Toxicology and Applied Pharmacology 353 (2018) 1–14

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap

Pesticides and cardiotoxicity. Where do we stand?

Nikolaos Georgiadis[a,g,1], Konstantinos Tsarouhas[b,1], Christina Tsitsimpikou[c,1], Alexandros Vardavas[d], Ramin Rezaee[e], Ioannis Germanakis[f], Aristides Tsatsakis[d], Dimitrios Stagos[g], Demetrios Kouretas[g,*]

[a] European Food Safety Authority, Via Carlo Magno 1A, 43126 Parma, Italy
[b] Department of Cardiology, University Hospital of Larissa, Mezourlo, Larissa 41110, Greece
[c] Generalr Chemical State Laboratory of Greece, 16 An. Tsocha Str., 11521 Athens, Greece
[d] Laboratory of Toxicology, Medical School, University of Crete, Voutes, Heraklion, 71003 Crete, Greece
[e] Clinical Research Unit, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Paediatric Cardiology Unit, Department of Paediatrics, University Hospital Voutes, Heraklion, 71409 Crete, Greece
[g] Department of Biochemistry- Biotechnology, School of Health Sciences, University of Thessaly, Viopolis, Larissa 41500, Greece

ARTICLE INFO

Keywords:
Pesticides
Cardiotoxicity
Heart
Oxidative stress
Myocardial infarction
CLP Regulation

ABSTRACT

Cardiovascular diseases are among the most significant causes of mortality in humans. Pesticides toxicity and risk for human health are controlled at a European level through a well-developed regulatory network, but cardiotoxicity is not described as a separate hazard class. Specific classification criteria should be developed within the frame of Regulation (EC) No 1272/2008 in order to classify chemicals as cardiotoxic, if applicable to avoid long-term cardiovascular complications. The aim of this study was to review the cardiac pathology and function impairment due to exposure to pesticides (i.e. organophosphates, organothiophisphates, organochlorines, carbamates, pyrethroids, dipyridyl herbicides, triazoles, triazines) based on both animal and human data. The majority of human data on cardiotoxicity of pesticides come from poisoning cases and epidemiological data. Several cardiovascular complications have been reported in animal models including electrocardiogram abnormalities, myocardial infarction, impaired systolic and diastolic performance, functional remodeling and histopathological findings, such as haemorrhage, vacuolisation, signs of apoptosis and degeneration.

1. Introduction

The term “pesticides” is commonly used as a synonym for plant protection products. Pesticides are mainly used to keep crops healthy and protect them from diseases and infestation. However, pesticides could also have broader applications to cover also products like biocides, which are intended for non-plant uses to control pests and disease vectors, such as insects, rats and mice. (Food and Agriculture Organization of the United Nations, 2002).

Plant protection products contain at least one active substance, which could be either a chemical or micro-organisms (e.g. viruses). When grouped into chemical families, the dominant pesticides groups include organochlorines, organophosphates and carbamates. According to the Stockholm Convention on Persistent Organic Pollutants, nine out of the twelve most dangerous and persistent organic chemicals are organochlorine pesticides (United Nations Environment Programme, 2005; Gilden et al., 2010). Organochlorine pesticides are chlorinated hydrocarbons. Representative and notorious compounds in this group include dichlorodiphenyltrichloroethane (DDT), methoxychlor, dieldrin, chlordane, toxaphene, mirex, chlordecone (Kepone), and gamma hexachlorocyclohexane (lindane) (Centers for Disease Control and Prevention, 2015). Nowadays, organophosphates and carbamates have replaced organochlorines world-wide. The chemical structures of the main classes of pesticides reviewed hereafter are presented in Fig. 1.

Regulation (EC) No 1107/2009 and Regulation (EU) No 528/2012 lay down rules and procedures for approval of the usage of active substances in plant protection and biocidal products at European Union (EU) level and for the authorisation of plant protection and biocidal products in the European market.

Authorisation of plant protection and biocidal products is based on the risk assessment thereof for human health and the environment, based on the identified hazards and classification of their active substances according to the Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008. The CLP Regulation is based on the

* Corresponding author.
E-mail address: dkouret@uth.gr (D. Kouretas).
[1] Contributed equally.

https://doi.org/10.1016/j.taap.2018.06.004
Received 23 February 2018; Received in revised form 30 May 2018; Accepted 3 June 2018
Available online 06 June 2018
0041-008X/

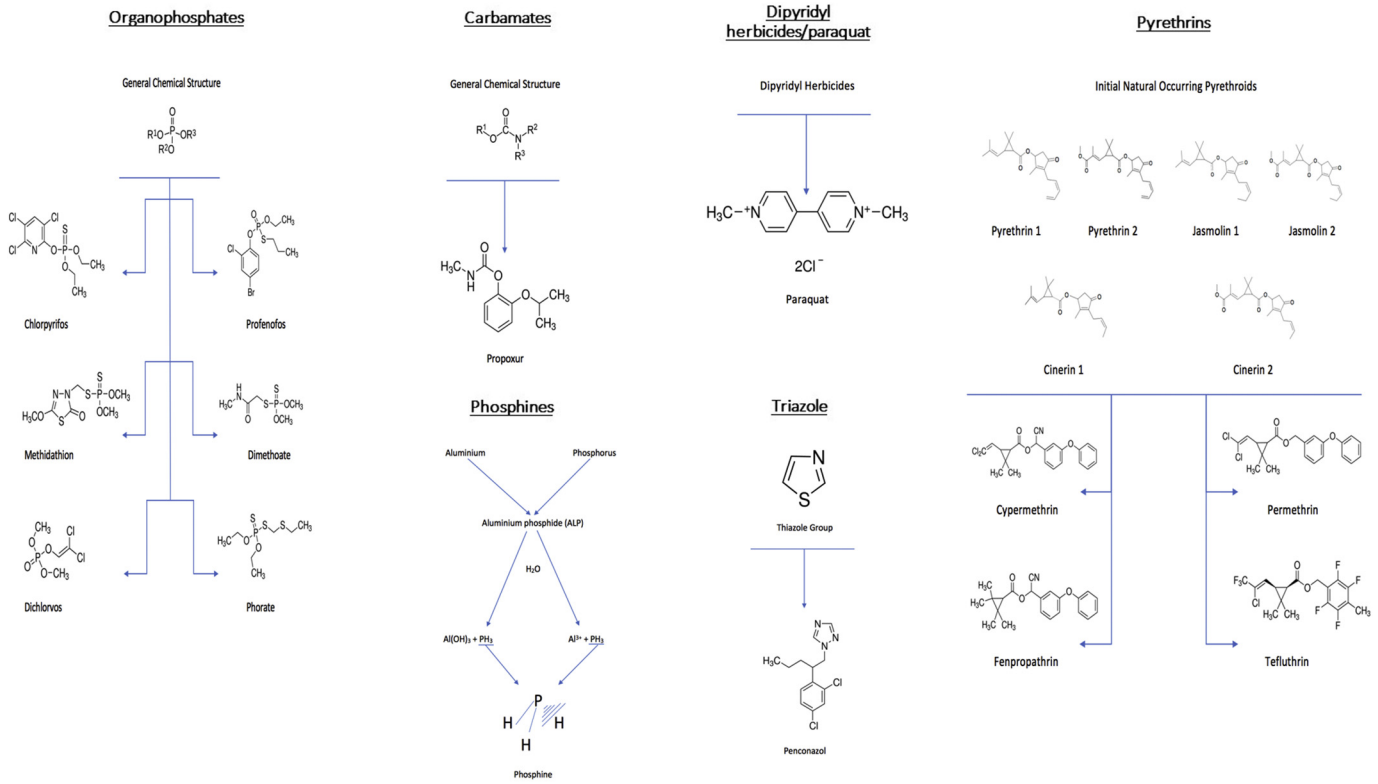

Fig. 1. Chemical structures of main classes of pesticides discussed.

United Nations' Globally Harmonised System (GHS) and is the only legislation in force in the EU for classification and labelling of substances and mixtures. CLP requires manufacturers, importers or downstream users of substances or mixtures to classify, label and package their hazardous chemicals before placing them on the market. One of the main aims of CLP is to determine whether a substance or mixture displays hazardous properties that lead to a classification.

