Published in final edited form as:

Food Chem Toxicol. 2017 July ; 105: 456–474. doi:10.1016/j.fct.2017.05.003.

Potential contribution of insecticide exposure and development of obesity and type 2 diabetes

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Abstract

The introduction of insecticides has greatly improved agricultural productivity and human nutrition; however, the wide use of insecticides has also sparked growing concern over their health impacts. Increased rate of cancers, neurodegenerative disorders, reproductive dysfunction, birth defects, respiratory diseases, cardiovascular diseases and aging have been linked with insecticide exposure. Meanwhile, a growing body of evidence is suggesting that exposure to insecticides can also potentiate the risk of obesity and type 2 diabetes. This review summarizes the relationship between insecticide exposure and development of obesity and type 2 diabetes using epidemiological and rodent animal studies, including potential mechanisms. The evidence as a whole suggests that exposure to insecticides is linked to increased risk of obesity and type 2 diabetes.

Keywords

Insecticide; obesity; glucose metabolism; type 2 diabetes

1. Introduction

The prevalence of obesity among adults in the United States more than doubled since the 1960s, increasing from 13.4 in 1962 to 35.7 percent in 2010 (NCHS, 2012). As obesity is a well known risk factor for other diseases, especially type 2 diabetes, the incidences of type 2 diabetes are also rising (ADA, 2013; CDC, 2014; WHO, 2013). The current epidemic of obesity and type 2 diabetes cannot be fully explained by changes in societal, genetic, behavioral, or dietary habits of individuals, suggesting unknown factors contribute to these disease outbreaks.

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The challenge of growing more food to feed the world's expanding population has driven need to control pest insects, which are harmful to crop yield. Application of insecticides are considered to be a major contributing factor for increased agricultural productivity in the 20th century (van Emden and Peakall, 1996). In addition to its role in agriculture, insecticides are widely used in industry, households, and military to control insect pests that are disease vectors, suggesting its essential role in human life (Sparks, 2013). However, insecticides are one of the major environmental contaminations and the extensive use of insecticides has caused wide public concern over their potential risk of inducing human chronic diseases, including obesity and diabetes (Hectors et al., 2011; Karami-Mohajeri and Abdollahi, 2011; Kuo et al., 2013; Lee et al., 2014a; Rezg et al., 2010b). Among insecticides, organochlorines and organophosphorus are the most investigated insecticides linked with obesity and/or type 2 diabetes in humans and rodents (Karami-Mohajeri and Abdollahi, 2011). Although limited, other types of insecticides, such as carbamates, pyrethroids, and neonicotinoids, are associated with development of obesity and/or type 2 diabetes as well (Montgomery et al., 2008; Narendra et al., 2008; Saldana et al., 2007; Sun et al., 2016b; Wang et al., 2011b). More recently, *in vitro* and *in vivo* studies reported that pyrethroids, a neonicotinoid, and a phenylpyrazole (fipronil), all were involved in potentiated adipogenesis and/or altered glucose responsiveness, as representative of obesity and type 2 diabetes, respectively (Kim et al., 2013, 2014a; Park et al., 2013; Shen et al., 2017; Sun et al., 2016a; Sun et al., 2016b). Moreover, reports of interaction between dietary fat and insecticides on these markers, further begs the question of the role of insecticides and health. Thus, this review focuses on summarizing the current reports on insecticide exposure and development of obesity and type 2 diabetes, including suggested mechanisms, to further expand our current understanding.

2. Methods

Bibliographic databases including PubMed and Web of Science were searched for the keywords 'insecticide' and 'obesity'; 'insecticide' and 'diabetes'; 'insecticide' and 'body weight'; 'insecticide' and 'glucose metabolism'; and 'insecticide' and 'lipid metabolism'. Data were collected from 1966 to December 2016. From the initial search of PubMed and Web of Science, each article was reviewed to evaluate title and abstract content, and to eliminate duplicates and those were not related to our purposes. A total of 111 articles were selected and their full texts were reviewed including 52 human studies and 59 animal studies. Our exclusion criteria were (1) publications containing no original research (reviews, editorials, or non-research letters); (2) studies not carried out in humans, mice, or rats; or (3) human studies without providing information on markers of obesity or diabetes as described below. We collected the following data for human studies: authors, journal, year of publication, country, insecticide, study design, study population, changes in body weight and/or body mass index, waist circumference, diabetes risk (increased blood glucose levels, insulin resistance, or gestational diabetes), lipid markers (triglycerides and/or cholesterol), and other critical comments. Variables extracted from animal studies include: authors, journal, year of publication, species, treatment methods (dose, route, and duration), sex, body weight change, major markers of glucose homeostasis (glucose, insulin, or insulin resistance) and lipid metabolism (triglycerides and/or cholesterol), and other metabolic

markers involved in glucose and lipid metabolisms (e.g., blood leptin, other lipids, glycogen content, markers of adipogenesis, gluconeogenesis, glycogenolysis, glycolysis, and/or inflammation). The findings are presented in Tables.

3. Insecticide classification and action

Insecticides can be classified based primarily on their chemical structures and mode of actions. Major classes of insecticides include organochlorines, organophosphorus, carbamates, pyrethroids, and neonicotinoids. A few examples are shown in Table 1.

Organochlorine insecticides can be divided into dichlorodiphenyltrichloroethane (DDT)-type and chlorinated alicyclic-type (cyclodienes) based on their distinctive mechanisms of action. DDT-type insecticides (such as DDT, DDE, and DDD) are known to inhibit the closing of voltage-sensitive sodium channel (VSSC) in neurons, resulting in repetitive firing of action potentials, while chlorinated alicyclic-type insecticides (e.g. aldrin, dieldrin, heptachlor, and endosulfan) bind to γ -aminobutyric acid (GABA) chloride ionophore complex, which inhibits chloride influx into the nerve (Coats, 1990; Karami-Mohajeri and Abdollahi, 2011). Even though most countries have not used organochlorines for the last several decades, due to extremely stable chemical characteristics, DDE (as a major metabolite of DDT) can currently be found in human serum, adipose tissue, and many foods (Karami-Mohajeri and Abdollahi, 2011; USDA, 2014).

Organophosphorus insecticides are irreversible inhibitors of cholinesterases, including acetyl cholinesterase, resulting in hyper-stimulation of cholinergic nerves (e.g. muscarinic and nicotinic acetylcholine receptor) (Abou-Donia, 2003). As the largest insecticide class in the world in 1980s, organophosphorus insecticides occupied 71% of world insecticides market in 1987; however, the use of organophosphorus insecticides dropped to around 52% in 1999 and to 13% in 2013 due to its environmental persistence and mammalian toxicity (Casida and Quistad, 2004; Nauen and Bretschneider, 2002; Sparks, 2013).

Carbamates, which account for 6% of global insecticides (Sparks, 2013), have the similar mechanism of action with organophosphorus insecticides, but their neurotoxic effects are relatively more moderate than organophosphorus because the inhibition of acetyl cholinesterase is reversible and carbamates are known to be rapidly metabolized by human and animals (Karami-Mohajeri and Abdollahi, 2011; Risher et al., 1987).

Pyrethroids are structural analogs to naturally occurring insecticide, pyrethrin, found in *Chrysanthemum* flower heads. Pyrethroids can cause over excitation of the neuron by delaying the closing of VSSC, producing an effect similar to, but more pronounced than, DDT due to its better sodium channel binding capacity (Davies et al., 2007; Soderlund et al., 2002). By 2013, pyrethroids accounted for approximately 17% of the global insecticide market (Sparks, 2013).

Neonicotinoids are a relatively new family of insecticides with structural resemblance to nicotine (Casida and Durkin, 2013). Acting on nicotinic acetylcholine receptors, neonicotinoids can stimulate these receptors at low doses, while blocking these receptors at high doses, leading to paralysis and death (Gervais et al., 2012). Neonicotinoids have

become the fastest growing class of insecticides, representing ~27% of the global insecticide market in 2013, which makes them the largest single insecticide class on the market (Sparks, 2013; Sparks and Nauen, 2015). Due to the potential link between use of neonicotinoids and the reduction of bee population, the European Commission has banned use of three neonicotinoids (imidacloprid, thiamethoxam, and clothianidin) in 2013 (The European Commission).

4. Effects of insecticide exposure on glucose and lipid metabolisms

4.1. Effects of insecticides on the risk of diabetes in human

Numerous epidemiological studies have found a potential association between insecticide exposure with increased risks of diabetes (summarized in Table 2). For this table, we have included elevated fasting blood glucose levels and insulin resistance as evidence of diabetes risk. Organochlorine and organophosphorus insecticides are the most studied, but few others reported on the role of pyrethroids, carbamates and neonicotinoids on diabetes.

Most studies of organochlorines linked the blood levels of organochlorines or their metabolites with increased risk of diabetes in humans, as these are known to be persistent in human tissues, particularly fatty tissues (Table 2). Overall there is strong indication that exposure to these insecticides leads to increased risk of diabetes. In addition, Boada *et al.* (Boada et al., 2007) reported a negative correlation between blood levels of aldrin and p,p'-DDD and insulin-like growth factor-1, which are also known to have implications for development of insulin resistance (Aguirre et al., 2016).

