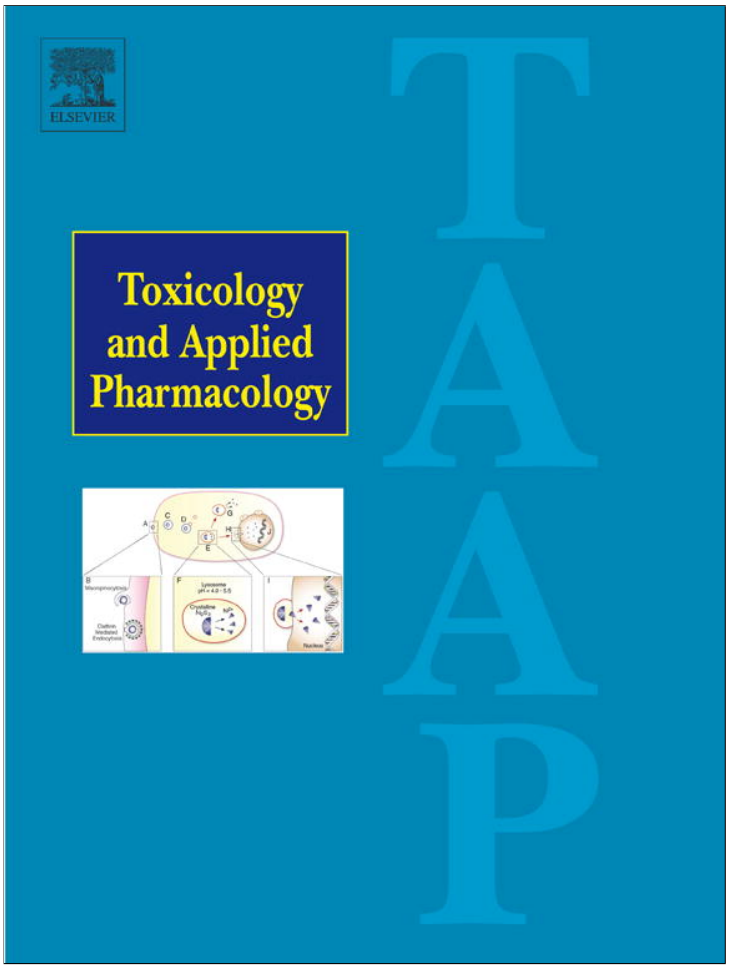


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Invited Review Article

# Pesticides and human chronic diseases: Evidences, mechanisms, and perspectives

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ABSTRACT

Along with the wide use of pesticides in the world, the concerns over their health impacts are rapidly growing. There is a huge body of evidence on the relation between exposure to pesticides and elevated rate of chronic diseases such as different types of cancers, diabetes, neurodegenerative disorders like Parkinson, Alzheimer, and amyotrophic lateral sclerosis (ALS), birth defects, and reproductive disorders. There is also circumstantial evidence on the association of exposure to pesticides with some other chronic diseases like respiratory problems, particularly asthma and chronic obstructive pulmonary disease (COPD), cardiovascular disease such as atherosclerosis and coronary artery disease, chronic nephropathies, autoimmune diseases like systemic lupus erythematous and rheumatoid arthritis, chronic fatigue syndrome, and aging. The common feature of chronic disorders is a disturbance in cellular homeostasis, which can be induced via pesticides' primary action like perturbation of ion channels, enzymes, receptors, etc., or can as well be mediated via pathways other than the main mechanism. In this review, we present the highlighted evidence on the association of pesticide's exposure with the incidence of chronic diseases and introduce genetic damages, epigenetic modifications, endocrine disruption, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress and unfolded protein response (UPR), impairment of ubiquitin proteasome system, and defective autophagy as the effective mechanisms of action.



**Contents**



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## Introduction

Pesticides are considered as one of the main factors involved in environmental contamination of today's world. These chemicals are on purpose designed to be toxic to pest and vectors of diseases. These compounds are among more than 1000 active ingredients that are marketed as insecticide, herbicide, and fungicide. Nevertheless, formulation of new and potent pesticides is increasingly on the order of researchers and manufacturers because of pest resistance, hygienic controls, and major human need for more food as the world population grows. Although pesticides have largely benefited the human life through enhancement of agricultural products and controlling infectious diseases, their extensive use, in turn, has offended human health from side to side of occupational or environmental exposures. Long-term contact to pesticides can harm human life and can disturb the function of different organs in the body, including nervous, endocrine, immune, reproductive, renal, cardiovascular, and respiratory systems. In this regard, there is mounting evidence on the link of pesticide's exposure with the incidence of human chronic diseases, including cancer, Parkinson, Alzheimer, multiple sclerosis, diabetes, aging, cardiovascular and chronic kidney disease (Abdollahi et al., 2004c; De Souza et al., 2011; Mostafalou and Abdollahi, 2012a). In this overview, we discuss the association of pesticide's exposure with the incidence of different types of human chronic diseases as well as general mechanisms of disease's process, which can be involved in pesticide-induced toxicities.

## Evidences for the link between pesticide exposure and incidence of chronic diseases

Chronic diseases are characterized by their generally slow progression and long term duration, which are considered as the leading cause of mortality in the new world, representing over 60% of all deaths. According to the WHO report, 36 million people died from chronic disease in 2008, of which nine million were under 60 and 90% of these premature deaths occurred in low- and middle-income countries (http://www.who.int/topics/chronic_diseases/en/).

### *Cancer*

The first reports on the association of pesticides with cancer were presented around 50 years ago regarding higher prevalence of lung and skin cancer in the farmers using insecticides in grape fields (Jungmann, 1966; Roth, 1958; Thiers et al., 1967). During the past half century, a wide spectrum of population-based studies has been carried out in this respect leading to a significant progress in understanding the relationship of pesticides to the incidence of different types of malignancies (Penel and Vansteene, 2007). The International Agency for Research on Cancer (IARC) has conducted several cohort studies on the incidence of cancers in people exposed to pesticides somehow during their lives (Baldi and Lebailly, 2007). Based on rising evidence given by epidemiological and agricultural health studies associated with exposure to pesticides, different types of neoplasm have been reported such as breast cancer, prostate cancer, lung cancer, brain cancer, colorectal cancer, testicular cancer, pancreatic cancer, esophageal cancer, stomach cancer, skin cancer and non-Hodgkin lymphoma (Alavanja and Bonner, 2012; Jaga and Dharmani, 2005; Weichenthal et al., 2010). Van Maele-Fabry et al. (2006, 2007, 2008) pointed out exposure to pesticides as a possible risk factor for prostate cancer and leukemia by a meta-analysis of risk estimates in pesticide manufacturing workers. In a series of agricultural health studies, Lee et al. (2004a,b, 2007) found an association between exposure to pesticides and cancer incidence, particularly lymphohematopoietic cancers for alachlor, lung cancer for chlorpyrifos, and colorectal cancer for aldicarb. Nowadays, chronic low-dose exposure to pesticides is considered as one of the important risk factors for cancer expansion. Therefore, carcinogenicity tests are now applied to detect carcinogenic potential of pesticides before allowing them to be marketed. Carcinogenicity testing is a long-term (around two years) rodent bioassay using two species of both sexes. According to a new list of Chemicals Evaluated for Carcinogenic Potential by EPA's Pesticide Program published in 2010, more than 70 pesticides have been classified as a probable or possible carcinogen. This classification has been accomplished based on the information extracted from animal studies, metabolism studies, structural relationship with other carcinogens, and if available, epidemiologic findings in human (http://www.epa.gov/pesticides/carlist/).

Carcinogenic properties of pesticides can be influenced by a series of complex factors including age, sex, individual susceptibility, amount and duration of exposure, and simultaneous contacts with other cancer causing chemicals. However, carcinogenic mechanisms of pesticides can be explored in their potential to affect genetic material directly via induction of structural or functional damage to chromosomes, DNA, and Histone proteins, or indirectly disrupting the profile of gene expression through impairment of cellular organelles like mitochondria and endoplasmic reticulum, nuclear receptors, endocrine network, and the other factors involved in maintenance of cell homeostasis (George and Shukla, 2011; Rakitsky et al., 2000). Table 1 is indicating data extracted from epidemiological studies implicating on the relation between exposure to specific pesticides and increased risk of some kind of cancers.