When relevant toxicological data on a substance or mixture meets the classification criteria in CLP, the hazards of a substance or mixture are identified by assigning a certain hazard class and category. The hazard classes in CLP cover physical, health, environmental and human health hazards. More specifically for human health hazards the classifications are listed below:

- Acute toxicity (oral, dermal, inhalation)
- Skin corrosion/skin irritation
- Serious eye damage/eye irritation
- Respiratory sensitisation
- Skin sensitisation
- Mutagenicity
- Carcinogenicity
- Toxicity for reproduction
- Specific target organ toxicity STOT (single exposure, SE)
- Specific target organ toxicity STOT (repeated exposure, RE)
- Aspiration hazard

In CLP Regulation, cardiotoxicity is not described as a separate hazard class and no definite criteria are set in order to classify a chemical as cardiotoxic. In the CLP hazard class of STOT, on the contrary, criteria have been developed for toxic damage to the liver, the kidneys, the hematopoietic system, the various glands, like the thyroid gland, etc. Cardiotoxocity has been mainly linked to side effects of pharmaceuticals and it could be diagnosed many years post-exposure at the time of clinical manifestations (Berardi et al., 2013; Germanakis et al., 2013; Madeddu et al., 2016; Vasilaki et al., 2016; Baggish et al., 2017). As a result, allegedly cardiotoxic substances or products face no market restrictions at a regulatory level. In general, cardiotoxicity testing is an unmet need in the current screening programs of environmental chemicals (Sirenko et al., 2017).

There is a long-lasting discussion in the literature linking pesticides with several human pathologies, such as endocrine disruption, diabetes mellitus, Parkinson (Yan et al., 2018; Paul et al., 2018; Mesnage and Antoniou, 2018; Hennig et al., 2018; Adeyinka and Pierre, 2018; Hosseini et al., 2013; Clark, 2018; Hassani et al., 2018). Nevertheless, from a regulatory point of view pesticides can be classified only to the hazard classes of the CLP Regulation, listed above. Since 2012, when the European regulatory framework for pesticides came into force, several hazards for human health and the environment have been officially recognized for 79 pesticide active substances that were evaluated to be placed on the European market. These results are summarised in Table 1 and Fig. 2. Acute toxicity either orally or dermally or via inhalation is the most popular hazard identified, while for STOT RE the vast majority has to do with the liver and for STOT SE for respiratory irritation. Active substances identified as carcinogens have to be replaced and withdrawn from the market.

The current review summarises for the first time the various side-effects on the cardiovascular system reported either in animal models (in vivo and ex vivo experiments) or in humans (epidemiological studies, case reports) after exposure to organophosphates, carbamates, organothiophosphates, pyrethroids, organochlorines, dipyridyl herbicides (paraquat), triazines, triazoles, thiazoles. An effort is being made to classify these side effects into various classes of cardiotoxic disorders, based on the cardiovascular toxicity guidelines developed for cancer treatment (Zamorano et al., 2016), which are so far the only relevant guidelines for cardiotoxicity and refer to direct effects of the cancer treatment on heart function and structure, or may be due to accelerated development of cardiovascular disease, especially in the presence of traditional cardiovascular risk factors. In addition, the underlying mechanisms of the adverse outcomes are investigated in correlation with the mode of action of the various pesticides discussed.

Table 1
List of harmonised classification for human health and environmental hazards of pesticides (79) according to the CLP Regulation (Risk Assessment Committee opinions 2012 – April 2018).

Chemical identification	CAS No	Classification
		Hazard class and category code(s)
Pirimicarb (ISO)	23103-98-2	Carc. 2, Acute Tox. 3 (oral, inhalation), Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Bendiocarb (ISO)	22781-23-3	Acute Tox. 2 (oral), Acute Tox. 3 (dermal, inhalation), Aquatic Acute 1, Aquatic Chronic 1
Fenoxycarb (ISO)	72490-01-8	Carc. 2, Aquatic Acute, Aquatic Chronic 1
Calcium phosphide; tricalcium diphosphide	1305-99-3	Water-react. 1, Acute Tox. 1(inhalation), Acute Tox. 2 (oral), Acute Tox. 3 (dermal), Eye Dam. 1, Aquatic Acute 1
Fenamiphos (ISO)	22224-92-6	Acute Tox. 2 (oral, dermal, inhalation), Eye Irrit. 2, Aquatic Acute 1, Aquatic Chronic 1
Ethephon	16672-87-0	Acute Tox. 3 (dermal), Acute Tox. 4 (oral, inhalation), Acute Tox. 4, Skin Corr. 1C, Aquatic Chronic 2
Potassium (E,E)-hexa-2,4-dienoate	24634-61-5	Eye Irrit. 2
Dicopper oxide; copper (I) oxide	1317-39-1	Acute Tox. 4 (oral, inhalation), Eye Dam. 1, Aquatic Acute 1, Aquatic Chronic 1
Dicopper chloride trihydroxide	1332-65-6	Acute Tox. 3 (oral), Acute Tox. 4 (inhalation), Aquatic Acute 1, Aquatic Chronic 1
Copper flakes (coated with aliphatic acid)		Acute Tox. 3 (inhalation), Acute Tox. 4 (oral), Eye Irrit. 2, Aquatic Acute 1, Aquatic Chronic 1
Copper(II) carbonate–copper(II) hydroxide (1:1)	12069-69-1	Acute Tox. 4 (oral, inhalation), Eye Irrit. 2, Aquatic Acute 1, Aquatic Chronic 1
Copper dihydroxide; copper(II) hydroxide	20427-59-2	Acute Tox. 2 (inhalation), Acute Tox. 4 (oral), Eye Dam. 1, Aquatic Acute 1, Aquatic Chronic 1
Bordeaux mixture; reaction products of copper sulphate with calcium dihydroxide	8011-63-0	Acute Tox. 4 (inhalation), Eye Dam. 1, Aquatic Acute 1, Aquatic Chronic 1
Copper sulphate pentahydrate	7758-99-8	Acute Tox. 4 (oral), Eye Dam. 1, Aquatic Acute 1, Aquatic Chronic 1
Tebuconazole (ISO)	107534-96-3	Repr. 2, Acute Tox. 4 (oral), Aquatic Acute 1, Aquatic Chronic 1
Chlorophacinone (ISO)	3691-35-8	Repr. 1B, Acute Tox. 1 (oral, dermal, inhalation), STOT RE 1, Aquatic Acute 1, Aquatic Chronic 1
Isoxaflutole (ISO)	141112-29-0	Repr. 2, Aquatic Acute 1, Aquatic Chronic 1
Abamectin (combination of avermectin B1a and avermectin B1b) (ISO)	71751-41-2 [1] 65195-55-3 [2]	Repr. 2, Acute Tox. 1 (inhalation), Acute Tox. 2 (oral), STOT RE 1, Aquatic Acute 1, Aquatic Chronic 1
Acequinocyl (ISO)	57960-19-7	STOT SE 1, STOT RE 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Sulcotrione (ISO)	99105-77-8	Repr. 2, STOT RE 2, Skin Sens. 1A, Aquatic Acute 1, Aquatic Chronic 1
Tralkoxydim (ISO)	87820-88-0	Carc. 2, Acute Tox. 4 (oral), Aquatic Chronic 2
Cycloxydim (ISO)	101205-02-1	Repr. 2
Carvone (ISO)	99-49-0 [1] 2244-16-8 [2] 6485-40-1 [3]	Skin Sens. 1
Tembotrione (ISO)	335104-84-2	Repr. 2, STOT RE 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Clethodim (ISO)	99129-21-2	Acute Tox. 4 (oral), Skin Sens. 1, Aquatic Chronic 3
Anthraquinone	84-65-1	Carc. 1B
Warfarin (ISO)	81-81-2 [1] 5543-57-7 [2] 5543-58-8 [3]	Repr. 1A, Acute Tox. 1 (dermal, inhalation), Acute Tox. 2 (oral), STOT RE 1, Aquatic Chronic 2
Coumatetralyl (ISO)	5836-29-3	Repr. 1B, Acute Tox. 2 (inhalation), Acute Tox. 3 (oral), STOT RE 1, Aquatic Chronic 1
Difenacoum (ISO)	56073-07-5	Repr. 1B, Acute Tox. 1 (oral, dermal, inhalation), STOT RE 1, Aquatic Acute 1, Aquatic Chronic 1
Brodifacoum (ISO)	56073-10-0	Repr. 1A, Acute Tox. 1 (oral, dermal, inhalation), STOT RE 1, Aquatic Acute 1, Aquatic Chronic 1
Indoxacarb (ISO)	173584-44-6 [1] 144171-61-9 [2]	Acute Tox. 3 (oral), Acute Tox. 4 (inhalation), STOT RE 1, Skin Sens. 1B, Aquatic Acute 1, Aquatic Chronic 1
Benzoic acid	65-85-0	STOT RE 1, Skin Irrit. 2, Eye Dam. 1
Methyl 2,5-dichlorobenzoate	2905-69-3	Acute Tox. 4 (oral), STOT SE 3, Aquatic Chronic 2
Fenoxaprop-P-ethyl (ISO)	71283-80-2	STOT RE 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Spirotetramat (ISO)	203313-25-1	Repr. 2, STOT SE 3, Eye Irrit. 2, Skin Sens. 1A, Aquatic Acute 1, Aquatic Chronic 1
Dodemorph acetate; 4-cyclododecyl-2,6-dimethylmorpholin-4-ium acetate	31717-87-0	Repr. 2, STOT RE 2, Skin Corr. 1C, Skin Sens. 1A, Aquatic Chronic 1
Fenpyroximate (ISO)	134098-61-6	Acute Tox. 2 (inhalation), Acute Tox. 3 (oral), Skin Sens. 1B, Aquatic Acute 1, Aquatic Chronic 1
Triflusulfuron-methyl	126535-15-7	Carc. 2, Aquatic Acute 1, Aquatic Chronic 1
Bifenazate (ISO)	149877-41-8	STOT RE 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Bromadiolone (ISO)	28772-56-7	Repr. 1B, Acute Tox. 1 (oral, dermal, inhalation), STOT RE 1, Aquatic Acute 1, Aquatic Chronic 1
Tefluthrin (ISO)	79538-32-2	Acute Tox. 1 (inhalation), Acute Tox. 2 (oral, dermal), Aquatic Acute 1, Aquatic Chronic 1
Aclonifen (ISO)	74070-46-5	Carc. 2, Skin Sens. 1A, Aquatic Acute 1, Aquatic Chronic 1
Spiroxamine (ISO)	118134-30-8	Repr. 2, Acute Tox. 4 (oral, dermal, inhalation), STOT RE 2, Skin Irrit. 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Fluazinam (ISO)	79622-59-6	Repr. 2, Acute Tox. 4 (inhalation),vEye Dam. 1, Skin Sens. 1A, Aquatic Acute 1, Aquatic Chronic 1
Bupirimate (ISO)	41483-43-6	Carc. 2, Skin Sens. 1B, Aquatic Chronic 1
Triflumizole (ISO)	68694-11-1	Repr. 1B, Acute Tox. 4 (oral), STOT RE 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Fuberidazole (ISO)	3878-19-1	Carc. 2, Acute Tox. 4 (oral), STOT RE 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Imazalil (ISO)	35554-44-0	Carc. 2, Acute Tox. 3 (oral), Acute Tox. 4 (inhalation), Eye Dam. 1, Aquatic Chronic 1
Dodemorph (ISO)	1593-77-7	Repr. 2, STOT RE 2, Skin Corr. 1C, Skin Sens. 1A, Aquatic Acute 1, Aquatic Chronic 1
Chlorsulfuron (ISO)	64902-72-3	Aquatic Acute 1, Aquatic Chronic 1
Etridiazole (ISO)	2593-15-9	Carc. 2, Acute Tox. 4 (oral), Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Pyridaben (ISO)	96489-71-3	Acute Tox. 3 (oral, inhalation), Aquatic Acute 1, Aquatic Chronic 1
Flumioxazin (ISO)	103361-09-7	Repr. 1B, Aquatic Acute 1, Aquatic Chronic 1

