We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Molecular Mechanisms of Pesticide Toxicity

Olfa Tebourbi, Mohsen Sakly and Khémais Ben Rhouma
Laboratory of Integrated Physiology, Science Faculty of Bizerte
Tunisia

1. Introduction

The environment represents a key contributor to human health and disease. Exposure to many environmental stressors such as pesticides have detrimental effects on health and are considered to contribute substantially to most diseases of major public health significance. Pesticide toxicity has been clearly demonstrated to alter a variety of physiological functions. In addition, evidence suggests that pesticide exposure increases the risk of cancer and neurodegenerative diseases. Recent evidence also demonstrates the ability of pesticides to act as endocrine disruptors, contributing to various adverse effects associated with reproductive and developmental toxicity (Colborn, 2006; Eskenazi et al., 1999). Thus, it is now evident that research towards understanding how pesticides influence the development and progression of disease will lead to further improvements in public health. A key for Environmental Sciences is identifying and understanding the basic biological processes that are altered or regulated by environmental factors, and that stimulate disease processes to begin, or the course of the disease to be substantially altered. For this, basic biology research with potential for future translation into the clinic must be pursued to understand the fundamental changes caused by exposure to environmental agents especially pesticides that will drive the scientific basis for health decisions. Cells respond and adapt to environmental signals such as toxicants or stressors through multiple mechanisms that involve communication pathways or signal transduction processes. A number of receptors sense the presence of foreign compounds in the cell and induce a cascade of events that is intended to lead to neutralization and excretion of these compounds. However, in many cases the metabolism of xenobiotic substances can give rise to toxic metabolites or to reactive oxygen species (ROS) that can harm the cell further. Additionally, the metabolism of foreign compounds can disturb other essential processes in the body, such as production and metabolism of certain hormones. Alterations in biochemical systems are often more sensitive indicators than those at higher levels of biological organization. Indeed, changes at the molecular level will underlie the effects at higher levels of organization.

In this chapter, we focus on a number of molecular pathways implicated in responses to pesticides. In many cases, these responses are adaptive. However, the same systems are involved in reactions leading to toxic effects. They are crucial to the health effects associated with pesticide insult and can be linked to adverse toxic effects and pathologies at higher levels of organization. These systems are:

- Endocrine disruption that can take place at different physiological levels: A) Altering (inhibiting or stimulating) the secretion of hormones. This possible effect is related to

mechanisms that control both the release of hormones from endocrine cells and synthesis of these hormones. B) Interfering with hormone-receptor interaction. C) Modifying the metabolism of circulating hormones, that is, by increasing or decreasing their excretion rate and/or biotransformation in the liver and other organs.

- Oxidant-mediated responses enhance the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the cell. Increased fluxes of these species can induce a number of antioxidant enzymes, alter concentrations of other antioxidants, and/or produce biochemical lesions associated with oxidative damage.

The present effort expands upon those earlier works, benefiting from the advances made in biochemistry and molecular biology in recent years. This chapter is meant to be substantive, but not exhaustive. Each section could be a chapter in itself.

2. Endocrine disruption

An "Endocrine Disrupting Chemical" (EDC) is best defined as "an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function" (European workshop on the impact of endocrine disrupters on human health and wildlife [EEC], 1996). Endocrine disruption refers to a mechanism of toxicity that hinders the ability of cells, tissues and organs to communicate hormonally, resulting in a wide variety of adverse health outcomes including reduced fertility and fecundity, spontaneous abortion, skewed sex ratios within the offspring of exposed communities, male and female reproductive tract abnormalities, precocious puberty, polycystic ovary syndrome, neurobehavioral disorders, hypothyroidism, hyperthyroidism, impaired immune function and a wide variety of cancers. Links between exposure to pesticides and endocrine disruption were suggested as early as 1949 when low sperm counts were observed in men involved in the aerial application of dichlorodiphenyltrichloroethane (DDT) (Singer, 1949). More recently, exposure to endocrine disrupting pesticides (EDPs) has been implicated in the etiologies of various cancers (Garry, 2004; Mathur et al., 2002), miscarriage and other reproductive disorders (Garry, 2004; Nicolopoulou and Stamanti, 2001), genital deformities (Baskin et al., 2001), other birth defects (Schreinemachers, 2003), behavioral abnormalities (Zala & Penn, 2004) and skewed offspring sex ratios (Garry, 2004; Mackenzie & Constanze, 2005). EDPs can affect the endocrine systems of an organism in a wide variety of ways. These include mimicking natural hormones, antagonizing their action or modifying their synthesis, metabolism, and transport. Moreover, these substances can act via multiple pathways including membrane receptors, or the enzymatic machineries involved in hormone biosynthesis/metabolism. However, most of the reported harmful effects of EDPs are attributed to their interference with hormonal signaling mediated by nuclear hormone receptors (NRs) (Swedenborg et al., 2009; Toppari, 2008).

In this section, we first describe receptors that mediate toxicity. We then give a short overview of pesticides that induce receptor-mediated events and finally discuss mechanisms of endocrine disruption.

2.1 Nuclear receptors involved in pesticide toxicity

Human NRs are a family of 48 transcription factors, many of which have been shown to be activated by ligands. NRs regulate cognate gene networks involved in key physiological functions such as cell growth and differentiation, development, homeostasis, or metabolism (Germain et al., 2006; Gronemeyer et al., 2004).

Receptors mediating toxicity can be roughly divided into two groups: dedicated xenosensors and hormone receptors with no primary role in the defense against xenobiotic insult. Upon binding of a xenobiotic compound, the dedicated xenosensors induce a response intended to metabolize and excrete the compound. Activation of the hormone receptors by xenobiotic substances leads to interference with the hormonal system of the exposed organism. To eliminate the harmful effects of an exogenous chemical, the cell attempts to change the compounds to an inactive state, make them water soluble, and excrete them. Metabolism of xenobiotics occurs in three phases: in phase I, the chemical is oxidized; in phase II, the oxidized products are conjugated to glutathione, sulfuric acid, or glucuronic acid, resulting in hydrophilic molecules; and finally in phase III, these substances are transported out of the cell by ATP-dependent export pumps (Nakata et al., 2006). In mammals, three different transcription factor superfamilies are responsible for the induction of xenobiotic metabolizing enzymes, basic-helix-loop-helix/Per-ARNT-Sim (bHLH-PAS) proteins, nuclear receptors (NRs) and basic leucine zipper (bZIP) proteins (Kliewer & Willson, 2002). Although bZIP proteins are important in the detoxification process, they do not bind xenobiotics but rather mediate the cellular response to oxidative stress.

Other receptors involved in the xenobiotic recognition are the NRs constitutive androstane receptor (CAR), rodent pregnane X receptor/steroid and its human orthologue human steroid X receptor (PXR/SXR) (Tolson & wang, 2010). Together with PXR, the constitutive androstane receptor (CAR) acts as an intracellular sensor for foreign chemicals and endogenous lipophilic substances (Willson & Kliewer, 2002). However, CAR differs from PXR in having high constitutive activity in the absence of ligand (Xu et al., 2004) and has been only identified in mammals (Reschly & Krasowski, 2006 ; Tolson & wang, 2010). The NRs farnesoid X receptor (FXR), liver X receptor (LXR), and peroxisome proliferator-activated receptor (PPAR) are also able to induce enzymes involved in the metabolism of xenobiotics. However, as these receptors are not primarily activated by xenobiotics, they are not considered xenosensors.

2.2 Pesticides that induce receptor-mediated toxicity

Receptor-mediated toxicity is induced by a number of pesticides. In contrast to genotoxic substances that are directly carcinogenic by inducing DNA damage, the receptor-mediated effects are versatile and often more subtle, and thus more difficult to identify. In this section, we give examples of pesticides inducing receptor-mediated events that can ultimately lead to toxicity to the organism. 127 pesticides were identified as having endocrine disrupting properties, including the 91 listed by the Pesticide Action Network (PAN) (2005). These pesticides have been used widely over the last 50 years, and the incidences of the diseases linked to them have increased markedly over the same time period and has led many scientists to suggest a connection, despite the inherent difficulty in proving any connection using epidemiological data (Mc Kinlay et al., 2008).

Many of these pesticides are structurally related to steroid hormones and may thus act on the respective hormone receptor. Actually, the first man-made chemicals identified as estrogen receptor (ER) disruptors were pesticides. Symptoms in men working with the manufacture of these compounds led to the identification of dichloro-diphenyl-trichloroethane (DDT) as an ER agonist. Other examples of pesticides that activate the ER are the DDT metabolite dichloro-diphenyl-dichloroethylene (DDE), methoxychlor, and dieldrin (Lemaire et al., 2006). In addition DDE and the fungicide vinclozolin can also affect the function of other hormone receptors: they both act as androgen receptor (AR) antagonists (Kavlock & Cummings, 2005), while vinclozolin can further antagonize the

activity of progesterone receptor (PR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR) *in vitro* (Molina-Molina et al., 2006). Androgen receptors are also affected by carbendazim. Premating exposures of male and female rats to carbendazim produced androgen-mediated birth defects in the resultant offspring which could be prevented by cotreatment with the androgen-receptor antagonist flutamide (Morinaga et al., 2004). Tetramethrin and Bioallethrin have also been shown to be estrogen antagonists (Garey and Wolff, 1998). The endocrine disrupting properties of pyrethroid metabolites are poorly understood. Cypermethrin and permethrin both produce a variety of metabolites with structures similar to 17-β-estradiol, some of which have been shown to be weakly estrogenic in vitro (McCarthy et al., 2006). The effects of these metabolites *in vivo* and in combination with other chemicals are unknown, as are the effects of other pyrethroid metabolites.

It has been demonstrated that some pesticides can act as endocrine disrupters on the basis of their basic chemistry, including Quantitative Structure Activity Relationships (QSAR), experimental studies on laboratory animals, wildlife studies and some human epidemiological studies like the International Program on Chemical Safety (IPCS, 2002). The effects of different groups of pesticides on hormone systems and their modes of action are listed in Table 1.

Pesticide	Uses	Hormones affected	Mechanism	References
Organochlorines	Insecticides	Androgens, oestrogens, prolactin	Competitive inhibitor of androgen receptors, inhibits oestrogen-sensitive reporter binding to androgen receptors. Some induce the production of aromatase, an enzyme that converts androgen to oestrogen	Daxenberger, 2002, Lemaire et al., 2004 ; Scippo, 2004 ; Sonnenschein & Soto,1998;
Organophosphates	Mostly Insecticides	Oestrogens, thyroid hormones binding.	Prevents thyroid hormone-receptor Increases the expression of oestrogen responsive genes	Gwinn et al., 2005 ; Jeong et al., 2006, Kang et al., 2004
Carbamates	Herbicides Fungicides	Androgens, oestrogens, Steroids	Still largely unknown. Thought to affect androgen- and androgen-receptor-dependant mechanisms. Shown to interfere with cellular microtubule formation in oestrogen-sensitive cells.	Daxenberger, 2002 ; Goad et al., 2004 ; Lu et al., 2004, Morinaga et al., 2004
Triazines	Herbicides	Androgens	Inhibition of natural ligands that bind to androgen receptors and androgen-binding proteins. Some induce or inhibit the production of aromatase, an enzyme that converts androgen to oestrogen	Hayes et al., 2002 ; Ishihara et al., 2003 ; Meulenberg, 2002
Pyrethroids	Insecticides	Oestrogens, Progesterone	Different compounds antagonise or potentiate the action of oestrogen by acting on the oestrogen receptor or possibly an alternative signalling pathway. Some inhibit the action of progesterone by affecting the hormone itself.	Garey & Wolff, 1998 ; Kim et al., 2004

Table 1. Common endocrine disrupting pesticides: their effects and modes of action

2.3 Pesticide-induced endocrine disruption mechanisms

The human endocrine system is a body-wide network of signaling pathways in which hormones deliver messages, directly or indirectly affecting all aspects of physiology. The phenomenon of exogenous compounds causing dysregulation of the endocrine system has been termed endocrine disruption, and the compounds are collectively referred to as endocrine disrupting chemicals (EDCs). Although pesticides could theoretically disturb the function of all hormone receptors, research to date has mainly focused on their effects on ER, AR and TR. In particular, the ER is recognized as a target for many pesticides. There are two main pathways by which a pesticide can disrupt hormone signaling through receptor-mediated mechanisms: (1) by directly binding to the hormone receptors (Fig. 1), or (2) by binding to xenosensors like PXR and CAR and indirectly affecting hormone signaling by various mechanisms (Fig. 2). Direct binding to hormone receptors is by far the most studied mechanism of endocrine disruption. However, there are several other mechanisms by which pesticides may indirectly affect hormonal pathways, such as inhibition of steroidogenic enzymes and binding to steroid transport proteins, reflecting how complex and interwoven the endocrine and pesticide detoxification systems are.
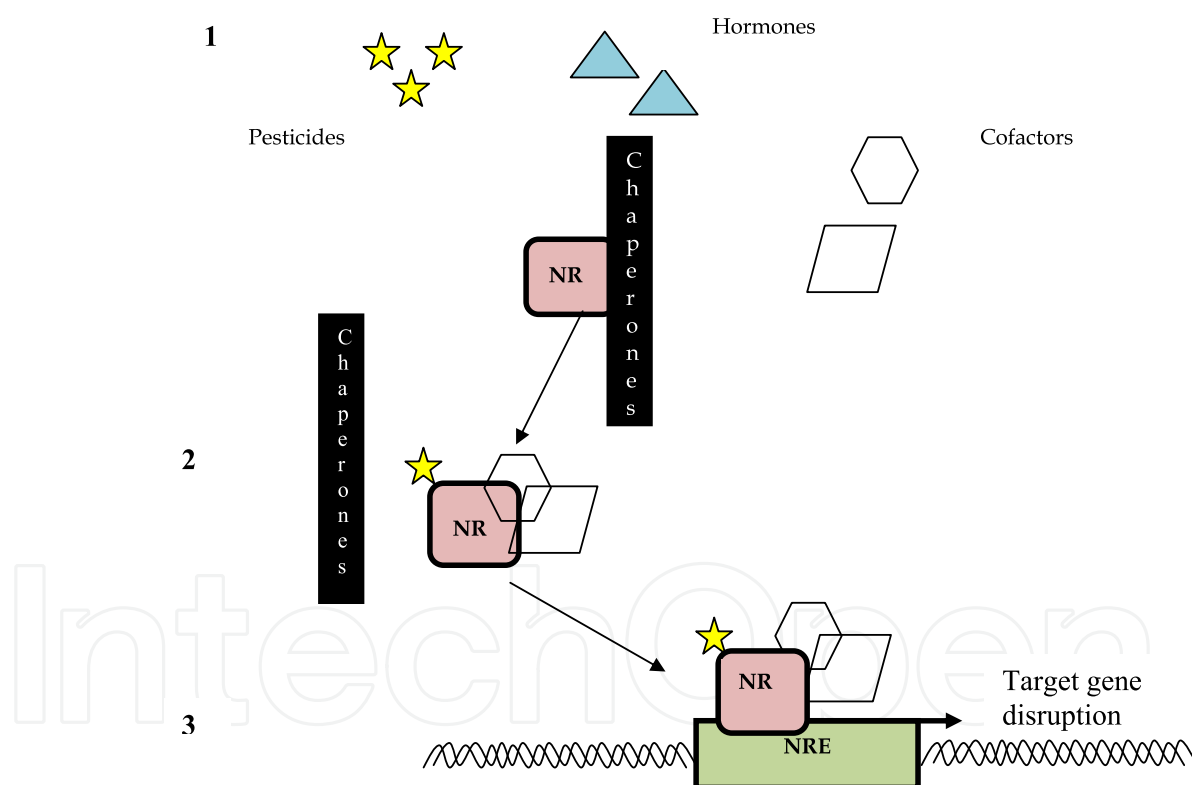

Fig. 1. Mechanistic representation of receptor-mediated endocrine disruption. (1) Endocrine disruptive Pesticides of suitable structure and affinity (illustrated with stars) bind to a nuclear receptor (NR) instead of the cognate hormone (illustrated with triangles). (2) Depending on the receptor conformation induced by the ligand, different cofactors are recruited to the ligand-NR complex. (3) The transcriptional activity of the receptor is governed through the ligand and cofactors, and may lead to inappropriate activation or repression of genes containing NR response elements (NRE) in their regulatory regions (Adapted from Rüegg et al., 2009, with modification).