Organophosphorus and carbamate insecticides have also been generally linked with increased risk of diabetes in humans, including pesticide applicators who were exposed to dichlorvos and trichlorfon (Montgomery et al., 2008). Interestingly, Saldana et al. (Saldana et al., 2007) reported that wives of pesticide applicators of organophosphorus insecticides (diazinon and phorate) along with carbamate insecticide (carbofuran) have increased risks of gestational diabetes mellitus, while no association was found for other organophosphorus (malathion and terbufos) or carbamate insecticide (carbaryl). In addition, a study reported that patients with acute organophosphorus poisoning due to suicide attempts had hyperglycemia (Amanvermez et al., 2010).

Reports on the effects of pyrethroids on diabetes from human studies are rather limited and no human study on neonicotinoids and diabetes is available currently. One study reported that pyrethroid mixture increases the risk of diabetes among pesticide factory workers in China (Wang et al., 2011a). Another study reported that exposure to pyrethroid insecticides (allethrin and prallethrin) increased plasma glucose levels in Indian men (Narendra et al., 2008). Since neonicotinoids have been used in the last few decades and they are designed to be relatively quickly degraded in biological systems, it is more challenging to investigate the exposure to neonicotinoids and human health perspectives (Casida, 2011). Overall, the majority of human studies have shown a positive association between exposure to certain type of insecticides and risk of diabetes.

4.2. Effects of insecticides on the risk of obesity in human

Compared to the large number of epidemiological studies on insecticide and diabetes, a relatively small number of studies reported a link between insecticide exposure and obesity (summarized in Table 3). Three reported positive association between organochlorine exposure (DDE and β -hexachlorocyclohexane) and body mass index (BMI) (Dirinck et al., 2011; Lee et al., 2011b; Mendez et al., 2011), while others found no association between organochlorine insecticide exposure (including DDE and β -HCH) and BMI (Dirinck et al., 2011; Glynn et al., 2003; Lee et al., 2011b; Mendez et al., 2011).

For other markers of lipid metabolism, there were no effects of organochlorines on high-density lipoprotein cholesterol (HDL-cholesterol), except one study reported negative correlation between DDE and HDL (Lee et al., 2007b). Others reported that pyrethroid insecticides, allethrin and prallethrin, were linked with disturbed lipid metabolism by increasing triglycerides, phospholipids, very low-density lipoprotein cholesterol (VLDL-C), but no effects on HDL (Narendra et al., 2008).

4.3. Effects of insecticides on glucose and lipid metabolisms in animals

Although different classes of insecticides have slightly different mechanism of insecticidal actions, many share common characteristics by acting on the nerve system. Common symptoms after exposure to insecticides include spasm, muscular tremors, and convulsions (Casida and Durkin, 2013; Nauen and Bretschneider, 2002). Overstimulation of the nervous system increases the energy demands and disturbs the functions of several organs, resulting in the disorder of energy homeostasis that can lead to altered glucose and lipid metabolisms (Matin et al., 1990a; Matin et al., 1990b; Pournourmohammadi et al., 2007; Rezg et al., 2008).

4.3.1. Effects of insecticides on blood glucose level in rodents—Studies have shown that exposure to all major types of insecticides induced hyperglycemia in experimental mice and/or rats (summarized in Table 4). Among them, organochlorine and organophosphorus compounds are the most documented with relatively less reports on carbamates, pyrethroids, and neonicotinoids. Studies have demonstrated that exposure to certain organochlorines, organophosphorus, pyrethroids, and neonicotinoids elevated blood glucose levels, although inconsistent results have also been reported (Table 4). This inconsistency might derive from the difference in dose and route of exposure, animal species, exposure duration, as well as methods to determine insulin resistance (Rezgi et al., 2006). In fact, others suggested that insecticide-induced hyperglycemia is only temporary: blood glucose concentration increased initially and then decreased with the possibility of reaching hypoglycemia (Gupta, 1974; Rezgi et al., 2006; Rezgi et al., 2007). More importantly, our group recently reported that low doses of orally administrated permethrin or imidacloprid (levels lower than NOAEL) potentiate insulin resistance, only when high-fat diet was provided in mice (Sun et al., 2016b; Xiao et al., 2015; Xiao et al., 2016). These results suggest that low dose insecticide exposure should be evaluated along with other factors contributing to development of diabetes.

4.3.2. Effects of insecticides on body weight in rodents—Although it is known that overstimulation of the nervous system increases the energy demands that are potentially linked to reduced weight, a number of studies reported that exposure to insecticides can lead to increased body weight gain, while other studies found inconsistent results (summarized in Table 4) (Matin et al., 1990a; Matin et al., 1990b; Pournourmohammadi et al., 2007; Rezg et al., 2008). Exposures to organochlorine insecticides (DDE, HCB, and γ -HCH) have led to increased body weight gain in rodents (Table 4) (Chadwick et al., 1988; Howell et al., 2014; Howell et al., 2015; Villeneuve et al., 1977), including a study of parental trans-generational exposure to DDT linked to increased obesity rate in the offspring (Skinner et al., 2013). Similarly, others reported that perinatal exposure to DDT was linked to significant weight gain, but only in female offspring (La Merrill et al., 2014) or reduced weight was reported after dieldrin exposure (Shakoori et al., 1984).

Organophosphorus insecticides have also been demonstrated to have moderate obesogenic effects. Chronic exposure to chlorpyrifos under manifestation of cholinergic toxicity was reported to increase body weight in mice (Peris-Sampedro et al., 2015) and rats (Meggs and Brewer, 2007), including developmental exposure of chlorpyrifos on weight gain in male, but not female offspring (Lassiter and Brimijoin, 2008). Others, however, reported reduced or no changes in weight after exposure to chlorpyrifos, dichlorvos, or dimethoate (Kamath and Rajini, 2007; Sarin and Gill, 1999; Slotkin et al., 2005).

Limited data are available for effects of pyrethroids and neonicotinoids on weight gain. Exposure to cypermethrin (a pyrethroid) or imidacloprid (a neonicotinoid) significantly decreased body weight in mice or rats (Arfat et al., 2014; Bhardwaj et al., 2010; Ince et al., 2012), while no effects of deltamethrin on weight in mice was reported (Armstrong et al., 2013). Recently, our group reported that low doses of orally administered permethrin or imidacloprid (levels of NOAEL and ADI) potentiate weight gain in male mice only when high-fat diet was provided (Sun et al., 2016b; Xiao et al., 2016). Taken collectively, the effects of insecticide exposure on body weight change are rather limited and inconsistent, likely depending on various factors, such as dose and route of administration, species, sex, and treatment duration. With new reports on low doses of insecticide and dietary fat interaction, it is possible that effects of insecticide exposure will be significant, particularly for relatively long-term low-dose exposure, when combined with other known contributing factors of obesity.

5. Mechanisms of insecticide-induced change in glucose and lipid metabolisms

Recent studies indicate that insecticides are reported to influence various organs and tissues, such as endocrine organs, liver, pancreas, muscle, and adipose tissue, which may lead to altered glucose and lipid metabolisms (Abdollahi et al., 2004c; Hectors et al., 2011; Hernandez et al., 2013; Karami-Mohajeri and Abdollahi, 2011; Kuo et al., 2013; McKinlay et al., 2008; Mostafalou and Abdollahi, 2013; Rahimi and Abdollahi, 2007; Rezg et al., 2010b; Soltaninejad and Abdollahi, 2009). A number of mechanisms were suggested to be influenced by insecticides; including oxidative stress and endoplasmic reticulum stress.

5.1. Liver

The liver, as one of the principal organs in regulation of glucose homeostasis, contributes to blood glucose level by maintaining a balance between storage of glucose via glycolysis and glycogenesis and release of glucose via glycogenolysis and gluconeogenesis (Abdollahi et al., 2004a; Hers, 1990; Nordlie et al., 1999; Rezg et al., 2006; Yang et al., 2000). It was suggested that since insecticides are designed to target the nervous system, exposure to insecticides may attribute to increased liver glucose production to meet the increased energy demand caused by overstimulation of the nervous system (Teimouri et al., 2006). In fact, studies have demonstrated that exposure to certain insecticides can increase the activities of key enzymes involved in hepatic gluconeogenesis and glycogenolysis (Abdollahi et al., 2004a; Basiri et al., 2007; Bergman, 1997; Deotare and Chakrabarti, 1981; Kauffman et al., 1990; Matin et al., 1990a; Romero-Navarro et al., 2006; Teimouri et al., 2006).

Organophosphorus insecticides were shown to increase hepatic phosphoenolpyruvate carboxykinase (a key enzyme for gluconeogenesis) and glycogen phosphorylase (a key enzyme for glycogenolysis) in both *in vitro* and *in vivo* (Abdollahi et al., 2004a; Basiri et al., 2007; Kauffman et al., 1990; Teimouri et al., 2006); however, others reported that insecticides increased hepatic glycogen levels by organochlorine (dieldrin) and organophosphorus (malathion) (Bhatia and Venkitasubramanian, 1972; Gupta, 1974). The inconsistent results obtained from different studies may be explained by initially increased blood glucose level caused by gluconeogenesis and glycogenolysis (the maximum increase was noted at 2 h after administration), followed by glycogenesis, and a return to normal blood glucose level 6–24 h after malathion treatment (Rezg et al., 2006; Rezg et al., 2007).