(*continued on next page*)

Table 1 (*continued*)

Chemical identification	CAS No	Classification
		Hazard class and category code(s)
Epoxiconazole (ISO)	133855-98-8	Carc. 2, Repr. 1B, Aquatic Chronic 2
Penconazole (ISO)	66246-88-6	Repr. 2, Acute Tox. 4 (oral), Aquatic Acute 1, Aquatic Chronic 1
Fenpyrazamine (ISO)	473798-59-3	Aquatic Acute 1, Aquatic Chronic 1
Lenacil (ISO)	2164-08-1	Carc. 2, Aquatic Acute 1, Aquatic Chronic 1
Triadimenol (ISO)	55219-65-3	Repr. 1B, Lact., Acute Tox. 4 (oral), Aquatic Chronic 2
Terbuthylazine (ISO)	5915-41-3	Acute Tox. 4 (oral), STOT RE 2, Aquatic Acute 1, Aquatic Chronic 1
Quinolin-8-ol; 8-hydroxyquinoline	148-24-3	Repr. 1B, Acute Tox. 3 (oral), Eye Dam. 1, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Thiacloprid (ISO)	111988-49-9	Carc. 2, Repr. 1B, Acute Tox. 3 (oral), Acute Tox. 4 (inhalation), STOT SE 3, Aquatic Acute 1, Aquatic Chronic 1
Cyanamide; carbamonitril	420-04-2	Carc. 2, Repr. 2, Acute Tox. 3 (oral, dermal), STOT RE 2, Skin Corr. 1, Eye Dam. 1, Skin Sens. 1, Aquatic Chronic 3
Cymoxanil (ISO)	57966-95-7	Repr. 2, Acute Tox. 4 (oral), STOT RE 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Acetochlor (ISO)	34256-82-1	Carc. 2, Repr. 2, Acute Tox. 4 (inhalation), STOT SE 3, STOT RE 2, Skin Irrit. 2, Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Metazachlor (ISO)	67129-08-2	Carc. 2, Skin Sens. 1B, Aquatic Acute 1, Aquatic Chronic 1
Flufenoxuron (ISO)	101463-69-8	Repro Lact., Aquatic Acute 1, Aquatic Chronic 1
Tebufenpyrad (ISO)	119168-77-3	Acute Tox. 3 (oral), Acute Tox. 4 (inhalation), STOT RE 2, Skin Sens. 1B, Aquatic Acute 1, Aquatic Chronic 1
Proquinazid (ISO)	189278-12-4	Carc. 2, Aquatic Acute 1, Aquatic Chronic 1
Metosulam (ISO)	139528-85-1	Carc. 2, STOT RE 2, Aquatic Acute 1, Aquatic Chronic 1
Dimethenamid-P (ISO)	163515-14-8	Acute Tox. 4 (oral), Skin Sens. 1, Aquatic Acute 1, Aquatic Chronic 1
Flonicamid (ISO)	158062-67-0	Acute Tox. 4 (oral)
Sulfoxaflor (ISO)	946578-00-3	Acute Tox. 4 (oral), Aquatic Acute 1, Aquatic Chronic 1
Benzovindiflupyr (ISO)	1072957-71-1	Acute Tox. 3 (oral, inhalation), Aquatic Acute 1, Aquatic Chronic 1
Carbetamide (ISO	16118-49-3	Carc. 2, Repr. 1B, Acute Tox. 4 (oral), Aquatic Chronic 2

2. Methods

In this evaluative literature review, the literature was screened up to April 2018 with due emphasis given to the past five years. MEDLINE and Embase databases were searched, using the following key words: pesticides, pesticide toxicity, pesticides exposure, cardiotoxicity, mode of action, cardiac effects, organophosphate & cardiotoxicity, organochlorine & cardiotoxicity, carbamates & cardiotoxicity, pyrethroids & cardiotoxicity, triazole & cardiotoxicity, triazines & cardiotoxicity, either in the title, abstracts, or in the text. The relevance of the subject and eligibility in all the publications detected was further evaluated based on the title and abstract. Human data and animal data from rodents were assessed. Data on zebrafish were excluded.