2.3.1 Direct binding to the nuclear hormone receptors

The nuclear hormone receptors regulate gene transcription in response to their cognate ligands. Nuclear receptor (NR) is bound to chaperone proteins in the absence of ligand. Upon ligand binding, the chaperone complex dissociates from the receptor, leading to increased affinity of the receptor for cofactors and nuclear receptor response elements (NRE) on DNA. The activated receptor complex binds to the response elements and regulates the expression of the target gene (activation or inhibition). As many pesticides structurally resemble these cognate ligands, they too can bind to the receptors causing inappropriate signals in the cell. A pesticide with suitable structural features binds to the hormone-binding cavity or in some instances to some other part of the receptor, causing a conformational change of the receptor. This change determines the activity of the receptor: an agonistic conformation leads to recruitment of coactivators and thus increased transcriptional activity of the receptor, whereas an antagonistic conformation prevents coactivator recruitment and/or attracts corepressors, leading to decreased transcriptional activity of the receptor (Rüegg et al., 2009) (Fig. 1).

2.3.2 Xenosensor-mediated endocrine disruption competition for common coactivators

The biological function of transcription factors, including the NRs, is dependent on the availability of transcriptional cofactors. Many of these cofactors are not receptor specific but are used in several different signaling pathways in the cell. Hence, the cofactors are a potential target for endocrine disruption. If one receptor is persistently activated, the continuous recruitment of cofactors to this receptor may reduce the availability of the cofactors to other receptors, thereby impairing their activity (Fig. 2A).

2.3.3 Dysregulation of hormone metabolism

Steroid hormones are small lipophilic molecules that are synthesized from cholesterol. They have a cyclopentano-perhydrophenanthrene four-ring hydrocarbon nucleus, the so-called steroid nucleus, as a core structure. The synthesis of steroid hormones occurs primarily in the adrenal cortex, gonads (testes and ovaries) and placenta. The catabolism of sex steroids occurs in the liver in a process that closely resembles the metabolism of pesticides. To render the steroid hormones hydrophilic, they are hydroxylated and conjugated. Hydroxylation reactions are carried out by steroid hydroxylases of the cytochrome P450 family (CYP), whereas sulfotransferases and the UDP-glucuronosyltransferases are responsible for steroid conjugation. As a consequence of the similarities between pesticide and steroid metabolism, activation of the pesticide response can affect metabolism of hormones (Fig. 2B). Enzyme activation upon exposure to pesticides can lead to alterations in the endogenous levels of hormones in the organism, and subsequently compromise hormone signaling. The most important regulators of the activity of these enzymes are PXR and CAR. For example, DDT and its metabolite DDE activate PXR and CAR in rodents. In turn, they induce CYP2B, CYP3A and other steroid hydroxylases, thereby potentially perturbing normal steroid metabolism (You, 2004). We have demonstrated previously that treatment of rats with 50 and 100 mg/kg of p,p'-DDT or with 3 and 6 mg/kg of dieldrin for 10 consecutive days induced a dose-dependent decrease of the number and the motility of epididymal spermatozoa and we have hypothesized that DDT/dieldrin induction of testosterone metabolism may play a role by reducing testosterone concentrations (Ben Rhouma et al., 2001; Hallègue et al., 2003). Thyroid metabolism is another target for endocrine disruption by pesticides.
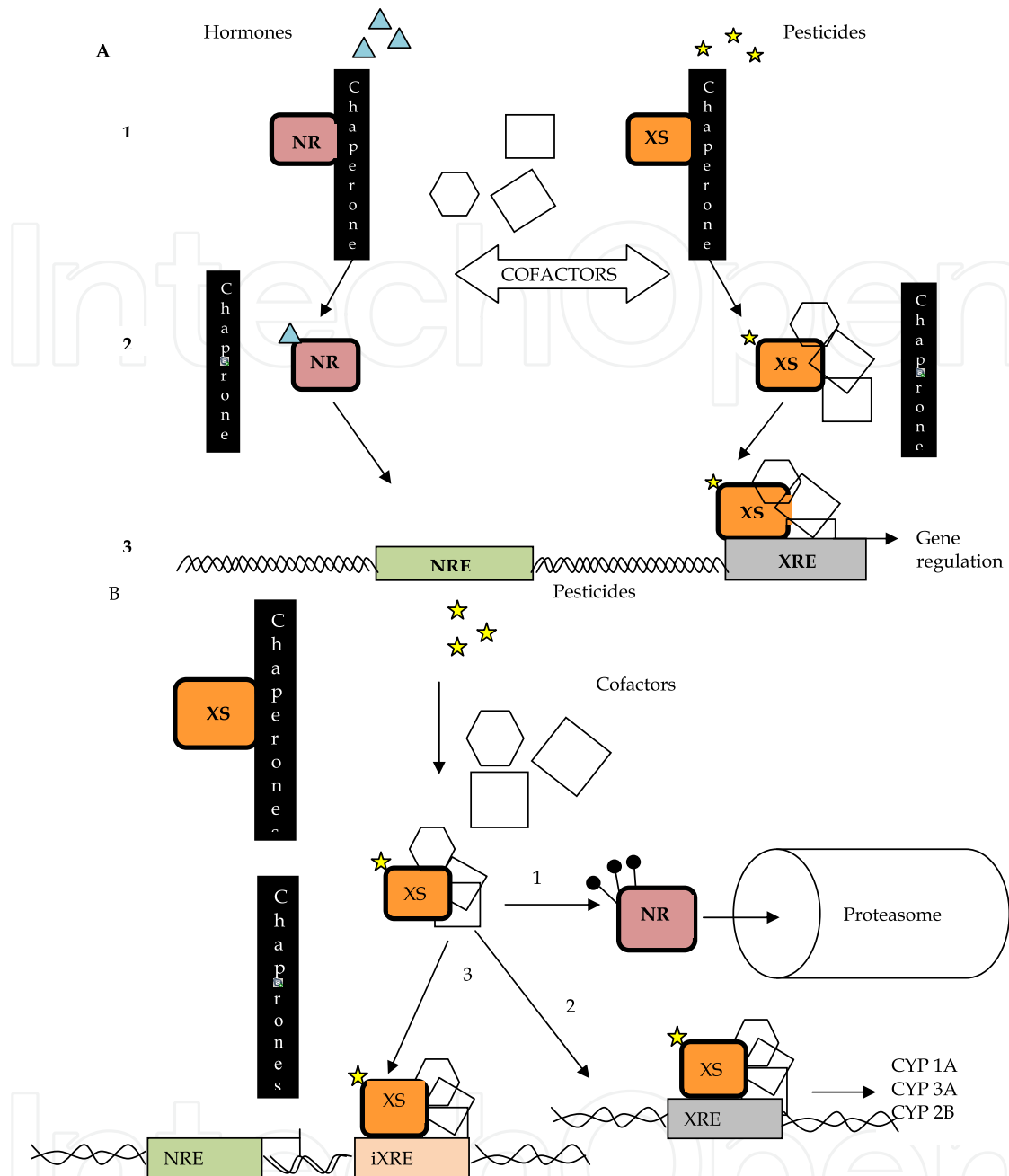
Fig. 2. Indirect mechanisms of receptor-mediated endocrine disruption. (A) Pesticides can disrupt nuclear receptor (NR) activity indirectly through competition for common cofactors: (1) When both NR and xenosensor (XS)-mediated signaling occurs in the same cell, common cofactors may become limiting factors in the signaling event. (2) When the cofactors are recruited to XS pathway, they are not sufficiently available for NR signaling. (3) NR signaling is hampered, while XS-mediated activity occurs normally. (B) More indirect mechanisms of endocrine disruption include: (1) Targeted degradation of NR in proteasome as a consequence of XS-induced ubiquitination (depicted with pins) of the receptor; (2) XS-induced transcription of enzymes involved in hormone metabolism; and (3) Binding of XS to inhibitory xenobiotic response elements (iXRE) in close proximity of NREs on DNA, blocking gene regulation through the NRE (Adapted from Rüegg et al., 2009, with modification).

We have recently shown that the same treatment with p,p'-DDT increased the metabolism of thyroid hormones and led to a decrease in serumT4 levels and hypothyroidism in rats (Tebourbi et al., 2010). Alteration of the enzymes involved in the thyroid hormone metabolism has been described as a mechanism for reducing the amount of available hormone (Curran and De Groot, 1991). Yet, we and others have shown that hepatic microsomal enzyme inducers, like DDT enhanced the glucuronidation and biliary excretion of thyroid hormones *via* induction of the hepatic T4 uridinediphospho-glucuronyltransferase (UDP-GT) (Bastomsky, 1974; Tebourbi et al., 2010).

2.3.4 Dysregulation of receptor stability

The stability of hormone receptors is an integral feature of receptor biology. Since cells need to rapidly respond to fluctuating hormone levels, the amount of the receptors has to be tightly and rapidly regulated. For example, in the absence of estrogens the ER levels are up-regulated and upon estrogen treatment, the levels quickly decrease. The degradation of several NRs occurs in the ubiquitin-proteasome pathway. Receptors are targeted for degradation with ubiquitin, a 76-amino acid protein. Polyubiquitinated proteins are transported to the proteasome, a multi-protein complex, where they are degraded. Inhibition of this pathway affects different hormone receptors differently. For instance, upon ubiquitination the transcriptional activity of AR (Lin et al., 2002) or GR (Deroo et al., 2002) is increased, whereas the activity of ER is decreased (Wijayaratne & McDonnell, 2002). Therefore, activation of CAR/PXR by pesticides may alter the amount of steroid hormone receptors in the cell, leading to disrupted estrogen and androgen signaling (Fig. 2B).

2.3.5 Inhibitory xenobiotic response elements

Ligand-activated xenosensors bind to xenobiotic response elements (XREs) in the DNA and induce the expression of target genes. Interestingly, many NR-regulated genes have also XRE-like elements in their promoters. These inhibitory XREs (iXREs) differ slightly in base composition from the response elements on xenobiotic-responsive genes, rendering the sequence capable of binding xenosensors but not of activating the downstream gene. Binding of the xenosensor (XS) to inhibitory xenobiotic response elements (iXRE) in close proximity of NREs on DNA, blocks gene regulation through the NR response elements (NRE) (Fig. 2B) (Nagel et al., 2001; Rüegg et al., 2009).

2.4 Endocrine disruption as a common causal mechanism of pesticide-induced carcinogenesis

The increased incidence of cancer over the last 50–60 years may be largely attributed to two factors: the ageing of the population and the diffusion of carcinogenic agents, present not only in the occupational, but also in the general environment. There are studies supporting evidence that lifespan exposure to carcinogenic agents, beginning during developmental life, produces an overall increase in carcinogenic processes (Soffritti et al., 2008). There are scientific evidences linking environmental changes over the time period preceding the growing incidence of some types of cancer. These changes have not stopped and the accumulation of carcinogens keeps growing (Irigaray et al., 2007). Genetic alterations, immune suppression, and malignant transformation are phenomena linked to the origin of cancer. Cancer is generally believed to arise from a single cell which has become "initiated" by mutation of a few crucial genes, caused by random errors in DNA replication or a

reaction of the DNA with free radicals or other chemical species of exogenous or endogenous origin (Hanahan & Weinberg, 2000). Carcinogenesis is indeed an extremely complex and long lasting biological process involving initiation, promotion and progression, which are three individualized steps that chronologically and sequentially contribute to cancer genesis and development through the interplay of a myriad of endogenous and exogenous causal factors (Belpomme et al., 2007). Among the numerous man made environmental chemicals used, pesticides, because of their estrogenic properties and carcinogenic potential, may in fact be common causal agents of cancers.

2.4.1 Pesticides as tumor promoters

Some xenoestrogens may possess a 1000 times lower affinity for nuclear estrogen receptors (ERs) than estradiol (Lemaire et al., 2006), meaning that they could not efficiently combine with and activate or inhibit ERs. However activation or inhibition of ERs is an extremely complex ligand-structure-dependent phenomenon, which also depends on several other factors including cell tumor-specific expression of coactivator/coregulatory proteins, gene promoters and cell environment (Katzenellenbogen et al., 1996). More precisely, mechanisms of estrogen activation involve ligand-induced dimerization of ERs, interactions with estrogen responsive elements in target gene promoters and transcriptional activation (Hall et al., 2001). ERα and ERβ are two major ER subtypes that have been evidenced in estrogen-dependent tissues. Activation of ERα stimulates cell proliferation and is associated with cancer-causing effects through tumor promotion, whereas activation of ERβ stimulates terminal cell differentiation and may contribute to anticancer effects (Foster et al., 2004). Many xenoestrogens, especially organochlorine pesticides have been shown to disrupt endocrine processes by acting as agonists on ERα and/or antagonists on ERβ (Lemaire et al., 2006) and also possibly as antagonists on androgenic receptors (ARs) (Escriva et al., 2004; Sonnenschein & Soto, 1998). Indeed, in addition to the induction of a more or less agonistic effects by interacting with ERα, many pesticides used such as chlordecone, endosulfan, aldrin, dieldrin and endrin have been shown to be associated with antagonistic effects by activating ERβ, meaning that agonistic effects involving ERα in addition to antagonistic effects involving ERβ may strongly contribute to the tumor promoting effects of these pesticides (Lemaire et al., 2006). In addition, several of the aforementioned pesticides or their metabolites have been shown to exhibit antiandrogenic effects by binding to ARs and competing with endogenous androgens, a property that reinforce their estrogenic effect. This is particularly true for p,p′-DDE (Kelce et al., 1995), HCH (Schrader & Cooke, 2000), dieldrin (Andersen et al., 2002) and chlordecone (Schrader & Cooke, 2000). Pesticides which stimulate α-aromatase that converts testosterone to 17β-estradiol and androstenedione to estrone, more precisely p,p′-DDE (You et al., 2001), chlordanes, aldrin and dieldrin (Laville et al., 2006), toxaphene (Yang & Chen, 1999) and atrazin (Laville et al., 2006; Sanderson & van den Berg, 2003) may also indirectly contribute to prostate and breast cancer promotion by increasing concentration of endogenous natural estrogens in peripheral tissues as well as in the intratumoral milieu. Also, it has been shown *in vitro* that p,p′-DDE at high concentrations could function as an inhibitor of 5α-reductase, an intraprostatic enzyme that converts testosterone to dihydrotestosterone (DHT) (Lo et al., 2007). However because it cannot be aromatized to estrogen, DHT hardly induces prostate cancer, suggesting that in addition to androgens, estrogens may play locally a major critical role in prostate carcinogenesis (Bosland, 2006).

2.4.2 Pesticides as tumor initiators

In addition to tumor promotion-induced endocrine disruption mechanisms, pesticides may be directly or indirectly mutagenic through free radical production (Cassidy et al., 2005) and may cause both tumor initiation and subsequent tumor promotion by inhibiting Gap junctional intercellular communication (GJIC) (Kang et al., 1996). Inhibition of GJIC has clearly been shown in normal epithelial breast tissue exposed to relatively high concentrations of organochlorine pesticides. Indeed DDT, dieldrin, toxaphene or mixtures of one of these pesticides with HCB (Kang et al., 1996) have been shown to inhibit GJIC and therefore may contribute to carcinogenesis through this mechanism. Indeed, during tumor initiation, blockage of GJIC between normal and preneoplasic cells consequently create an appropriate intratissue microenvironment leading initiated cells to escape growth control from normal surrounding cells and therefore indirectly contribute to tumor promotion (Klaunig et al., 1990; Klaunig & Ruch, 1990). This may also be the case for several non organochlorine pesticides more recently used, such as the quinonoid herbicide Paraquat (Ruch & Klaunig, 1988), which has been proved to block GJIC in mouse hepatocytes (Klaunig et al., 1990; IARC, 1997) and thus possibly contribute to carcinogenesis through this mechanism.

3. Oxidant-mediated responses to pesticide exposure

The areas of oxidative stress have received intensive investigation by the biomedical community in recent years. These studies have elucidated endogenous and xenobiotic-mediated mechanisms of reactive oxygen specie (ROS) and reactive nitrogen specie (RNS) production, antioxidant defense mechanisms and deleterious consequences of oxyradical fluxes that outstrip detoxification pathways. Oxidant-mediated effects include adaptive responses (such as increased activities of antioxidant enzymes) and oxidant-mediated toxicities (such as oxidations of proteins, lipids, nucleic acids and disrupted tissue redox status). Oxidative stress in the context of pesticide metabolism is briefly reviewed here and specific biochemical responses to examples of pesticides with relevance to some common diseases are discussed.