5.2. Pancreas

Excessive stimulation of the cholinergic receptors by insecticides can result in disturbance of insulin and glucagon secretions, potentially due to pancreas tissue damage. Thus, insecticides that influence either acetylcholine level or its receptors by inhibiting acetylcholine esterase (organophosphorus and carbamates) or by acting as agonists to nicotinic acetylcholine receptors (neonicotinoids) can all potentially stimulate insulin release from the pancreas. Studies have found that exposure to malathion, an organophosphorus insecticide, resulted in elevated blood insulin levels in rats (Pournourmohammadi et al., 2005; Pournourmohammadi et al., 2007). Another study, however, found that exposure to malathion resulted in decreased glucose-stimulated insulin secretion accompanied with patchy degenerative changes in the islets of Langerhans (Pournourmohammadi et al., 2007). Similarly, other human and animal studies also found that organophosphorus and carbamate insecticide can cause acute pancreatitis, which potentially influence insulin secretion (Dressel et al., 1978; Gokel et al., 2002; Goodale et al., 1993; Harputluoglu et al., 2003; Hsiao et al., 1996; Kandalaft et al., 1991; Lankisch et al., 1990; Marsh et al., 1988; Moore and James, 1981; Moritz et al., 1994; Panieri et al., 1997; Weizman and Sofer, 1992).

5.3. Muscle

Muscle is tightly linked with the nervous system by neuromuscular junctions, thus susceptible to insecticide-induced neurotoxic effects. Previous reports have exhibited that exposure to malathion, an organophosphorus insecticide, decreased glycogen content in

muscles (Pournourmohammadi et al., 2005; Rezg et al., 2007). In particular, Pournourmohammadi et al. (Pournourmohammadi et al., 2005) reported that this was due to increased activities of glycogen phosphorylase and phosphofructokinase (PFK), which are the key enzymes regulating glycogenolysis and glycolysis, respectively. In addition, permethrin (a pyrethroid insecticide) and imidacloprid (a neonicotinoid insecticide) were previously shown to induce insulin resistance in C2C12 muscle cells via Akt signaling (Kim et al., 2013, 2014a).

5.4. Adipose tissue

It is suggested that many lipophilic insecticides, such as DDE, malathion, or permethrin, can be easily trapped and stored in adipose tissues (Karmaus et al., 2009; Morgan et al., 2007; Pournourmohammadi et al., 2007). In addition, *in vitro* studies using 3T3-L1 adipocytes demonstrated that DDT (Kim et al., 2016; Moreno-Aliaga and Matsumura, 2002), DDE (Kim et al., 2016; Mangum et al., 2015), imidacloprid (Park et al., 2013), and permethrin (Kim et al., 2014a) potentiated adipogenesis. Another study found that treatment of DDE to 3T3-L1 cells did not alter adipogenesis or lipolysis, but increased basal free fatty acid uptake and the release of leptin, resistin, and adiponectin, which may be potentially linked to increased risk of obesity and type 2 diabetes (Howell and Mangum, 2011). The same study also reported that oxychlordan and dieldrin (both organochlorines) increased basal free fatty acid uptake, but not insulin-stimulated glucose uptake in 3T3-L1 adipocytes (Howell and Mangum, 2011).

5.5. Endocrine organs and brain

Currently more than 101 pesticides have been listed as proven or possible endocrine disruptors by the Pesticide Action Network UK (Mostafalou and Abdollahi, 2013). Some of the insecticides disrupt the endocrine system by mimicking the action of estrogen. For example, certain organochlorines and carbamates were reported to inhibit androgen receptors; some organophosphorus insecticides were reported to increase the expression of estrogen responsive genes; and certain pyrethroids potentiate the action of estrogen (McKinlay et al., 2008). The endocrine disrupting activities of pesticides may potentiate the risk of obesity and type 2 diabetes and other related diseases (Alonso-Magdalena et al., 2011; Gore et al., 2015).

Along with altered glucose homeostasis, organophosphorus compounds have been demonstrated to elevate catecholamine levels (Abdollahi et al., 2003a; Abdollahi et al., 2003b; Fukuyama and Adie, 1963; Gowda et al., 1983; Matin et al., 1990b; Pournourmohammadi et al., 2005; Ramu et al., 1973; Sungur and Guven, 2001), which are abolished by adrenalectomy (Matin et al., 1990a; Matin et al., 1990b). This suggests a role of adrenal glands in organophosphorus-induced disturbance of glucose homeostasis.

Pyrethroids were reported to inhibit progesterone action, organophosphorus insecticides were shown to inhibit thyroid hormone receptor (McKinlay et al., 2008), and exposure to an organophosphorus, diazinon, was previously reported to increase the serum testosterone levels (Alahyary et al., 2008). Organochlorine and carbamate insecticides showed anti-androgenic effects by inhibition of binding natural ligand to androgen binding receptors

(Mostafalou and Abdollahi, 2013). All these hormones are known to influence insulin sensitivity and glucose homeostasis (Bruns and Kemnitz, 2004; Fernandez-Real et al., 2006; Polderman et al., 1994). It was suggested that insecticides were able to act as an agonist or an antagonist towards aryl hydrocarbon receptors and certain nuclear receptors, such as retinoic acid receptors, pregame X receptors, and peroxisome proliferator-activated receptors (Kojima et al., 2010; Lemaire et al., 2005).

Studies have reported decreased brain glycogen content with increased activity of glycogen phosphorylase by organophosphorus insecticide, malathion (Matin and Husain, 1987; Matin et al., 1990a) and dichlorvos (Sarin and Gill, 1999). It was suggested that malathion could interfere with oxygen uptake and promoted glycogenolysis and glycolysis in favor of anaerobic conditions to counteract the neurotoxic effects in rats (Matin and Husain, 1987). Malathion was also shown to increase lactic acid concentration without altering pyruvate content in the brain (Matin et al., 1990b). Others reported that an organochlorine insecticide (dieldrin) was previously reported to cause apoptosis and neural degeneration by increasing acetylation of core histone H3 and H4 in neuronal cells (Song et al., 2010). Limited studies reported that exposure to insecticides could affect feeding behavior by acting on the neural circuits (Mostafalou and Abdollahi, 2013). When low doses of imidacloprid or permethrin (at or lower than NOAEL) were administered in mice, no significant effects of either insecticide on food intake were observed (Sun et al., 2016b; Xiao et al., 2015; Xiao et al., 2016).

5.6. Cellular Responses

5.6.1. Oxidative stress—Oxidative stress was often suggested to be associated with insecticide-induced toxicity *in vitro* and *in vivo* (Abdollahi et al., 2004b; Bagchi et al., 1995; Begum and Rajini, 2011; Kalender et al., 2005; Mostafalou and Abdollahi, 2012; Mostafalou and Abdollahi, 2013; Mostafalou et al., 2012; Slaninova et al., 2009; Soltaninejad and Abdollahi, 2009; Teimouri et al., 2006; Yang and Dettbarn, 1996). It is also known that oxidative stress is linked with obesity and type 2 diabetes (Furukawa et al., 2004). Thus, many mechanistic studies have suggested that insecticides disrupt glucose and lipid metabolisms via oxidative stress-mediated mechanisms, such as lipid peroxidation, mitochondrial dysfunction, inhibition of paraoxonase and glucose-6-phosphate dehydrogenase (G6PD), and nitrosative stress (Abdollahi et al., 2004b; Abdollahi et al., 2004c; Akhgari et al., 2003; Karami-Mohajeri and Abdollahi, 2011; Matsuoka et al., 1997; Mostafalou and Abdollahi, 2013; Ranjbar et al., 2002; Rezg et al., 2008; Shadnia et al., 2005; Soltaninejad and Abdollahi, 2009).

Glucose plays a critical role as an antioxidant against free radicals via the pentose phosphate pathway, in which nicotinamide adenine dinucleotide phosphate (NADP) is reduced to NADPH, which is subsequently used for the reduction of oxidized glutathione (GSH) from disulfides of GSH and cellular proteins (Teimouri et al., 2006). The increased demand of glucose to counteract the increased reactive oxygen species induced by insecticides has been suggested to cause hyperglycemia, leading to stimulated hepatic glycogenolysis and gluconeogenesis pathways (Teimouri et al., 2006). In fact, some studies found that

antioxidants could attenuate insecticide-induced hyperglycemia (Basiri et al., 2007; Yousef et al., 2006).

Abnormal mitochondrial respiratory chain functions can cause disturbance in intracellular energy homeostasis and has been involved in many diseases, including diabetes (Abdul-Ghani and DeFronzo, 2008; Kim et al., 2008; Lowell and Shulman, 2005; Ma et al., 2012). Exposure to insecticides can cause muscle fasciculation, which greatly increase the oxygen flow into corresponding tissues and organs (Abdollahi et al., 2004b; Abdollahi et al., 2004c; Basiri et al., 2007; Mostafalou and Abdollahi, 2012). And this increased oxygen flow caused by insecticides may lead to elevated oxidative phosphorylation in mitochondria, which subsequently increase the production of reactive oxygen species as byproducts. In addition, some insecticides (rotenone or pyridaben) are known to disrupt mitochondrial respiratory chain reaction, mainly by inhibiting Complex I, II, III and V electron transport chain (Gomez et al., 2007).