In general, the cardiovascular complications mainly as a results of cancer therapy can be divided into nine categories: myocardial dysfunction and heart failure (HF); coronary artery disease (CAD); valvular disease; arrhythmias, especially those induced by QT-prolonging drugs; arterial hypertension; thromboembolic disease; peripheral vascular disease and stroke; pulmonary hypertension and pericardial complications (Zamorano et al., 2016). Having those categories in mind and based on the findings of the studies discussed in the present review, the following classes of cardiovascular disorders have been identified and used hereafter: (1) Myocardial dysfunction, (2) Electrical, (3) Biochemical (oxidative damage), (4) Anatomical, (5) Cytopathological, (6) Histopathological, (7) Biochemical (functional implications), (8) Coronary artery disease, (9) Biochemical (lipidemic profile and other), (10) Blood pressure disorders (hypertension, hypotension). The precise timing of the cardiovascular disorders associated with pesticide

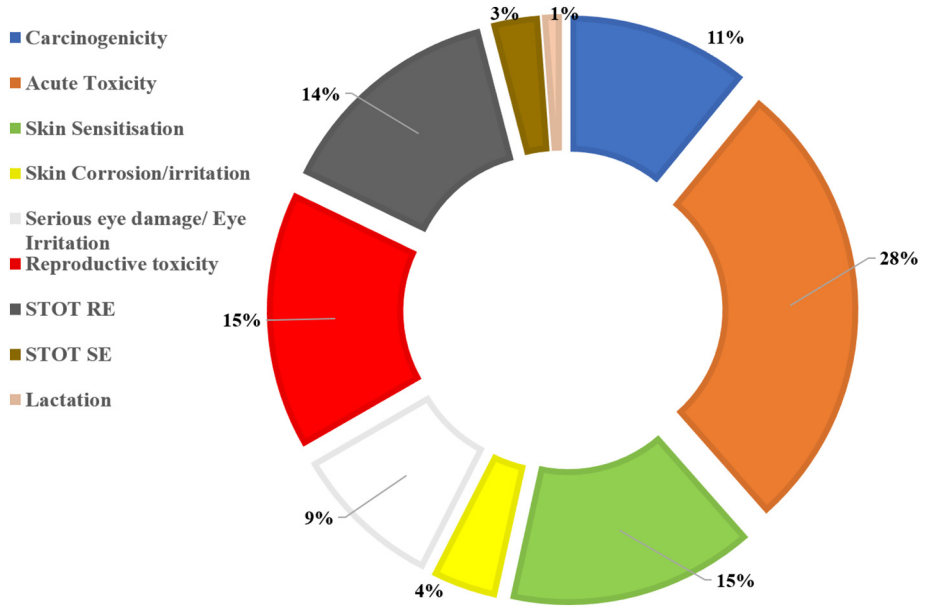

Fig. 2. The most common hazard classes identified for pesticides under CLP.

exposure is an issue to be addressed, while more than one of the classes described above can co-exist in a specific cardiovascular manifestation due to pesticide exposure. Whether a specific class precedes the others in a specific toxicity setting is also an issue for further study. Myocardial function suppression, for example, can be the result of an earlier myocardial insult that leads to cardiac remodeling. Biochemical disorders in the form of oxidative stress leading to membrane lipid peroxidation can provoque subclinical cardiovascular disease and precede myocardial echocardiographic findings. In many cases subcellular insults affect many organs, not only the heart. Heart has a limited regenerative capacity, though. Therefore, when aggregated toxicity exceeds a certain threshold of damage, a process of ventricular remodeling common to multiple forms of cardiac injury is initiated (Sawyer et al., 2010).

Scientific uncertainties: The main uncertainty remains the fact that, according to the statistical meta-analysis performed by the authors (goodness of fit), not all classes of disorders/side effects have been equally explored in each study analyzed in this report nor, in each mode of action of pesticides recognized, the same toxicity evaluation methods were performed.

3. Results

The mode of action of the most common classes of pesticides reviewed in the present study is summarised in Table 2. The more interesting and comprehensive published cardiotoxic effects of organophosphates (diazinon, chlorpyrifos, methidathion, malathion, profenofos, monoctotophos, dimethoate, and dichlorvos), organothiophosphates (phorate), carbamates (propoxur), pyrethroids (tefluthrin, fenpropathrin, cypermethrin, tetramethrin, prallethrin and permethrin), organochlorines (endosulfan and lindane), dipyridyl herbicides (paraquat), phosphides (aluminum phosphide), triazines (atrazine) and thiazoles (penconazole, itraconazole) on experimental animals and humans are summarised in Tables 3-7.

> 40% of the studies reviewed reporting cardiotoxicity deal with pesticides acting through inhibition of carboxyl ester hydrolases, particularly acetylcholinesterase (AChE). The most prominent side effect reported in this mode of action is oxidative stress induced in the myocardial tissue (ca 30%), which is also common in all mode of actions reviewed (ca24%). One third of the effects noted due to exposure to pesticides that alter the function of voltage-gated sodium channels are electrical disorders, which account for 14% of the total number of disorders discussed. Myocardial dysfunction accounts for ca 15% of the disorders observed and coronary artery disease for almost 8% of the disorders, with a universal distribution in all modes of actions. A more detailed discussion follows.

3.1. Inhibition of acetylcholinesterase (AChE) – organophospathes

Early studies using in vivo experimental models provide evidence for dose-dependent direct cardiotoxic effects of organophosphate pesticides. Even back in 1968, experiments by Wolthuis et al. (Wolthuis and Meeter, 1968) showed that the organophosphate diisopropyl fluorophosphate (DFP) could induce cardiac failure in rats. At the same time, clinical observations (Kabrawala et al., 1965) and abnormal electrocardiogram (ECG) patterns (Kiss and Fazekas, 1979) supported the early thoughts of organophosphates' cardiotoxicity in humans. Nevertheless, a meta-analysis on myocardial infarction incidences in licensed organophosphates and carbamates applicators, primarily farmers with pesticide licenses, in North Carolina and Iowa from the Agricultural Health Study, reported limited association between the lifetime use of 49 pesticides and fatal and nonfatal myocardial infarction (Mills et al., 2009).

The vast majority of the cardiotoxic effects of organophosphates in animals are reported after subchronic/chronic exposure (14 days to 12 months) (Table 3). In humans data boh form epidemiology and from acute poisoning point to coronary artery disease as the manin cardiotoxic outcome of organophosphates. It seems that there are complex and multifactorial pathways involved in the development of the abovementioned cardiac toxicity, which also lead to disturbed cardiac rhythms and arrhythmias in organophosphate poisoning. Following acute exposure to organophosphates, acetylcholinesterase inhibition occurs and parasympathetic over-activity predominates (Roth et al., 1993; Tsatsakis et al., 1996a; Tsatsakis et al., 1996b). It has been reported that selenium or vitamin E supplementation restored acetylcholinesterase and Na1K1-ATPase activity in the heart after exposure to organophosphates (Amara et al., 2013). Long-term cardiac manifestations include QT prolongation, with or without simultaneous troponin increase, and in many cases without obvious anatomical or histopathological abnormalities (Shiyovich et al., 2018; Yavuz et al., 2004; Velmurugan et al., 2013). In humans, though, fatally exposed to organophospahtes and with similar QT prolongation, ST- and T-abnormalities, histopathological evidence of focal necrosis and regeneration were noted (Kiss and Fazekas, 1979; Bar-Meir et al., 2007; Ludomirsky et al., 1982). On the other hand, elevated levels of Creatine Kinase Isoenzyme MB (CK-MB) have been reported (Razavi et al., 2013; Velmurugan et al., 2013). Apoptosis, as depicted by Bax/Bcl2 ratio elevation (at both protein and mRNA levels), cytochrome c cytosolic release and caspase-3 activation in cardiac tissue, is suggested to be involved in the myocardial damage induced by organophosphates (Razavi et al., 2015). Uncommon arrhythmias may appear late after organophospate poisoning even after apparent clinical recovery and can be attributed to cardiotoxic effects, metabolic (acidosis) and electrolyte derangements or even to recovery and healing mechanisms of the damaged myocardium. Despite the usual lack of severe echocardiographic anomalies in organophosphate poisoning, patchy myocardial involvement has been found in histopathological analysis post mortem, suggesting a possible origin of late electrical anomaly (Anand et al., 2009). It has been reported that following intoxication, the levels of free fatty acids increase and lipid homeostasis is altered (Kiss and Fazekas, 1979; Zaki,

Table 2
Most important Mode of Actions of groups of pesticides found in the literature (Shaon Kumar Das, 2013).