3.1 Overview of oxygen toxicity and antioxidant defenses

Oxidative stress is caused by an imbalance between the production of reactive oxygen and the ability to: (1) detoxify the reactive intermediates produced or (2) repair the resulting damage. Ultimately, oxidative stress conveys the biomolecular alteration in cellular function caused by the reaction of reactive species with cellular constituents. Reactive oxygen species (ROS) include oxygen (O_2)-derived free radicals (defined as molecules with one or more unpaired electrons in an outermost valence shell) such as superoxide anion ($\bullet O_2^-$) and the hydroxyl radical ($\bullet OH$), as well as nonradical derivatives of O_2 such as hydrogen peroxide (H_2O_2). ROS production is the result of an aerobic environment. A significant amount of O_2 consumed by mitochondria is converted to $\bullet O_2^-$, although it can be produced through various enzymatic oxidation reactions catalyzed by cytochrome P450 (phase I detoxifying enzymes), other oxidoreductases and also by nicotinamide adenine dinucleotide phosphate)-oxidase (NADPH oxidase). $\bullet O_2^-$ reacts at diffusion-controlled rates with nitric oxide ($\bullet NO$) produced by $\bullet NO$ synthases (NOS) leading to the formation of a wide diversity of oxidizing and nitrosating/nitrating species such as peroxynitrite ($ONOO^-$) (Fig. 3). $\bullet O_2^-$ is also dismutated non enzymatically or
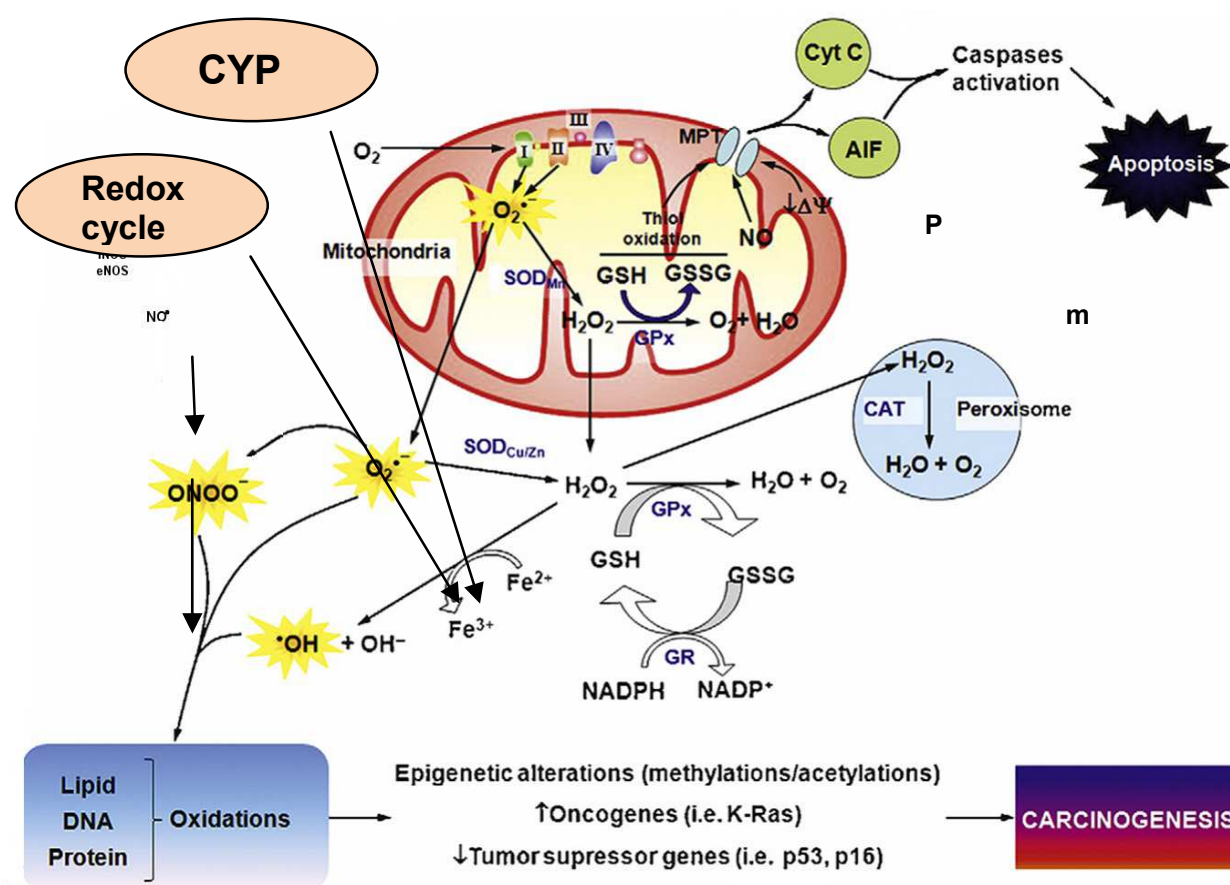
Fig. 3. Pesticides promote oxidative stress leading to cell death or procarcinogenic mutations. This figure schematically illustrates the complex molecular network activated different pesticides. Abbreviations used are: AIF, apoptosis-inducing factor; CAT, catalase; CYP, Cytochrome P450; CytC, cytochrome C; eNOS, endothelial nitric oxide synthase; GSH, glutathione; GSSG, glutathione disulphide; iNOS, inducible nitric oxide synthase; MPTP, mitochondrial permeability transition pore; SODCu/Zn, copper/zinc-type superoxide dismutase; SODMn, mangano-type superoxide dismutase; GPx, glutathione peroxidase; GR, glutathione reductase; $\Delta\Psi$m, mitochondrial transmembrane potential (Adapted from Mena et al., 2009, with modification).

enzymatically with the aid of superoxide dismutases (SODs) to hydrogen peroxide (H_2O_2). H_2O_2 can be also utilized by myeloperoxidases (MPO) to produce hypochlorous acid and other noxious chlorine-derived oxidants. Furthermore, H_2O_2 can be reduced to $\bullet OH^-$ through Fenton type reactions (Fig. 3). Thus it is clear that the formation of a reactive species can ultimately lead to an amplification chain generating other more toxic reactive species. Cells have intrinsic antioxidant mechanisms to detoxify ROS generated under both physiological and pathological conditions. Reduced glutathione (GSH) is the most important antioxidant molecule in the cell, and due to its high cytosolic concentration, it can directly scavenge ROS such as $\bullet O_2^-$, $\bullet OH$ and $\bullet NO$. H_2O_2 is reduced to H_2O by GSH peroxidases (GPX) and catalase (CAT). The GSH reductase (GR) and thioredoxin (Trx)/thioredoxin reductase systems regenerate cellular GSH or reduced Trx, respectively, at the expense of NADPH (Fig. 3). Other antioxidant molecules (such as ascorbate or

Pesticides in the Modern World
– Pests Control and Pesticides Exposure and Toxicity Assessment
308

vitamin E) and enzymes (such as peroxiredoxins) are important defenses against oxidative stress. Oxidative stress arises if detoxification systems and antioxidants are compromised or if ROS production is excessive, resulting in DNA, protein, and lipid oxidation (Fig. 3) (Franco et al., 2009, 2010; Ryter et al., 2007). Oxidative damage to DNA leads to the formation of lesions such as 8-oxo-deoxyguanosine, 8-oxo-deoxyadenosine, and deoxythymidine glycol which are selectively excised from DNA by DNA glycosylases. Lipid peroxidation refers to the oxidative degradation of lipids. Lipid peroxidation is initiated through a radical-mediated abstraction of a hydrogen atom from polyunsaturated fatty acids to make water and a fatty acid radical. Lipid peroxyl radicals (LOO•) are formed by the reaction of free fatty acid radicals with oxygen that subsequently reacts with another free fatty acid producing a different fatty acid radical and a lipid peroxide propagating the damage. Lipid peroxidation generates a number of lipid hydroperoxide products such as malondialdehyde, 4-hydroperoxy-2-nonenal, 4-oxo-2-nonenal and 4-hydroxy-2-nonenal (4HNE). These aldehyde products react with individual nucleotides and nucleophilic amino acids, thus inducing several signaling effects (West & Marnett, 2006). Oxidative protein modifications have been shown to regulate the activity of a wide variety of proteins such as kinases, phosphatases, proteases (caspases), molecular adaptors and chaperones, and transcription factors. Amino acids such as cysteine, methionine, tryptophan, and tyrosine residues are prone to specific oxidative modification. Oxidative protein modifications in general can be classified as reversible and irreversible. Highly reactive oxidant species such as hypochlorous acid, $ONOO^-$, and •OH are thought to oxidize biomolecules leading to the irreversible formation of, for example, 3-nitrotyrosine and protein carbonyls. Physiological oxidants such as •NO, •O_2^- and H_2O_2, have been implicated in reversible protein modifications at the cysteine level (nitrosylation, hydroxylation, glutathionylation, disulfide bond formation) that underlie homeostatic control and diverse biological responses. A wide variety of enzymes regulate these post-translational modifications including sulfiredoxins, thioredoxins, glutaredoxins and methionine sulfoxide reductases (Dalle-Donne et al., 2008; Janssen-Heininger et al., 2008).

Pesticides are known to induce oxidative stress by: (1) the induction of reactive oxygen species (ROS) as byproducts of detoxifying metabolism, (2) alterations in the mitochondrial respiration or (3) by their own redox (reduction/oxidation) cycling properties per se. In the redox cycle, the parent compound typically is the first enzymatically reduced by a NADPH-dependent reductase (such as NADPH-cytochrome P450 reductase) to yield the pesticide radical. This radical donates its unshared electron of O2, yielding (•O2-) and the parent compound. The latter can undergo another cycle. At each turn of the cycle, therefore, two potentially deleterious events have occurred: a reductant has been oxidized and an oxyradical has been produced.

3.2 Oxidative stress and cell death
3.2.1 Types of cell death
It is well known that environmental toxicants exert their toxicity, at least in part, by triggering cell death. Cell death is classified by biochemical and morphological criteria. According to the recommended classification of cell death (Kroemer et al., 2009), three distinct types of cell death pathways can be defined according to morphological criteria which are necrosis, apoptosis and autophagy, although there are numerous examples in which cell death displays mixed features.

Necrotic cell death is characterized by a gain in cell volume, swelling of organelles, plasma membrane rupture and subsequent loss of intracellular contents. It is now recognized that execution of necrotic cell death may be regulated by a series of signal transduction pathways and catabolic processes (Kroemer et al., 2009).

Autophagy is a major catabolic pathway by which eukaryotic cells degrade and recycle macromolecules and organelles, leading to cell survival. It plays an essential role in differentiation and development, as well as in cellular response to stress. Autophagy can be activated during amino acid deprivation and has been associated with neurodegenerative diseases. Autophagy is initiated by the surrounding of cytoplasmic constituents by the crescent-shaped isolation membrane/phagophore, which forms a closed double membrane structure, called autophagosome. The autophagosome subsequently fuses with a lysosome to become an autolysosome, and its content is degraded by acidic lysosomal hydrolases. When autophagy is prolonged, this could lead to cell death. Autophagic cell death is morphologically defined by massive autophagic vacuolization of the cytoplasm in the absence of chromatin condensation (Kroemer et al., 2009).

Apoptosis, or programmed cell death, is an evolutionary conserved homeostatic mechanism involved in a variety of biological processes. Under physiological conditions, apoptosis is important not only for the constant turnover of cells in all tissues but also during the normal development and senescence of the organism. Apoptosis is a highly organized process characterized by the progressive activation of precise signaling pathways leading to specific biochemical and morphological alterations. Initial stages of apoptosis are characterized by cell shrinkage, loss of membrane lipid asymmetry and chromatin condensation, while later stages are associated with the activation of execution caspases (cysteine-dependent aspartate-directed proteases) and endonuclease, apoptotic body formation and cell fragmentation Galluzzi et al., 2007; Hengartner, 2000). Both extrinsic and intrinsic pathways have been described for the activation of apoptosis. Induction of apoptosis via the extrinsic pathway is triggered by the activation of death receptors leading to the formation of the death-inducing signaling complex (DISC) by the recruitment of the Fas-associated death domain (FADD) and initiator caspase 8. Death receptor-induced apoptosis is amplified by cleavage of the B-cell lymphoma 2 (Bcl-2) family protein Bid by caspase 8, which triggers the mitochondrial pathway of apoptosis (Barnhart et al., 2003; Khosravi-Far & Esposti, 2004) (Fig. 4). The intrinsic pathway of apoptosis, also referred to as the mitochondrial pathway, is activated by a wide variety of cytotoxic stimuli or environmental stressors. Although the mechanisms by which these stimuli trigger apoptosis differ between them, they convey the opening of mitochondrial permeability transition pores (MPTP) that mediates the disruption of the mitochondrial transmembrane potential ($\Delta\Psi$m) and the release of pro-apoptotic proteins from the mitochondria including cytochrome C (Fig. 3 & Fig. 4).

However, the exact mechanisms mediating cytochrome C release are still controversial (Franco et al., 2010). Distinct mitochondrial components and mitochondrial released proteins such as apoptosis inducing factor (AIF), endonuclease G (EndoG), adenine nucleotide translocase (ANT), cyclophilin D, Bit1, p53-regulated Apoptosis Inducing Protein 1 (p53AIP), gene associated with retinoic-interferon-induced mortality 19 (GRIM-19), death associated protein 3 (DAP3), Nerve Growthfactor IB (Nur77/TR3/NGFB-1), HtrA serine peptidase 2 (HtrA2)/ second mitochondria-derived activator of caspases (Omi and Smac)/Diablo have been proposed to participate in the mitochondrial pathway to apoptosis (Ekert & Vaux, 2005). The intrinsic pathway is also regulated by the Bcl-2 family of proteins.
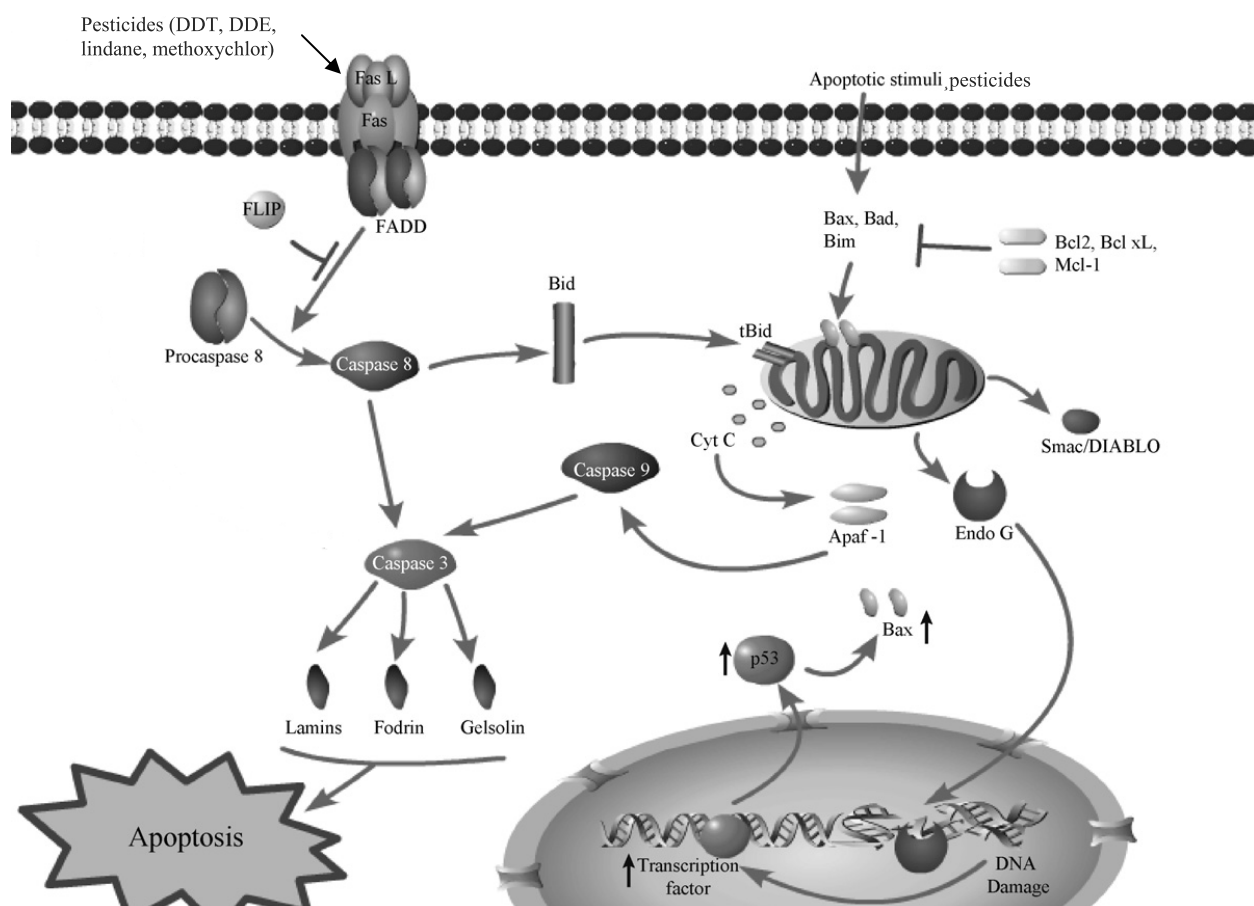
Fig. 4. A schematic diagram shows the various molecular components involved in the extrinsic and the intrinsic pathways of apoptosis. Two pathways are represented. The intrinsic pathway involving the mitochondria and the extrinsic pathway with the Fas/FasL with their corresponding downstream regulators are shown. The substrates of caspase 3, including lamins, fodrin and gelsolin are indicated as these are the primary components that are acted upon by caspase 3 leading to fragmentation of the cell. The activation of p53 after DNA damage is shown (Adapted from Tripathi et al., 2009, with modification)

