one of the most frequent and it is responsible for conformational changes of proteins that generated AGEs (Finot, 2005). A lot of studies showed that this modification could influence the allergenicity of proteins, mainly by increasing it (Teodorowicz et al., 2017). However, modifying the allergenicity is not the only way for these neoformed compounds to modulate the immune and therefore allergic response. Indeed, neoformed compounds may predispose to inflammation. It was shown that consumption of dietary AGEs is correlated with an increased release of biomarkers of the inflammatory reaction and/or oxidative stress in both humans and animals (Elmhiri et al., 2015; Poulsen et al., 2014; Uribarri et al., 2007). Another argument is that RAGE, the receptor of these neoformed compounds, is present on immune cells and plays an important role in the regulation of the immune response (for review (Leerach et al., 2021)). Smith et al suggest that neoformed compounds, by binding to RAGEs, could act as alarmins and promote both Th2 response and pro-inflammatory cytokines synthesis, resulting in the development of allergic phenotypes (Smith et al., 2017). Clinical studies suggest also this link between AGEs and allergy. It was thus showed that exposure to AGEs through children's diet is associated to allergic outcomes. However, no association was found between maternal AGEs intake during pregnancy and allergic outcomes in offspring (Venter et al., 2021). The mechanisms therefore appear to be complex and further studies are needed to understand how AGEs can influence the allergic response.

4.3. Epigenetic dysregulation and allergies

Our knowledge of molecular and cellular mechanisms linked to food allergy shows how environnmental factors could lead to allergy. At this step it is clear that perinatal period appear to be the most susceptible period to contribute to this process and that epigenetic mechanisms play a pivotal role by programming the genome and influencing its future expression (Hong and Wang, 2014). The positive effect of nutrition during pregnancy and lactation on the epigenetic signature and its influence on the risk for developing allergic disease (Acevedo et al., 2021) has been shown, but a potential increase of developing allergic disease has not yet been correlated with a particular exposure to a food contaminant, and more precise researches are needed.

Reference	**Size human population/animal model/cells/exposure**	**Samples/markers analyzed**
Maillard Reaction Products and allergies		
Finot, 2005	Review on MRPs	
Teodorowicz et al., 2017	Review on food processing and the role of MR on allergenicity and immunogenicity of food proteins	
Elmhiri et al., 2015	IUGR piglets fed a low temperature heated formula (n = 8) or a high temperature heated formula (n = 8), 3 weeks	CML was measured in plasma, feces, and formula by HPLC/MS-MS
Poulsen et al., 2014	Humans, 19 healthy overweight patients, effects of AGE contents in a single meal on postprandial appetite and markers of inflammation, endothelial activation, and oxidative stress	Postprandial blood samples, levels of CML, appetite-regulating gut hormones, glucose, insulin, triacylglycerol, and markers of inflammation and endothelial activation

Uribarri et al., 2007	Review on the generation of AGEs during the cooking of food, the gastrointestinal absorption of these compounds, and their biological effects *in vitro* and *in vivo*	
Leerach et al., 2021	Review, role of RAGE in immunity and social behavior	
Smith et al., 2017	Review, role of AGE in allergy	
Venter et al., 2021	Pregnant women ≥16 years, prospective pre-birth cohort from Colorado (N=1410), children (<8 years-old, N=462) diagnosed for asthma and allergies	Cord sera cytokines and chemokines in children
Hong and Wang, 2014	Humans, review on the latest advance on epigenetics in the development of food allergy	
Acevedo et al., 2021	Humans, review on the current knowledge on the relationship between immunometabolism and allergy mediated by epigenetic mechanisms	

Table 7: References related to Maillard Reaction Products and allergies. Different parameters are indicated as the size of human cohorts, the animal model or cells used, the type of exposure, and the samples and markers analyzed.