Type of pesticide	Mode of action
Organophosphates/Carbamates	Inhibition of carboxyl ester hydrolases, particularly acetylcholinesterase (AChE)
Pyrethroids	Alter the function of voltage-gated sodium channels in insect neuronal membranes, thereby disrupting electrical signalling in the nervous system
Organochlorines	Ligand-gated ion channel activity (GABA-gated chlorine channel blockers)
Phosphines	Cellular hypoxia due to the effect on mitochondria, inhibition of cytochrome C oxidase and formation of highly reactive hydroxyl radicals (mitochondrial complex IV electron transport inhibitors)
Triazoles	Block the cytochrome P450-dependent enzyme C-14 alpha-demethylase, which is needed to convert lanosterol to ergosterol
Triazines	Inhibition of primary events in photosynthesis in the chloroplast: binding to the D-1 protein in photosynthetic electron transport. This binding stops photosynthesis. Inhibition requires the presence of light and transpiration to move the chemical to foliage (Photosystem II (PSII) inhibition)
Dipyridyl	Photosystem I (PSI) inhibition: photosynthesis is affected leading to destruction of cell membranes; the specific effect is much faster than other desiccators (Summers, 1980)

Table 3
Cardiotoxic effects of organophosphates, carbamates and organothiophosphates in experimental animals and human data.

Subject	Substance/Dose	Exposure Route/Period	Evaluation Method	Signs of Cardiotoxicity (class of disorder[a])	Reference
New Zealand Rabbits	Diazinon (2.6 and 5.2 mg/kg/day) Propoxur (8.8 and 18 mg/kg/day) Chlorpyrifos (8.7 and 18 mg/kg/day)	Oral daily administration for 12 months	Echocardiography Biochemical and histpathological evaluations	• Reduced systolic and diastolic performances (1) • Increased oxidative stress of the cardiac tissues. Diazinon and propoxur increased lipid peroxidation in plasma (3) • Increased oxidative modifications in the genomic DNA content of the cardiac tissues (3) • Thin-walled left ventricles with reduced myocardial mass, impaired systolic (radial and longitudinal) and diastolic LV function assessed by M-Mode, PW and TDI Doppler (1) • Diazinon and propoxur retained in the cardiac tissue	(Zafiropoulos et al., 2014; Akturk et al., 2006)
Male Wistar rats	Methidathion (5 mg/kg)	Oral administration (5 days/week) for 4 weeks	Biochemical and histpathological evaluations	• Increase of lipid peroxidation (3)	(Yavuz et al., 2004)
Male Wistar rats	Chlorpyrifos (5.4 mg/kg equal to 1/25 of the oral LD50)	Oral administration for 4 weeks	Biochemical and histopathological evaluations	• Increased levels of MDA, SOD and CAT; decreased GPx and GST activities in heart (3)	(Bas and Kalender, 2011)
Male New Zealand rabbits	Chlorpyrifos (0, 125, 250 or 375 ppm in drinking water)	Oral administration for 90 days	Echocardiography	• Significant decrease ($p < .05$) in HR, cardiac output (CO), left ventricular fractional shortening (FS), left ventricular ejection fraction (EF), percentage thickening of left ventricle posterior wall (PWT) (1) • Significant increase ($p < .05$) in left atrial diameter (LA), left ventricular internal diameter in end diastole (LVIDD), left ventricular end diastolic (EDV) and end systolic volumes (ESV) compared to controls (1)	(Cetin et al., 2007)
Rats	Chlorpyrifos (1 or 5 mg/kg)	Subcutaneous injections on gestational days 9–12 or 17–20 or on postnatal days (PN) 1–4 or 11–14 Assessments done on PN60	Cardiac and Hepatic Cell Signalling	• Cell signalling cascades (7)	(Meyer et al., 2004)
Sexually mature male white rats	Profenofos (47.5 mg/kg for acute toxicity and 23.75 mg/kg for subchronic toxicity)	Oral administration Acute intoxication: 120 h Subchronic exposure: 14 days Withdrawal group: 14 days	Biochemical and Enzymes activities assays	• Alters lipid metabolism (9) • Increase the activities of cytotoxicity enzymes biomarkers (5)	(Zaki, 2012)
Female Sprague-Dawley rats	Diazinon (8, 10, 12 and 20 mg/kg) (oral LD50 = 300 mg/kg)	Oral administration for 3 weeks	Biochemical assays Histopathological evaluations	• Induced varying degrees of oxidative damage (3) • The histological analysis of cardiac and skeletal muscle fibers demonstrated large areas of degenerating muscle fibers with evident loss of transverse striations and wide interfascicular spaces (6)	(Abdou and ElMazoudy, 2010)
Adult female rats	Dimethoate (0.2 g/l drinking water)	Oral administration 30 days	Biochemical assays Histopathological evaluations	• Promoted oxidative stress with a rise in malondialdehyde, advanced protein oxidation, and protein carbonyl levels. An increase of glutathione peroxidase, superoxide dismutase, and catalase activities was also noted (3) • Derease in acetylcholinesterase and Na, K -ATPase activities (2) • Plasma levels of cholesterol, triglycerides, and low density lipoprotein-cholesterol increased and those of high density lipoprotein-cholesterol decreased (9)	(Amara et al., 2013)
Male Wistar albino rats	Diazinon (20 mg/kg)	Oral administration for 28 days	Biochemical assays	• A significant increase in cardiac MDA and NO content was observed compared with the control group, but cardiac antioxidants were significantly ($p \leq .05$) decreased (3)	(Abdel-Daim et al., 2016)
Rats	Diazinon (15 mg/kg/day)	Oral administration for 28 days	Biochemical assays	• Increased MDA level (3) • Lower level of reduced GSH (3) • Induction of apoptosis (5)	(Razavi et al., 2013)
Adult male Wistar rats	Diazinon (15 mg/kg/day)	Oral administration for 28 days	Biochemical assays	• Total ubiquitylation[b] of myocardial proteins was increased by 79% (7)	(Razavi et al., 2015)
Male Wistar rats		Oral administration for 14 days			(Saquib et al., 2012)

(*continued on next page*)

Table 3 (*continued*)

Subject	Substance/Dose	Exposure Route/Period	Evaluation Method	Signs of Cardiotoxicity (class of disorder[a])	Reference
	Phorate (0.046, 0.092 or 0.184 mg/kg)		Histopathological evaluations	• Congestion and haemorrhage, cardiac myofiber degeneration and round and shrunken focal degenerating myocytes (6)	
Adult male Sprague–Dawley rats	Dichlorvos (0.25 LD50, 7.5 mg/kg), (0.35 LD50, 10.5 mg/kg), (0.5 LD50, 15.0 mg/kg), (0.75 LD50, 22.5 mg/kg), and (1.4 LD50, 42.0 mg/kg)	Intraperitoneal administration, evaluation at 2 and 6 weeks post-exposure	Echocardiography Histopathological evaluations	• QT prolongation without anatomical or histopathological abnormalities (2)	(Shiyovich et al., 2018)
Wistar rats	Monocrotophos (MCP) (0.36 mg/kg/day equal to 1/50 oral LD50)	Oral administration for 3 weeks	Biochemical assays Histopathological evaluations	• Cardiac oxidative stress was conferred by accumulation of protein carbonyls, lipid peroxidation and glutathione production. The cardiac markers (cTn-I, CK-MB and LDH) were showed elevated expression in blood plasma, which signals the cardiac tissue damage (3) • The histopathology of the heart tissue authenticated the MCP induced tissue damage by showing signs of nonspecific inflammatory changes and oedema between muscle fibers (6)	(Velmurugan et al., 2013)
Meta-analysis in the Agricultural Health Study, USA	Organophosphates Carbamates	Self-reporting use (1993–1997)		• Myocardial infarction mortality, insecticide use Hazard Ratio (HR) = 0.93 (8) • Non-fatal myocardial infarction incidence, insecticide use HR = 0.85 (8)	(Mills et al., 2009)
Ex vivo study	Malathion (10, 15, 20 and 25 μg/ml)	Direct effect on human cardiac myocytes	MTT cell proliferation assay	• Toxicity in cardiac cells (5) LD50 calculated as 20 μg/ml	(Atale et al., 2014)
41 patients at emergency care unit	Dichlorvos (dosage not specified)	Acute oral poisoning		• Sinus tachycardia (2) • ST-T changes (8) • Decreases in wall motion of the interventricular septum and left ventricle (reversible) (8) • Abnormal left ventricle perfusion (1)	(He et al., 2011)

[a] Classes of cardiovascular disorders: (1) Myocardial dysfunction, (2) Electrical, (3) Biochemical (oxidative damage), (4) Anatomical, (5) Cytopathological, (6) Histopathological, (7) Biochemical (functional implications), (8) Coronary artery disease, (9) Biochemical (lipidemic profile and other), (10) Blood pressure disorders (hypertension, hypotension).