The Bcl-2-associated death promoter (Bad), Bcl-2-interacting domain (Bid), Bcl-2-interacting killer (Bik), NOXA, and p53 upregulated modulator of apoptosis (PUMA) regulate the anti-apoptotic Bcl-2 proteins : Bcl-2 and B-cell lymphoma-extra large (Bcl-xl) to promote apoptosis. Bcl-2 and Bcl-xl inhibit Bcl-2–associated X protein (Bax) and Bcl-2 homologous antagonist/killer (Bak) by direct binding and inhibition of Bcl-2 and other anti-apoptotic family members. Bax and Bak are known to mediate the release of cytochrome C. Released cytochrome C leads to the recruitment of the apoptotic protease activating factor 1 (APAF1) into the apoptosome and activation of caspase-9 (Ravagnan et al., 2002; Youle & Strasser, 2008) (Fig. 4). Once activated, initiator caspases converge in the cleavage/activation of execution caspases 3, 6 and 7 which further cleave different cellular substrate leading to the organized demise of the cell. A wide variety of enzymes such as protein kinases, phosphatases, calpains, transcription factors and several other adaptor or scaffolding proteins have been described to participate in several pathways of apoptosis in distinct ways (Saelens et al., 2004; Youle & Strasser, 2008). Other intrinsic pathways of apoptosis, such as endoplasmic reticulum (ER) stress and DNA damage, have been described, which can be dependent or independent from the mitochondrial pathway. The ER is highly

sensitive to stressors that perturb cellular energy levels, the redox state and/or Ca^{2+} concentration. Such stress results in the accumulation and aggregation of unfolded proteins which are toxic to cells. ER stress leads to the activation of the stress-activated protein kinase (SAPK), c-Jun N-terminal kinases (JNK) and induction of C/EBP homologous protein (CHOP), which by impairment of the anti-apoptotic function of Bcl-2, lead to the activation of Bim, Bax and Bak, transmission of the signal from the ER to the mitochondria and execution of death by activation of caspases (Boyce & Yuan, 2006; Szegezdi et al., 2006). DNA damage is also known to trigger apoptosis. Blockage of DNA replication associated with DNA damage leads to the activation of p53 which induces the transcriptional activation of pro-apoptotic factors. However, non-transcriptional regulation of apoptosis by p53 and p53-independent pathways have also been described (Roos & Kaina, 2006).

3.2.2 Oxidative stress and apoptosis

Although oxidative stress has been largely linked to the activation of distinct apoptotic enzymes, the direct mechanisms involved have remained largely elusive. Oxidative stress-induced apoptosis has been largely associated to the activation of the intrinsic pathways of apoptosis at the level of the mitochondria. One important target of ROS is the mitochondrial DNA (mtDNA) due to the close proximity to the electron transport chain and the lack of protective histones. Oxidative mtDNA damage induced by ROS leads to lethal cell injury due to mitochondrial genomic instability leading to respiratory dysfunction through the disruption of electron transport, mitochondrial membrane potential, and ATP generation. ROS in the mitochondria can also directly oxidize and inactivate proteins such as mitochondrial aconitase and complex I NADH oxidase leading to further ROS overload. Lipid peroxidation at the level of the mitochondria also impairs mitochondrial metabolism and induction of the mitochondrial permeability transition pores (MPTP) (Ott et al., 2007). In addition, oxidative reactions causing glutathione (GSH) exhaustion, followed by thiol oxidation would favor MPTP opening (Marchetti et al., 1997). Similarly, loss of GSH *via* non oxidative mechanisms, as in the case after Fas-cross-linking, might indirectly favor this induction of MPTP (Vandendobberlsteen et al., 1996). However, the relationship between MPTP and thiol redoxidation processes is probably not unilateral. Thus, MPTP itself affects cellular GSH levels. Due to its uncoupling effect on the respiratory chain, MPTP causes an immediate depletion of reduced $NADH_2/NADPH_2$, which, in turn, causes the oxidation of mitochondrial and cytosolic GSH *via* the glutathione peroxidase reaction (Hoek & Rydström, 1988). Moreover, one consequence of MPTP is uncoupling of the respiratory chain with hyperproduction of superoxide anions, which would favor GSH depletion (Zamzami et al, 1995). This depletion can be prevented by Bcl2, which functions as an endogenous inhibitor of MPTP induction and thus acted as an antioxidant (Hockenberry et al., 1993). Finally, cytochrome C which is bound to the inner mitochondrial membrane by an association with the anionic phospholipid cardiolipin has been shown to be released *via* oxidation of cardiolipin during apoptosis which precedes its release to the cytosol (Ott et al., 2007). ROS and RNS have been shown to directly trigger the activation of distinct signaling cascades induced by ER stress including activation of JNK and dissociation of the tumor necrosis factor receptor-associated factor-apoptosis signal-regulating kinase1 (TRAF2–ASK1) complex, transcriptional activation of CHOP, and caspase activation (Fig. 5). Protein disulfide isomerase (PDI) which is the most abundant chaperone in the ER facilitates the folding and disulfide bond formation of its protein substrates. PDI is regulated not only by post-translational oxidative modifications (nitrosylation and glutathionylation) but also by the ER oxidase (ERO1), which restores reduced PDI to an oxidized state through disulfide exchange with ERO1. ERO1 activity is also
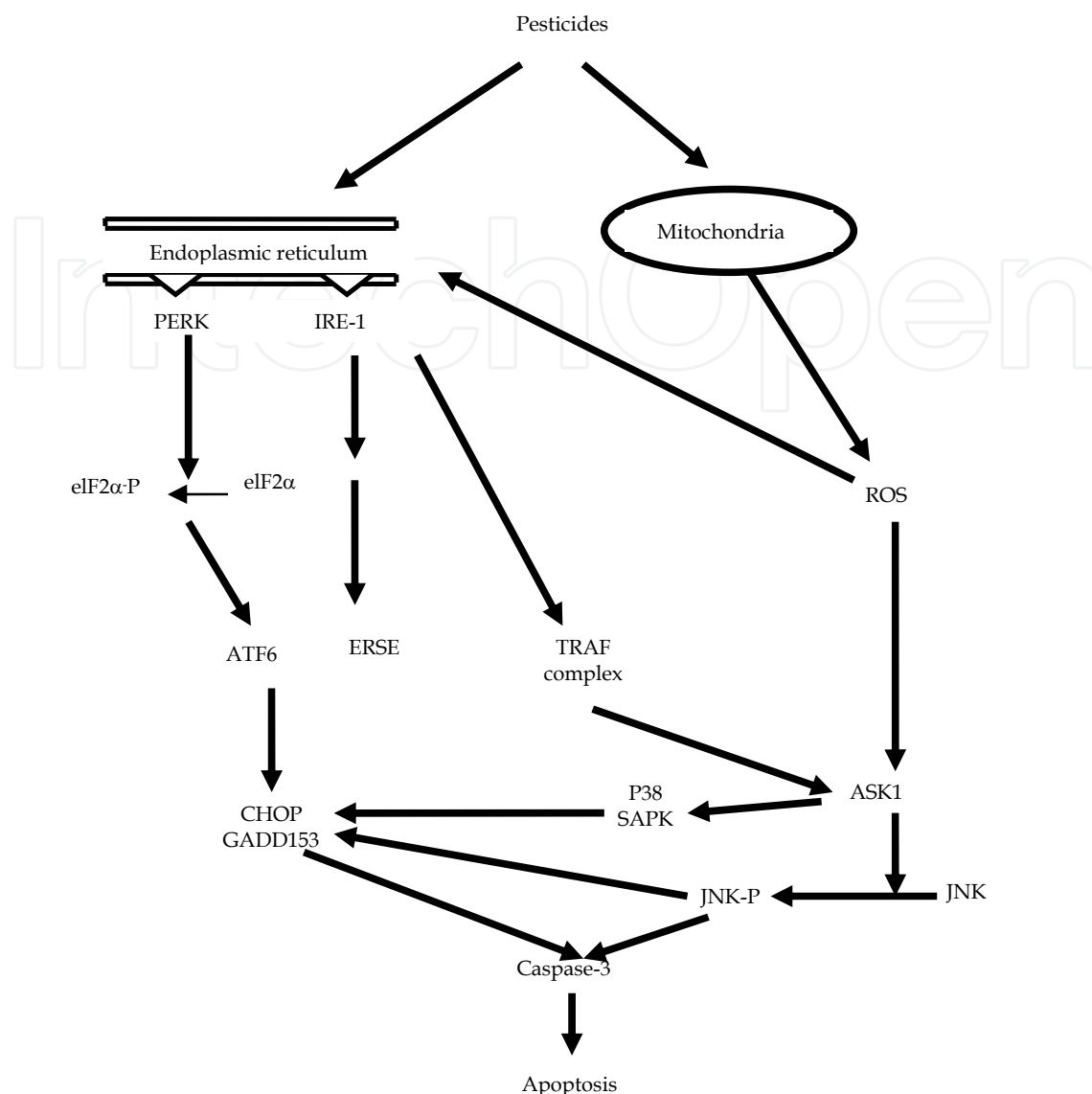
Fig. 5. Oxidant and ER stress pathways involved in apoptosis. Abbreviations used are: ASK, apoptosis signal-regulating kinase; ATF, activating transcription factor; CHOP, C/EBP homologous protein; elF2α, eukaryotic initiation factor 2α; ERSE, endoplasmic stress response element; GADD, growth arrest and DNA damage; IRE, inositol-requiring ER-to-nucleus signal kinase; JNK, c-jun N-terminal kinase; PERK, protein kinase-like ER kinase; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; TRAF, tumor necrosis factor receptor-associated factor (Adapted from Katsoulieris et al., 2010, with modification).

regulated through modulation of non catalytic cysteine residues and has been shown to be inhibited under oxidized conditions in the ER (Townsend, 2007). Redox imbalance in the ER lumen is the most frequent cause of ER stress-induced apoptosis, which involves the impairment of oxidative protein folding, the accumulation of unfolded/misfolded proteins in the lumen and the initiation of the unfolded protein response (UPR). In the ER, changes in the luminal redox state are sensed by secretory proteins to be folded (via ER chaperone Bip),

and also directly by transmembrane proteins involved in signaling such as activating transcription factor 6 (ATF6) (Fig. 5).

Several antioxidant protective systems such as glutathione, ascorbate, flavin adenine dinucleotide (FAD), tocopherol and vitamin K exist in the ER. Formation of disulfide bonds is required for the proper folding of secretory and membrane proteins in the ER and thus, redox imbalance leads to the accumulation of unfolded/misfolded proteins in the ER lumen. Redox-sensitive thiols in the ryanodine receptor calcium channel are also targets for oxido-reduction that regulates the open probability of the channel. More recently, the InsP3 receptor (InsP3R) has also been demonstrated to be regulated by ER luminal redox status through a direct interaction with ERp44, a thioredoxin family member (Banhegyi et al., 2007).

Thiram chemicals have been reported to induce GSH depletion which is paralleled by protein carbonylation, lipid peroxidation and subsequent apoptotic cell death (Grosicka et al., 2005). Carbamate derivatives such as mancozeb and pyrethroids such as cyermethrin have also been shown to induce oxidative stress, DNA damage and activation of the mitochondrial pathway of apoptosis (Calviello et al., 2006; Jin et al., 2011).

3.2.3 Oxidative stress and autophagy

Interaction mechanisms between autophagy and oxidative stress induction are still not clear. It was demonstrated that ROS can induce autophagy through several distinct mechanisms involving autophagic gene 4 (Atg4), catalase, and the mitochondrial electron transport chain (mETC). This leads to both cell survival and cell death responses. $\cdot O_2^-$ is the major ROS regulating autophagy (Chen et al., 2009). Recent studies provide strong evidences for the involvement of mitochondrially-generated ROS production in the induction of autophagy (Chen & Gibson, 2008; Chen et al., 2009). Recently, it has been demonstrated that targeting mETC complex I by rotenone, induces autophagic cell death through a ROS-mediated mechanism (Chen et al., 2007).

3.2.4 Oxidative stress and necrosis

Exposure to oxidants causes multiple intracellular alterations, including elevation of cytosolic Ca^{2+}, depletion of ATP, oxidation of NADH, reduced glutathione (GSH) and lipids (Slater et al., 1995). Necrosis is the characteristic end point of such a dramatic disturbance in cell homeostasis. Many studies have demonstrated that raising the concentration of the oxidant was observed to shift the form of cell death away from apoptosis towards necrosis, probably via a rapid ATP and GSH depletion induced by acute oxidant doses (Orrenius, 1993; Slater et al., 1995). Inhibition of caspase activity or transient inhibition of the production of caspase can switch cells from an apoptotic to necrotic death mode (Nicotera & Melino, 2004). Cells with low levels of Bcl-xL die by apoptosis, whereas high levels of Bcl-xL can induce necrotic cell death (Abdelhaleem, 2002). Cell lysis seems to be a more prominent route of cell death when apoptosis is defective, presumably due to the limited options by which a cell has to die (Degenhardt et al., 2006). Autophagy can delay cell death by apoptosis in response to metabolic stress. Moreover, cells with defective apoptosis, and in which the autophagic pathway is disrupted, are forced to die by necrosis when stressed (White, 2008). Recently, it has been shown that lindane disrupts the autophagic pathway and inhibits spontaneous apoptosis, leading to necrosis in primary cultured rat hepatocytes (Zucchini-Pascal et al., 2009).

4. Oxidative stress-mediated cell death/survival of pesticides: relevance to common diseases

The majority of cases of diseases are not inherited and thus it has been proposed that a complex array of environmental factors and gene interactions might exert synergetic effects toward the predisposition to sporadic diseases. In this section, we will focus on the pesticide-induced oxidative stress as possible mechanism involved in the regulation of death/survival signaling pathways in cells due to their relevance to some diseases.

4.1 Cancer

It is generally accepted that ROS eventually cause DNA damage. In addition phase I pesticide detoxifying enzymes generate electrophilic compounds like carcinogenic epoxides, whereby insufficient cellular repair mechanisms may contribute to premature aging and apoptosis. Conversely, ROS-induced imbalances of the signaling pathways for metabolic protein turnover may also result in opposite effects to recruit malfunctioning aberrant proteins and compounds that trigger tumorigenic processes (Wang, 2008). Consequently, DNA damage plays a role in the development of carcinogenesis, but is also associated with an aging process in cells and organisms (Bertram & Hass, 2008). Hence, additional actions of ROS must be important, possibly their effects on p53, cell proliferation, invasiveness and metastasis. Chronic inflammation predisposes to malignancy, but the role of ROS in this is likely to be complex because ROS can sometimes act as anti-inflammatory agents (Halliwell, 2007). The mutagenic origin of cancer may be due, in some cases, to exposition to different carcinogens present in our environment (Claxton & Woodall, 2007). These mutations can affect genes of relevant xenobiotic metabolizing enzymes, produce polymorphisms leading to altered ligand affinity and activity, or influencing the expression of downstream target genes (Dong et al., 2008). Besides, although polymorphisms in oxidative stress-related genes (e.g. mangano-type superoxide dismutase, catalase, or glutathione peroxidase) may not be directly associated with cancer risk, it is possible that accumulative defects in protection from oxidative stress may result in increased risk of the disease (Ryter et al., 2007).