### *Birth defects and developmental toxicity*

Birth defects or congenital disorders are defined as structural or functional abnormalities existing at birth or before birth that causes physical or mental disabilities. Ranging from mild to fatal, diverse types of birth defects have been recognized and deliberated as the principal cause of death for infants during the first years of life. Any material which can induce birth defects is called teratogen (Rogers and Kavlock, 2008). The history of sensibility on the topic of developmental toxicity of pesticide returns to an incidence of congenital disorders induced by DDT and other organochlorines in the wildlife in Laurentian Great Lakes (Hamlin and Guillette, 2010). That concern was more intensified when reports associating with elevated rate of birth defects in defoliant sprayed areas of Vietnam appeared after

**Table 1**
Pesticides associated with elevated incidence of cancer in epidemiological studies.

| Type of cancer | Pesticide | Reference |
|---|---|---|
| Leukemia | Chlordane/heptachlor | Purdue et al. (2007) |
| | Chlorpyrifos | Lee et al. (2004b) |
| | Diazinon | Beane Freeman et al. (2005) |
| | EPTC | van Bemmel et al. (2008) |
| | Fonofos | Mahajan et al. (2006) |
| Non-Hodgkin's lymphoma | Lindane | Purdue et al. (2007) |
| | Oxychlordane/chlordane | Spinelli et al. (2007) |
| Multiple myeloma | Permethrin | Rusiecki et al. (2009) |
| Brain cancer | Chlorpyrifos | Lee et al. (2004b) |
| Prostate cancer | Fonofos | Mahajan et al. (2006) |
| | Methylbromide | Alavanja et al. (2003) |
| | Butylate | Lynch et al. (2009) |
| | Clordecone | Multigner et al. (2010) |
| | DDT, lindane, simazine | Band et al. (2011) |
| Colon cancer | Aldicarb | Lee et al. (2007) |
| | Dicamba | Samanic et al. (2006) |
| | EPTC | van Bemmel et al. (2008) |
| | Imazethapyr | Koutros et al. (2009) |
| | Trifluralin | Kang et al. (2008) |
| Rectum cancer | Chlordane | Purdue et al. (2007) |
| | Chlorpyrifos | Lee et al. (2004b) |
| | | Lee et al. (2007) |
| | Pendimethalin | Hou et al. (2006) |
| Pancreatic cancer | EPTC, pendimethalin | Andreotti et al. (2009) |
| | DDT | Garabrant et al. (1992) |
| Lung cancer | Chlorpyrifos | Lee et al. (2004b) |
| | Diazinon | Beane Freeman et al. (2005) |
| | Dicamba | Alavanja et al. (2004) |
| | Dieldrin | Purdue et al. (2007) |
| | Metolachlor | Alavanja et al. (2004) |
| | Pendimethalin | Hou et al. (2006) |
| Bladder cancer | Imazethapyr | Koutros et al. (2009) |
| Melanoma | Carbaryl | Mahajan et al. (2007) |
| | Toxaphene | Purdue et al. (2007) |
| | Carbaryl, parathion, maneb/mancozeb | Dennis et al. (2010) |

war in late 1960. Defoliant or the famous Agent Orange is composed of phenoxy herbicides, which included small amounts of highly toxic dioxin (TCDD) as a byproduct (Ngo et al., 2006). Currently, there is much epidemiological evidence linking pre- and post-natal exposures to pesticides with congenital disorders (Weselak et al., 2007). A meta-analysis of literature published from 1966 to 2008 by Rocheleau et al. (2009) indicated that higher incidence of hypospadias resulted from parental exposure to pesticides. Parental exposure to Agent Orange has also been associated with increased risk of birth defects given by a meta-analytical review of epidemiological studies (Ngo et al., 2006). Furthermore, experimental data have indicated adverse developmental outcomes of some pesticides in laboratory animals as evidenced by intrauterine death, in utero growth retardation, visceral and skeletal malformations or dysfunctions (Cavieres, 2004).

In addition to the rate of placental transfer and systemic absorption as a determinant factor for chemicals to be teratogen, their potential in induction of genetic damage, neuronal cell defects, endocrine disruption, and oxidative stress has been proposed as the main mechanism of developmental toxicity (van Gelder et al., 2010).

*Reproductive disorders*

Reproductive disorders are defined as conditions prejudicing the capacity of the reproductive system to reproduce. Vast body of literature has detailed adverse effects of environmental exposures, particularly pesticides on both male and female reproductive systems (Kumar, 2004; Shojaei Saadi and Abdollahi, 2012). Decreased fertility in both sex, demasculinization (antiandrogenic effects), elevated rate of miscarriage, altered sex ratio, and change in the pattern of maturity are among the most reported reproductive dysfunctions induced by chronic exposure to pesticides (Frazier, 2007). These effects of pesticides deemed more important when their link to endocrinal disruption was explained. A number of pesticides, mostly the old organochlorine types like aldrin, chlordane, DDT, dieldrin, and endosulfan, the herbicide atrazine, and the fungicide vinclozolin have been identified as commonly believed endocrine disrupting chemicals (PAN, 2009). Interfering with functions of the endocrine system has been implicated in most pesticides that caused reproductive toxicities (Cocco, 2002; Figa-Talamanca et al., 2001; Tiemann, 2008).

*Parkinson*

Parkinson disease is a motor progressive disorder of CNS characterized by degeneration of dopaminergic neurons in the substantia nigra. The cause of this degeneration is not well-known but post-mortem studies have indicated that oxidative stress and mitochondrial dysfunction play the main role in development of this late-onset disorder. There are large numbers of population studies that prove higher incidence of Parkinson disease in the people exposed to pesticides (Bonetta, 2002; Freire and Koifman, 2012; Van Maele-Fabry et al., 2012). A new meta-analysis published by van der Mark et al. (2012) reviewed updated literature, including 39 case–control studies, four cohort studies, and three cross-sectional studies and found that exposure to insecticides, and herbicides can lead to augmented risk of Parkinson disease. Furthermore, elevated levels of some pesticides in the serum of patients with Parkinson disease have been reported (Richardson et al., 2009). These results were followed up by other researchers who designed developmental models to analyze the link between Parkinson disease and pesticide exposure in several environmental health studies (Cory-Slechta et al., 2005). It can be said that Parkinson and other neurodegenerative disorders have been most studied in case of exposure to neurotoxic pesticides such as organophosphates, carbamates, organochlorines, pyrethroids and some other insecticides since they interfere with neurotransmission and function of ion channels in the nervous system (Costa et al., 2008).

*Alzheimer*

Evidence implicating on the role of pesticide in developing Alzheimer's disease is lesser than that of Parkinson. Most of the studies carried out in this respect are relatively small and vague until a longitudinal population-based cohort study was published in 2010 (Jones, 2010). Elderly people living in an agricultural area who contributed in the survey for 10 years showed a higher rate of cognitive performance and risk of Alzheimer's disease. When researchers specifically tested CNS affecting pesticides, they found a direct and significant association between occupational exposure to organophosphates, acetylcholinesterase inhibitor compounds, and developing Alzheimer's disease later in life (Hayden et al., 2010). Furthermore, in an ecologic study, Parron et al. (2011) showed that people living in areas with high level of pesticides usage had an elevated risk of Alzheimer's disease.

*Amyotrophic lateral sclerosis (ALS)*

Amyotrophic lateral sclerosis (ALS) is the nearly all common form of the motor neuron diseases characterized by degeneration of both upper and lower motor neurons. The symptoms include rapidly progressive weakness, muscle atrophy and fasciculations, muscle spasticity, dysarthria (difficulty speaking), dysphagia (difficulty swallowing), and a decline in breathing ability. Irrespective of familial ALS which can be easily ruled out, there is no known cause for this disease but many evidence-based potential risk factors have been proposed for its development where chemical exposures have been bolded (Morahan and Pamphlett, 2006; Sutedja et al., 2009). A population-based case–control study conducted by McGuire and colleagues in 1997 was almost the starting point of pesticide-focused investigations in association with ALS. In that study, occupational exposure to three

**Table 2**
The list of studies whose results implicate on the association of exposure to pesticides with incidence of chronic diseases.

| Disease | Types | Reports | | | |
|---|---|---|---|---|---|
| | | Case control | Cohort | Ecological | Others |
| Cancer | Childhood leukemia | Alderton et al. (2006)<br>Alexander et al. (2001)<br>Buckley et al. (1989)<br>Buckley et al. (1994)<br>Infante-Rivard et al. (1999)<br>Lafiura et al. (2007)<br>Laval and Tuyns (1988)<br>Leiss and Savitz (1995)<br>Lowengart et al. (1987)<br>Ma et al. (2002)<br>Magnani et al. (1990)<br>Meinert et al. (1996)<br>Menegaux et al. (2006)<br>Monge et al. (2007)<br>Mulder et al. (1994)<br>Rau et al. (2012)<br>Reynolds et al. (2005)<br>Rudant et al. (2007)<br>Rull et al. (2009)<br>Shu et al. (1988)<br>Soldin et al. (2009) | | Carozza et al. (2008) | Turner et al. (2010) |
| | Adult leukemia | Alavanja et al. (1990)<br>Brown et al. (1990)<br>Ciccone et al. (1993)<br>Clavel et al. (1996)<br>Miligi et al. (2006) | Beane Freeman et al. (2005)<br>Beard et al. (2003)<br>Blair et al. (1983)<br>Bonner et al. (2010)<br>Cantor and Silberman (1999) | Chrisman Jde et al. (2009)<br>Delzell and Grufferman (1985)<br>Mills (1998) | Cuneo et al. (1992)<br>Merhi et al. (2007)<br>Van Maele-Fabry et al. (2008) |
| | Hodgkin's lymphoma | Orsi et al. (2007)<br>Persson et al. (1993)<br>Rudant et al. (2007)<br>van Balen et al. (2006) | Flower et al. (2004) | Carozza et al. (2008)<br>Cerhan et al. (1998) | |
| | Non-Hodgkin's lymphoma | Alavanja et al. (1990)<br>Buckley et al. (2000)<br>Cantor (1982)<br>Cantor et al. (1992)<br>Chiu et al. (2006)<br>De Roos et al. (2003)<br>Eriksson et al. (2008)<br>Hardell and Eriksson (1999)<br>Hardell et al. (2002)<br>Hoar et al. (1986)<br>McDuffie et al. (2001)<br>Meinert et al. (2000)<br>Miligi et al. (2006)<br>Nordstrom et al. (1998)<br>Pearce et al. (1985)<br>Rudant et al. (2007)<br>Schroeder et al. (2001)<br>t Mannetje et al. (2008)<br>Vajdic et al. (2007)<br>Woods et al. (1987)<br>Zahm et al. (1990)<br>Zahm et al. (1993) | Bonner et al. (2010)<br>Kristensen et al. (1996b)<br>Kross et al. (1996)<br>Morrison et al. (1994)<br>Purdue et al. (2007)<br>Ritter et al. (1990)<br>Zhong and Rafnsson (1996) | | Khuder et al. (1998)<br>Merhi et al. (2007) |
| | Multiple myeloma | Burmeister et al. (1983)<br>Pearce et al. (1985) | Kristensen et al. (1996b)<br>Landgren et al. (2009)<br>Lope et al. (2008) | Cerhan et al. (1998) | Merhi et al. (2007) |
| | Neuroblastoma | Daniels et al. (2001)<br>Walker et al. (2007) | Feychting et al. (2001)<br>Giordano et al. (2006)<br>Kristensen et al. (1996b)<br>Littorin et al. (1993) | Carozza et al. (2008) | |
| | Soft tissue sarcoma | Kogevinas et al. (1995)<br>Leiss and Savitz (1995)<br>Magnani et al. (1989) | | Carozza et al. (2008)<br>Chrisman Jde et al. (2009) | |
| | Childhood brain cancer | Bunin et al. (1994)<br>Cordier et al. (1994)<br>Davis et al. (1993)<br>Efird et al. (2003)<br>Gold et al. (1979)<br>Holly et al. (1998)<br>Pogoda and Preston-Martin (1997)<br>Rosso et al. (2008)<br>Ruder et al. (2006)<br>Searles Nielsen et al. (2010) | Kristensen et al. (1996a) | | |