[b] Ubiquitin (Ub) is a small protein which covalently binds to lysine (Lys) residues of target proteins to presumably mark targeted proteins for degradation. At the same time, ubiquitylation regulates a number of biological processes, including DNA repair and replication, gene expression and apoptosis (Haglund and Dikic, 2005; Razavi et al., 2015).

Table 4
Cardiotoxic effects of pyrethroids in experimental animals and human data.

Subject	Substance/Dose	Exposure Route/Exposure Period	Evaluation Method	Signs of Cardiotoxicity (class of disorder[a])	Reference
Wistar rats and guinea pig	Tefluthrin Fenpropathrin Cypermethrin Tetramethrin (10 μM for each one)	Ex vivo study, direct action on Isolated heart ventricular myocytes	Electrophysiology	• Prolonged ventricular action potentials revoked after depolarizations (1) • Modified the time course of INa by altering the relative proportions of fast and slowly inactivating current (2) • Altered the voltage dependence of INa (2)	(Spencer et al., 2001)
Male and Female 500-day-old rats	Permethrin (4 ml/kg equal to 1/50 of LD50)	Oral administration from the 6th to 21st day of life	Gene expression Calcium levels Heart surface area Histopathology	• Cardiac hypotrophy (4) • Increased calcium and Nrf2 gene expression levels in old age (3) The histological analysis of cardiac and skeletal muscle fibers demonstrated large areas of degenerating muscle fibers with evident loss of transverse striations and wide interfascicular spaces (6)	(Vadhana et al., 2013)
Case Report 28-year-old Female	Prallethrin (20 ml of a preparation containing prallethrin (1.6%) and piperonyl butoxide (5%)	Intentional ingestion		• Metabolic acidosis (7) • Sinus arrest (2)	(Bhaskar et al., 2010)
Epidemiological study, 72 CHD patients and 136 healthy individuals	Pyrethroids and pyrethroids metabolites	Exposure that led to urinary excretion		• Increased levels in Coronary Heart Disease (CHD) patients (8)	(Han et al., 2017)
Freshly isolated rat heart cells (in vitro)	Permethrin (5, 10, 20 μM)		DNA damage assessed by comet assay	• Significant difference in % tail DNA between all concentrations of permethrin (7)	(Vadhana et al., 2010)

[a] Classes of cardiovascular disorders: (1) Myocardial dysfunction, (2) Electrical, (3) Biochemical (oxidative damage), (4) Anatomical, (5) Cytopathological, (6) Histopathological, (7) Biochemical (functional implications), (8) Coronary artery disease, (9) Biochemical (lipidemic profile and other), (10) Blood pressure disorders (hypertension, hypotension).

2012), which can contribute to the arrhythmogenicity. In addition, exposure to organophosphates, like profenofos, increases cytotoxicity enzymes activity, rendering them a possible cause for dysfunction of organs, such as the liver, kidney, heart and muscles (Zaki, 2012). A generally distorted redox status has been reported for experimental animals exposed to organophosphates (Bas and Kalender, 2011; Yavuz et al., 2004; Razavi et al., 2015). It should be noted that the heart is particularly sensitive to peroxidative insults due to its limited antioxidant defenses that can enzymatically counteract hydroxyl radicals (Doroshow et al., 1980). It has also been suggested that the developmental toxicity of several organophosphates, such as chlorpyrifos, extends beyond the nervous system to other organs' cell signalling cascades, which could be proven vital to cardiac and hepatic homeostasis (Meyer et al., 2004). In two recent studies (Zafiropoulos et al., 2014; Koutroulakis et al., 2014) residues of diazinon and chlorpyrifos were detected in the cardiac tissue and the amniotic fluid. Residues of pesticides in the heart is not expected, since heart is not directly involved in the toxicokinetics of pesticides, as it is the liver and the kidneys; distribution of the chemicals to the organs differs by their log K_{OW} and generally follows the blood flow path after the gastrointestinal tract (Dang et al., 2016).

3.2. Altered function of voltage-gated sodium channels – pyrethroids

Pyrethroid insecticides are known to affect the functions of sodium channels, which are present both in neuronal and cardiac cells. Pyrethroids are thought to be able to shift both voltage-dependent activation and inactivation of Na channels to hyperpolarized potentials (Trainer et al., 1997; Spencer et al., 2001). Cardiac myocytes are rich in sodium channels. The type I pyrethroid, tefluthrin, and the type II pyrethroids, fenpropathrin and α-cypermethrin (see Fig. 1), modify the time course of sodium channel current {I(Na)} by altering the relative proportions of fast and slowly inactivating current and alter the voltage dependence of I(Na), prolong the ventricular action potentials and evoke after-depolarizations, indicating an arrythmogenic activity (Spencer et al., 2001). Similarly, in a 28-year-old female having accidentally consumed prallethrin, metabolic acidosis and sinus arrest with escape junctional rhythm were developed, which persisted for 3 days, despite the correction of metabolic acidosis. Consequently, sinus rhythm with bradycardia was established, possibly due to pyrethroid effect on myocardial cells sodium channels. The human poisoning cases due to pyrethroids are limited, probably due to the high excretion rate of pyrethroids (Scheme and Team, 2005). Nevertheless, epidemiology could support a possible positive association between pyrethroids exposure and the risk of coronary heart disease (Han et al., 2017). In the same context of ion signalling, cytosol calcium levels are important for the cardiac muscle contractile state. A transient increase in cytosolic calcium is required for each cardiac cycle. It was found that early-life exposure to low doses of permethrin led to rats' cardiac muscle hypotrophy along with increased heart cells' calcium (de la Cerda et al., 2002; Vadhana et al., 2013). Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor found in the cardiovascular system that controls the expression of a number of antioxidant genes and other cytoprotective phase-II detoxifying enzymes (Li et al., 2009). Increased Nrf2 gene expression levels were observed following pyrethroid exposure, especially in older animals (Vadhana et al., 2013). Similar to organophosphates, ROS generation in heart tissues has been implicated in pyrethroid toxicity, as it was found that pyrethroids increase lipid peroxidation, alter the antioxidant capacity in heart cells' plasma membrane and induce oxidative DNA base modifications (Kale et al., 1999; You et al., 2000; Vadhana et al., 2010). Permethrin has also been shown to accumulate in heart cells (0.1–0.2% of dietary intake) (Vadhana et al., 2010).

Table 5
Cardiotoxic effects of organochlorines and dipyridyl pesticides (paraquat) in experimental animals and human data.

Subject	Substance/dose	Exposure Route/Exposure Period	Evaluation Method	Signs of Cardiotoxicity (class of disorder[b])	Reference
Male Wistar rats	Endosulfan 2 mg/kg/day	Oral administration for 6 weeks	Measurement of antioxidant enzymes activities	• SOD, GPx, CAT activities and MDA level increased in the endosulfan-treated group heart tissue compared to control group (3) • Cytoplasmic edema and swelling and vacuolization of mitochondria of myocardial cells in endosulfan-treated group (6)	(Kalender et al., 2004)
Male rats	Endosulfan 2 mg/kg/day	Oral administration for 28 days	Histopathological evaluations	• Sever congestion; Haemorrhages with interstitial oedema; Diapedesis of leukocytes; Myocardium showed different degrees of degeneration; Some of the myofibrils were found to be granular with pyknotic nuclei (6) • Thickening of wall of arteries (4)	(Jalili et al., 2007a)
Case Report 50-years-old female	Lindane (dose not mentioned)	Accidental ingestion		• NSTEMI (non-ST segment elevation myocardial infarction) (8) • Left Ventricular (LV) dysfunction (1)	(Ramachandra and Rachel, 2013)
Review article	Endosulfan	Poisoning		• Hypotension, (10) • ECG abnormalities (2)	(Ozmen, 2011)
Rats	Lindane (100 mg/kg)	Oral administration for 30 days	Biochemical analysis Histopathology	• Elevated activity for serum marker enzymes, lipid peroxidation (LPO), and membrane-bound Ca^{2}+ ATPase, with a concomitant decrease in the level of non-enzymatic antioxidant (GSH), enzymatic antioxidants such as SOD, CAT, GPx, and GST, and membrane-bound ATPases like Na +/K+ ATPase and Mg2+ ATPase in heart tissue (3) • Pathological changes(6)	(Vijaya Padma et al., 2013)
Adult male wild-type (WT) and TLR4 knockout (TLR42/2) mice	Paraquat[a] 45 mg/kg	Intraperitoneal administration	Histopathological evaluations done after 48 h	Myocardial functional and geometric alterations including enlarged left ventricular end systolic diameter (LVESD), reduced fractional shortening, decreased sarcomere shortening, maximal velocities of sarcomere shortening and relengthening associated with unchanged LV posterior wall thickness, septal thickness, LV end diastolic diameter (LVEDD), heart rate, sarcomere length, time-to-peak shortening and time-to-90% relengthening (1)	(Lei et al., 2017)
Akt2 knockout mice	Paraquat[a] (45 mg/kg)	A single intraperitoneal injection	Echocardiography followed by isolation of cardiomyocytes for evaluation of mechanical properties of myocytes and intracellular Ca^{2+} levels. Aconitase and citrate synthase activities were measured in heart homogenates.	• Decreased intracellular Ca^{2+} release (2) • Significant decreases in fractional shortening, but no changes in other geometric parameters (1) • Increased myocardial apoptosis as reflected by upregulated Bax, downregulated Bcl-2 and elevated caspase-3 activity (5)	(Wang et al., 2017)
Cardiac-specific overexpression catalase mice and FVB littermates as wild type	Paraquat[a] (75 mg/kg)	A single intraperitoneal injection, examination48 h later	Echocardiography, edge detection, caspase-3 activity, immunoblotting	• Enlarged left ventricular (LV) end diastolic and systolic diameters; increased LV mass and resting myocyte length; reduced fractional shortening, cardiomyocyte peak shortening, and maximal velocity of shortening/ relengthening; and prolonged relengthening duration in the FVB group (1) • increased apoptosis ablated by the catalase transgene (5 with underlying 3)	(Ge et al., 2010)