5. Conclusion

We could very well end this review by saying "to stay healthy, eat healthy and balanced but also varied" without necessarily falling into the extreme of "eat organic at all costs". It would be more reasonable to launch the slogan "to stay healthy throughout life, eat a variety of foods, healthy, of good quality and in reasonable quantities together with the mastering of domestic as well as the industrial food process ". Nutrition is a major factor contributing to child growth and maintaining the individual's health. During the early life period, the quality of foodstuff and risk management bound to food contaminants is a prerequisite to limit the risk of developing chronic diseases later in life. Even if it appears difficult to get totally rid of preformed and neoformed pollutants and contaminants in food, it seems more reasonable to limit their presence in food. For several years now, real awareness of the deleterious effects of pesticides has allowed the emergence of a collective and international desire to limit the use of pesticides in agriculture (Ecophyto plan), without unfortunately achieving, so far, the objectives set. Furthermore, for most of these pesticides, since their presence in the environment lasts several years, it is of peculiar importance to understand their risks on health especially in vulnerable persons. On the other side, a better understanding of the chemical structure and genesis of MRPs during the heat treatment of food has also made it possible to characterize their health effects thanks to various studies in humans and animals. Thanks to a large set of experiments, different factors have been evidenced as inducers of major contributors of fetal and postnatal programming modifications which will increase the risk of developing NCDs. Several lines of evidence indicate that the exposure to these substances could alter the epigenome, disrupting the mRNA expression and protein levels of key genes involved in normal functions and thus, producing negative consequences. These epigenetic modifications could be heritable and could have a manifestation in health impacts and disease after the exposure has ended. Clinical, experimental and epidemiological studies on epigenetic changes induced by contaminants exposure have increased our understanding and knowledge of the mechanisms of action by which those molecules can alter gene expression and modify perinatal programming. Most of the studies conducted so far have been centered on DNA methylation, whereas only a few recent investigations have studied the effects on histone acetylation and miRNAs synthesis and release. These two sets of markers of epigenetic modifications represent the future studies to be carried out in order to deeper characterize the origin of the effects of the molecules studied. Many questions remain

open, among which the origin of the observed effects as being the result of the exposure to a single pesticide compound or to a complex mixture of chemicals of different origins, such as pesticides residues and MRPs. These studies also provided relevant data on the impacts of the timepoint and duration of exposure to these contaminants on future human health. However, despite of the actual knowledge on their fate on health, more studies are needed to identify more epigenetic marks, to define how they are modulated in human disease and their role, and to characterize the critical windows of vulnerability induced by those exposures. Whether children or adults, the population finds itself confronted in real conditions of consumption not with a single molecule but with cocktails of molecules in highly variable concentrations and over exposure times that are sometimes even more variable. The scientific scope of the studies is even more limited, due to the fact that few studies available in the literature have focused on the impacts of cocktails of molecules. This is certainly one of the aspects to which the scientific community must succeed in responding in the future, while keeping in mind that the ideal cocktail and the most representative of the exposure of the population does not exist. These points would influence environmental risk assessment and contribute to the development of prevention strategies for health outcomes. Far from being conclusive, the reported evidences suggest that epigenetic modifications may be one of the mechanisms by which pesticides and MRPs can have noxious effects on human health. Further studies are warranted to evaluate if epigenetic modifications may act as a causal link between exposure and health effects, or rather be a sensitive marker of exposure.

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FIGURES LEGENDS

Figure 1 : Hypothesis on the impacts of food contaminants as pesticides and Maillard Reaction Products on the growing fetus, baby and child and their consequences on the etiology of non-communicable chronic diseases. During pregnancy and infancy, a repeated exposure of fetus and later in life the infant to food contaminants is highly suspected to be at the origin of NCDs as metabolic syndrome and obesity, inflammatory bowel diseases and allergies by altering gut homeostasis, microbiota diversification and densification, and the settlement of neuro-immuno-endocrine cross talks as well as brain-gut axis. MRPs: Maillard Reaction Products.

Figure 2 : Impacts of food contaminants on gut homeostasis and maturation during growth and at the origin of chronic non-communicable diseases. During the *in utero* period and at birth, the digestive tract is immature in terms of microbiota, layer of mucus, communications between the various cellular actors of the intestinal wall (epithelium, immune cells, nerve cells). Maturation takes place very gradually after birth with dietary diversification and contact with environmental factors. Certain factors such as pesticides or the products of the Maillard reaction can alter the maturation of neuroimmunoendocrine relationships. This could then be responsible for gut permeability increase responsible for a mild « leaky gut », predisposing to intestinal neuroimmunoendocrine communications alterations and be the cause of the occurrence of chronic non-communicable diseases in the growing child or in adulthood. A: Expected conditions; B: Altered conditions. MRPs: Maillard Reaction Products, MC: mast cells, EEC: epithelial endocrine cells, Th1: Thelper 1 response, Th2: Thelper 2 response, Treg: Tregulatory response, SCFA: short chain fatty acids.