**Table 2** (*continued*)

| Disease | Types | Reports | | | |
|---|---|---|---|---|---|
| | | Case control | Cohort | Ecological | Others |
| Cancer | Childhood brain cancer | van Wijngaarden et al. (2003)<br>Wilkins and Koutras (1988)<br>Wilkins and Sinks (1990) | | | |
| | Adult brain cancer | Lee et al. (2005)<br>Musicco et al. (1988)<br>Provost et al. (2007)<br>Rodvall et al. (1996)<br>Samanic et al. (2008)<br>Zheng et al. (2001) | Blair et al. (1983)<br>Figa-Talamanca et al. (1993)<br>Kross et al. (1996)<br>Viel et al. (1998) | Delzell and Grufferman (1985)<br>Mills (1998)<br>Wesseling et al. (1999) | Smith-Rooker et al. (1992) |
| | Bone cancer | Merletti et al. (2006)<br>Moore et al. (2005) | Holly et al. (1992) | Carozza et al. (2008)<br>Wesseling et al. (1999) | |
| | Prostate cancer | Cerhan et al. (1998)<br>Dosemeci et al. (1994)<br>Forastiere et al. (1993)<br>Meyer et al. (2007)<br>Mills and Yang (2003)<br>Settimi et al. (2003) | Alavanja et al. (2003)<br>Chamie et al. (2008)<br>Dich and Wiklund (1998)<br>Fleming et al. (1999)<br>Kross et al. (1996)<br>MacLennan et al. (2002)<br>Morrison et al. (1993) | Chrisman Jde et al. (2009)<br>Delzell and Grufferman (1985)<br>Mills (1998) | Keller-Byrne et al. (1997)<br>Sharma-Wagner et al. (2000) |
| | Breast cancer | Band et al. (2000)<br>Brophy et al. (2002)<br>Duell et al. (2000)<br>Mills and Yang (2005)<br>Teitelbaum et al. (2007) | Dolapsakis et al. (2001) | | Ortega Jacome et al. (2010) |
| | Colorectal cancer | Cerhan et al. (1998)<br>Forastiere et al. (1993)<br>Lo et al. (2010) | Kang et al. (2008)<br>Koutros et al. (2009)<br>Kross et al. (1996)<br>Lee et al. (2007)<br>Samanic et al. (2006)<br>van Bemmel et al. (2008)<br>Zhong and Rafnsson (1996) | Wesseling et al. (1999) | |
| | Pancreatic cancer | Alguacil et al. (2000)<br>Forastiere et al. (1993)<br>Ji et al. (2001)<br>Kauppinen et al. (1995)<br>Lo et al. (2007)<br>Partanen et al. (1994) | Andreotti et al. (2009)<br>Cantor and Silberman (1999) | Chrisman Jde et al. (2009) | |
| | Kidney cancer | Buzio et al. (2002)<br>Fear et al. (1998)<br>Forastiere et al. (1993)<br>Hu et al. (2002)<br>Karami et al. (2008)<br>Mellemgaard et al. (1994)<br>Olshan et al. (1993)<br>Sharpe et al. (1995)<br>Tsai et al. (2006) | Kristensen et al. (1996b) | Carozza et al. (2008) | |
| | Lung cancer | Brownson et al. (1993)<br>Bumroongkit et al. (2008)<br>Pesatori et al. (1994) | Alavanja et al. (2004)<br>Barthel (1981)<br>Beane Freeman et al. (2005)<br>Blair et al. (1983)<br>Lee et al. (2004b)<br>Rusiecki et al. (2006)<br>Samanic et al. (2006) | Wesseling et al. (1999) | |
| | Stomach cancer | Forastiere et al. (1993)<br>Mills and Yang (2007) | | Van Leeuwen et al. (1999) | |
| | Esophageal cancer | Jansson et al. (2006) | | Chrisman Jde et al. (2009)<br>Wesseling et al. (1999) | |
| | Liver cancer | | Giordano et al. (2006) | Carozza et al. (2008)<br>Wesseling et al. (1999) | |
| | Testicular cancer | Mills et al. (1984) | Fleming et al. (1999) | Mills (1998) | |
| | Bladder cancer | Forastiere et al. (1993) | Koutros et al. (2009) | Wesseling et al. (1999) | |
| | Gallbladder cancer | | Giordano et al. (2006) | Wesseling et al. (1999) | |
| | Thyroid cancer | | Ward et al. (2010) | Carozza et al. (2008) | |
| | Melanoma | Fortes et al. (2007) | Dennis et al. (2010)<br>Mahajan et al. (2007) | Carozza et al. (2008)<br>Wesseling et al. (1999) | |
| | Eye cancer | Carozza et al. (2008) | Kristensen et al. (1996b) | | |
| | Lip cancer | | Wiklund (1983) | Cerhan et al. (1998)<br>Chrisman Jde et al. (2009) | |
| | Mouth cancer | | Tarvainen et al. (2008) | | |
| | Larynx cancer | | | Wesseling et al. (1999) | |
| | Sinonasal cancer | | | | Tisch et al. (2002) |
| | Ovarian cancer | Donna et al. (1989) | | Wesseling et al. (1999) | |
| | Uterine cancer | | | Wesseling et al. (1999) | |
| | Cervical cancer | | Fleming et al. (1999) | | |

(*continued on next page*)