(*continued on next page*)

Table 5 (*continued*)

Subject	Substance/dose	Exposure Route/Exposure Period	Evaluation Method	Signs of Cardiotoxicity (class of disorder[b])	Reference
Wild-type and transgenic mice with overexpression of a mutant AMPK	Paraquat[a] (45 mg/kg)	A single intraperitoneal injection	Echocardiography followed by isolation of cardiomyocytes for evaluation of cell shortening/relengthening, intracellular Ca^{2+} transients, measurement of mitochondrial membrane potential	• Cardiac mechanical anomalies and compromised echocardiographic parameters (elevated left ventricular end-systolic diameter and reduced factional shortening) (1) • Suppressed cardiomyocyte contractile function, intracellular Ca^{2+} handling (2) • overt mitochondrial damage (loss in mitochondrial membrane potential) (2) • promoted phosphorylation of AMPK and autophagy, reduced cell survival (5)	(Wang et al., 2014)
Toll-like receptor 4 (TLR4) knockout (TLR4 − / −) mice	Paraquat[a] (45 mg/kg)	A single intraperitoneal injection	Heart rate measurement followed by isolation of cardiomyocytes for evaluation of mechanical properties of myocytes and intracellular Ca^{2+} levels.	• No effect was observed in terms of diastolic, systolic and mean blood pressures following exposure to paraquat. • No effect was observed in cell length. • Paraquat significantly increased intracellular Ca^{2+} decay rate. (2)	(Wang et al., 2016)

[a] Paraquat is quaternary nitrogen dipyridyl pesticide with a Cl^- moiety.

[b] Classes of cardiovascular disorders: (1) Myocardial dysfunction, (2) Electrical, (3) Biochemical (oxidative damage), (4) Anatomical, (5) Cytopathological, (6) Histopathological, (7) Biochemical (functional implications), (8) Coronary artery disease, (9) Biochemical (lipidemic profile and other), (10) Blood pressure disorders (hypertension, hypotension).

3.3. GABA-gated chlorine channel blockers – organochlorines

The Na^+/K^+ ATPase activity is crucial for the maintenance of the ionic balance and the resting electric potential of the cell membrane. It also serves as a signal transducer-regulator of cell enzymes and intracellular calcium levels acting in parallel with Ca^{2+} ATPase (Bers et al., 2003). Lindane increased membrane-bound Ca^{2+} ATPase activity, while both Na^+/K^+ ATPase and Mg^{2+}ATPase activities were suppressed (Vijaya Padma et al., 2013). Redox status of the myocardial tissue was also distorted by organochlorines, with lipid peroxidation being the most prominent effect (Vijaya Padma et al., 2013; Kalender et al., 2004). It is interesting that endosulfan affected myocardial cells from rats even at doses lower than LD_{50} values. It should be also considered that even at doses that are quite below the legally permitted limits of contamination/exposure, combinations of chemicals may produce unpredicted toxicities necessitating evaluation of cardiotoxic effects of pesticides (at doses below the acceptable levels), when accidental co-exposure with other frequently used chemicals takes place (Tsatsakis et al., 2016). In humans, organochlorines poisoning led to hypotension and electrocardiographic abnormalities, myocardial infarction and left ventricular myocardial dysfunction (Ramachandra and Rachel, 2013; Ozmen, 2011). Lindane accumulates in appreciable amounts in the heart and causes oxidative stress by modifying the scavenger enzymes activity (Ramachandra and Rachel, 2013). Chronic application of low doses of lindane shortened the action potential duration in rat papillary muscle. These effects were similar to those induced by hyperthyroidism (Sauviat and Pages, 2002).

3.4. Cellular hypoxia, inhibition of cytochrome C oxidase – aluminum phosphide (AlP)

Aluminum phosphide (AlP) reacts with water or acids to release phosphine: $AlP + 3H_2O \rightarrow Al(OH)_3 + PH_3$, $AlP + 3H^+ \rightarrow Al^{3+} + PH_3$. Phosphine is a strong inhibitor of electron transport chain in mitochondria, specifically mitochondrial complex IV (cytochrome-c oxidase) (Nath et al., 2011). AlP reduced heart mitochondrial complexes II, IV and V activity, accompanied by increased lipid peroxidation and decreased ADP/ATP ratio in myocardial cells. ATP levels and ADP/ATP ratio are thought to be important biochemical end-points for evaluating the status of mitochondrial respiratory chain performance (Hosseini et al., 2013). AlP interrupted electron transfer between mitochondrial complexes and protons in mitochondrial inter-membrane space, which led to the loss of proton gradient and consequently led to mitochondrial permeability transition pore (MPT) opening and mitochondrial membrane potential (MMP) decline. Thus, mitochondrial membrane integrity was compromised and this outcome resulted in cardiomyocytes death (Solgi et al., 2015). Augmented oxidative stress (elevated ROS and plasma iron levels) along with myocardial energy ATP depletion and apoptosis induction in exposed animals has also been associated with the cardiotoxic effects of AlP (Baghaei et al., 2016). In addition, clinical manifestations such as decrements in heart rate (HR) and blood pressure (BP) as well as ECG changes such as abnormal QRS complexes, QTc prolongation and ST height decrease are also reported (Abdolghaffari et al., 2015). All the above effects refer to acute exposure. In humans, a characteristic feature of AlP poisoning is myocardial suppression and resistant hypotension (Bogle et al., 2006; Chauhan et al., 2015).

3.5. Inhibition of photosynthesis – atrazine, paraquat

Atrazine is a herbicide of the triazine class, which significantly decreased GSH and total thiol (T-SH) content both in serum and in cardiac tissue and significantly increased cardiac tissue Heme oxygenase-1 (HO-1) activity, while promoting oxidative DNA damage (Keshk et al., 2014). Apoptosis is also present in atrazine poisoning, as caspase-3, the "point-of-no-return" in the apoptotic signalling cascade (Green and

Table 6
Cardiotoxic effects of phosphines in experimental animals and human data.