Studies have demonstrated that pancreatic beta cell failure induced by insecticide exposure could be the result of underlying mitochondrial dysfunction in the pancreas (Lee, 2011; Lim et al., 2009; Mostafalou and Abdollahi, 2013). It is reported that the pancreas is more susceptible to reactive oxygen species than other tissues because of its relative low expression of defensive enzymes against reactive oxygen species (Grankvist et al., 1981; Ho and Bray, 1999; Kakkar et al., 1998).

Besides their inhibiting effect on acetylcholine esterase activity, organophosphorus compounds were reported to inhibit other esterase, such as the paraoxonase, a key enzyme involved in hydrolysis of oxons (active organophosphorus metabolites), which may potentially increase oxidative stress (Mackness et al., 1991).

cAMP and cGMP signaling may also play an important role in insecticide-induced oxidative stress. Previous studies have found that increased cyclic nucleotides using phosphodiesterase inhibitors could protect against organophosphorus-induced lipid peroxidation in rat submandibular saliva (Abdollahi et al., 2003a) and liver cells (Abdollahi et al., 2003b). Similarly, another report supported that increased intracellular levels of cAMP and cGMP by intraperitoneal administration of phosphodiesterase inhibitors could exert protective effects against organophosphorus-induced hyperglycemia and oxidative/nitrosative stress in Langerhans islets cells in rat (Ghafour-Rashidi et al., 2007).

5.6.2. Endoplasmic reticulum (ER) stress—Recent studies have found ER stress play key roles in development of several chronic diseases, including obesity and type 2 diabetes (Cao and Kaufman, 2013; Hotamisligil, 2010; Hummasti and Hotamisligil, 2010; Ozcan et al., 2004; van der Kallen et al., 2009). There are a few studies reporting a correlation between several types of insecticides and ER stress. An organochlorine (endosulfan), carbamates (formetanate, methomyl, pyrimicarb), and a pyrethroid (bifenthrin) were reported to increase 78 kDa glucose-regulated protein GRP78, also known as binding immunoglobulin protein (BiP), which is one of the ER stress markers in human pulmonary A549 cells (Skandrani et al., 2006a; Skandrani et al., 2006b). Another pyrethroids insecticide, deltamethrin, was reported to induce ER stress in SK-N-AS neuroblastoma cells

via elevation of intracellular calcium level and activation of eukaryotic translation initiation factor 2 α (eIF2 α) (Hossain and Richardson, 2011). Currently there is no study directly determining the role of ER stress caused by insecticides and development of obesity and type 2 diabetes.

6. Conclusion

Previous studies have largely focused on organochlorine and organophosphorus insecticides, with less on carbamates, pyrethroids, and neonicotinoids and the link between development of obesity and type 2 diabetes. The human and animal studies included in this review generally suggest that exposure to insecticides increases the risk of developing obesity and type 2 diabetes with some inconsistent results. This inconsistency may have contributed from other factors, such as dose, duration of exposure, methods used to determine variables, diet, and experimental design especially for animal studies. Although limited, current knowledge suggest that there is great need to determine the effects of low level exposure to insecticides, at or lower than NOAEL, and interaction with other known factors, such as sex and diet, that contributing in development of obesity and type 2 diabetes. In addition, knowledge on specifics of various exposures of new types of insecticides is still very limited, and there is a great need to develop proper strategy for evaluating the exposure levels for insecticides, particularly for those known to be metabolized and eliminated rather quickly in the biological system. Lastly, although we have not focused on the developmental exposure of insecticides in the current review, it would be significant to understand developmental exposure of insecticides and health implication of the next generation. Overall, we conclude that the majority of studies reporting exposures to insecticides are associated with increased risk of developing obesity and type 2 diabetes. More clinical and epidemiological studies, as well as mechanistic studies are needed to understand the insecticide-induced disturbances in glucose and lipid metabolisms, which may contribute to the development of obesity and type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Authors would like to thank Ms. Brooke T. Pearson and Jayne M. Storkson for help in writing manuscript. This project is supported in part by NIH funding R21ES023676.

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Highlights

- Exposure to insecticides are positively associated with the risk of obesity and type 2 diabetes.
- Exposure to insecticides may disturb glucose and lipid metabolisms.
- Insecticide may induce oxidative and/or endoplasmic reticulum stresses.

Table 1

Major classes of insecticides with examples and their structures

Organochlorines	Organophosphorus	Carbamates	Pyrethroids	Neonicotinoids
Aldrin	Chlorpyrifos	Aldicarb	Allethrin	Acetamiprid
DDT/DDE	Diazinon	Bendiocarb	Bifenthrin	Clothanidin
Dieldrin	Dichlorvos	Carbaryl	Cismethrin	Dinotefuran
Heptachlor	Malathion	Dioxacarb	Cyhalothrin	Imidacloprid
Lindane	Parathion	Fenobucarb	Deltamethrin	Niternpyram
Methoxychlor	Profenofos	Isoprocab	Permethrin	Thiacloprid
		Methomyl	Tefluthrin	Thiamethoxam

Table 2

Effects of insecticide exposure on risk of diabetes in human

Insecticide ^a	Country	Subject	Risk of diabetes ^c	Other comments	Reference
Organochlorine					
Aldrin	USA	Pesticide applicators	↑		(Montgomery et al., 2008)
Chlordane	USA	General population	↑		(Lee et al., 2006)
	USA	Pesticides applicators	↑		(Montgomery et al., 2008)
	South Korea	Age 40	×		(Son et al., 2010)
p,p'-DDD	Sweden	Aged 50–74 years old	×		(Glynn et al., 2003)
	Sweden	Fishermen and theirwives	↑		(Rylander L., 2005)
	USA	General population	↑		(Lee et al., 2006)
USA	USA	Native Americans	↑		(Codru et al., 2007)
	USA	Mexican Americans	↑		(Cox et al., 2007)
	Sweden	Fishermen's wives	↑		(Rignell-Hydbom et al., 2007)
USA	USA	Non-diabetic	↑ ^c		(Lee et al., 2007b)
p,p'-DDE	Canada	First Nation Community members	↑		(Philibert et al., 2009)
	Sweden	50–59 years old	↑		(Rignell-Hydbom et al., 2009)
	USA	Great Lakes sport fish consumer	↑		(Turyk et al., 2009)
	USA	General population	↑		(Everett and Matheson, 2010)
	USA	African and White Americans	×		(Lee et al., 2010)
	South Korea	Age 40	↑		(Son et al., 2010)
	Slovakia	Polluted area	↑		(Ukropec et al., 2010)
	Finland	57–70 years old	↑		(Airaksinen et al., 2011)
	Belgium	Hospital patients, staff and volunteers	×		(Dirinck et al., 2011)
	USA	Non-diabetic	↑ ^d		(Lee et al., 2011b)
	Sweden	Age > 70	×		(Lee et al., 2011a)
	Denmark	General population	↑		(Faerch et al., 2012)
Spain	Spain	General population	×		(Gasull et al., 2012)
	Spain	Hospital patients	↑		(Arrebola et al., 2013)

Insecticide ^a	Country	Subject	Risk of diabetes ^c	Other comments	Reference
o,p'-DDE	Canada	First Nations community members	×	↑ Blood DDE in diabetic individuals	(Pal et al., 2013)
	Benin	18–65 years old	↑		(Azandjeme et al., 2014)
	Russia	8–9 years old boys	× ^d		(Burns et al., 2014)
	Belgium	General population	↑		(Dirinck et al., 2014)
	South Korea	Hospital patients	↑		(Kim et al., 2014b)
	Slovakia	Polluted area	↑		(Langer et al., 2014)
	Thailand	General population	↑		(Teeyapant et al., 2014)
	Saudi Arabia	30–50 years old	↑		(Al-Othman et al., 2015)
	USA	Great Lake Sport fish consumer	↑		(Turyk et al., 2015)
	Belgium	Aged 50–65 years old	↑	only in men	(Van Larebeke et al., 2015)
	France	Newborns	×	↓ Insulin & adiponectin level in female newborns	(Debost-Legrand et al., 2016)
	Canada	Pregnant women	× ^e		(Shapiro et al., 2016)
	Denmark	General population	↑		(Faerch et al., 2012)
	USA	Mexican Americans	↑		(Cox et al., 2007)
	USA	General population	↑		(Everett et al., 2007)
	USA	Non-diabetic	× ^d		(Lee et al., 2007a)
p,p'-DDT	USA	General population	↑		(Everett and Matheson, 2010)
	USA	African and White Americans	×		(Lee et al., 2010)
	South Korea	Age 40	↑		(Son et al., 2010)
	Slovakia	Polluted area	↑		(Ukropec et al., 2010)
	USA	Non-diabetic	× ^d		(Lee et al., 2011b)
	Denmark	General population	↑		(Faerch et al., 2012)
	Spain	General population	×		(Gasull et al., 2012)
	Benin	18–65 years old	↑		(Azandjeme et al., 2014)
	South Korea	Hospital patients	↑		(Kim et al., 2014b)
	Saudi Arabia	30–50 years old	↑		(Al-Othman et al., 2015)
o,p'-DDT	South Korea	Age 40	↑		(Son et al., 2010)
	Denmark	General population	↑		(Faerch et al., 2012)