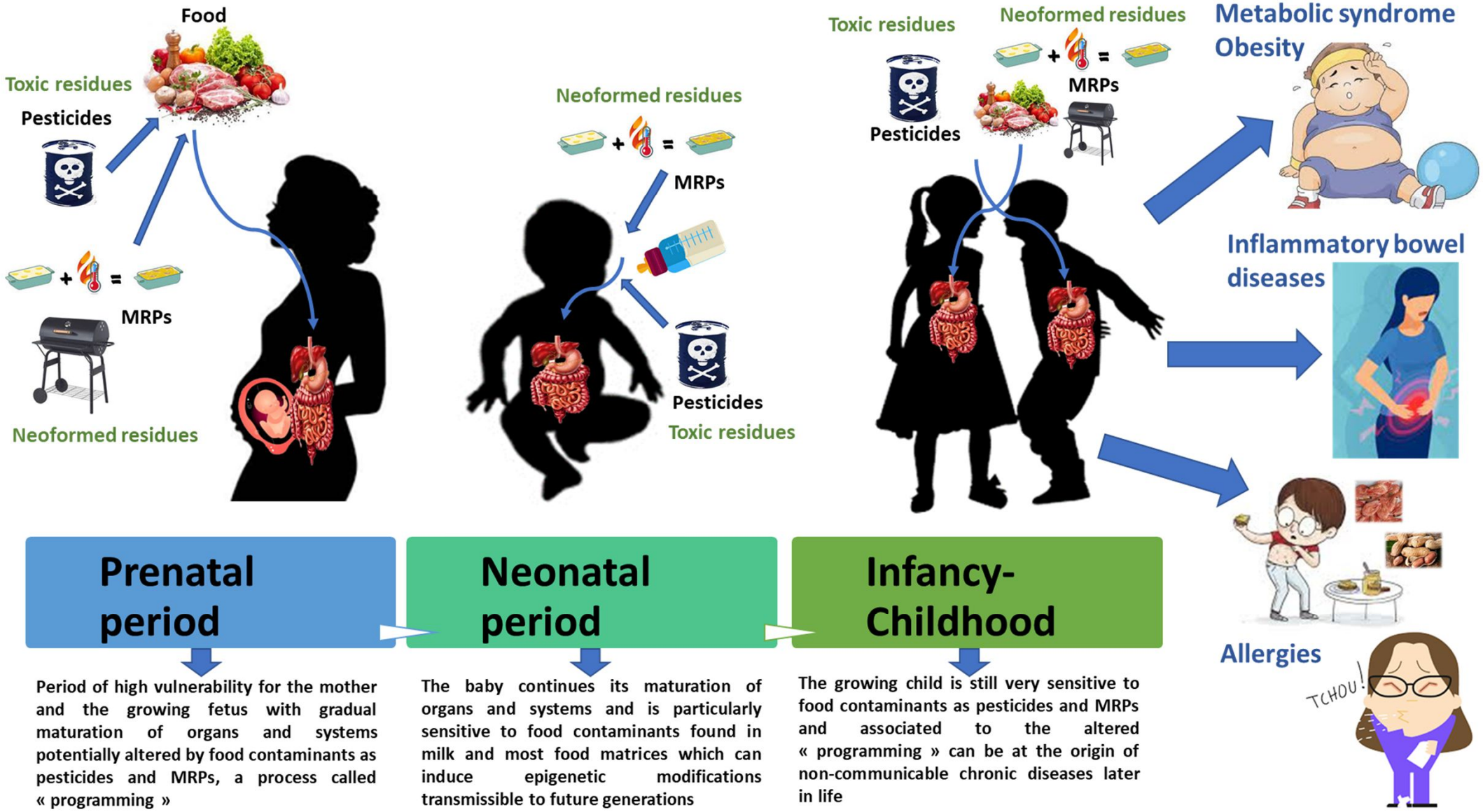
Food
Toxic residues
Pesticides
MRPs
Neoformed residues
Neoformed residues
MRPs
Pesticides
Toxic residues
Toxic residues
Pesticides
Neoformed residues
MRPs
Metabolic syndrome
Obesity
Inflammatory bowel
diseases
Allergies
TCHOU!
Prenatal period
Neonatal period
Infancy-Childhood
Period of high vulnerability for the mother and the growing fetus with gradual maturation of organs and systems potentially altered by food contaminants as pesticides and MRPs, a process called « programming »
The baby continues its maturation of organs and systems and is particularly sensitive to food contaminants found in milk and most food matrices which can induce epigenetic modifications transmissible to future generations
The growing child is still very sensitive to food contaminants as pesticides and MRPs and associated to the altered « programming » can be at the origin of non-communicable chronic diseases later in life