**Table 2** (*continued*)

| Disease | Types | Reports | | | |
|---|---|---|---|---|---|
| | | Case control | Cohort | Ecological | Others |
| Birth defects | | Brender et al. (2010)<br>Brucker-Davis et al. (2008)<br>Dugas et al. (2010)<br>Nassar et al. (2010)<br>Ren et al. (2011) | Chevrier et al. (2011)<br>Perera et al. (2003)<br>Petit et al. (2010) | de Siqueira et al. (2010)<br>Garry et al. (1996)<br>Schreinemachers (2003)<br>Winchester et al. (2009) | Benachour and Seralini (2009)<br>Enoch et al. (2007)<br>Greenlee et al. (2004)<br>Qiao et al. (2001)<br>Rauch et al. (2012)<br>Richard et al. (2005)<br>Rocheleau et al. (2009)<br>Sherman (1996) |
| Reproductive disorders | | Greenlee et al. (2003)<br>Swan et al. (2003b) | Saiyed et al. (2003)<br>Snijder et al. (2011)<br>Tiido et al. (2005)<br>Tiido et al. (2006) | Swan et al. (2003a) | Anway et al. (2005)<br>Cavieres et al. (2002)<br>Fei et al. (2005)<br>Gray et al. (1999)<br>Joshi et al. (2011)<br>Meeker et al. (2006)<br>Oliva et al. (2001)<br>Orton et al. (2011)<br>Stanko et al. (2010)<br>Wang et al. (2011b) |
| Neuro degenerative diseases | Parkinson | Baldi et al. (2003a)<br>Butterfield et al. (1993)<br>Chan et al. (1998)<br>Costello et al. (2009)<br>Dick et al. (2007)<br>Dutheil et al. (2010)<br>Elbaz et al. (2009)<br>Fall et al. (1999)<br>Firestone et al. (2005)<br>Fong et al. (2007)<br>Frigerio et al. (2006)<br>Gatto et al. (2009)<br>Gorell et al. (1998)<br>Hancock et al. (2008)<br>Hertzman et al. (1994)<br>Hubble et al. (1993)<br>Hubble et al. (1998)<br>Koller et al. (1990)<br>Manthripragada et al. (2010)<br>Menegon et al. (1998)<br>Ritz et al. (2009)<br>Seidler et al. (1996)<br>Semchuk et al. (1992)<br>Stephenson (2000)<br>Tanner et al. (2009)<br>Tanner et al. (2011)<br>Wang et al. (2011a)<br>Zorzon et al. (2002) | Ascherio et al. (2006)<br>Baldi et al. (2003b)<br>Kamel et al. (2007)<br>Petrovitch et al. (2002)<br>Tuchsen and Jensen (2000) | Barbeau et al. (1987)<br>Ritz and Yu (2000)<br>Schulte et al. (1996) | Barlow et al. (2004)<br>Barlow et al. (2005)<br>Caudle et al. (2005)<br>Chou et al. (2008)<br>Jia and Misra (2007)<br>Priyadarshi et al. (2000)<br>Priyadarshi et al. (2001)<br>Purisai et al. (2007)<br>Richardson et al. (2006) |
| | Alzheimer | | Baldi et al. (2003b)<br>Hayden et al. (2010)<br>Tyas et al. (2001) | Parron et al. (2011) | |
| | ALS | Bonvicini et al. (2010)<br>Das et al. (2012)<br>McGuire et al. (1997)<br>Morahan and Pamphlett (2006)<br>Pamphlett (2012)<br>Qureshi et al. (2006) | Burns et al. (2001) | | Choy and Kim (2011)<br>Doi et al. (2006)<br>Kanavouras et al. (2011) |
| Cardio-vascular diseases | Hypertension | | Morton et al. (1975) | | |
| | Atherosclerosis | | | | Fokina and Bezuglyi (1978)<br>Antov and Aianova (1980) |
| | Coronary artery disease | | | | Zamzila et al. (2011) |
| Respiratory diseases | Asthma | Salam et al. (2004) | Beard et al. (2003)<br>Hoppin et al. (2002)<br>Hoppin et al. (2008)<br>Slager et al. (2009) | | Draper et al. (2003)<br>Kolmodin-Hedman et al. (1982)<br>Lessenger (1992)<br>Moretto (1991)<br>Salameh et al. (2003)<br>Vandenplas et al. (2000)<br>Wagner (2000)<br>Weiner and Worth (1969) |
| | COPD | Arifkhanova et al. (2007)<br>Ubaidullaeva (2006) | Chakraborty et al. (2009)<br>Hoppin et al. (2007)<br>LeVan et al. (2006)<br>Valcin et al. (2007) | | Barczyk et al. (2006)<br>Faria et al. (2005) |
| Diabetes | Type 1, 2 and gestational | Lee et al. (2010) | Montgomery et al. (2008)<br>Saldana et al. (2007) | Kouznetsova et al. (2007) | Everett and Matheson (2010)<br>Patel et al. (2010) |

**Table 2** (*continued*)

| Disease | Types | Reports | | | |
|---|---|---|---|---|---|
| | | Case control | Cohort | Ecological | Others |
| Chronic renal diseases | Chronic renal failure | | | | Peiris-John et al. (2006) |
| | | | | | Wanigasuriya et al. (2007) |
| | Chronic kidney disease | | | | Siddharth et al. (2012) |
| Autoimmune diseases | Rheumatoid arthritis | | Parks et al. (2011) | | Gold et al. (2007) |
| | Systemic lupus erythematous | Cooper et al. (2004) | Parks et al. (2011) | | Gold et al. (2007) |

groups of chemicals, including solvents, metals, and pesticides in relation to the incidence of ALS was evaluated and the results showed the role of agrochemicals in most of the cases (McGuire et al., 1997). During the past decade, several reports indicated the association of ALS development with exposure to pesticides (Bonvicini et al., 2010; Doi et al., 2006; Freedman, 2001). Pesticides have reserved the most prominent role in the most of the surveys focusing on the association of environmental and occupational exposures with ALS, which have been carried out up to now, and it would not be unlikely to consider them as a risk factor for developing this neurological disorder (Johnson and Atchison, 2009; Kamel et al., 2012; Vinceti et al., 2012).

*Diabetes*

Diabetes can be said that has become epidemic since 347 million people worldwide are appraised to be diabetic and based on WHO belief, diabetes deaths are expected to double between 2005 and 2030 (http://www.who.int/diabetes/en/index.html). Unlike diseases mentioned above, diabetes, particularly type 2 has some identified risk factors, including rich diet, obesity and sedentary manner of living but the extent of reports implicating on the relation of exposure to environmental pollutants, particularly pesticides and development of diabetes is rapidly growing (Mostafalou and Abdollahi, 2012b; Rahimi and Abdollahi, 2007). The possibility of studying diabetes in experimental models allowed researchers to investigate effects of exposure to pesticides on glucose homeostasis in laboratory animals. In this regard, there were lots of reports on disrupting effects of pesticides particularly organophosphates and organochlorines on glucose metabolism in association with imbalanced insulin secretion and response in animals (Abdollahi et al., 2004a; Karami-Mohajeri and Abdollahi, 2011; Pournourmohammadi et al., 2007). A couple of epidemiological studies whose results published during the past few years indicated that exposure to pesticides can be a potential risk factor for developing diabetes (Everett and Matheson, 2010; Montgomery et al., 2008; Saldana et al., 2007). It has also been suggested that exposure to some pesticides can be a promoter for other risk factors of diabetes like obesity by distressing neural circuits that regulate feeding behavior or altering differentiation of adipocytes (Thayer et al., 2012).

*Cardiovascular diseases*

About the relationship between pesticide's exposure and cardiovascular diseases, there are just a few random reports carried out in varied forms. In addition to a report concerning hypertension in Oregon pesticide formulating workers (Morton et al., 1975), there have been a few evidences on the link between exposure to pesticides and atherosclerosis (Antov and Aianova, 1980; Fokina and Bezuglyi, 1978). Recently, it was reported that chronic exposure to organophosphate pesticides can potentiate the risk of coronary artery disease presumably through diminished paraoxonase activity (Zamzila et al., 2011).

*Chronic nephropathies*

Higher incidence of the late-onset nephropathies like chronic kidney disease and chronic renal failure has been reported in middle-aged people (40–60 years) living in the agricultural areas with more prevalence in men. The results of a survey in North Central Province of Sri Lanka have presented a significant relationship between chronic renal failure and environmental factors in farming areas (Wanigasuriya et al., 2007). Exposure to acetylcholinesterase inhibiting pesticides was associated with chronic renal failure (Peiris-John et al., 2006). Furthermore, higher level of organochlorine pesticides was detected in chronic kidney disease patients along with a reduced glomerular filtration and increased oxidative stress (Siddharth et al., 2012).

*Chronic respiratory disease*

Asthma is considered as the most common disorder among chronic respiratory dysfunctions affecting both children and adults. Its close relationship with work-related exposures has been known from 18 centuries so that occupational asthma is characterized as a disease in medicine. There have been several reports on increased rate of asthma in people occupationally exposed to pesticides (Hernandez et al., 2011). Moreover, the result of an agricultural health study indicated that exposure to some pesticides may increase the risk of chronic obstructive pulmonary disease (COPD) in farmers (Hoppin et al., 2007).

*Other chronic diseases*

However, there are sporadic reports on the association of exposure to pesticides with different types of human chronic diseases, including chronic fatigue syndrome (Behan and Haniffah, 1994), autoimmune diseases like systemic lupus erythematous and rheumatoid arthritis (Cooper et al., 2004; Gold et al., 2007; Parks et al., 2011) which need further investigations for more proof (Table 2).

## Molecular mechanisms linking pesticide exposure to chronic diseases

*Genetic damages*

Genetic damages are caused by direct interaction with genetic material resulting in DNA damage or chromosomal aberrations and considered as a primary mechanism for chronic diseases within the context of carcinogenesis and teratogenesis. They are studied in the field of genetic toxicology and can be detected by distinctive kinds of genotoxicity tests. Growing body of data concerning genetic toxicity of pesticides have been collected from epidemiological and experimental studies using different types of examinations, including chromosomal aberrations, micronucleus, sister chromatid exchanges and comet assay (Bolognesi, 2003; Bull et al., 2006).

Indeed, genetic damages are classified into three groups as follows: 1. Premutagenic damages like DNA strand breaks, DNA adducts or unscheduled DNA synthesis; 2. Gene's mutation which means insertion or deletion of a couple of base pairs; 3. Chromosomal aberrations, including loss or gain of whole chromosome (aneuploidy), deletion or breaks (clastogenicity), and chromosomal segments or rearrangements. Premutagenic damages may be repaired prior to cell division while the damages in the second and third groups are permanent and have the