Insecticide ^a	Country	Subject	Risk of diabetes ^c	Other comments	Reference
Dieldrin	USA	General population	×		(Everett and Matheson, 2010)
	Sweden	50–74 years old	↑		(Glynn et al., 2003)
	USA	Native Americans	↑		(Codru et al., 2007)
	USA	Mexican Americans	×		(Cox et al., 2007)
HCB	USA	African and White Americans	×		(Lee et al., 2010)
	South Korea	Age 40	↑		(Son et al., 2010)
	Slovakia	Polluted area	×	↑ only prediabetes	(Ukropec et al., 2010)
	USA	Non-diabetic	× ^d		(Lee et al., 2011b)
	Sweden	Age > 70	×		(Lee et al., 2011a)
	Denmark	General population	↑		(Faerch et al., 2012)
	Spain	General population	↑		(Gasull et al., 2012)
	Spain	Hospital patients	×		(Arrebola et al., 2013)
	Canada	First Nations community members	×	↑ Blood HCB	(Pal et al., 2013)
	Russia	8–9 years old boys	↑ ^d		(Burns et al., 2014)
<i>cis</i> -nonachlor	Slovakia	Polluted area	↑		(Langer et al., 2014)
	South Korea	> 40 years old	↑		(Lee et al., 2014b)
	South Korea	Hospital patients	↑		(Kim et al., 2014b)
	Belgium	50–65 years old	↑		(Van Larebeke et al., 2015)
CB-153	Canada	First Nations community members	↑		(Pal et al., 2013)
	South Korea	Hospital patients	↑		(Kim et al., 2014b)
	Sweden	Fishermen and their wives	↑	only in men	(Rylander L., 2005)
	USA	General population	↑		(Lee et al., 2006)
β-HCH	Sweden	50–74 years old	×		(Glynn et al., 2003)
	USA	Mexican Americans	↑		(Cox et al., 2007)
	USA	Non-diabetic	× ^d		(Lee et al., 2007a)
	USA	Non-diabetic	× ^c		(Lee et al., 2007b)
	USA	General population	↑		(Everett and Matheson, 2010)
	USA	African and White Americans	×		(Lee et al., 2010)

Insecticide ^a	Country	Subject	Risk of diabetes ^c	Other comments	Reference
	South Korea	Age 40	↑		(Son et al., 2010)
	Slovakia	Polluted area	×	↑ only prediabetes	(Ukropec et al., 2010)
	Belgium	Hospital patients, staff and volunteers	↑		(Dirinck et al., 2011)
	USA	Non-diabetic	× ^d		(Lee et al., 2011b)
	Denmark	General population	×		(Faerch et al., 2012)
	Spain	General population	×		(Casull et al., 2012)
	Spain	Hospital patients	↑		(Arrebola et al., 2013)
	Canada	First Nations community members	×	↑ Blood β-HCH	(Pal et al., 2013)
	Benin	18–65 years old	↑		(Azandjeme et al., 2014)
	Saudi Arabia	18–65 years old	↑		(Al-Othman et al., 2014)
γ-HCH	Russia	8–9 years old boys	× ^d		(Burns et al., 2014)
	South Korea	Aged > 40 years	↑		(Lee et al., 2014b)
	South Korea	Hospital patients	×		(Kim et al., 2014b)
	USA	African and White Americans	×		(Lee et al., 2010)
	USA	Non-diabetic	× ^d		(Lee et al., 2011b)
Heptachlor	Saudi Arabia	18–65 years old	↑		(Al-Othman et al., 2014)
	USA	Pesticide applicators	↑		(Montgomery et al., 2008)
	USA	General population	↑		(Everett and Matheson, 2010)
	USA	General population	↑		(Patel et al., 2010)
	South Korea	Age 40	↑		(Son et al., 2010)
Mirex	South Korea	Age > 40	↑		(Lee et al., 2014b)
	USA	Native Americans	↓		(Codru et al., 2007)
	USA	General population	×		(Everett and Matheson, 2010)
	USA	African and White Americans	↑		(Lee et al., 2010)
	South Korea	Age 40	↑		(Son et al., 2010)
Oxychlordane	USA	Non-diabetic	× ^d		(Lee et al., 2011b)
	Canada	First Nations community members	×	↑ Blood mirex in diabetic individuals	(Pal et al., 2013)
	Sweden	50–74 years old	×		(Glynn et al., 2003)

Insecticide ^a	Country	Subject	Risk of diabetes ^c	Other comments	Reference
TNC	USA	General population	↑		(Lee et al., 2006)
	USA	Mexican Americans	↑		(Cox et al., 2007)
	USA	Non-diabetic	↑ ^d		(Lee et al., 2007a)
	USA	Non-diabetic	× ^c		(Lee et al., 2007b)
	USA	General population	↑		(Everett and Matheson, 2010)
	USA	African and White Americans	×		(Lee et al., 2010)
	South Korea	Age 40	↑		(Son et al., 2010)
	Finland	57–70 years old	↑		(Airaksinen et al., 2011)
	USA	Non-diabetic	× ^d		(Lee et al., 2011b)
	Canada	First Nations community members	↑	↑ Blood oxychlordan in diabetic individuals	(Pal et al., 2013)
	South Korea	Aged > 40 years	↑		(Lee et al., 2014b)
	Canada	Pregnant women	× ^e		(Shapiro et al., 2016)
	Sweden	50–74 years old	×		(Glynn et al., 2003)
	USA	General population	↑		(Lee et al., 2006)
	USA	Mexican Americans	↑		(Cox et al., 2007)
	USA	Non-diabetic	↑ ^d		(Lee et al., 2007a)
	USA	Non-diabetic	× ^c		(Lee et al., 2007b)
	USA	General population	↑		(Everett and Matheson, 2010)
	USA	African and White Americans	×		(Lee et al., 2010)
	South Korea	Age 40	↑		(Son et al., 2010)
	Finland	57–70 years old	↑		(Airaksinen et al., 2011)
Organophosphorus	USA	Non-diabetic	× ^d		(Lee et al., 2011b)
	Sweden	age > 70	↑		(Lee et al., 2011a)
	Canada	First Nations community members	↑		(Pal et al., 2013)
	Benin	18–65 years old	↑		(Azandjeme et al., 2014)
	Canada	Pregnant women	× ^e		(Shapiro et al., 2016)

Insecticide ^a	Country	Subject	Risk of diabetes ^c	Other comments	Reference
Dialkylphosphate (Metathalites)	France	Newborns	×	↑ Insulin level	(Debost-Legrand et al., 2016)
Dimethylphosphate (Metathalites)	France	Pregnant women	↓ ^e		(Shapiro et al., 2016)
Dimethylthiophosphate (Metathalites)	France	Pregnant women	↓ ^e		(Shapiro et al., 2016)
Mixture	Turkey	Overdose patients	↑ ^c	Case report	(Amanvermez et al., 2010)
	Iran	Farmers	↑		(Malekiran et al., 2013)
	India	A 15-year-old girl	↑ ^c	Case report	(Swaminathan et al., 2013)
Diazinon	Israel	Children	↑ ^c		(Weizman and Sofer, 1992)
	USA	Wives of pesticide applicators	↑ ^e		(Saldana et al., 2007)
Dichlorvos	USA	Pesticides applicators	↑		(Montgomery et al., 2008)
Malathion	Canada	81-year-old mother and her 39-year old son	↑ ^c	Case report	(Meller et al., 1981)
	USA	Wives of pesticide applicators	× ^e		(Saldana et al., 2007)
	Egypt	Non-diabetic male farmers	↑		(Raafat et al., 2012)
Phorate	USA	Wives of pesticide applicators	↑ ^e		(Saldana et al., 2007)
Terbufos	USA	Wives of pesticide applicators	×		(Saldana et al., 2007)
Trichlorfon	USA	Pesticides applicators	↑		(Montgomery et al., 2008)
Carbamates					
Carbaryl	USA	Wives of pesticide applicators	× ^e		(Saldana et al., 2007)
Carbofuran	USA	Wives of pesticide applicators	↑ ^e		(Saldana et al., 2007)
Pyrethroids					
Allethrin	India	Mosquito repellent coils or mats users	↑ ^c		(Narendra et al., 2008)
Permethrin	USA	Pesticides applicators	×		(Montgomery et al., 2008)
Prallethrin	India	Mosquito repellent coils or mats users	↑ ^c		(Narendra et al., 2008)
Pyrethroid mixture	China	Pesticide factory workers	↑		(Wang et al., 2011a)
Pyrethroid mixture	Bolivia	Male pesticide sprayers	↑		(Hansen et al., 2014)
Other insecticide					

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Insecticide ^a	Country	Subject	Risk of diabetes ^c	Other comments	Reference
Amitraz	Turkey	Overdose patients	↑ ^c	Case report	(Avsarogullari et al., 2006)
Mixture of chlorpyrifos & cypermethrin	Morocco	A 30-year-old man	↑ ^c	Case report	(Badrane et al., 2014)

^a Abbreviation for insecticides: 2,2'-bis (4-chlorophenyl)-1,1-dichloroethylen (p,p'-DDD), 2,2'-bis (4-chlorophenyl)-1,1-dichloroethylene (p,p'-DDE); 2,2'-bis (4-chlorophenyl)-1,1,1-trichloro-ethane (p,p'-DDT); Hexachlorobenzene (HCB); 2,2',4,4',5,5'-Hexachlorobiphenyl (CB-153); β-Hexachlorocyclohexane (β-HCH); γ-Hexachlorocyclohexane (γ-HCH); trans-nonachlor (TNC).