Piperonyl butoxide (PBO), is a pesticide widely used along with pyrethroids as grain protector and domestic insecticide (Muguruma et al., 2007). PBO is capable of increasing the gene expression of *CYP1A1*, a cytochrome P-450 isoform and the most active enzyme catalyzing procarcinogens (Canistro et al., 2002). PBO has a liver-tumor-promoting effect increasing production of ROS as a byproduct of hepatic microsomal oxidation in mice (Muguruma et al., 2007). The increase of ROS is due to PBO-induced regulation of glutathione reductase (GR), NADPH: quinone oxidoreductase 1 (NQO_1), and other antioxidant enzymes. This regulation is under the nuclear factor erythroid 2 p45-related factor 2 (Nrf2) (Ellinger-Ziegelbauer et al., 2005). NQO_1 that detoxifies quinones and thus decreases ROS formation (Yang et al., 2005), has been found within solid tumors of the breast, ovary, lung, colon, thyroid, and adrenal gland in an elevated concentration (Siegel & Ross, 2000). Organochlorine pesticides like DDT and dieldrin, are persistent organic pollutants that may accumulate in the environment and food. They are lipophilic and can be detected, after ingestion, in human breast milk and adipose tissue (Cok et al., 1997; Malarvannan et al., 2009). They are particularly harmful during pregnancy (these compounds cross the placenta and reach the fetus blood) and after birth (neonates are exposed through the breast milk) (Perera et al., 2005). These pesticides induce hepatic cell proliferation and are known as non genotoxic hepatocarcinogens (Stevenson et al., 1999).

4.2 Parkinson's disease

Parkinson's disease (PD) is characterized by abnormalities of motor control such as resting tremors, bradykinesia (slowness of voluntary movement), rigidity, and a loss of postural reflexes. A number of epidemiologic studies have found an association between PD and exposure to pesticides. Furthermore, increased levels of pesticides have been found in brains of PD cases versus controls. Contradictory studies have also been published demonstrating no association between PD and pesticide exposure (Brown et al., 2006; Hatcher et al., 2008; Landrigan et al., 2005). It is clear now that PD is a multi-factorial disease with a complex etiology including genetic risk factors, environmental exposure and aging (Benmoyal-Segal & Soreq, 2006; Palomo et al., 2004). Nevertheless, the study of neurotoxic properties of paraquat, diquat, maneb (Meco et al., 1994; Zhang et al., 2003), rotenone (Coulom & Birman, 2004; Hartley et al., 1994), glyphosate pesticides (Negga et al., 2011) and organochlorine pesticides (DDT and dieldrin) (Fleming et al., 1994), has provided valuable information regarding the potential mechanisms involved in the progression of neurodegeneration associated with environmental toxicity. Parkinson's disease (PD) is characterized by a selective degeneration of dopaminergic neurons in the *substantia nigra* (SN) *pars compacta* attributed to the toxic accumulation and aggregation of proteins, mitochondrial dysfunction and oxidative stress. The occurrence of oxidative stress has been observed in the SN of PD brains as evidenced by increased lipid, protein, and DNA oxidation, increased total iron content, and significant decreases in GSH and GSH/glutathione disulfide (GSSG) ratio (Mattson, 2006). The main pathway of cell toxicity in PD involves misfolding and aggregation of α-synuclein (Okouchi et al., 2007). Failure of α-synuclein clearance by the ubiquitin-proteasome system (UPS) leads to its accumulation over time and to the formation of fibrillar aggregates and Lewy bodies. α-Synuclein protofibrils can directly lead to oxidative stress that can further impair the UPS by reducing ATP levels, inhibiting the proteasome, and by the oxidation of parkin. Exposure to paraquat maneb rotenone and dieldrin has been shown to induce proteasome dysfunction and α-synuclein aggregation (Barlow et al., 2005; Ding & Keller, 2001; Fei et al., 2008; Sun et al., 2005; Zhou et al., 2004). Furthermore, paraquat has been shown to potentiate α-synuclein-induced toxicity (Norris et al., 2007). It has been hypothesized that mutated α-synuclein induces a reduction in vesicle number and the accumulation of cytoplasmic dopamine in association with enhanced ROS generation and initiation of the apoptotic cascade (Wood-Kaczmar et al., 2006). In the cytosol, dopamine is metabolized by monoamine oxidase which generates H_2O_2, or is auto-oxidized generating $\bullet O_2^-$, H_2O_2 and dopamine-quinone species (Abou-Sleiman et al., 2006). In the brain, specific cell types have been reported to express cytochrome P450 enzymes. The presence of cytochrome P450 enzymes in the brain should also be important in inducing bioactivation and cellular damage of pesticides. Many results support the possibility of a local metabolism of pesticides and other pollutants in the brain by cytochrome P450 enzymes into neurotoxic compounds, suggesting that brain metabolism could be a factor modulating the individual susceptibility to Parkinson's disease during pesticide exposure. Moreover, the involvement of mitochondrial superoxide in the neurodegenerative process is demonstrated. Recently, paraquat, maneb and dieldrin was reported to act at the level of complex III to generate ROS, whereas rotenone inhibit electron flow through complex I (Castello et al., 2007; Drechsel & Patel, 2009). It is clear that oxidative stress is a central player in the regulation of paraquat-induced neuronal cell death. The ability of paraquat to cause oxidative damage through a free radical mechanism may explain the selective vulnerability of dopaminergic neurons which are highly susceptible to oxidative damage

due to the pro-oxidant properties of dopamine. Interactions with glial cell types play a role in potentiating or reducing oxidative stress (Vogt et al., 1998). Paraquat has been reported to induce necrosis when injected into different areas of the rat brain. However, this effect might be observed just at high doses (Calo et al., 1990). Neurons from patients with PD display characteristics of autophagy. Recent studies have demonstrated that low concentrations of paraquat induce autophagy which is followed by apoptosis. Because inhibition of autophagy potentiated apoptosis induced by paraquat, it was proposed that autophagy might be acting as a protective mechanism against cell death progression (Gonzalez-Polo et al., 2007). Neurodegenerative diseases are most commonly associated with selective neuron loss by apoptosis. Paraquat-induced neural cell death has been demonstrated to involve primarily the activation of apoptosis (Franco et al., 2010). In PD, cell death by apoptosis has been proposed to result from mitochondrial dysfunction, leading to an increase in oxidative stress and a decline in ATP production. Paraquat and rotenone induce cytochrome C release (Ahmadi et al., 2003; Fei et al., 2008) and caspase-9 activation, which are preceded by the induction/activation of pro-apoptotic Bax and Bak (Fei et al., 2008; Yang & Tiffany-Castiglioni, 2008). Induction of pro-apoptotic Bax and apoptosis in response to paraquat have also been reported to be dependent on p53 (Yang & Tiffany-Castiglioni, 2008). Paraquat neurotoxicity has also been recently reported to require the activation of stress activated protein kinases (SAPK) (Niso-Santano et al. 2010; Yang et al., 2009). Interestingly, exposure to maneb enhances Bax-dependent cell death through an increased induction of Bax-activators Bik and Bim (Fei & Ethel, 2008). Dieldrin has been shown to induce apoptosis *via* GSH depletion and oxidative stress, triggering the intrinsic mitochondrial apoptotic pathway (Kitazawa et al., 2004). Dichlorodiphenyltrichloroethane (DDT) derivatives have been shown to induce neural cell death by apoptosis through the activation of mitogen-activated protein kinases (MAPKs) (Shinomiya & Shinomiya, 2003). Recently, paraquat and rotenone have been shown to induce DNA damage and ER stress. ER stress was associated with the activation of the inositol-requiring enzyme 1 (IRE1), apoptosis signal regulating kinase 1 (ASK1), and JNK (Niso-Santano et al. 2010; Yang et al., 2009). Rotenone has also been reported to trigger ER stress via the activation of the PKR-like ER kinase (PERK) (Ryu et al., 2002). Rotenone has been demonstrated to induce activation of the glycogen synthase kinase 3 (GSK-3), JNK and p38 kinases, whose activity seems to be required for the progression of apoptosis (Newhouse et al., 2004).The molecular mechanisms linking paraquat-induced oxidative stress and neural apoptosis are still largely elusive. Recently, paraquat-induced oxidation of Trx has been reported as a possible mechanism for the activation of the ASK1/JNK signaling pathways. Accordingly, Nrf2-dependent regulation of Trx levels determines the sensitivity of paraquat toxicity by activation of the ASK1/JNK p38 signaling (Niso-Santano et al. 2010). Paraquat-induced tyrosine nitration and lipid peroxidation (4HNE) have been recently demonstrated (McCormack et al., 2005). However, the molecular targets for these signaling events remain to be elucidated. It was recently demonstrated that oxidative stress induced by paraquat generates protein aggregation of the plasma membrane Ca2+-ATPase (PMCA) and its degradation by calpain (Zaidi et al., 2009).

4.3 Reproductive disorders

A scientific finding on human reproduction showed that infertility may affect 15–20% of couples in industrialized countries (Oehninger, 2001) compared to 7–8% during early 1960s. The concern over decreased sperm count and male reproductive capacity was triggered by a

report of Carlsen et al. (1992) on the meta-analysis of 61 sperm count studies which showed a nearly 50% decrease in sperm counts between 1940 and 1990 worldwide and this decrease amounts to about two percent per year over the last two decades (Auger et al., 1995). The full mechanism of male infertility is poorly understood. The testis is one tissue where a large incidence of apoptosis occurs to discard excessive germ cells, or whereby germ cells damaged by toxins are removed (Hikim et al., 2003). Few studies have been conducted on pesticide-induced cell death in reproductive tract. Song et al. (2008) showed that p,p'-DDE could activate apoptosis of cultured rat Sertoli cells in a pro-oxidant and mitochondria-dependent manner by activating the intrinsic programmed cell death pathway. The same authors have demonstrated also that p,p'-DDE increased the apoptotic rate of isolated Sertoli cells (Shi et al., 2009) and germinal cells *in vivo* (Shi et al., 2010), by a mechanism possibly involving FasL-dependent pathway. Exposure to p,p'-DDE can enhance ROS and oxidative stress, then induce activation of Fas-FasL. Consequently, an intrinsic program of apoptotic death is stimulated in a target cell leading to the activation of caspase 8. Finally, apoptosis of Sertoli cells and germinal cells is mediated by a terminal executioner, caspase 3, thereby disturbing the spermatogenic process (Shi et al., 2010). More recently, p,p'-DDE has also been reported to induce Sertoli cell apoptosis via p38 MAPK pathway (Song et al., 2011). Similarly, lindane and methoxychlor have been shown to induce testicular apoptosis in rats through the involvement of Fas-FasL and mitochondria-dependent pathways (Saradha et al., 2009; Vaithinathan et al., 2010). These data provided additional mechanisms explaining pesticide-induced endocrine disruption. However, there's a striking lack of data concerning pesticide-induced cell death in females.

4.4 Immune dysfunction

It is important to remember that apoptosis plays a variety of important roles under normal physiological conditions, but when it is out of regulation, apoptosis can contribute to several diseases as immunodeficiency, autoimmunity diseases and cancer. It seems evident that the uncontrolled elimination of immune cells may account for immunosupression or immune dysregulation (Gougeon et al., 1996). In a previous study, we have reported the induction of apoptosis in rat thymocytes exposed for 6 hours to p,p'-DDT at a concentration of 7 µg/mL (20 µM/mL) (Tebourbi et al., 1998). As shown in Fig. 6, DNA fragmentation is negligible in thymocytes immediately after isolation and for control cells after 6 hours of incubation in free medium, whereas thymocyte exposure to DDT resulted in a DNA ladder, typical of apoptosis, similar to that observed in dexamethasone (DEXA)-treated cells. Furthermore, as for DEXA, DDT fragmentation induced by DDT is inhibited by zinc (1mM) which is known as an antioxidant. This result suggests the involvement of oxidative stress mechanism in the apoptotic action of DDT. By this apoptotic effect, DDT could have a profound immunotoxic action similar to that caused by corticosteroid hormones (Tebourbi et al., 1998). Pérez-Maldonado et al. (2004) have demonstrated that *in vitro* o'p-DDT, p'p-DDT, p'p-DDE and p'p-DDD are able to induce apoptosis of human peripheral blood mononuclear cells (PBMC), through the production of reactive oxygen species (Pérez-Maldonado et al., 2005). Furthermore, a preliminary association between the percentage of apoptotic cells and the levels of DDT and its metabolites in blood of exposed children was reported in a pilot study (Pérez-Maldonado et al., 2006).

Organophosphorus pesticides induce apoptosis in immune cells *via* the mitochondrial pathway (Das et al., 2006; Saleh et al., 2003). Chlorpyrifos and dichlorvos have been shown

to induce caspase-dependent apoptosis associated to oxidative stress. This apoptosis was detected in human natural killer lymphocytes (Li, et al., 2007), in human T cells (Li et al., 2009) and in human monocyte cell line (Nakadai et al., 2006). Recently, phosphamidon and endosulfan have been shown to induce apoptosis of human peripheral blood mononuclear cells *via* cytochrome C release. Coadministration of the antioxidants N-acetylcysteine, which enhances GSH synthesis, attenuated phosphamidon-induced apoptosis. This work supports the hypothesis that oxidative stress, as indicated by GSH depletion, results in the induction of apoptosis by release of cytochrome C (Ahmed et al., 2008; Ahmed et al., 2010).

Fig. 6. Agarose gel analysis of DNA samples obtained from thymocytes not incubated (lane a) and incubated 6 hours in control medium (lane b), medium containing 10^{-5} M DEXA (lane c), 1 mM zinc (lane d), 10^{-5} M DEXA plus 1 mM zinc (lane e), 2.10^{-5} M DDT (lane f), 2.10^{-5} M DDT plus 1 mM zinc (lane j), 1 Kb molecular weight DNA marker (lane M) (Tebourbi et al.; 1998).

5. Conclusion

Through food, water and air, humans are exposed daily to a diversity of pesticides, which are new to the cellular detoxification system and may present a hazard to health. As described in this chapter, many problems may arise upon exposure to pesticides, for example endocrine disruption and oxidative stress. Indeed, it is alarming that, while the manufacture and use of pesticides has drastically increased during the last decades, the incidence of hormone/oxidative stress-related diseases, such as cancers of breast and prostate and neurodegenerative diseases, has increased markedly all over the world. Moreover, the difficulty of identifying receptor-mediated human health hazards based on *in vitro* methodology depends partly on poor understanding of the function of the receptors with respect to disease development. It is not clear which endpoints should be considered alarming, or which end-points should be used to identify all possible biological effects of pesticides. To tackle these problems, basic research on the function of xenosensors and

hormone receptors is needed. The growing field of genomics, proteomics (analysis of protein expression and interactions), and structural biology will contribute to a more detailed understanding of the complexity of the signaling of these receptors. Research should also consider the action of pesticides on other hormonal systems other than steroid and thyroid hormone signaling. To date, only little is known about how pesticides can affect the pathways of peptide hormones and fatty acid derivatives. The data summarized above demonstrate that redox signaling is one of the central mechanisms by which many of these pesticides modulate/trigger apoptosis. In certain circumstances pesticides might trigger other types of cell death pathways such as necrosis and autophagy. Redox signaling induced by pesticides involves both alterations in antioxidant defenses and accumulation of ROS leading to oxidative stress. These biochemical events mediate a number of redox-dependent processes such as oxidative protein modifications, oxidative DNA damage, ER stress and alterations in mitochondrial function which in turn trigger the activation of specific signaling cascades. Activation of SAPKs such as JNK and of transcription-dependent p53 signaling cascades act as important sensors for xenobiotic stress and the induction of apoptotic cell death. Interestingly, pesticides also induce the activation of survival responses including, DNA repair mechanisms, Mitogen-activated protein kinase/ phosphatidylinositol 3-kinase (MAPK/ PI3K) signaling cascades and up-regulation of antioxidant defenses in an attempt to counteract the deleterious effects of cell death pathways. In fact, in most cases both apoptotic and survival signaling cascades have been observed to be activated in parallel in response to pesticide toxicity. Tipping the balance towards either cell death or survival depends in most cases on the intensity, length and type of exposure. In this case, not only the extent and duration of redox signals are important to determine subsequent cell fate, but also the intracellular localization of the redox signaling and the surrounding cellular environment. Finally, deregulated activation of survival signals as a consequence of mutagenesis is well-known to promote cellular transformation aroused by the impairment of apoptotic signaling. When facing this challenge it is important to state that for many pesticides, there is a lack of research and information about complete mechanistic events involved in the induction of cell death/survival by these toxicants. Thus, future research in the understanding of both pesticide-induced cytotoxicity and pesticide-induced cellular transformation is necessary for a complete understanding of the human health consequences to pesticide exposure, in order to establish improved usage regulations and reduction of exposure risk.