**Table 3**
Genotoxicity biomarkers determined in populations occupationally exposed to different types of pesticides.

| Genetic damage | Pesticides | Reference |
|---|---|---|
| DNA strand breaks | Acephate, chlorpyrifos, dimethoate, monocrotophos, phorate, cypermethrin, fenvalerate, carbendazim | Grover et al. (2003) |
| | Dimethoate, ethephon, omethoate, oxydemeton-methyl, thiometon, befenthrin, B-cyfluthrin, deltamethrin, mancozeb, carbendazim, endosulfan, chlorothalanil, iprodione, diflufenicanil, L-cyhalothrin, pyrimethanil, fluroxypyr, cyproconazole, epoxyconazole, flutriafol, tebucanazole, atrazine | Lebailly et al. (1998) |
| DNA adducts | Glyphosate, methamidophos, monocrotophos, parathion methyl, methomyl, metam-sodium, dazomet, zineb, benomyl, carbendazim, paraquat, captan, folpet, endosulfan | Peluso et al. (1996) |
| Chromosomal aberration | Acephate, chlorpyrifos, dimethoate, fenitrothion, fenthion, fosetyl, isofenphos, methamidophos, naled, pyrazophos, cypermethrin, deltamethrin, fenpropathrin, fenvalerate, methiocarb, methomyl, oxamyl, mancozeb, propineb, zineb, benomyl, diquat, paraquat, captan, folpet, procymidone, endosulfan, abamectin, kasugamycin, iprodione, oxadixyl, buripimate, metribuzin, linuron, methabenzthiazuron, triforine, vinclozolin, bitertanol, fenbutatin oxide, amitraz, propargite, dithiocarbamate | Carbonell et al. (1993) |
| | Diazinon, dichlorvos, dimethoate, malathion, ethylazinophos, monocrotophos, parathion, parathion methyl, phorate, prothoate, terbufos, trichlorofon, cypermethrin, fenpropathrin, permethrin, maneb, thiram, dazomet, mancozeb, zineb, ziram, thiabendazole, paraquat, captan, folpet, endosulfan, dodemorph, chlorothalonil, iprodione, acetic metaldehyde, barium polysulfide, copper oxychloride, copper sulfate, sulfur, white oil, dinocap, DNOC, alachlor, simazine, MCPA, linuron, vinclozolin, phenmedifam, methalaxyl, ethofumesate, 2,4-D, dicofol | De Ferrari et al. (1991) |
| | Dimethoate, mevinphos, monocrotofos, parathion, parathion methyl, aldicarb, maneb, dazomet, propineb, zineb, captan, endosulfan, aldrin, aramite, chlordimeform, heptachlor, tetradifon | Dulout et al. (1985) |
| | 2,4-D | Garry et al. (2001) |
| | Chlorpyriphos, cypermethrin, deltamethrin, fenpropathrin, methomyl, thiram, pirimicarb, benomyl, carbendazim, endosulfan, chlorothalonil, iprodione, buprofezin, atrazine, triforine, vinclozolin, cyhexatin, fetin acetate, carboxin, 2,4-D, chloridazon, defenamide, oxadiazon, propargyl | Lander et al. (2000) |
| Micronucleus formation | Metham sodium, dodemorph, zineb, antracol, captan, dazomet, dichloropropane, dichloropropene | Bolognesi et al. (1993) |
| | Diazinon, dichlorvos, fosetyl-aluminum, malathion, ethamidophos, parathion methyl, cypermethin, carbaryl, methomyl, mancozeb, pirimicarb, benomyl, captan, endosulfan, lindane, diuron, 2,4-D, aldrin, ametrina, BHC, DDT, dacomil, dieldrin, di-syxtox, endrin, furadan, gusathion, javelin, metalaxyl, nuvacron, oxidemeton methyl, talstar, tordon | Gomez-Arroyo et al. (2000) |
| | Deltamethrin, carbaryl, mancozeb, propineb, benomyl | Pasquini et al. (1996) |
| Sister chromatid exchange | Azynphos methyl, dimethoate, malathion, methyl parathion, 2,4,5-T, 2,4-D | Laurent et al. (1996) |
| | Mancozeb-contained fungicide | Jablonicka et al. (1989) |
| | A complex mixture of pesticides (atrazine, alachlor, cyanazine, 2,4-dichlorophenoxyacetic acid, and malathion) | Zeljezic and Garaj-Vrhovac (2002) |
| | DDT, BHC, endosulfan, malathion, methyl parathion, phosphamidon, dimethoate, monocrotophos, quinalphos fenvelrate, and cypermethrin | Rupa et al. (1991) |
| | DDT, BHC malathion, parathion, dimethoate, fenitrothion, urea and gromor | Rupa et al. (1988) |

ability of transmission to daughter cells after cell division (Guy, 2005) (Fig. 1).

Between chromosomal assessments, micronucleus has been recognized as the most reliable and successful test as verified by the Organisation for Economic Co-operation and Development (OECD). A micronucleus is referred to the third nucleus formed during the metaphase/anaphase transition of mitosis. The group of these cytoplasmic bodies is called micronuclei having a portion of acentric chromosome or whole chromosome, which does not integrate in the opposite poles during the anaphase. This results in the formation of daughter cells without a part or all of a chromosome. Regarding sensitivity, reliability, and cost-effectiveness of this test, it has been proposed as a biomarker for genotoxicity calculations, and has been used in different studies on pesticide-exposed populations. Most of these surveys implied on the increased level of micronucleus formation in people dealing with pesticides for a long time (Costa et al., 2011; Ergene et al., 2007; Garaj-Vrhovac and Zeljezic, 2002).

Sister chromatid exchange (SCE) or exchange of genetic material between sister chromatids is another testing for chemicals suspected to be mutagenic. Elevated level of SCE has been observed in some diseases, including Bloom syndrome and Behçet's syndrome and maybe tumor formation. There are some reports on increased frequency of SCE in pesticide applicators who worked in agricultural fields (Carbonell et al., 1990; Rupa et al., 1991; Zeljezic and Garaj-Vrhovac, 2002).

Single-cell gel electrophoresis (SCGE) or Comet assay is a simple and sensitive testing for evaluation of DNA strand breaks in eukaryotic cells (Dhawan et al., 2009). This technique has been frequently used for biomonitoring genotoxic effect of pesticides in a large number of studies most of which implicate on induction of DNA damage by these chemicals (Grover et al., 2003; Mostafalou and Abdollahi, 2012c; Shadnia et al., 2005; Zeljezic and Garaj-Vrhovac, 2001).

Although, genotoxicity assays are among necessary tests applying for pesticides prior to introducing to the market, collected data from post-market monitoring studies have been evident for potential of allowed pesticides in induction of genetic damages. Considering genetic damages as one of the main events for cancer induction or development, further studies focusing on genotoxicity of pesticides, of course in appropriate models like exposure to their mixtures along with some other promoting factors, are required to understand the carcinogenic and tumorigenic mechanisms of pesticides (Table 3).

*Epigenetic modifications*

Epigenetic is referred to the heritable changes in gene expression or cellular phenotype without any alterations in the DNA sequence, and its mechanisms include DNA methylation, histone modifications and expression of non-coding RNAs. A growing body of evidence has implicated on the role of environmental exposures, particularly in early development, in the induction of epigenetic changes that may be transmitted to subsequent generations or may serve as a basis of diseases developed later in life. Furthermore, it has become so likely that epigenetics contribute to the causes or transmission of chronic disorders from one generation to another (Weinhold, 2006) (Fig. 2).

Several evidence collected from animal studies during the past decade suggested that exposure to pesticides can induce epigenetic changes. Heritable alterations of DNA methylation in male germline along with testis and ovarian dysfunction have been reported after exposure to some pesticides like vinclozolin and methoxychlor (Anway and Skinner, 2006; Anway et al., 2005; Guerrero-Bosagna et al., 2010; Zama and Uzumcu, 2009). Exposure to dichloroacetic acid and trichloroacetic acid has been associated with decreased methylation in promoter regions of *c-jun* and *c-myc* in liver of mice (Tao et al., 2000a,b). Global DNA hypomethylation has also been reported in