Figure 1

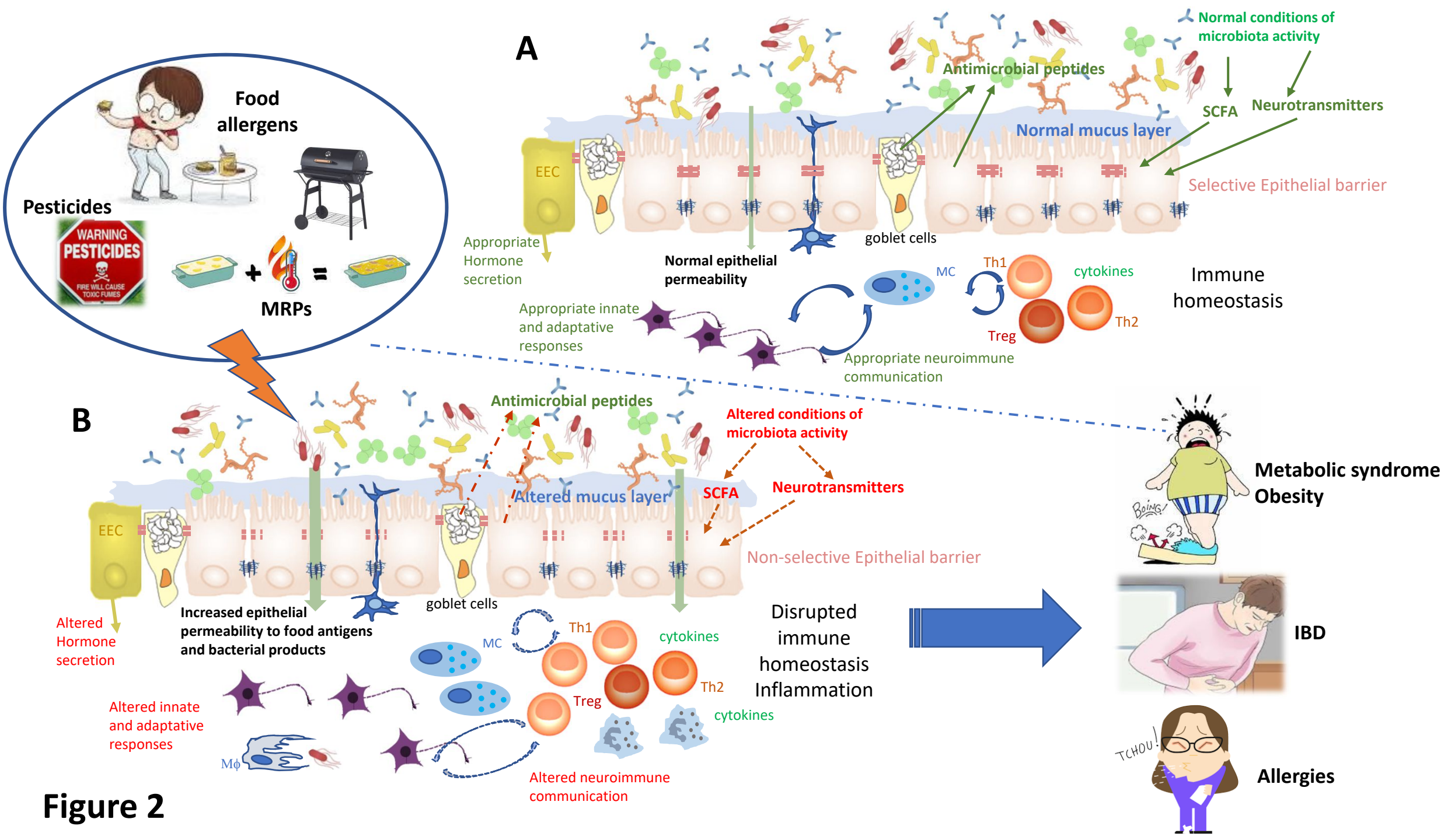
A
Food allergens
Pesticides
WARNING PESTICIDES
FIRE WILL CAUSE TOXIC FUMES
MRPs
Normal conditions of microbiota activity
Antimicrobial peptides
SCFA
Neurotransmitters
Normal mucus layer
Selective Epithelial barrier
EEC
Appropriate Hormone secretion
Normal epithelial permeability
goblet cells
MC
Th1
cytokines
Th2
Treg
Appropriate innate and adaptative responses
Appropriate neuroimmune communication
Immune homeostasis
B
Antimicrobial peptides
Altered conditions of microbiota activity
Altered mucus layer
SCFA
Neurotransmitters
Non-selective Epithelial barrier
EEC
Altered Hormone secretion
Increased epithelial permeability to food antigens and bacterial products
goblet cells
MC
Th1
cytokines
Th2
Treg
cytokines
Altered innate and adaptative responses
Mϕ
Altered neuroimmune communication
Disrupted immune homeostasis Inflammation
Metabolic syndrome
Obesity
IBD
Allergies
TCHOU!

Figure 2