^b Abbreviation: ↑, increase; ×, no association with; Gestational diabetes mellitus (GDM).

Risk of diabetes including elevated blood glucose level^c, insulin resistance^d, and gestational diabetes mellitus^e.

Table 3
Effects of insecticide exposure on body weight change and other lipid markers in humans

Insecticide ^a	Study information			Results ^b	Reference
	Country	Description	BMI Others		
Organochlorine	Sweden	Women	=		(Glynn et al., 2003)
	USA	Non-diabetic	N/A = TG		(Lee et al., 2007b)
	Belgium	Obese and lean men & women	=		(Dirinck et al., 2011)
	USA	African and White Americans	↑ ↑ TG ↓ HDL-C		(Lee et al., 2011b)
<i>p,p'</i>-DDE	Spain	Women in early pregnancy & their newborn children	↑ ↑ Weight in the first 6 months; ↑ BMI at 14 months in infancy		(Mendez et al., 2011)
	Denmark	General Population	N/A ↑ Lipid oxidation; ↑FFA		(Faerch et al., 2012)
	Slovakia	Polluted area	↑ ↑ TG & cholesterol; ↓ testosterone in males		(Langer et al., 2014)
	Belgium	Aged 50–65 years old	↑ Only in men		(Van Larebeke et al., 2015)
<i>p,p'</i>-DDT	USA	African and White Americans	= = TG = HDL-C		(Lee et al., 2011b)
	Sweden	Women	=		(Glynn et al., 2003)
HCB	USA	African and White Americans	= = TG = HDL-C		(Lee et al., 2011b)
	Spain	Women in early pregnancy & their newborn children	=		(Mendez et al., 2011)
	Denmark	General Population	N/A ↑ Lipid oxidation		(Faerch et al., 2012)
	Saudi Adults	30–50 years old	N/A ↑ TG; ↓ HDL-cholesterol		(Al-Othman et al., 2014)

Insecticide ^a	Study information		Results ^b		Reference
	Country	Description	BMI	Others	
γ-HCH	Slovakia	Polluted area	↑	↑ TG & cholesterol; ↓ testosterone in males	(Langer et al., 2014)
	Belgium	Aged 50–65 years old	↑	Only in women	(Van Larebeke et al., 2015)
	Sweden	Women	=		(Glynn et al., 2003)
	USA	Non-diabetic	N/A	= TG	(Lee et al., 2007b)
	Belgium	Obese and lean men & women	↑	↑ Waist & subcutaneous abdominal fat mass	(Dirinck et al., 2011)
β-HCH	USA	African and White Americans	=	= TG = HDL-C	(Lee et al., 2011b)
	Spain	Women in early pregnancy & their newborn children	=		(Mendez et al., 2011)
γ-HCH	USA	African and White Americans	=	= TG = HDL-C	(Lee et al., 2011b)
	Sweden	Women	=		(Glynn et al., 2003)
Oxychlordan	USA	Non-diabetic	N/A	↑ TG	(Lee et al., 2007b)
	USA	African and White Americans	=	↑ TG = HDL-C	(Lee et al., 2011b)
	Sweden	Women	=		(Glynn et al., 2003)
TNC	USA	Non-diabetic	N/A	= TG	(Lee et al., 2007b)
	USA	African and White Americans	=	= TG = HDL-C	(Lee et al., 2011b)
	USA	African and White Americans	=	= TG = HDL-C	(Lee et al., 2011b)
Mirex	USA	African and White Americans	=	= TG = HDL-C	(Lee et al., 2011b)
	USA	African and White Americans	=	= TG = HDL-C	(Lee et al., 2011b)
Organophosphorus					
Malathion	Egypt	Non-diabetic male farmers	↑	↑ Waist circumference	(Raafat et al., 2012)

Insecticide ^a	Study information		Results ^b	Reference	
	Country	Description			
Pyrethroids					
Allethrin	India	Men	N/A	↑ TG, phospholipids, lipid peroxides, & VLDL-C; ↓ Cholesterol & glycolipids; = HDL-C & LDL-C	(Narendra et al., 2008)
Prallethrin	India	Men	N/A	↑ TG, phospholipids, lipid peroxides, & VLDL-C; ↓ Cholesterol & glycolipids; = HDL-C & LDL-C	(Narendra et al., 2008)

^a Abbreviation for insecticides: 2,2'-bis (4-chlorophenyl)-1,1-dichloroethylene (p,p'-DDE); 2,2'-bis (4-chlorophenyl)-1,1,1-trichloro-ethane (p,p'-DDT); Hexachlorobenzene (HCB); β-Hexachlorocyclohexane (β-HCH); γ-Hexachlorocyclohexane (γ-HCH); trans-nonachlor (TNC).

^b Abbreviation for results: ↑, increase; ↓, decrease; =, no change; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/A, not available; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol.

Table 4
Effects of insecticide-induced alteration of glucose and lipid metabolisms in mice and rats

Insecticide	Treatment			Sex ^d	Results ^e					Reference
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol	
Mice										
Organochlorine										
	0.4 & 2	Oral	Daily for 5 d, tested after 7, 14, 21 & 28d	M	↑ (2)	↑ (2; 7 & 21 d)	=	N/A	N/A	= Glucagon; = Insulin resistance; = pAkt Ser473/Akt (liver, muscle & fat); = Leptin & resistin

Insecticide	Treatment			Sex ^d	Results ^e					Reference	
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol		Other comments
	1.7	Oral	Daily for 16 d (GND11.5- PND5)	F & pups	↓ in ♂ (PND5); ↑ in adult ♀	↓ (PND5); = (6 m post- wean)	↑ in ♀ w/ HFD; = (6 m post-wean)	↑ in ♀ w/ HFD	↑ in ♀ w/ HFD;	↑ Insulin resistance in ♀ w/ HFD & ♂ w/ LFD; ↑ Fat mass in adult ♀; = Lipid level (during 6 m of post-weaning); = Food intake; = FFAs	(La Merrill et al., 2014)
Organophosphorus											
Chlorpyrifos	2	Oral (Diet)	8 wk	M ^f	↑	↑	↑	=	↑	↑ Insulin resistance; ↑ Food intake; ↑ Leptin in ApoE3f	(Peris- Sampedro et al., 2015)
Diazinon	6.5 (1/10 LD ₅₀)	i.p.	5 times weekly for 7 wk	M	N/A	↑	N/A	↑	↑	Tea and olive leaves extract prevented diazinon-disturbed glucose and lipid metabolism	(Al-Attar and Abu Zeid, 2013)
Carbamates											
Furadan	0.125, 0.25, & 0.5	i.p.	Weekly for 2.4, & 6 wk	M	N/A	N/A	N/A	↑	↑	↑ Lipid content in serum, liver & kidney; ↑ Phospholipid in serum, liver, & kidney; ↓ Phospholipid in brain; = FFAs; ↓ Lipase activity in liver and serum	(Gupta et al., 1986)
Pyrethroids											
Cypermethrin	10	Oral	Daily for 28 d	M	↓	↓	N/A	↑	↑; ↑ VLDL, ↓ HDL		(Ince et al., 2012)

Insecticide	Treatment			Sex ^d	Results ^e					Reference	
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol		Other comments
Deltamethrin	1 & 3 (1/4 of NOAEL)	Oral (Diet)	Every 3 d in gestation & lactation in dams	F & ♂ pups	= in ♂ pups	N/A	N/A	N/A	N/A	Gene expression in fat of ♂ pups: ↓ Glucose transport: Glut4 (1) & Glut2; ↓ Lipogenic gene (1) : SREBP1, ACC-1, FABP4, CD36, LPL & SCD-1; ↓ Adipogenesis (1): PPARγ & CEBPα	(Armstrong et al., 2013)
Neonicotinoids											
Imidacloprid	5, 10, & 15	Oral	Daily for 15 d	M	↓ (15)	N/A	N/A	N/A	N/A	↑ Liver & kidney weight (15)	(Arfat et al., 2014)
	0.06, 0.6 & 6	Oral	Daily for 12 wk	M	↑	↑	↑	↑	=	↑ Leptin; = FFA; Fat: ↑ cell size; ↑ CD36, SREBP1, TNFα; ↓ CaMKKβ, pAMPKα/AMPKα, pACC/ACC; Liver: ↑ PEPCK; ↓ CaMKKβ, PPARα, pAMPKα/AMPKα, pACC/ACC, Sirt1, PGC-1α; Muscle: ↓ GLUT4; ↑ PDK4; = CPT1	(Sun et al., 2016b)
Rats											
Organochlorine											