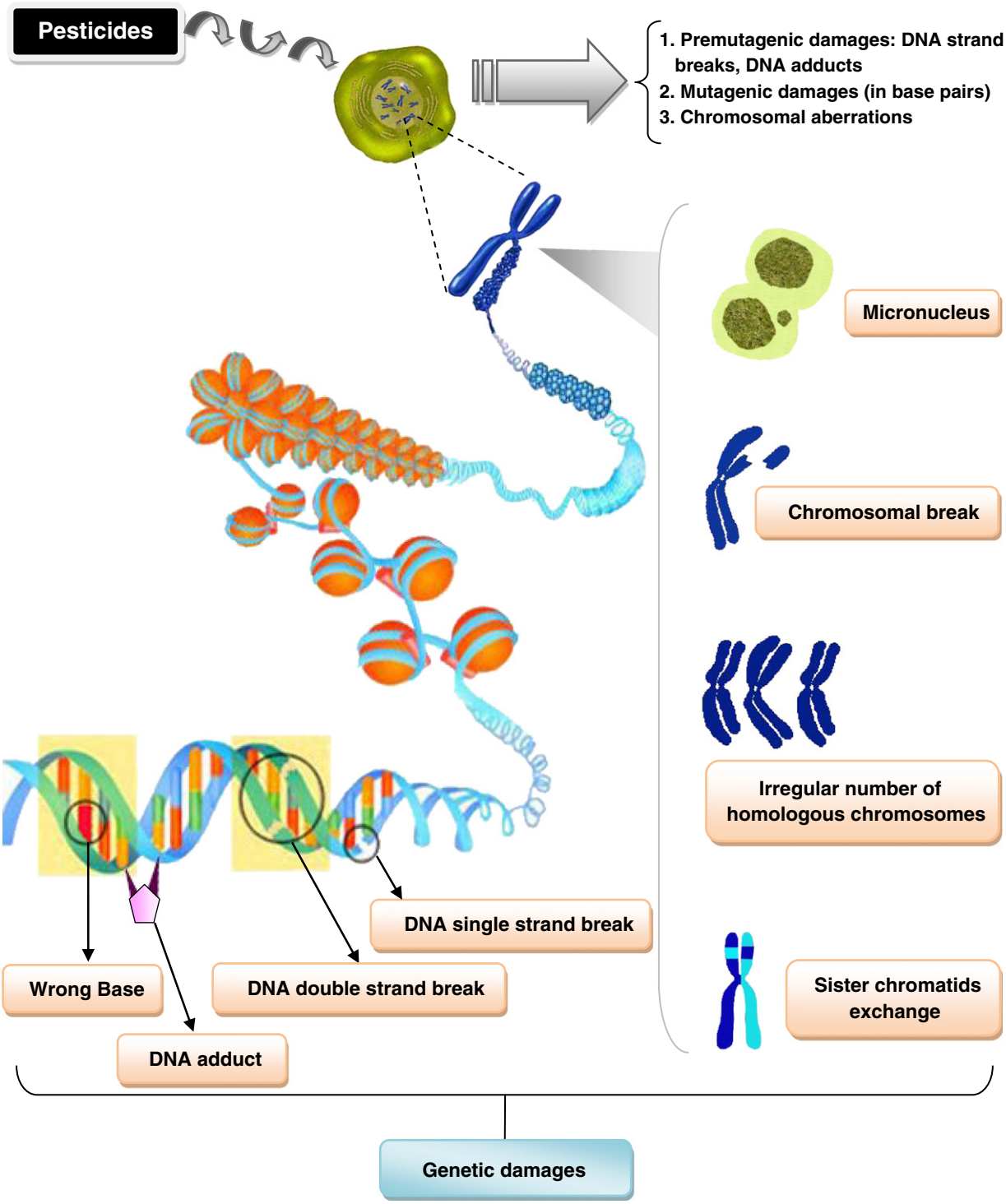


**Fig. 1.** A schematic model for induction of genetic damages including premutagenic, mutagenic and chromosomal effects by exposure to pesticides.

people who had an elevated blood level of pesticides and persistent organic pollutants in two surveys (Kim et al., 2010; Rusiecki et al., 2008). Furthermore, increased acetylation of core histones H3 and H4 has been reported by dieldrin, an organochlorine pesticide, in mouse models (Song et al., 2010).

On the other hand, growing progress has been made in the recognition of epigenetic modifications in human chronic diseases, particularly cancer. Cancer is now considered as an epigenetic disease the same as a genetic disease. There is tremendous evidence on the contribution of epigenetic events in the initiation, promotion and progression of different types of cancers, mainly through silencing of tumor suppressor genes and/or activation of proto-oncogenes. These modifications have allocated such a fundamental role in cancer development that epigenetic therapy of cancer is rapidly growing in medical sciences (Jones and Baylin, 2002). In addition, epigenetic changes currently have been a powerful tool for studying the carcinogenesis mechanisms of occupational and environmental exposures (Ziech et al., 2010). The first note on pesticide-induced carcinogenesis through epigenetic mechanisms was from a study carried out by Maslansky and colleagues in 1981. They reported hepatocarcinogenesis of organochlorine pesticides with no genotoxic effects in hepatocytes and suspected to epigenetic modifications disrupting intracellular

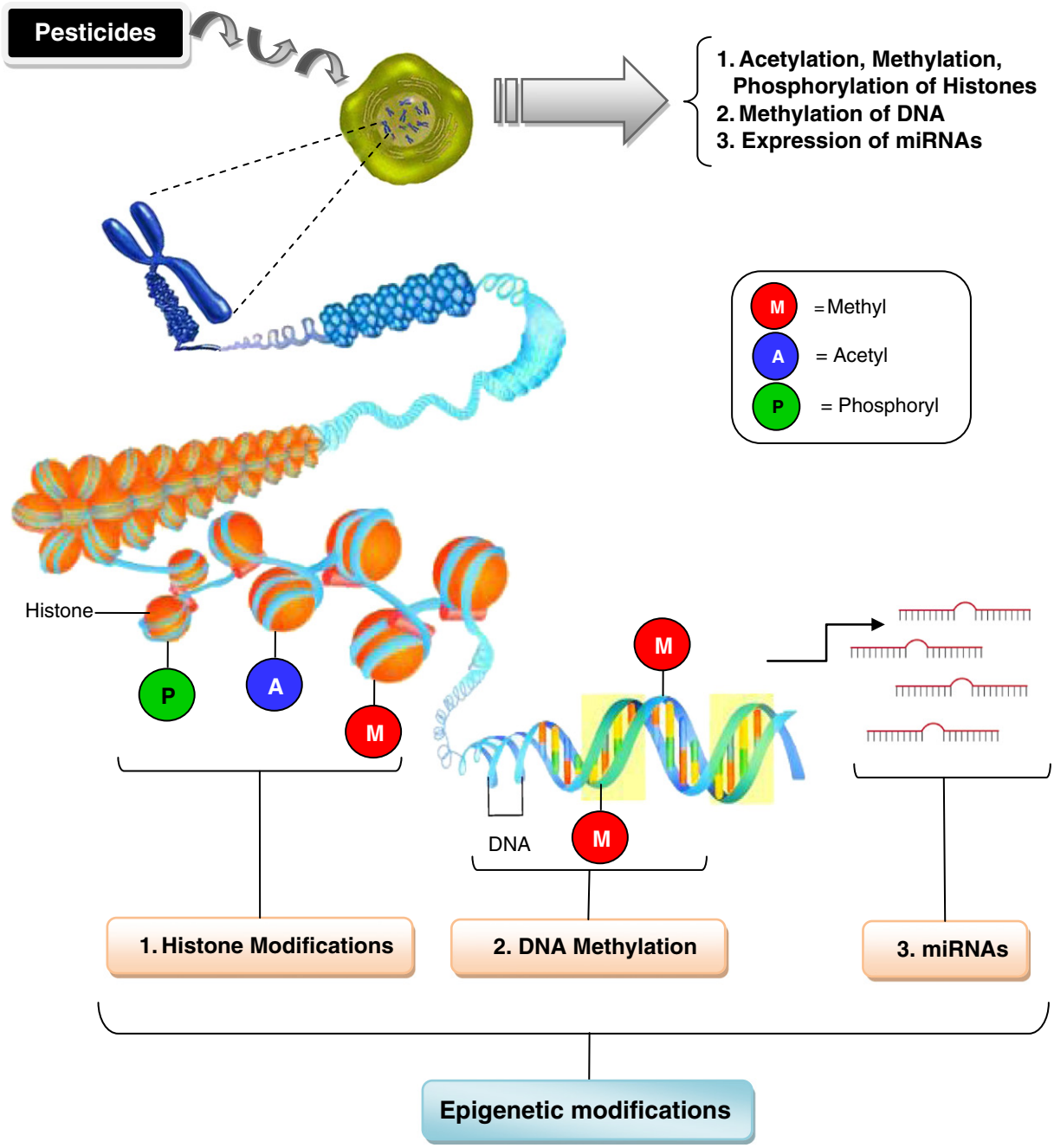


**Fig. 2.** A schematic model for induction of epigenetic modifications including DNA methylation, histone modification, and expression of miRNAs by pesticides.

communications (Maslansky and Williams, 1981). Later, reports presented about epigenetic actions of vinclozolin, a fungicide known to be an environmental endocrine disruptor, in association with adult-onset diseases, particularly tumor development (Skinner and Anway, 2007). Pesticides were introduced as carcinogens acting through epigenetic or nongenotoxic mechanisms (Rakitsky et al., 2000).

Other than cancer, epigenetic alterations have increasingly been detected and investigated in neurodegenerative diseases, including Parkinson (Habibi et al., 2011), Alzheimer (Kwok, 2010), ALS (Oates and Pamphlett, 2007), and multiple sclerosis (Burrell et al., 2011). On the role of epigenetic changes in pesticide-induced neurodegenerative disorder, recently neurotoxic insecticides were found to promote apoptosis in dopaminergic neurons through hyper-acetylation of core histones H3 and H4 (Song et al., 2010).

Epigenetic alterations have also been reported to be involved in some other late-onset diseases like diabetes (Simmons, 2007), aging (Gravina and Vijg, 2010), chronic kidney disease (Dwivedi et al., 2011), and atherosclerosis (Lund and Zaina, 2011). Nevertheless, presenting epigenetic modifications as a mechanism by which pesticides develop these chronic diseases depends on the future studies.

However, epigenetics has opened a new field for studying the influence of environmental exposures on transcriptional regulation of genes in association with human diseases. There are a lot of findings about changing the pattern of gene expressions in exposure to pesticides, which can be used as a tool in studying the process of human diseases (Pournourmohammadi and Abdollahi, 2011), but further studies are still required to determine the role of epigenetic mechanisms in these variations.

## Other mechanisms involved in pesticide-induced chronic diseases

### *Endocrine disruption*

At a cellular level, endocrine disruption refers to a mechanism of toxicity that interferes the ability of the cells to communicate hormonally and results in a wide variety of adverse health effects including birth defects, reproductive, developmental, metabolic, immune, and neurobehavioral disorders as well as hormone dependent cancers. The term "endocrine disruptor" (ED) was first introduced in 1991 referring to the substances that interfere with synthesis, secretion, transport, binding, action, metabolism or elimination of hormones in the body (Crisp et al., 1998). Up to now, a huge body of evidence has brought up on endocrine disrupting properties of pesticides so that currently a total of 101 pesticides have been listed as proven or possible EDs by the Pesticide Action Network UK (PAN, 2009). Most endocrine disrupting pesticides mimic estrogen function by acting as a ligand for receptor, converting other steroids to active estrogen or increasing the expression of estrogen responsive genes as shown by some organochlorines, organophosphates, carbamates, and pyrethroids. Antiandrogenic effects have also been reported for organochlorine and carbamate insecticides, as well as triazines, a group of herbicides through inhibition of binding natural ligand to receptors and androgen binding receptors. Competitive inhibition of thyroid hormone receptors by organophosphates and inhibition of progesterone action by pyrethroids are other findings regarding endocrine disruption by pesticides (McKinlay et al., 2008). However, the results of various transactivation assays using mammalian and yeast cells indicated agonistic or antagonistic activity of pesticides toward aryl hydrocarbon receptors and some members of the nuclear receptor superfamily including retinoic acid receptors, pregnane X receptors, and peroxisome proliferator-activated receptors (Kojima et al., 2010; Lemaire et al., 2005).