6. Acknowledgment

7. References

Abdelhaleem, M. (2002). Differential effect of Bcl-xl over-expression on cell death of the monocytic leukemia cell line U937. *Anticancer Research,* 22., 3911–3915.

Abou-Sleiman, P.M.; Muqit, M.M. & Wood, N.W. (2006). Expanding insights of mitochondrial dysfunction in Parkinson's disease. *Nature Reviews Neuroscience*, 7., 207–219.

Ahmadi, F.A.; Linseman, D.A.; Grammatopoulos, T.N.; Jones, S.M.; Bouchard, R.J. Freed, C.R.; Heidenreich, K.A. & Zawada, W.M. (2003). The pesticide rotenone induces caspase-3-mediated apoptosis in ventral mesencephalic dopaminergic neurons. *Journal of Neurochemistry*, 87., 914–921.

Ahmed, T.; Tripathi, A.K. ; Ahmed, R.S.; Das, S., Suke, S.G.; Pathak, R.; Chakraboti, A. & Banerjee, B.D. (2008). Endosulfan-induced apoptosis and glutathione depletion in human peripheral blood mononuclear cells: Attenuation by N-acetylcysteine. *Journal of Biochemical and Molecular Toxicology*, 22., 299-304.

Ahmed, T.; Tripathi, A.K.; Ahmed, R.S. & Banerjee, B.D. (2010). Assessment of phosphamidon-induced apoptosis in human peripheral blood mononuclear cells: protective effects of N-acetylcysteine and curcumin. *Journal of Biochemical and Molecular Toxicology*, 24., 286-292.

Andersen, H.R.; Vinggaard, A.M.; Rasmussen, T.H.; Gjermandsen, I.M. & Bonefeld-Jørgensen, E.C. (2002). Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. *Toxicology and Applied Pharmacology*, 179., 1-12.

Auger, J.; Kunstmann, J.M.; Czyglik, F. & Jouannet, P. (1995). Decline in sperm quality among fertile men in Paris during the past 20 years. *The New England Journal of Medicine*, 332., 281–285.

Banhegyi, G.; Benedetti, A.; Csala, M. & Mandl, J. (2007). Stress on redox. *The Federation of European Biochemical Societies Letters*, 581., 3634–3640.

Barlow, B.K.; Lee, D.W.; Cory-Slechta, D.A. & Opanashuk, L.A. (2005). Modulation of antioxidant defense systems by the environmental pesticide maneb in dopaminergic cells. *Neurotoxicology*, 26., 63–75.

Barnhart, B.C.; Alappat, E.C.M. & Peter, E. (2003). The CD95 type I/type II model. *Seminars in Immunology*, 15., 185-193.

Baskin, L.S.; Himes, K. & Colborn, T. (2001). Hypospadias and endocrine disruption: Is there a connection? *Environmental Health Perspectives*, 109., 1175-1183.

Bastomsky, C.H. (1974). Effects of a polychlorinated biphenyl mixture (Aroclor 1254) and DDT on biliary thyroxine excretion in rats. *Endocrinology*, 95., 1150-1155.

Belpomme, D.; Irigaray, P.; Hardell, L.; Clapp, R.; Montagnier, L. & Epstein, S. (2007). The multitude and diversity of environmental carcinogens. *Environmental Research*, 105., 414-429.

Ben Rhouma, K.; Tebourbi, O.; Krichah, R. & Sakly, M. (2001). Reproductive toxicity of DDT in adult male rats. *Human and Experimental Toxicology*, 20., 393-397.

Benmoyal-Segal, L. & Soreq, H. (2006). Gene–environment interactions in sporadic Parkinson's disease. *Journal of Neurochemistry*. 97., 1740–1755.

Bertram, C. & Hass, R. (2008). Cellular responses to reactive oxygen species-induced DNA damage and aging. *Biological Chemistry*, 389., 211–220.

Bosland, MC. (2006). Sex steroids and prostate carcinogenesis: integrated, multifactorial working hypothesis. *Annals of the New York Academy of Sciences*, 1089., 168-176.

Boyce, M.& Yuan, J. (2006). Cellular response to endoplasmic reticulum stress: a matter of life or death, *Cell Death and Differentiation*, 13., 363-373.

Brown, T.P.; Rumsby, P.C.; Capleton, A.C.; Rushton, L. & Levy, L.S. (2006). Pesticides and Parkinson's disease is there a link? *Environmental Health Perspectives*, 114., 156–164.

Calo, M.; Iannone, M.; Passafaro, M. & Nistico, G. (1990). Selective vulnerability of hippocampal CA3 neurones after microinfusion of paraquat into the rat substantia nigra or into the ventral tegmental area. *Journal of Comparative Pathology*, 103., 73–78.

Calviello, G.; Piccioni, E.; Boninsegna, A.; Tedesco, B.; Maggiano, N.; Serini, S. & Wolf, F.I.; & Palozza, P. (2006). DNA damage and apoptosis induction by the pesticide Mancozeb in rat cells: involvement of the oxidative mechanism. *Toxicology and Applied Pharmacology,* 211., 87–96.

Canistro, D.; Cantelli-Forti, G.; Biagi, G.L.& Paolini, M. (2002). Re: dioxin increases reactive oxygen production in mouse liver mitochondria. *Toxicology and Applied Pharmacology*, 178., 15–21.

Carlsen, E.; Giwercman, A.; Keiding, N. & Skakkebaek, N.E. (1992). Evidence for the decreasing quality of semen during the past 50 years. *British Medical Journal,* 305., 609–613.

Cassidy, R.A.; Natarajan, S.& Vaughan, G.M. (2005). The link between the insecticide heptachlor epoxide, estradiol, and breast cancer. *Breast Cancer Research and Treatment,* 90., 55-64.

Castello, P.R.; Drechsel, D.A. & Patel, M. (2007). Mitochondria are a major source of paraquat-induced reactive oxygen species production in the brain. *Journal of Biological Chemistry*, 282., 14186–14193.

Chen, Y.; McMillan-Ward, E.; Kong, J.; Israels, S.J. & Gibson, S.B. (2007). Mitochondrial electron-transport-chain inhibitors of complexes I and II induce autophagic cell death mediated by reactive oxygen species. *Journal of Cell Science,* 120., 4155-4166.

Chen, Y. & Gibson, S.B. (2008). Is mitochondrial generation of reactive oxygen species a trigger for autophagy? *Autophagy,* 16., 246-248.

Chen, Y.; Azad, M.B & Gibson, S.B. (2009). Superoxide is the major reactive oxygen species regulating autophagy. *Cell Death and Differentiation,* 16., 1040-1052.

Claxton, L.D. & Woodall, G.M. (2007). A review of the mutagenicity and rodent carcinogenicity of ambient air, *Mutation Research,* 636., 36–94.

Cok, I.; Bilgili, A.; Ozdemir, M.; Ozbek, H.; Bilgili, N. & Burgaz, S. (1997). Organochlorine pesticide residues in human breast milk from agricultural regions of Turkey, 1995–1996. *Bulletin of Environmental Contamination and Toxicology*, 59., 577–582.

Colborn, T. (2006). A case for revisiting the safety of pesticides: a closer look at neurodevelopment, *Environmental Health Perspectives*, 114., 10-17.

Coulom, H. & Birman, S. (2004). Chronic exposure to rotenone models sporadic Parkinson's disease in Drosophila melanogaster. *Journal of Neuroscience*, 24., 10993–10998.

Curran, P.G. & De Groot, L.J. (1991). The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. *Endocrine Reviews*, 12., 135-150.

Dalle-Donne, I.; Rossi, R.; Colombo, R.; Giustarini, D. & Milzani, A. (2006). Biomarkers of oxidative damage in human disease. *Clinical Chemistry*, 52., 601–623.

Dalle-Donne, I.; Milzani, A.; Gagliano, N.; Colombo, R.; Giustarini, D. & Rossi, R. (2008). Molecular mechanisms and potential clinical significance of S-glutathionylation, *Antioxidants and Redox Signaling*, 10., 445-473.

322
Pesticides in the Modern World
– Pests Control and Pesticides Exposure and Toxicity Assessment

Das, G.P.; Shaik, A.P. & Jamil, K. (2006). Estimation of apoptosis and necrosis caused by pesticides in vitro on human lymphocytes using DNA diffusion assay. *Drug and Chemical Toxicology,* 29., 147–156.

Daxenberger, A.A. (2002). Pollutants with androgen-disrupting potency. *European Journal of Lipid Science and Technology*, 104., 124–130.

Degenhardt, K.; Mathew, R.; Beaudoin, B.; Bray, K.; Anderson, D.; Chen, G.; Mukherjee, C.; Shi, Y.; Gélinas, C.; Fan, Y.; Nelson, D.; Jin, S. & White, E. (2006). Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. *Cancer Cell,* 10., 51–64.

Deroo, B.J.; Rentsch, C.; Sampath, S.; Young, J.; DeFranco, D.B. & Archer, T.K. (2002). Proteasomal inhibition enhances glucocorticoid receptor transactivation and alters its subnuclear trafficking. *Molecular and Cellular Biology*, 22., 4113-4123.

Dhalla, N.S.; Temsah, R.M. & Netticadan, T. (2000). Role of oxidative stress in cardiovascular diseases. *Journal of Hypertension*, 18., 655–673.

Ding, Q. & Keller, J.N. (2001). Proteasome inhibition in oxidative stress neurotoxicity: implications for heat shock proteins. *Journal of Neurochemistry,* 77., 1010–1017.

Dong, L.M.; Potter, J.D.; White, E.; Ulrich, C.M.; Cardon, L.R. & Peters, U. (2008). Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. *Journal of the American Medical Association,* 299., 2423–2436.

Drechsel, D.A. & Patel, M. (2009). Differential contribution of the mitochondrial respiratory chain complexes to reactive oxygen species production by redox cycling agents implicated in parkinsonism. *Toxicological Sciences*, 112., 427-434.

European workshop on the impact of endocrine disrupters on human health and wildlife (EEC). (1996). Weybridge: UK.

Ekert, P.G. & Vaux, D.L. (2005). The mitochondrial death squad: hardened killers or innocent by standers? *Current Opinion in Cell Biology*, 17., 626-630.

Ellinger-Ziegelbauer, H.; Stuart, B.; Wahle, B.; Bomann, W. & Ahr, H.J. (2005). Comparison of the expression profiles induced by genotoxic and nongenotoxic carcinogens in rat liver. *Mutation Research*, 575., 61–84.

Escriva, H.; Bertrand, S. & Laudet, V. (2004). The evolution of the nuclear receptor superfamily. *Essays in Biochemistry*, 40., 11-26.

Eskenazi, B.; Bradman, A.; Castorina, R. (1999). Exposures of children to organophosphate pesticides and their potential adverse health effects, *Environmental Health Perspectives*, 107., 409-419.

Fei, Q. & Ethel, D.W. (2008). Maneb potentiates paraquat neurotoxicity by inducing key Bcl-2 family members. *Journal of Neurochemistry*, 105., 2091-2097.

Fei, Q.; McCormack, A.L.; Di Monte, D.A. & Ethel, D.W. (2008). Paraquat neurotoxicity is mediated by a Bak-dependent mechanism. *Journal of Biological Chemistry*, 283., 3357–3364.

Fleming, L.; Mann, J.B.; Bean, J. & Briggle, T. & Sanchez-Ramos, J.R. (1994). Parkinson's disease and brain levels of organochlorine pesticides. *Annals of Neurology*, 36., 100–103.

Foster, W.G.; Younglai, E.V.; Boutross-Tadross, O.; Hughes, C.L. & Wade, M.G. (2004). Mammary gland morphology in sprague-dawley rats following treatment with an organochlorine mixture in utero and neonatal genistein. *Toxicological Sciences*, 77., 91-100.

Franco, R.; Sanchez-Olea, R.; Reyes-Reyes, E.M. & Panayiotidis, M.I. (2009). Environmental toxicity, oxidative stress and apoptosis: ménage à trois. *Mutation Research*, 674., 3-22.

Franco, R.; Li, S.; Rodriguez-Rocha, H.; Burns, M.; Panayiotidis, M.I. (2010). Molecular mechanisms of pesticide-induced neurotoxicity: Relevance to Parkinson's disease. *Chemico-Biological Interactions,* 188., 289-300.

Galluzzi, L.; Maiuri, M.C.; Vitale, I.; Zischka, H.; Castedo, M.; Zitvogel, L. & Kroemer, G. (2007). Cell Death Modalities: classification and pathophysiological implications. *Cell Death and Differentiation*, 14., 1237-1243.

Garey, J. & Wolff, M.S. (1998). Estrogenic and antiprogestagenic activities of pyrethroid insecticides. *Biochemical and Biophysical Research Communications*, 251., 855-859.

Garry, V.V. (2004). Pesticides and children. *Toxicology and Applied Pharmacology,* 198., 152-163.

Germain, P.; Staels, B.; Dacquet, C.; Spedding, M. & Laudet, V. (2006). Overview of nomenclature of nuclear receptors. *Pharmacological Reviews*, 58., 685-704.

Goad, R.; Goad, J.; Atieh, B. & Gupta, R. (2004). Carbofuran-induced endocrine disruption in adult male rats. *Toxicology Mechanisms and Methods,* 14., 233–239.

Gonzalez-Polo, R.A.; Niso-Santano, M.; Ortiz-Ortiz, M.A.; Gomez-Martin, A; Moran, J.M.; Garcia-Rubio, L.; Francisco-Morcillo, J.; Zaragoza, C.; Soler, G. & Fuentes, J.M. (2007). Relationship between autophagy and apoptotic cell death in human neuroblastoma cells treated with paraquat: could autophagy be a "brake" in paraquat-induced apoptotic death? *Autophagy,* 3., 366–367.

Gougeon, M.L.; Lecoeur, H. & Dulioust, A. (1996). Programmed cell death in peripheral lympocytes from HIV-infected persons. *Journal of Immunology,* 156., 3509–3520.

Gronemeyer, H.; Gustafsson, JA. & Laudet, V. (2004) Principles formodulation of the nuclear receptor superfamily. *Nature Reviews : Drug Discovery*, 3., 950-964.

Grosicka, E.; Sadurska, B.; Szumilo, M.; Grzela, T.; Lazarczyk, P.; Niderla-Bielinska, J. & Rahden-Staron, I. (2005). Effect of glutathione depletion on apoptosis induced by thiram in Chinese hamster fibroblasts. *International Immunopharmacology,* 5., 1945–1956.

Gwinn, M.R.; Whipkey, D.L.; Tennant, L.B. & Weston, A. (2005). Differential gene expression in normal human mammary epithelial cells treated with malathion monitored by DNA microarrays. *Environmental Health Perspectives,* 113., 1046–1051.

Hall, J.M.; Couse, J.F. & Korach, K.S. (2001). The multifaceted mechanisms of estradiol and estrogen receptor signaling. *Journal of Biological Chemistry*, 276., 36869-36872.

Hallegue, D.; Ben Rhouma, K.; Tebourbi, O. & Sakly, M. Impairment of testicular endocrine and exocrine functions after dieldrin exposure in adult rat. *Polish Journal of Environmental Studies*, 12., 557-561.

Halliwell, B. (2007). Oxidative stress and cancer: have we moved forward? *Biochemical Journal*. 401., 1–11.

Hanahan, D. & Weinberg, R.A. (2000). The hallmarks of cancer. *Cell*. 100., 57–70.

Hartley, A.; Stone, J.M.; Heron, C.; Cooper, J.M. & Schapira, A.H. (1994). Complex I inhibitors induce dose-dependent apoptosis in PC12 cells: relevance to Parkinson's disease. *Journal of Neurochemistry*, 63., 1987–1990.

Hatcher, J.M.; Pennell, K.D. & Miller, G.W. (2008). Parkinson's disease and pesticides: a toxicological perspective. *Trends in Pharmacological Sciences*, 29., 322–329.

Hayes,T.; Haston, K.; Tsui, M.; Hoang, A.; Haeffele, C. & Vonk, A. (2002). Herbicides: feminization of male frogs in the wild. *Nature,* 419., 895–896.

Hengartner, M.O. (2000). The biochemistry of apoptosis. *Nature,* 407., 770-776.

Hikim, A.P.; Lue, Y.; Yamamoto, C.M.; Vera, Y.; Rodriguez, S.; Yen, P.H.; Soeng, K.; Wang, C. & Swerdloff, R.S. (2003). Key apoptotic pathways for heat-induced programmed germ cell death in the testis. *Endocrinology,* 144., 3167–3175.

International Program on Chemical Safety (IPCS). (2002). Global assessment of the state-of-the-science of endocrine disruptors. *World Health Organization*:
[http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/].