Insecticide	Treatment			Sex ^d	Results ^e					Reference
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol	Other comments
DDT	1	Oral (Diet)	180 d	M	N/A	N/A;	↓ in sedentary rats;	N/A	↓ in sedentary rats; ↑ in exercised rats;	= Food intake, carcass & liver lipids;
							Significant interaction DDT × Exercise		Significant interaction DDT × Exercise (glucose tolerance)	(Berdanier and de Dennis, 1977)
	20	Oral	Daily for 189 d	F	=	N/A	N/A	N/A	N/A	(Chadwick et al., 1988)
Dieldrin	25 & 50	i.p.	Daily for 6 d (GND8-14)	F/M	↑ in F3	N/A	N/A	N/A	N/A	Gestational rats (F0) were treated and the third generation (F3) were observed
	30	Oral	Single, test after 24h	M	=	N/A	N/A	N/A	N/A	↑ Liver glycogen & TG; = Liver phospholipid & cholesterol
	2	Oral	6 m	M	↓	↑	N/A	N/A	=	(Shakoori et al., 1984)
HCB	*20 & 100;				↑ σ (40) w/ food deprivation, ↑ in σ (20 & 100) w/o food deprivation					= Food intake;
	40 & 200 w/ food deprivation;	Oral (Diet)	4 wk	F/M		N/A	N/A	N/A	N/A	↑ Liver weight w/ food restriction (20);
										↑ Liver hypertrophy w/ food deprivation (200)
γ-HCH (lindane)	5, 10, 20, & 40	Oral	Daily for 189 d; daily for 15 wk	F	↑ (20 & 40)	N/A	N/A	N/A	N/A	↑ Food intake & food efficiency (20 & 40); ↑ Liver weight; 40 caused death
Organophosphorus										

Insecticide	Treatment			Sex ^d	Results ^e						Reference
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol	Other comments	
Acephate	2.5	s.c.	Daily for 8 wk	M	N/A	↑	N/A	N/A	N/A	↓ Liver glycogen; ↑ Pyruvic acid and lactic acid in liver, heart, kidney, brain & blood	(Deotare and Chakrabarti, 1981)
										↓ Total lipids; Liver: ↑ Total lipids (↓ microsome, ↑ mitochondria, ↑ cytosol); ↑ Phospholipids & total cholesterol (↓ microsome, ↓ mitochondria, & ↑ cytosol); ↑ FFA & TG;	(Choudhary and Chakrabarti, 1984)
	600	Oral	Daily for 8 wk	F/M	N/A	N/A	N/A	↓	=		
	140 (1/10 LD ₅₀)	Oral	Single, tested after 2–8h	M	N/A	↑ at 2h and return to normal	N/A	N/A	↓ in adrenal (2 & 6 h)	↑ Corticosterone (2 & 6 h); ↑ Liver glycogen (6 h) ↓ Gluconeogenesis (G6P & TAT) at 6 h; = Weights of adrenals & liver	(Joshi and Rajini, 2009)
Chlorpyrifos	1	s.c.	Daily for 4 d (PND1–4), test in adulthood	F/M	=	=	↑ in post-prandial ♂, = in fasting ♂; ↓ in ♀ (<i>p</i> < 0.08)	↑ in ♂	↑ in ♂	= FFAs	(Slotkin et al., 2005)
	5	s.c.	Daily for 4 m	F	↑ (starting at 2 m)	N/A	N/A	N/A	N/A	↑ Perinephric fat weight; = Weights of heart, liver & gastrocnemius muscle	(Meggs and Brewer, 2007)

Insecticide	Treatment			Sex ^d	Results ^e					Reference	
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol		Other comments
Diazinon	1, 2.5, & 4	Oral	Daily for 35 d, GND7-PND21 to dams	F& pups	↑ in ♂ pups starting at PND 51 (2.5); = in ♀ pups	N/A	N/A	N/A	N/A	↑ Body volume in ♂ pups at PND 100; ↓ Weight/volume ratio in ♂ pups at PND 100; ↓ Leptin	(Lassiter and Brimijoin, 2008)
	40 (1/3 LD ₅₀)	i.p.	Single, tested after 2 h	F	N/A	↑	N/A	N/A	N/A	↓ Brain glycogen; ↑ GP & PGM; = G6P; Atropine (cholinergic blocker), tolazoline (α-adrenergic blocker) and propranolol (β-adrenergic blocker) abolished or reduced diazinon-induced hyperglycemia & brain glycogenolysis	(Husain and Ansari, 1988)
	40	i.p.	Single, tested after 2 h	F	N/A	↑; abolished by adrenalectomy	N/A	N/A	N/A	↑ Lactic acid; = Pyruvic acid; Liver & brain: ↓ Glycogen; ↑ Glycogenolysis (↑ GP & PGM, = G6P); ↑ Glycolysis (↑ HK & LDH, brain only; = G6PD); ↑ Gluconeogenesis (↑ F1,6D & PEPCK, liver only); Adrenalectomy abolished above changes	(Matin et al., 1990a)
	128 (LD ₅₀) -1 d;	Oral	1 (single), 2, 8 or 32 d	M	N/A	N/A	N/A		10, 15 d post-treatment: ↓ (64); ↑ at 128; ↓ (16);	↓ Phospholipids	(Ibrahim and El-Gamal, 2003)

Insecticide	Treatment			Sex ^d	Results ^e						Reference
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol	Other comments	
	64 – 2d; 16 – 8d; 8 – 32 d									= other doses ^d ; ↓ HDL; ↑ LDL (except ↓ at 16)	
	15, 30, & 60	Oral	Single, tested after 2 h	M	N/A	↑	N/A	N/A	N/A	Liver: ↑ GP & PEPCK (30 & 60)	(Teimouri et al., 2006)
	15, 30, & 60 (1/20, 1/10, 1/5 LD ₅₀)	Oral	Single, tested after 2 h	M	N/A	↑	↓	N/A	N/A	↑ TNF-α; all effect abolished by cAMP & cGMP PDE inhibitor	(Ghafoor-Rashidi et al., 2007)
	75 (1/4 LD ₅₀)	Oral	Single, tested after 28 d	M	N/A	↑	N/A	N/A	N/A	↑ Testosterone	(Alahyari et al., 2008)
	6.5 (1/10 LD ₅₀)	i.p.	Single, (tested after 2 wk)	M ^g	=	=	=	↓	↓ (Wistar); = HDL	↓ Glucose tolerance in GK; = Glut4 in fat	(Ueyama et al., 2008)
	15, 30, & 60	i.p.	Single, tested after 1 & 18 h	M	N/A	N/A	↓ (1h); = (18h)	N/A	N/A	↑ Langerhans islet GDH (1h, 30 & 60; 18h); ↑ Glutamate (1h; = 18 h) ↑ C-peptide; ↓ GDH gene expression (18h, 60)	(Jamshidi et al., 2009)
Dichlorvos	4 (1/20 LD ₅₀), 40 (1/2 LD ₅₀)	Oral	Single; 3, 7, 14 d	M	N/A	↑ (40)	N/A	N/A	N/A	↓ Glucose tolerance; Liver: ↑ GP & GS (40); ↓ uridine diphosphate glucose pyrophosphorylase	(Teichert-Kuliszewska and Szymszyk, 1979)
	6	s.c.	Daily for 8 wk	M	↓	↑	N/A	N/A	N/A	Brain:	(Sarin and Gill, 1999)

Insecticide	Treatment			Sex ^d	Results ^e					Reference	
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol		Other comments
										↑ GP; ↓ Glycogen, HK, PFK, LDH & glucose uptake	
	20 (1/4 LD ₅₀)	N/A	Single, tested after 1 or 3 d	M	N/A	N/A	N/A	N/A	N/A	Liver: ↓ Glycogen & GK activity; ↑ GK mRNA level; Pancreas: = GK activity & mRNA; = Insulin mRNA	(Romero-Navarro et al., 2006)
	150	i.p.	15 & 30 d (every other days)	M	↑	= (15 d); ↑ (30 d)	↑		= (15 d); ↑ (30 d)		(Reena et al., 1989)
Dimethoate	20 & 40 (1/20 & 1/10 LD ₅₀)	Oral	Daily for 30 d	M	↓ (40)	↑	N/A	N/A	N/A	↑ Lipase & amylase; ↓ Pancreas lipase & amylase; ↓ Glucose tolerance; ↑ Pancreas weight; = Weights of liver, kidney & adrenals	(Kamath and Rajini, 2007)
Isofenphos	20	Oral	Single, tested after 3–72h	M	N/A	N/A	N/A	N/A	N/A	↑ Muscle lipid; ↓ Sarcoplasmic esterase; ↓ Muscle lipase (13– 18h)	(Calore et al., 1999)
Malathion	2000	s.c.	Single, tested after 0–6 h	F	N/A	↑	N/A	N/A	N/A		(Ramn and Drexler, 1973)
	500	i.p.	Single, tested after 0–48 h	F	N/A	↑ (first 6 h)	N/A	N/A	N/A	↑ Liver, kidney, heart, & spleen glycogen (all	(Gupta, 1974)