### *Mitochondrial dysfunction*

As dynamic multifunctional organelles, mitochondria are the main source of ATP and reactive oxygen species (ROS) in the cell and have important roles in calcium homeostasis, synthesis of steroids and heme, metabolic cell signaling, and apoptosis. Abnormal function of the mitochondrial respiratory chain is the primary cause of imbalanced cellular energy homeostasis and has been widely studied in different types of human diseases most of all diabetes (Abdul-Ghani and DeFronzo, 2008; Kim et al., 2008; Lowell and Shulman, 2005; Ma et al., 2012) and neurodegenerative disorders (Johri and Beal, 2012). Perturbation of this organelle has been accepted as one of the crucial mechanisms of neurodegeneration since there is broad literature supporting mitochondrial involvement of proteins like α-Synuclein, Parkin, DJ-1, PINK1, APP, PS1 & 2, and SOD1 that have some known roles in major neurodegenerative disorders, including Parkinson, Alzheimer, and ALS (Martin, 2012). Some evidence even proposed the involvement of mitochondrial DNA and its alterations in development of these diseases (Lin and Beal, 2006). Parkinson was almost the first disease in which the role of mitochondrial dysfunction was uncovered when the classical inhibitor of complex I electron transport chain, metabolite of MPTP, was reported to cause Parkinsonism in drug abusers (Langston, 1996). In 2000, developing the symptoms of Parkinson was also reported for a broad-spectrum pesticide, rotenone, whose mechanism of action is selective inhibition of complex I mitochondrial respiratory chain so that it has been widely used to create Parkinson model in laboratory animals (Caboni et al., 2004). In this regard, interfering with mitochondrial respiratory chain functions has made a pattern in development of different types of pesticides, and many agrochemicals are known to inhibit electron transport chain activity as their primary or secondary mechanism of action. Most of the pesticides interfering with mitochondrial respiratory chain activities are mainly inhibitors of complex I electron transport chain and some others partially inhibit complexes II, III, and V (Gomez et al., 2007). Moreover, a wide variety of pesticides has been known as uncouplers of mitochondrial oxidative phosphorylation (Ilivicky and Casida, 1969). Nevertheless, impairment of oxidative phosphorylation has been reported in exposure to a large number of pesticides particularly neurotoxic agents through inhibition of a biosynthetic pathway essential for mitochondrial function or extramitochondrial generation of ROS (Ranjbar et al., 2010). Likewise, there is enough evidence on the role of mitochondrial dysfunction in pathophysiological features of diabetes, including insulin deficiency and insulin resistance. Pancreatic beta cell failure has been reported to be associated with mitochondrial dysfunction and can be caused by exposure to pesticides (Jamshidi et al., 2009; Pournourmohammadi et al., 2007). On the other hand, exposure to pesticides inhibiting complex I and III mitochondrial respiratory chain can lead to a diminished oxygen consumption and cellular energy supply which in turn can result in reduced insulin signaling cascade. In this way, organochlorines, atrazine, and some dioxin-like pesticides have been shown to decrease mitochondrial capacity in beta oxidation of fatty acids resulting in accumulation of intracellular fat, a situation considered to develop obesity and insulin resistance (Lee, 2011; Lim et al., 2009).

### *Oxidative stress*

Increased production of ROS and/or decreased capacity of antioxidant defense can disrupt oxidative balance and result in damaging all components of the cell, including lipids, proteins, and DNA. Further, oxidative stress can disrupt various parts of cellular signaling because ROS are considered as one of the main messengers in redox signaling. However, the role of oxidative stress has been uncovered in induction and development of different kinds of human diseases, including cancer, diabetes, neurodegeneration, atherosclerosis, schizophrenia, chronic fatigue syndrome, and renal and respiratory disorders (Ahmad et al., 2010; Ciobica et al., 2011; Fendri et al., 2006; Lushchak and Gospodaryov, 2012; Nathan et al., 2011). On the other hand, there is a huge body of literature on induction of oxidative stress by pesticides, and it has been implicated in development of health problems mediated by exposure to pesticides (Grosicka-Maciag, 2011; Olgun and Misra, 2006; Slaninova et al., 2009; Soltaninejad and Abdollahi, 2009). It has been revealed that pesticides can disturb oxidative homeostasis through direct or indirect pathways, including mitochondrial or extramitochondrial production of free radicals, thiol oxidation, and depletion of cellular antioxidant reservoirs (Abdollahi et al., 2004b,c; Braconi et al., 2010; Mostafalou et al., 2012a). Considering the oxidative stress as a powerful promoter of other cellular pathways involved in disease process and as a unique attendant in inflammatory response, it has been put in the spotlight of the most mechanistic studies regarding the association of pesticide's exposure with chronic disorders. Oxidative stress has been implicated in the onset and progression of pesticide induced Parkinson disease (Singh et al., 2007). In this regard, organochlorine pesticides have been reported to cause degeneration of dopaminergic neurons by an oxidative dependent pathway in Parkinson model (Kanthasamy et al., 2002; Sharma et al., 2010). Additionally, disrupting effects of organophosphates on glucose homeostasis have been reportedly linked to oxidative damages and inflammatory cytokines and thought to be compensatory responses accompanied with reduced insulin signaling in insulin sensitive organs such as liver, muscle, and adipose tissue (Mostafalou et al., 2012b; Teimouri et al., 2006). As such further disruption of glucose homeostasis in diabetic models of laboratory animals exposed to organophosphate insecticides has been associated with enhanced lipid peroxidation and decreased activity of antioxidant enzymes (Begum and Rajini, 2011). Oxidative stress has also been reported to be involved in nephrotoxicity of some pesticides,

including diazinon, acephate, and paraquat (Poovala et al., 1998; Shah and Iqbal, 2010; Tomita et al., 2006).

*Endoplasmic reticulum stress and unfolded protein response*

As the first compartment of secretary pathway, endoplasmic reticulum (ER) is specialized for synthesis, folding, and delivery of proteins in addition to its fundamental role in the storage of calcium. Any disturbance in calcium homeostasis, redox regulation, and energy supply can cause perturbation of ER normal function resulting in accumulation of unfolded or misfolded proteins in this organelle, a situation which is called ER stress. Unfolded proteins occupy ER resident chaperones leading to release of transmembrane ER protein kinases which activate a series of phosphorylation cascades resulting in increased expression of genes, which act as molecular chaperones to reestablish ER folding capacity or promote ER associated degradation (ERAD) to remove misfolded proteins. This process is called unfolded protein response (UPR) aiming to adjust to the changing environment. In case if adaptation fails, ER stress results in expression of genes involved in programmed cell death pathways (Xu et al., 2005). Recent discoveries indicate that prolonged ER stress and UPR play an important role in the development of several human diseases particularly chronic ones, including insulin resistance, diabetes (Back et al., 2012; Kim et al., 2012; Scheuner and Kaufman, 2008), Parkinson, Alzheimer, ALS (Doyle et al., 2011; Lindholm et al., 2006; Nassif et al., 2010), tumor formation and progression (Koumenis, 2006; Lee and Hendershot, 2006), atherosclerosis, cardiomyopathy, chronic kidney diseases and renal failure (Dickhout et al., 2011; Tabas, 2010).