Hockenberry, D.M.; Oltvai, Z.N.; Yin, X.M.; Milliman, C.L. & Korsmeyer, S.J. (1993). Bcl-2 functions in an antioxidant pathway to prevent apoptosis. *Cell,* 75., 241-251.

Hoek, J.B. & Rydström, J. (1988). Physiological roles of nicotinamide nucleotide transhydrogenase. *Biochemical Journal,* 254., 1-10.

Irigaray, P.; Newby, J.A.; Clapp, R.; Hardell, L.; Howard, V.; Montagnier, L.; Epstein, S. & Belpomme, D. (2007). Lifestyle-related factors and environmental agents causing cancer: an overview. *Biomedicine and Pharmacotherapy*, 61., 640–658.

Ishihara, A.; Nishiyama, N.; Sugiyama, S.I. & Yamauchi, K. (2003). The effect of endocrine disrupting chemicals on thyroid hormone binding to Japanese quail transthyretin and thyroid hormone receptor. *General and Comparative Endocrinology*, 134., 36–43.

Janssen-Heininger, Y.M.; Mossman, B.T.; Heintz, N.H.; Forman, H.J.; Kalyanaraman, B.; Finkel, T.; Stamler, J.S.; Rhee, S.G. & Van Der Vliet, A. (2008). Redox-based regulation of signal transduction: principles, pitfalls, and promises. *Free Radical Biology and Medicine*, 45., 1-17.

Jeong, S.H.; Kim,B.Y.; Kang, H.G.; Ku, H.K. & Cho, J.H. (2006). Effect of chlorpyrifos-methyl on steroid and thyroid hormones in rat F0- and F1-generations. *Toxicology*, 220., 189–202.

Jin, Y.;Zheng, S.; Pu, Y.; Shu, L.; Sun, L.; Liu, W. & Fu, Z. (2011). Cypermethrin has the potential to induce hepatic oxidative stress, DNA damage and apoptosis in adult zebrafish (Danio rerio). *Chemosphere,* 82., 398-404.

Kang, K.S.; Wilson, M.R.; Hayashi, T.; Chang, C.C. & Trosko, J.E. (1996). Inhibition of gap junctional intercellular communication in normal human breast epithelial cells after treatment with pesticides, PCBs, and PBBs, alone or in mixtures. *Environmental Health Perspectives,* 104., 192-200.

Kang, H.G.; Jeong, S.H.; Cho, J.H.; Kim, D.G.; Park, J.M. & Cho, M.H. (2004). Chloropyrifos-methyl shows anti-androgenic activity without estrogenic activity in rats. *Toxicology*, 199., 219–230.

Katsoulieris , E.; Mabley, J.G.; Samai, M.; Sharpe, M.A.; Green, I.C. & Chatterjee, P.K. (2010). Lipotoxicity in renal proximal tubular cells: relationship between endoplasmic reticulum stress and oxidative stress pathways *Free Radical Biology and Medicine*, 48., 1654-1662.

Katzenellenbogen, J.A.; O'Malley, B.W. & Katzenellenbogen, B.S. (1996). Tripartite steroid hormone receptor pharmacological interaction with multiple effector sites as a basis for the cell- and promoter-specific action of these hormones. *Molecular Endocrinology,* 10., 119-131.

Kavlock, R. & Cummings, A. (2005). Mode of action: Inhibition of androgen receptor function-Vinclozolin-induced malformations in reproductive development. *Critical Reviews in Toxicology*, 35., 721-726.

Kelce, W.R.; Stone, C.R.; Laws, S.C.; Gray, L.E.; Kemppainen, J.A. & Wilson, E.M. (1995). Persistent DDT metabolite p,p′-DDE is a potent androgen receptor antagonist. *Nature,* 375., 581-585.

Khosravi-Far, R. & Esposti, M.D. (2004). Death receptor signals to mitochondria. *Cancer Biology and Therapy*, 3.,1051-1057.

Kim, I.Y.; Shin, J.H.; Kim, H.S.; Lee, S.J.; Kang, I.H. & Kim, T.S. (2004). Assessing estrogenic activity of pyrethroid insecticides using in vitro combination assays. *The Journal of Reproduction and Development*, 50., 245–255.

Kitazawa, M.; Anantharam, V.; Kanthasamy, A. & Kanthasamy, A.G. (2004). Dieldrin promotes proteolytic cleavage of poly(ADP-ribose) polymerase and apoptosis in dopaminergic cells: protective effect of mitochondrial anti-apoptotic protein Bcl-2. *Neurotoxicology,* 25., 589–598.

Klaunig, J.E. & Ruch, R.J. (1990). Biology of disease: role of inhibition of intercellular communication in carcinogenesis. *Laboratory Investigation,* 62., 135-146.

Klaunig, J.E.; Hartnett, J.A.; Ruch, R.J.; Weghorst, C.M.; Hampton, J.A. & Schafer, L.D. (1990). Gap junctional intercellular communication in hepatic carcinogenesis. *Progress in Clinical and Biological Research,* 340., 165-174.

Kliewer, S.A. & Willson, T.M. (2002). Regulation of xenobiotic and bile acid metabolism by the nuclear pregnane X receptor. *Journal of Lipid Research*, 43., 359-364.

Kroemer, G.; Galluzzi, L.; Vandenabeele, P.; Abrams, J.; Alnemri, E.S.; Baehrecke, E.H.; Blagosklonny, M.V.; El-Deiry, W.S.; Golstein, P.; Green, D.R.; Hengartner, M.; Knight, R.A.; Kumar, S.; Lipton, S.A.; Malorni, W.; Nunez, G.; Peter, M.E.; Tschopp, J.; Yuan, J.; Piacentini, M.; Zhivotovsky, B. & Melino, G. (2009). Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009, *Cell Death and Differentiation*, 16., 3-11.

Landrigan, P.J.; Sonawane, B.; Butler, R.N.; Trasande, L.; Callan, R. & Droller, D. (2005). Early environmental origins of neurodegenerative disease in later life. *Environmental Health Perspectives*, 113., 1230–1233.

Laville, N.; Balaguer, P.; Brion, F.; Hinfray, N.; Casellas, C.& Porcher, J.M. (2006). Modulation of aromatase activity and mRNA by various selected pesticides in the human choriocarcinoma JEG-3 cell line. *Toxicology*, 228., 98-108.

Lemaire, G.; Terouanne, B.; Mauvais, P.; Michel, S. & Rahmani R. (2004). Effect of organochlorine pesticides on human androgen receptor activation in vitro. *Toxicology and Applied Pharmacology*, 196.,235–246.

Lemaire, G.; Mnif, W.; Mauvais, P.; Balaguer, P. & Rahmani, R. (2006). Activation of alpha- and beta-estrogen receptors by persistent pesticides in reporter cell lines. *Life Sciences,* 79., 1160-1169.

Li, Q.; Kobayashi, M. & Kawada, T. (2007). Organophosphorus pesticides induce apoptosis in human NK cells, *Toxicology,* 239., 89–95.

Li, Q.; Kobayashi, M. & Kawada, T. (2009). Chlorpyrifos induces apoptosis in human T cells. *Toxicology*, 255., 53–57.

Lin, H.K.; Altuwaijri, S.; Lin, W.J.; Kan, P.Y.; Collins, L.L. & Chang, C. (2002). Proteasome activity is required for androgen receptor transcriptional activity via regulation of

326
Pesticides in the Modern World
– Pests Control and Pesticides Exposure and Toxicity Assessment

androgen receptor nuclear translocation and interaction with coregulators in prostate cancer cells. *Journal of Biological Chemistry*. 277., 36570-36576.

Lo, S.; King, I.; Allera, A. & Klingmuller, D. (2007). Effects of various pesticides on human 5alpha-reductase activity in prostate and LNCaP cells. *Toxicology in Vitro,* 21., 502-508.

Lu, S.Y.; Liao, J.W.; Kuo, M.L.; Wang, S.C.; Hwang, J.S. & Ueng, T.H. (2004). Endocrine disrupting activity in carbendazim-induced reproductive and developmental toxicity in rats. *Journal of Toxicology and Environmental Health Part A*, 67., 1501–1515.

Mackenzie, C.A. & Constanze, A. (2005). Declining sex ratio in a first nation community. *Environmental Health Perspectives*, 113., 1295-1298.

Malarvannan, G.; Kunisue, T.; Isobe, T.; Sudaryanto, A.; Takahashi, S.; Prudente, M.; Subramanian, A. & Tanabe, S. (2009). Organohalogen compounds in human breast milk from mothers living in Payatas and Malate, the Philippines: levels, accumulation kinetics and infant health risk. *Environmental Pollution*, 157., 1924–1932.

Manning-Bog, A.B.; McCormack, A.L.; Li, J.; Uversky, V.N.; Fink, A.L. & Di Monte, D.A. (2002). The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. *Journal of Biological Chemistry,* 277., 1641–1644.

Marchetti, P.; Decaudin, D.; Macho, A.; Zamzami, N.; Hirsch, T.; Susin, S.A. & Kroemer, G. (1997). Redox regulation of apoptosis: impact of thiol redoxidation on mitochondrial function. *European Journal of Immunology*, 27., 2889-2896.

Mathur, V.; Bhatnagar, P.; Sharma, R.G.; Acharya, V. & Sexana R. (2002). Breast cancer incidence and exposure to pesticides among women originating from Jaipur. *Environment International*, 228., 331-336.

Mattson, M.P. (2006). Neuronal life-and-death signaling, apoptosis, and neurodegenerative disorders, *Antioxidants and Redox Signaling,* 8., 1997–2006.

McCarthy, A.R.; Thomson, B.M.; Shaw, I.C. & Abella, A.D. (2006). Estrogenicity of pyrethroid insecticide metabolites. *Journal of Environmental Monitoring*, 8., 197-202.

McCormack, A.L.; Atienza, J.G.; Johnston, L.C.; Andersen, J.K.; Vu, S. & Di Monte, D.A. (2005). Role of oxidative stress in paraquat-induced dopaminergic cell degeneration. *Journal of Neurochemistry*, 93., 1030–1037.

McKinlay, R.; Plant, J.A. & Bell, J.N.B.; Voulvoulis, N. (2008). Endocrine disrupting pesticides: Implications for risk assessment. *Environment International,* 34., 168-183.

Meco, G.; Bonifati, V.; Vanacore, N. & Fabrizio, E. (1994). Parkinsonism after chronic exposure to the fungicidemaneb(manganese ethylene-bis-dithiocarbamate). *Scandinavian Journal of Work, Environment and Health*, 20., 301–305.

Mena, S.; Ortega, A. & Estrela, J.M. (2009). Oxidative stress in environmental-induced carcinogenesis. *Mutation Research,* 674., 36–44.

Meulenberg, E.E. (2002). A new test to identify endocrine disruptors using sex hormone binding globulins from human serum. *European Journal of Lipid Science and Technology*, 104., 131–136.

Molina-Molina, J.M.; Hillenweck, A.; Jouanin, I.; Zalko, D.; Cravedi, J.P.; Fernandez, M.F.; Pillon, A.; Nicolas, J.C.; Olea, N. & Balaguer, P. (2006). Steroid receptor profiling of vinclozolin and its primary metabolites. *Toxicology and Applied Pharmacology*, 216., 44-54.

Morinaga, H.; Yanase, T.; Nomura, M.; Okabe, T.; Goto, K. & Harada, N. (2004). A benzimidazole fungicide, benomyl, and its metabolite, carbendazim, induce aromatase activity in a human ovarian granulose-like tumor cell line (KGN). *Endocrinology,* 145., 1860-1869.

Muguruma, M.; Unami, A.; Kanki, M.; Kuroiwa, Y.; Nishimura, J.; Dewa, Y.; Umemura, T.; Oishi, Y.& Mitsumori, K. (2007). Possible involvement of oxidative stress in piperonyl butoxide induced hepatocarcinogenesis in rats. *Toxicology,* 236., 61–75.

Nagel, S.C.; Hagelbarger, J.L. & McDonnell, D.P. (2001). Development of an ER action indicator mouse for the study of estrogens, selective ER modulators (SERMs), and xenobiotics. *Endocrinology,* 142., 4721-4728.

Nakadai, A.; Li, Q. & Kawada, T. (2006). Chlorpyrifos induces apoptosis in human monocyte cell line U937. *Toxicology,* 224., 202–209.

Nakata, K., Tanaka, Y., Nakano, T., Adachi, T., Tanaka, H., Kaminuma, T. & Ishikawa, T. (2006). Nuclear receptor-mediated transcriptional regulation in phase I, II, and III xenobiotic metabolizing systems. *Drug Metabolism and Pharmacokinetics,* 21., 437-457.

Negga, R.;Rudd, D.A.; Davis, N.S.; Justice, A.N; Hatfield, H.E; Valente, A.L.; Fields, A.S. & Fitsanakis, V.A. (2011). Exposure to Mn/Zn ethylene-bis-dithiocarbamate and glyphosate pesticides leads to neurodegeneration in Caenorhabditis elegans. *Neurotoxicology,* doi:10.1016/j.neuro.2011.02.002.

Newhouse, K.; Hsuan, S.L.; Chang, S.H.; Cai, B.; Wang, Y. & Xia, Z. (2004). Rotenone-induced apoptosis is mediated by p38 and JNK MAP kinases in human dopaminergic SH-SY5Y cells. *Toxicological Sciences*. 79., 137–146.

Nicolopoulou, P. & Stamanti, P. (2001). The impact of endocrine disrupters on the female reproductive system. *Human Reproduction Update,* 7., 323-330.

Nicotera, P. & Melino, G. (2004). Regulation of the apoptosis-necrosis switch. *Oncogene,* 23., 2757–2765.

Niso-Santano, M.; Gonzalez-Polo, R.A.; Bravo-San Pedro, J.M.; Gomez-Sanchez, R.; Lastres-Becker, I.; Ortiz-Ortiz, M.A.; Soler, G.; Moran, J.M.; Cuadrado, A. & Fuentes, J.M. (2010). Activation of apoptosis signal-regulating kinase 1 is a key factor in paraquat-induced cell death. Modulation by the Nrf2/Trx axis. *Free Radical Biology and Medicine,* 48., 1370-1381.

Norris, E.H.; Uryu, K.; Leight, S.; Giasson, B.I.; Trojanowski, J.Q. & Lee, V.M. (2007). Pesticide exposure exacerbates alpha-synucleinopathy in an A53T transgenic mouse model. *American Journal of Pathology*, 170., 658–666.

Oehninger, S. (2001). Strategies for the infertile man. *Seminars in Reproductive Medicine,* 19., 231–237.

Okouchi, M. ; Ekshyyan, O.; Maracine, M. & Aw, T.Y. (2007). Neuronal apoptosis in neurodegeneration. *Antioxidants and Redox Signaling* 9., 1059–1096.

Orrenius, S. (1993). Mechanisms of oxidative cell damage. In: *Free Radicals: From Basic Science to Medicine*, Poli, G.; Albano, E. & Dianzani, M.U., pp. 47–64, Birkhauser Verlag, Basel, Switzerland.

Ott, M.; Gogvadze, V.; Orrenius, S. & Zhivotovsky, B. (2007). Mitochondria, oxidative stress and cell death, *Apoptosis,* 12., 913–922.

Palomo, T.; Archer, T.; Beninger, R.J. & Kostrzewa, R.M. (2004). Gene–environment interplay in neurogenesis and neurodegeneration, *Neurotoxicity Research*, 6., 415–434.

Pascussi, J.M., Gerbal-Chaloin, S., Drocourt, L., Assenat, E., Larrey, D., Pichard-Garcia, L., Vilarem, M.J. & Maurel, P. (2004). Cross-talk between xenobiotic detoxication and other signalling pathways: Clinical and toxicological consequences. *Xenobiotica,* 34., 633-664.

Perera, F.P.; Rauh, V.; Whyatt, R.M.; Tang, D.; Tsai, W.Y.; Bernert, J.T.; Tu, Y.H.; Andrews, H.; Barr, D.B.; Camann, D.E.; Diaz, D.; Dietrich, J.; Reyes, A. & Kinney, P.L. (2005). A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures. *Neurotoxicology,* 26., 573–587.

Pérez-Maldonado, I.N.; Athanasiadou, M.; Yáñez, L.; González-Amaro, R.; Bergman, A. & Díaz-Barriga, F. (2006). DDE-induced apoptosis in children exposed to the DDT metabolite. *Science of the Total Environment*, 370., 343–351.

Pérez-Maldonado, I.N.; Díaz-Barriga, F.; De la Fuente, H.; González-Amaro, R.; Calderón, J. & Yañez, L. (2004). DDT induces apoptosis in human mononuclear cells in vitro and is associated with increased apoptosis in exposed children. *Environmental Research*, 94., 38–46.