Insecticide	Treatment			Sex ^d	Results ^e						Reference
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol	Other comments	
										6–12 h, except liver 6–24 h); = Brain glycogen	
	46 (1/25 LD ₅₀)	i.p.	15 d	M	N/A	=	N/A	N/A	N/A	↑ Liver glycogen, Adrenaline (8 d), noradrenaline (8 d) & dopamine (4 d).	(Gowda et al., 1983)
	650	i.p.	Single, tested after 8 h	M	N/A	↑	N/A	N/A	N/A		(Rodrigues et al., 1986)
	500	i.p.	Single, tested after 2 h	F	N/A	↑	N/A	N/A	N/A	↑ Lactate; = pyruvate; Brain: ↓ Glycogen; ↑ GP, PGM & HK; = G6P & G6PD	(Matin and Husain, 1987)
	125, 250, & 500	i.p.	Single, tested after 0.5, 1, & 2 h	F	N/A	N/A	N/A	N/A	N/A	Brain (500 except glycogen): ↓ Glycogen (starting at 0.5 h); ↑ GP, PGM, HK & lactate; = G6P, G6PD, LDH & pyruvate; Adrenalectomy abolish these above changes; ↓ Succinic dehydrogenase; Adrenal: ↓ Ascorbic acid; ↓ Cholesterol	(Matin et al., 1990b)
	5, 10, & 20	Oral (Diet)	4 wk	M	N/A	↑	N/A	N/A	N/A	↑ Liver PEPCK & GP	(Abdollahi et al., 2004a)

Insecticide	Treatment			Sex ^d	Results ^e					Reference	
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol		Other comments
	5,10, & 20	Oral (Diet)	4 wk	M	N/A	↑ (10 & 20)	↑ (10 & 20)	N/A	N/A	Muscle: ↑ PFK & GP (20); = HK	(Pournourmoh ammadi et al., 2005)
										↓ Food intake;	
										Liver: ↑ Weight, HK, & glycogen; ↓ GP	
	100	Oral	Daily for 32 d	M	=	=	N/A	N/A	N/A	↓ Liver lipids; ↑ glycogen; ↓ Muscle glycogen	(Rezgi et al., 2006)
	100	Oral	Daily for 32 d	M	N/A	=	N/A	N/A	N/A		(Rezgi et al., 2007)
	20	Oral	Daily for 28 d	M	N/A	↑	N/A	N/A	N/A	Liver: ↑ PEPCK; ↑ Mitochondrial GP; Administration of <i>Satureja khuzestanica</i> essential oil (225 mg/kg/day) abolished the malathion induced effect	(Basiri et al., 2007)
	5,10, & 20	Oral (Diet)	28 d	M	N/A	↑ (10 & 20)	↑ (10 & 20)	N/A	N/A	↓ Pancreas insulin secretion (glucose stimulated); = (KCl stimulated)	(Pournourmoh ammadi et al., 2007)
	100 (1/21 LD ₅₀)	Oral	Single, tested after 24 h	M	N/A	N/A	N/A	N/A	N/A	↑ Liver glycogen & HK; ↓ Liver GP; Caffeic acid (100 mg/kg) abolished these effects;	(Rezgi et al., 2008)

Insecticide	Treatment			Sex ^d	Results ^e					Reference	
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol		Other comments
	100 (1/21 LD ₅₀)	Oral	Daily for 32 d	M	N/A	N/A	N/A	↑	=; = HDL & LDL	↓ Hypothalamic CRH mRNA; ↑ iNOS; = nNOS	(Rezgi et al., 2010a)
Parathion	0.1 & 0.2	s.c.	Daily for 4 d (PND1–4)	F & M	σ: ↑ (0.1); ♀: ↓ (0.1 & 0.2); ↓ in ♀ w/ HFD (0.2);	↑ (0.2) in only normal diet	=	↓ only ♀ in the fasted state	↑ in σ w/ HFD; ↓ in ♀	↓ Food intake in σ (0.2); ↑ Food intake in ♀ (0.1); ↓ HbA1c; ↓ FFA in ♀ w/ normal diet; ↓ β-hydroxybutyrate only in fasted σ	(Lassiter et al., 2008)
Carbamates											
Carbendazim	0.48, 0.96, 2.4, & 4.8	s.c.	Single, tested after 12 & 24h	M	N/A	↓ after 12h (0.48 & 0.96); ↑ after 12h (4.8); ↑ after 24h	N/A	N/A	= after 12h; ↑ after 24h		(Veerappan et al., 2012)
Pyrethroids											
Cismethrin	4	i.v.	Single	M	N/A	↑	N/A	N/A	N/A	↑ Noradrenaline, adrenaline, & lactate	(Cremer and Seville, 1982)
Cypermethrin	420 (1/10 LD ₅₀)	Oral (Diet)	6 m	M	N/A	=; ↑ in liver;	N/A	N/A	↓; = in liver	N/A	(Shakoori et al., 1988)
	0.06, 0.12, 0.3, & 0.6	s.c.	Single, tested after 12 & 24h	M	N/A	↑ after 12h (0.3 & 0.6); ↑ after 24h (0.06)	N/A	N/A	↑ after 12h (0.06 & 0.12); ↑ after 24 h (0.3 & 0.6)		(Veerappan et al., 2012)
Decamethrin	40	i.p.	Single	F	N/A	↑	N/A	N/A	N/A	↑ Lactate	(Ray and Cremer, 1979)

Insecticide	Treatment			Sex ^d	Results ^e						Reference
	Dose (mg/kg ^a)	Route ^b	Duration ^c		BW	Glucose	Insulin	TG	Cholesterol	Other comments	
Deltamethrin	1.28 (1/100 LD ₅₀)	Oral	Daily for 30 d	M	N/A	↑	N/A	↑	↑ LDL & VLDL; ↓ HDL	↑ Total lipid; Vitamin E attenuate adverse effect of deltamethrin	(Yousef et al., 2006)
	1.5 & 2.6	i.v.	Single	M	N/A	↑	N/A	N/A	N/A	↑ Noradrenaline, adrenaline, & lactate	(Cremer and Seville, 1982)
Neonicotinoids											
Imidacloprid	0, 5, 10, & 20	Oral	Daily for 90 d	F	↓ (20)	↑ (20)	N/A	=	=	↓ Food intake (20); ↑ Weight of liver, kidney, & adrenal (20)	(Bhardwaj et al., 2010)
	10, 30, & 90	Oral	Daily from GND 6-PND 21 to dams; Daily from PND21-PND 42 to pups	F& pups	=	N/A	N/A	N/A	N/A		(Gawade et al., 2013)

^a mg/kg bw/day unless otherwise specified (e.g. in diet).

^{*} doses are ppm in diet; NOAEL, no observed adverse effect level;

^b s.c., subcutaneous injection; i.p., intraperitoneal injection; i.v., intravenous injection

^c d, day(s); h, hour(s); m, month(s); wk, week(s); w/o, without; PND, postnatal days; GND, gestational day;

^d F, female; M, male;

^e Results are for all doses tested in each study, unless doses are indicated as numbers in parenthesis; all markers are from fasting blood samples unless otherwise specified; ↑, increase; ↓, decrease; = no change; w/, with; σ, male; ♀, female; N/A, not available;

^f apoE3 & C57BL/6N strain were used;

^g GK (Goto-Kakizaki) rats are a spontaneous animal model of non-insulin-dependent diabetes without obesity;

Acronyms used: ACC-1, Acetyl-CoA carboxylase 1; pACC, phosphorylated ACC; pAkt, phosphorylated Akt; AMPKα, AMP-activated protein kinase alpha; pAMPKα, phosphorylated AMPKα; BW, body weight; cAMP, cyclic adenosine monophosphate; CaMKKβ, calcium/calmodulin-dependent protein kinase β; CD36, cluster of differentiation 36; CEBPα, CCAAT/enhancer-binding protein α;

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cGMP, cyclic guanosine monophosphate; CPT1, carnitine palmitoyltransferase I; CRH, corticotropin-releasing hormone; FA, fatty acid; FFAs, free fatty acids; FABP4, fatty acid binding protein 4; F1,6D, fructose 1,6-bisphosphatase; GDH, glutamate dehydrogenase; GK, glucokinase; GK rat, Goto-Kakizaki rat; Glut2, glucose transporter 2; Glut4, glucose transporter 4; G6P, glucose-6-phosphatase; G6PD, glucose-6-phosphatase dehydrogenase; GP, glycogen phosphorylase; GS, glycogen synthase; GTT, glucose tolerance test; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HFD, high-fat diet; HK, hexokinase; HOMA-IR, homeostatic model assessment-insulin resistance; iNOS, inducible nitric oxide synthase; IL-6, interleukin 6; LDH, lactate dehydrogenase; LFD, low-fat diet; LPL, lipoprotein lipase; nNOS, neuronal nitric oxide synthase; PDE, phosphodiesterase inhibitor; PDK4, pyruvate dehydrogenase liposamide kinase isozyme 4; PEPC K, phosphoenolpyruvate carboxykinase; PFK, phosphofructokinase; PGC-1 α , peroxisome proliferator-activated receptor gamma co-activator 1 α ; PGM, phosphoglucomutase; PK, pyruvate kinase; PPAR γ , peroxisome proliferator-activated receptor gamma; SCD-1, stearoyl-CoA desaturase-1; Sirt 1, NAD-dependent deacetylase sirtuin-1; SREBP1, sterol regulatory element-binding protein 1; TAT, tyrosine aminotransferase; TG, triglycerides; TNF α , tumor necrosis factor- α ; VLDL, very low-density lipoprotein.