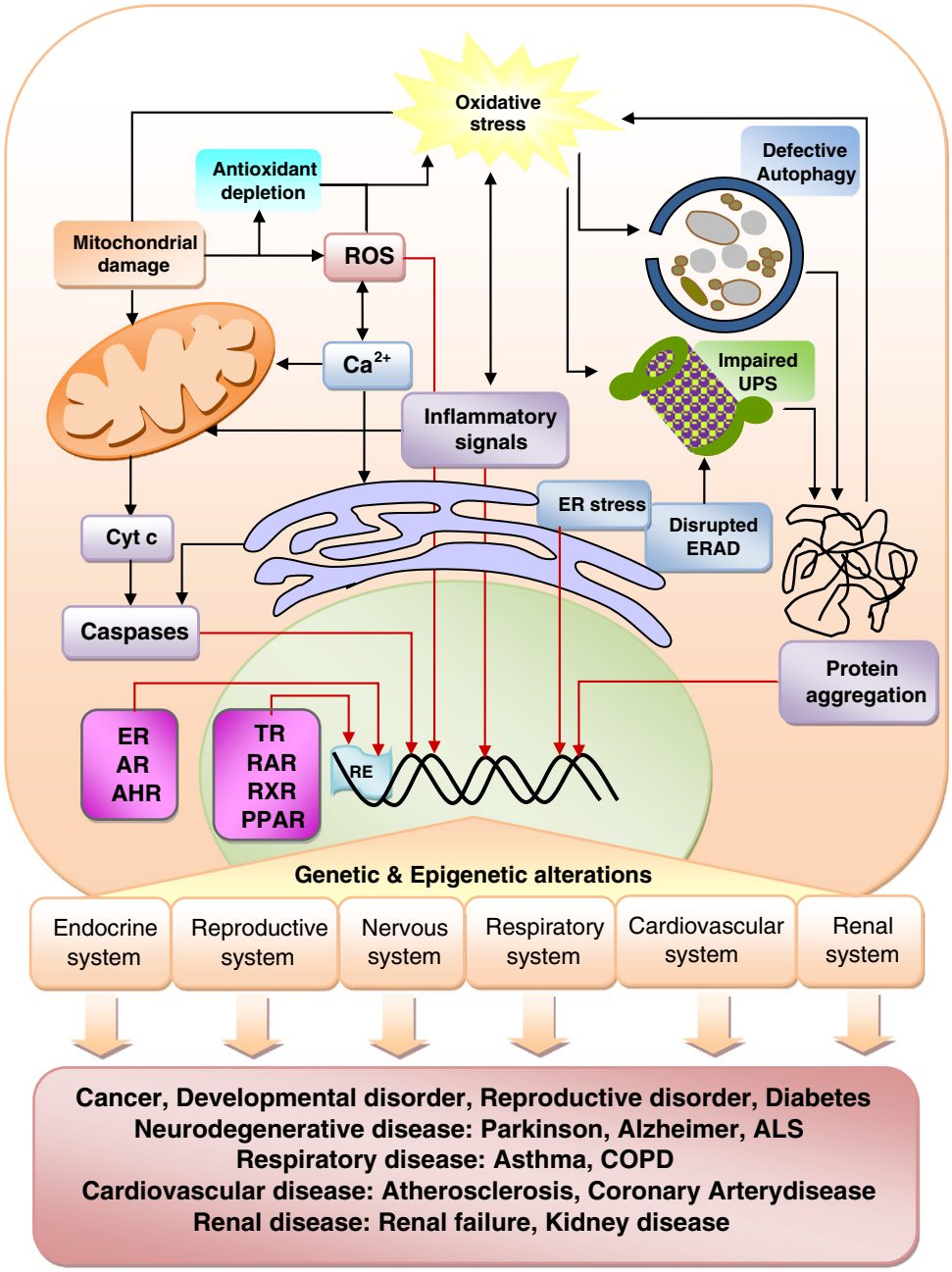


**Fig. 3.** A simplified model for mechanisms by which pesticides induce and develop chronic disease, ROS: reactive oxygen species, Cyt c: cytochrome c, UPS: ubiquitin proteasome system, ER stress: endoplasmic reticulum stress, ERAD: endoplasmic reticulum associated degradation, ER: estrogen receptor, AR: androgen receptor, AHR: aryl hydrocarbon receptor, TR: thyroid receptor, RAR: retinoic acid receptor, RXR: retinoid X receptor, PPAR: peroxisome proliferator-activated receptor, RE: response element, ALS: amyotrophic lateral sclerosis, COPD: chronic obstructive pulmonary disease.

On the other hand, ER stress and related pathways have been reported to be involved in cytotoxicity of some pesticides. Paraquat, a bipyridyl herbicide, which is suspected to increase the risk of Parkinson disease following chronic exposures, has been reported to induce ER stress and trigger dopaminergic cell death by enhanced cleavage of a small ER co-chaperone protein, p23, and inhibition of ERAD (Chinta et al., 2008). Elevated level of ER stress biomarkers like glucose-regulated protein 78 (GRP78), ER degradation-enhancing-α-mannosidase-like protein (EDEM), and C/EBP homologous protein (CHOP) has also been implicated in paraquat-induced toxicity in human neuroblastoma cells. Further, paraquat activated calpain and caspase 3 along with ER-induced cascade inositol-requiring protein 1 (IRE1)/apoptosis signal-regulating kinase 1 (ASK1)/C-Jun N-terminal kinase (JNK) (Yang et al., 2009). In another study carried out on neuroblastoma cells, rotenone-induced ER stress has become evident by increased phosphorylation of protein kinase RNA-like endoplasmic reticulum kinase (PERK), protein kinase RNA-activated (PKR), and eukaryotic initiation factor 2-a (eIF2a) as well as the expression of GRP78. Moreover, rotenone activates glycogen synthase kinase 3β (GSK3β), an ER related multifunctional serine/threonine kinase implicated in the pathogenesis of neurodegeneration (Chen et al., 2008). Deltamethrin, a pyrethroid pesticide, has been reported to induce apoptosis through ER stress pathway involving eIF2α, calpain and caspase 12 (Hossain and Richardson, 2011). Induction of apoptosis by pyrrolidine dithiocarbamate (PDTC)/Cu complex, a widely used pesticide, has also been linked to the ER stress-associated signaling molecules, including GRP78, GRP94, caspase-12, activating transcription factor 4 (ATF4), and CHOP in lung epithelial cells (Chen et al., 2010). Chloropicrin an aliphatic nitrate pesticide has been indicated to increase ER stress-related proteins, including GRP78, IRE1α, and CHOP/GADD 153 in human retinal pigment epithelial cells (Pesonen et al., 2012). Some other pesticides belonging to the organochlorines (endosulfan), carbamates (formetanate, methomyl, pyrimicarb), and pyrethroids (bifenthrin) have been evaluated for their effects on stress proteins among which upregulation of the ER chaperone GRP78 and downregulation of the cytosolic chaperone HSP72/73 were significant. These effects can occur when ER is under stress and the UPR result in increased expression of ER chaperones and decreased protein synthesis in the cytosol (Skandrani et al., 2006a,b).

*Protein aggregation*

Degradation of misfolded, damaged or unneeded proteins is a fundamental biological process which has a crucial role in maintenance and regulation of cellular function. There are two major cellular mechanisms for protein degradation; ubiquitin proteasome system (UPS) that mainly targets short-lived proteins by proteases, and autophagy that mostly clears long-lived and poorly soluble proteins through the lysosomal machinery (Gies et al., 2010). UPS is composed of ubiquitin for tagging and proteasomes for proteolysis of proteins, which are to be degraded. Deregulation of this system has been implicated in the pathogenesis of several chronic diseases, mostly neurodegeneration and cancers evidenced by decreased and increased proteasome activity, respectively (Paul, 2008). Environmental exposure to certain pesticides has been linked to proteasomal dysfunction in development of neurodegenerative diseases. The organochlorine pesticide dieldrin has been reported to decrease proteasome activity along with enhanced sensitivity to occurrence of apoptosis in dopaminergic neuronal cells (Sun et al., 2005). Proteasome inhibition has also been shown in neuroblastoma cells exposed to rotenone, ziram, diethyldithiocarbamate, endosulfan, benomyl, and dieldrin (Chou et al., 2008; Wang et al., 2006). Paraquat has also been noted to impair UPS given by decreased proteasome activity and increased ubiquitinated proteins in DJ-1 deficient mice and dopaminergic neurons (Yang and Tiffany-Castiglioni, 2007; Yang et al., 2007). Increased degradation of proteasome components has been presented as the mechanism of proteasome inhibition by rotenone, an inducer of Parkinson (Chou et al., 2010).

The lysosomal degradation pathway of autophagy is known as a self-digestion process by which cells not only get rid of misfolded proteins, damaged organelles and infectious microorganisms but also provide nutrients during fasting. Defect of this process has found an emerging role in many human diseases such as cancer, neurodegeneration, diabetes, aging, and disorders of the liver, muscle, and heart (Gonzalez et al., 2011; Levine and Kroemer, 2008; Shintani and Klionsky, 2004). There are a few reports on the involvement of defective autophagy in toxic effects of pesticides. A relationship between autophagy and paraquat-induced apoptosis in neuroblastoma cells was shown by Gonzalez-Polo and colleagues in 2007 (Gonzalez-Polo et al., 2007). This effect was confirmed in another study in which paraquat-induced autophagy was attributed to the occurrence of ER stress (Niso-Santano et al., 2011). Lindan, a broad-spectrum organochlorine pesticide, has been reported to promote its toxicity through disruption of an autophagic process in primary rat hepatocytes (Zucchini-Pascal et al., 2009) (Fig. 3).

## Conclusion

Taken together, chronic diseases discussed above are considered as the major disorders affecting public health in the 21st century. The relationship between these diseases and environmental exposures, particularly pesticides increasingly continues to strengthen. Near to all studies carried out in the area of pesticides, and chronic diseases are categorized in the field of epidemiologic evidence or experimental investigation with mechanistic insight into the disease process. Some epidemiologic studies have been debated on their uncertainty in elicitation of a definite conclusion because of some restrictions. However, existence of more than a few dozen reports on the association of one case like brain cancer with exposure to pesticide is enough to create concern even without finding a direct link. Abundance of evidence in this regard has promoted scientist to evaluate the mechanisms by which pesticides develop chronic diseases. Although there remains a lot to do in this way, several mechanisms and pathways have been clarified for pesticide-induced chronic diseases. It should not be forgotten that these mechanisms work alongside or sequentially rather than singly in most cases, or they even can potentiate genetically susceptible individuals. However, the body of studies in this respect has become massive enough to consider pesticide exposure as a potential risk factor for developing chronic diseases. Considering chronic diseases as the most important global health problems it is time to find a preventive approach in association with agrochemicals by logical reducing pesticide use or pesticide dependency and find efficient alternatives for hazardous ones.

## Conflict of interest statement

There is no competing interest.

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