Pérez-Maldonado, I.N.; Herrera, C.; Batres, L.E.; González-Amaro, R.; Díaz-Barriga, F. & Yañez L. (2005). DDT -Induced oxidative damage in human blood mononuclear cells. *Environmental Research,* 98., 177–184.

Pesticide Action Network (PAN). (2005). List of lists: a catalogue of lists of pesticides identifying those associated with particularly harmful health or environmental impacts.

Ravagnan, L.; Roumier, T. & Kroemer, G. (2002). Mitochondria, the killer organelles and their weapons. *Journal of Cell Physiology*, 192., 131-137.

Reschly, E.J. & Krasowski, M.D. (2006). Evolution and function of the NR1I nuclear hormone receptor subfamily (VDR, PXR, and CAR) with respect to metabolism of xenobiotics and endogenous compounds. *Current Drug Metabolism*, 7., 349-365.

Roos, W.P. & Kaina, B. (2006). DNA damage-induced cell death by apoptosis. *Trends in Molecular Medicine*, 12., 440-450.

Ruch, R.J. & Klaunig, J.E. (1988). Antioxidant prevention of tumor promoter induced inhibition of mouse hepatocyte intercellular communication. *Cancer Letters,* 33., 137-150.

Rüegg, J.; Penttinen-Damdimopoulou, P.; Makela, S; Pongratz, I. & Gustafsson, J.A. (2009). Receptors mediating toxicity and their involvement in endocrine disruption Molecular. Clinical and Environmental Toxicology, In: *Molecular Toxicology*, Luch, A., pp289-323, Birkhäuser Verlag, Switzerland.

Ryter, S.W.; Kim, H.P.; Hoetzel, A.; Park, J.W.; Nakahira, K.; Wang, X. & Choi, A.M. (200 7). Mechanisms of cell death in oxidative stress. *Antioxidants and Redox Signaling*, 9., 49-89.

Ryter, S.W.; Kim, H.P.; Hoetzel, A.; Park, J.W.; Nakahira, K.; Wang, X.& Choi, A.M. (2007). Mechanisms of cell death in oxidative stress. *Antioxidants and Redox Signaling,* 9., 49–89.

Ryu, E.J.; Harding, H.P.; Angelastro, J.M.; Vitolo, O.V.; Ron, D. & Greene, L.A. (2002). Endoplasmic reticulum stress and the unfolded protein response in cellular models of Parkinson's disease. *Journal of Neuroscience*, 22., 10690–10698.

Saelens, X.; Festjens, N.; Vande Walle, L.; Van Gurp, M.; G. Van Loo, G. & Vandenabeele, P. (2004). Toxic proteins released from mitochondria in cell death. *Oncogene,* 23., 2861-2874.

Saleh, A.M.; Vijayasarathy, C.; Fernandez-Cabezudo, M.; Taleb, M. & Petroianu, G. (2003). Influence of paraoxon (POX) and parathion (PAT) on apoptosis: a possible mechanism for toxicity in low-dose exposure. *Journal of Applied Toxicology,* 23., 23–29.

Sanderson, T. & Van Den Berg, M. (2003). Interactions of xenobiotics with the steroid hormone biosynthesis pathway. *Pure and Applied Chemistry*, 75., 1957-1971.

Saradha, B.; Vaithinathan, S. & Mathur, P.P. (2009). Lindane induces testicular apoptosis in adult Wistar rats through the involvement of Fas-FasL mitochondria-dependent pathways. *Toxicology,* 255., 131-139.

Sayre, L.M.; Smith, M.A. & Perry, G. (2001). Chemistry and biochemistry of oxidative stress in neurodegenerative disease. *Current Medicinal Chemistry*, 8., 721–738.

Schrader, T.J. & Cooke, G.M. (2000). Examination of selected food additives and organochlorine food contaminants for androgenic activity in vitro.*Toxicological Sciences*, 53., 278-288.

Schreinemachers, D.D. (2003). Birth malformations and other adverse perinatal out comes in four US wheat-producing states. *Environmental Health Perspectives*, 111., 1259-1264.

Scippo, M.L. (2004). Recombinant human estrogen, androgen and progesterone receptors for detection of potential endocrine disruptors. *Analytical and Bioanalytical Chemistry*, 378., 664–669.

Shi, Y.Q.; Song, Y.; Wang, Y.N.; Liang, X.M.; Hu, Y.F.; Guan, X.; Cheng, J. & Yang, K. (2009). P,p'-DDE induces apoptosis of rat Sertoli cells via a FasL-dependent pathway. *Journal of Biomedical Biotechnology*, ID181282 doi: 10.1155/181282.

Shi, Y.Q; Wang,Y.; Song, Y.; Li, H.W.; Liu, C.J.; Wu, Z.G. & Yang, K. (2010). P,p'-DDE induces testicular apoptosis in prepubertal rats via the Fas/FasL pathway. *Toxicology Letters*, 193., 79-85.

Shinomiya, N. & Shinomiya, M. (2003). Dichlorodiphenyltrichloroethane suppresses neurite outgrowth and induces apoptosis in PC12 pheochromocytoma cells. *Toxicology Letters*, 137., 175–183.

Siegel, D. & Ross, D. (2000). Immunodetection of NAD(P)H:quinone oxidoreductase 1(NQO1) in human tissues. *Free Radical Biology and Medicine,* 29., 246–253.

Singer, P.L. (1949). Occupational oligiospermia. *Journal of the American Medical Directors Association*, 140., 1249.

Slater, A.F.G.; Nobel, C.S.I.; Van den Dobbelsteen, D.J. & Orrenius, S. (1995). Signaling mechanisms and oxidative stress in apoptosis. *Toxicology Letters*, 82/83., 149–153.

Soffritti, M.; Belpoggi, F.; Esposti, D.D.; Falcioni, L. & Bua, L. (2008). Consequences of exposure to carcinogens beginning during developmental life. *Basic and Clinical Pharmacology and Toxicology*, 102., 118–124.

Song, Y.; Liang, X., Hu, Y.; Wang, Y.; Haige, Y. & Yang, K. (2008). P,p'-DDE induces mitochondria-mediated apoptosis of cultured rat Sertoli cells. *Toxicology*, 253., 53-61.

Song, Y.; Shi, Y.;Yu, H.; Hu, Y.; Wang, Y. & Yang, K. (2011). p,p'-Dichlorodiphenoxydichloroethylene induced apoptosis of Sertoli cells through
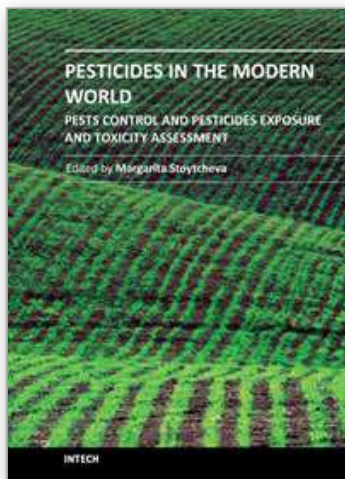
oxidativestress-mediated p38 MAPK and mitochondrial pathway. *Toxicology Letters,* doi:10.1016/j.toxlet.2011.01.020.

Sonnenschein, C. & Soto, A.M. (1998). An updated review of environmental estrogen and androgen mimics and antagonists. *Journal of Steroid Biochemistry and Molecular Biology*, 65., 143–150.

Stevenson, D.E.; Walborg Jr., E.F.; North, D.W.; Sielken Jr., R.L.; Ross, C.E.; Wright, A.S.; Xu, Y. Kamendulis, L.M. & Klaunig, J.E. (1999). Monograph: reassessment of human cancer risk of aldrin/dieldrin. *Toxicology Letters*. 109., 123–186.

Sun, F.; Anantharam, V.; Latchoumycandane, C.; Kanthasamy, A. & Kanthasamy, A.G. (2005). Dieldrin induces ubiquitin-proteasome dysfunction in alphasynuclein overexpressing dopaminergic neuronal cells and enhances susceptibility to apoptotic cell death. *Journal of Pharmacology and Experimental Therapeutics*, 315., 69–79.

Swedenborg, E.; Rüegg, J.; Makela, S.; Pongratz, I. (2009) Endocrine disruptive chemicals: mechanisms of action and involvement in metabolic disorders. *Journal of Molecular Endocrinology*, 43., 1-10.

Szegezdi, E.; Logue, S.E.; Gorman, A.M. & Samali, A. (2006). Mediators of endoplasmic reticulum stress-induced apoptosis. *The European Molecular Biology Organization Reports,* 7., 880-885.

Tebourbi, O., Ben Rhouma, K. & Sakly, M. (1998). DDT induces apoptosis in rat thymocytes. *Bulletin of Environmental Contamination and Toxicology.* 61 216-223.

Tebourbi, O.; Hallegue, D.; Yacoubi, M.T.; Sakly, M. & Ben Rhouma, K. (2010). Subacute toxicity of p,p'-DDT on rat thyroid: Hormonal and histopathological changes. *Environmental Toxicology and Pharmacology*. 29., 271-279.

Tolson, A.H.; Wang. H. (2010). Regulation of drug-metabolizing enzymes by xenobiotic receptors: PXR and CAR Advanced. *Drug Delivery Reviews,* 62., 1238-1249.

Toppari, J. (2008). Environmental endocrine disrupters. *Sexual Development,* 2., 260-267.

Townsend, D.M. (2007). *S*-glutathionylation: indicator of cell stress and regulator of the unfolded protein response, *Molecular Interventions*, 7., 313–324.

Tripathi, R.; Mishra, D.P.; Shaha, C. (2009). Male germ cell development: turning on the apoptotic pathways. *Journal of Reproductive Immunology*, 83., 31–35.

Vaithinathan, S.; Saradha, B. & Mathur, P.P. (2010). Methoxychlor induces apoptosis via mitochondria- and FasL-mediated pathways in adult rat testis. *Chemico-Biological Interactions,* 185., 110-118.

Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M.T.; Mazur, M. & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *International Journal of Biochemistry and Cell Biology*, 39., 44–84.

Vandendobberlsteen, D.J.; Nobel, C.S.I.; Schelegel, J.; Cotgreave, I.A.; Orrenius, S. & Slater, A.F.G. (1996). Rapid and specific efflux of reduced glutathione during apoptosis induced by anti-Fas/APO-1 antibody. *Journal of Biology and Biochemistry,* 271., 15420.

Vogt, M.; Bauer, M.K.; Ferrari, D. & Schulze-Osthoff, K. (1998). Oxidative stress and hypoxia/reoxygenation trigger CD95 (APO-1/Fas) ligand expression in microglial cells. *The Federation of European Biochemical Societies Letters*, 429., 67–72.

Wang, Y. (2008). Bulky DNA lesions induced by reactive oxygen species. *Chemical Research in Toxicology*. 21., 276–281.

West, J.D. & Marnett, L.J. (2006). Endogenous reactive intermediates as modulators of cell signaling and cell death. *Chemical Research in Toxicology*, 19., 173-194.

White, E. (2008). Autophagic cell death unraveled: pharmacological inhibition of apoptosis and autophagy enables necrosis. *Autophagy,* 4, 399-401.

Wijayaratne, A.L. & McDonnell, D.P. (2001). The human estrogen receptor is a ubiquitinated protein whose stability is affected differentially by agonists, antagonists, and selective estrogen receptor modulators. *Journal of Biological Chemistry*, 276: 35684-35692.

Willson, T.M. & Kliewer, S.A. (2002). PXR, CAR and drug metabolism. *Nature Reviews Drug Discovery*, 1., 259-266.

Wood-Kaczmar, A.; Gandhi, S. & Wood, N.W. (2006). Understanding the molecular causes of Parkinson's disease; *Trends in Molecular Medicine* 12., 521–528.

Xu, R.X.; Lambert, M.H.; Wisely, B.B.; Warren, E.N.; Weinert, E.E. & Waitt, G.M. (2004). A structural basis for constitutive activity in the human CAR/RXR alpha heterodimer. *Molecular Cell*, 16., 919-928.

Yang, C. & Chen, S. (1999). Two organochlorine pesticides, toxaphene and chlordane, are antagonists for ERRα-1 orphan receptor. *Cancer Research,* 59., 4519-4524.

Yang, L.Y.; Chen, W.L.; Lin, J.W.; Lee, S.F.; Lee, C.C.; Hung, T.I. & Wei, Y.H. & Shih, C.M. (2005). Differential expression of antioxidant enzymes in various hepatocellular carcinoma cell lines, *Journal of Cellular Biochemistry*, 96., 622–631.

Yang, W. & Tiffany-Castiglioni, E. (2008). Paraquat-induced apoptosis in human neuroblastoma SH-SY5Y cells: involvement of p53 and mitochondria. *Journal of Toxicology and Environmental Health Part* A, 71., 289–299.

Yang, W.; Tiffany-Castiglioni, E.; Koh, H.C. & Son, I.H. (2009). Paraquat activates the IRE1/ASK1/JNK cascade associated with apoptosis in human neuroblastoma SH-SY5Y cells. *Toxicology. Letters*, 191., 203-210.

You, L. (2004). Steroid hormone biotransformation and xenobiotic induction of hepatic steroid metabolizing enzymes. *Chemico-Biological Interactions*. 147., 233-246.

You, L.; Sar, M.; Bartolucci, E.; Ploch, S. & Whitt, M. (2001). Induction of hepatic aromatase by p, p'-DDE in adult male rats. *Molecular and Cellar Endocrinology,* 178., 207-214.

Youle, R.J. & Strasser, A. (2008). The BCL-2 protein family: opposing activities that mediate cell death. *Nature Reviews Molecular and Cellular Biology*, 9., 47-59.

Zaidi, A.; Fernandes, D.; Bean, J.L. & Michaelis, M.L. (2009). Effects of paraquat-induced oxidative stress on the neuronal plasma membrane Ca(2+)-ATPase. *Free Radical Biology and Medicine*, 47., 1507–1514.

Zala, S. & Penn, D.J. (2004). Abnormal behaviours induced by chemical pollution: a review of the evidence and new challenges. *Animal Behavior*, 68., 649-664.

Zamzami, N.; Marchetti, P.; Castedo, M.; decaudin, D.; Macho, A.; Hirsch, T.; Susin, S.A.; Petit, P.X.; Mignotte, B. & Kroemer, G. (1995). Sequential reduction of mitochondrial transmembrane potential and generation of reactive oxygen species in early programmed cell death. *Journal of Experimental Medicine,* 182., 367-377.

Zhang, J.; Fitsanakis, V.A.; Gu, G.; Jing, D.; Ao, M.; Amarnath, V. & Montine, T.J. (2003). Manganese ethylene-bis-dithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. *Journal of Neurochemistry*, 84., 336–346.

332
Pesticides in the Modern World
– Pests Control and Pesticides Exposure and Toxicity Assessment

Zhou, Y.; Shie, F.S.; Piccardo, P.; Montine, T.J. & Zhang, J. (2004). Proteasomal inhibition induced by manganese ethylene-bis-dithiocarbamate: relevance to Parkinson's disease. *Neuroscience,* 128., 281–291.

Zucchini-Pascal, N.; De Sousa, G. & Rahmani, R. (2009). Lindane and cell death: At the crossroads between apoptosis, necrosis and autophagy. *Toxicology,* 256., 32–41.

Pesticides in the Modern World - Pests Control and Pesticides Exposure and Toxicity Assessment

Edited by Dr. Margarita Stoytcheva

The present book is a collection of selected original research articles and reviews providing adequate and up-to-date information related to pesticides control, assessment, and toxicity. The first section covers a large spectrum of issues associated with the ecological, molecular, and biotechnological approaches to the understanding of the biological control, the mechanism of the biocontrol agents action, and the related effects. Second section provides recent information on biomarkers currently used to evaluate pesticide exposure, effects, and genetic susceptibility of a number of organisms. Some antioxidant enzymes and vitamins as biochemical markers for pesticide toxicity are examined. The inhibition of the cholinesterases as a specific biomarker for organophosphate and carbamate pesticides is commented, too. The third book section addresses to a variety of pesticides toxic effects and related issues including: the molecular mechanisms involved in pesticides-induced toxicity, fish histopathological, physiological, and DNA changes provoked by pesticides exposure, anticoagulant rodenticides mode of action, the potential of the cholinesterase inhibiting organophosphorus and carbamate pesticides, the effects of pesticides on bumblebee, spiders and scorpions, the metabolic fate of the pesticide-derived aromatic amines, etc.

INTECH
open science | open minds