Subject	Substance/Dose	Exposure Route/Exposure Period	Evaluation Method	Signs of Cardiotoxicity (class of disorder[a])	Reference
Male Wistar albino rats	Aluminum phosphide (AlP) 12 mg/kg (equal to LD50 value)	Oral administration; assessments were done 24 h later	ECG, blood pressure (BP) and heart rate (HR)	• Changes in ECG patterns such as decrement of HR (2) • BP (10) • Abnormal QRS complexes, QTc and ST height. (2)	(Abdolghaffari et al., 2015)
Male Wistar rats	Aluminum phosphide (AlP) 12 mg/kg	Oral administration; assessments were done 24 h later	Measurement of biochemical and mitochondrial factors	• Oxidative stress (elevated ROS and plasma iron levels) (3)	(Baghaei et al., 2016)
Male Wistar rats	Aluminum phosphide (AlP) 6 and 12 mg/kg	Oral administration; assessments were done 1, 2, 4, 8, 12 and 24 h later	Biochemical assays ECG Immuno-histochemistry	• Reducing of mitochondrial complexes (II, IV and V) followed by increasing lipid peroxidation and ADP/ATP ratio and declining mitochondrial membrane integrity that ultimately resulted in cell death (2,3) • Acute exposure (6 mg/kg) resulted in an increase in hydroxyl radicals and lipid peroxidation in a time-dependent fashion, suggesting an interaction of delivering electrons of phosphine with mitochondrial respiratory chain and oxidative stress induction(3) • Degeneration, fragmentation and loss of cross striation of the cardiac muscle fibers (4,6) • Showed marked caspase positivity in cardiac muscle with muscle fiber fragmentation and loss of cross striation (4,6)	(Solgi et al., 2015)
41 year old Indian woman Review of 93 cases reported to the National Poisons Information Service (London) 1997–2003	10 g sachet of Fumino (aluminum phosphide - AlP) 56% w/w; United Phosphorus)	Deliberate ingestion		• Bilateral pulmonary infiltrates and ECG findings of sinus tachycardia (broad complex) • Hypoxia and metabolic acidosis (9) • Normal left ventricle (LV) size with moderately impaired LV function and cardiac index of 1.5 l/min/m^2	(Bogle et al., 2006)
Case Report 17 year old Male	Aluminum phosphide 3 g	Intentional ingestion		• Metabolic acidosis (9) • Myocardial depression (1)	(Chauhan et al., 2015)

[a] Classes of cardiovascular disorders: (1) Myocardial dysfunction, (2) Electrical, (3) Biochemical (oxidative damage), (4) Anatomical, (5) Cytopathological, (6) Histopathological, (7) Biochemical (functional implications), (8) Coronary artery disease, (9) Biochemical (lipidemic profile and other), (10) Blood pressure disorders (hypertension, hypotension).

Table 7
Cardiotoxic effects of triazines/triazoles pesticides in experimental animals and human data.

Subject	Substance/Dose	Exposure Route/Exposure Period	Evaluation Method	Signs of Cardiotoxicity (class of disorder[a])	Reference
A report on two cases (one in early 30s and one in early 50s)	Itraconazole (triazole)	200 mg PO q8hr for 3 days, then 200 mg PO q12hr for 6–12 months		• Acute systolic heart failure (1) • Myocardial ejection fractions of 10–15% for the younger patient and 40–45% for the elder. (1)	Paul and Rawal, 2017
Male Wistar rats	Penconazole (triazole) 67 mg/kg	Intraperitoneal aministration every 2 days from day 7 until day 15	Biochemical assays	• Oxidative stress induction(3)	(Chaabane et al., 2016)
Albino rats	Atrazine 400 mg/kg/day (triazine)	Oral administration for 3 weeks	Biochemical assays	• Significantly decreased serum/cardiac tissue GSH and TSH levels; significantly increased cardiac tissue HO-1 activity; serum/cardiac tissue GPx and CAT activity, MDA and serum 8-OHdG level altered; significantly decreased cardiac tissue complex I activity (3)	(Keshk et al., 2014)
			Histopathology Immuno-histochemistry	• Degeneration, fragmentation, and loss of cross striation of the cardiac muscle fibers (4,6) • Showed marked caspase positivity in cardiac muscle with muscle fiber fragmentation and loss of cross striation (4,6)	

[a] Classes of cardiovascular disorders: (1) Myocardial dysfunction, (2) Electrical, (3) Biochemical (oxidative damage), (4) Anatomical, (5) Cytopathological, (6) Histopathological, (7) Biochemical (functional implications), (8) Coronary artery disease, (9) Biochemical (lipidemic profile and other), (10) Blood pressure disorders (hypertension, hypotension).

Amarante-Mendes, 1998), is increased in the heart tissue cytoplasm (Keshk et al., 2014).

Oxidative stress, myocardial inflammation, apoptosis and endoplasmic reticulum (ER) stress are associated with paraquat cardiotoxic effects (Wang et al., 2017; Wang et al., 2014; Ge et al., 2010) after acute exposure. ER is an extensive intracellular membranous network participating in cellular functions such as Ca^{2+} storage, Ca^{2+} signalling and glycosylation (Cominacini et al., 2015). Paraquat intoxication induced myocardial functional alterations and geometric transformation of the left ventricle including enlarged left ventricular end systolic diameter (LVESD) (Wang et al., 2014); however it did not induce significant changes in left ventricle (LV) posterior wall thickness, septal thickness and LV end diastolic diameter (LVEDD) (Lei et al., 2017). Therefore, myocardial contractility suppression seems to be the main myocardial effect of paraquat exposure.

3.6. Blockage of cytochrome P450-dependent enzyme C-14 alpha-demethylase – triazoles

Very few studies focus on triazole cardiotoxicity mainly after subchronic/chronic exposure (Table 7). The main cardiotoxic mechanism recognized after penconazole exposure is oxidative stress. The whole oxidative profile of the heart, including enzymatic (superoxide dismutase, GPx, and CAT) and non-enzymatic (MDA, protein carbonyls glutathione and vitamin C) parameters, along with the lipidemic profile was altered (Chaabane et al., 2016). Paul and Rawal (2017) presented two case reports that developed acute systolic heart failure when itraconazole was used, as a medication. Itraconazole is an antifungal medication used to treat a number of fungal infections, such as aspergillosis, blastomycosis, coccidioidomycosis etc. When Itraconazole treatment was withdrawn in both cases, the first patient did not improve even months after cessation of therapy and was referred for heart transplant, whereas the second patient stabilized after a few weeks and his myocardial ejection fraction augmented on repeat echocardiographic testing.

4. Conclusion

Exposure to pesticides has been associated with several cardiovascular complications including electrocardiogram abnormalities, myocardial infarction, impaired systolic and diastolic performance, functional remodeling, histopathological insults, such as haemorrhage, vacuolisation, signs of apoptosis and degeneration, various biochemical complications, such as distorted lipidemic profile and increased systemic and cardiac-tissue-specific oxidative stress and DNA alterations in cardiac cells that could lead to functional impairment. Very limited data point to retainment of pesticides (organophosphate, organochlorines) residues in the cardiac tissue. More research should be performed in this respect to verify if observed cardiotoxicity could be due to intense localised action.

In addition, several molecular pathways have been shown to be involved in pesticides cardiotoxicity. Organophosphates which significantly decrease serum acetylcholinesterase activity (Lopez-Carillo and Lopez-Cervantes, 1993) and organochlorines affect the redox status in the cardiac tissue and induce oxidative stress in a dose-dependent mode. Continuous exposure to organophosphates alters lipid metabolism and increases cytotoxicity enzymes activity, consequently leading to apoptosis (Zaki, 2012). The main mechanism involved in AlP cardiotoxicity is inhibition of cytochrome C oxidase in the myocardial cells mitochondria, resulting in decreased ATP production and induction of oxidative stress (Asghari et al., 2017). Pyrethroids have been found to modify neuronal sodium channels as they induce a persistent, steady-state sodium current within depolarized membranes leading to cardiac hypotrophy (Bhaskar et al., 2010), increase calcium release and enhance Nrf2 gene expression levels in older animals. Cytosolic calcium levels are important for the contractile state of cardiac muscle.

Permethrin also induced oxidative damage to purine bases in the heart cells (Vadhana et al., 2010). Organochlorines affect myocardial cells in rats even at doses lower than LD_{50} values (Kalender et al., 2004).

Pesticides toxicity and the risk they pose for human health are controlled at a European level through a well-developed regulatory network, but cardiotoxicity is not described as a separate hazard class. Specific classification criteria should be developed within the frame of Regulation (EC) 1272/2008 in order to classify chemicals as cardiotoxic, if applicable, to avoid long-term cardiovascular complications. Classification should be based on anatomical, histopathological, echocardiographic and biochemical criteria both in animals and in humans developed in a way that could exclude cofounding factors in the development of the observed cardiotoxicity.

Competing interests

All authors declare no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Abdel-Daim, M.M., Taha, R., Ghazy, E.W., El-Sayed, Y.S., 2016. Synergistic ameliorative effects of sesame oil and alpha-lipoic acid against subacute diazinon toxicity in rats: hematological, biochemical, and antioxidant studies. Can. J. Physiol. Pharmacol. 94, 81–88.

Abdolghaffari, A.H., Baghaei, A., Solgi, R., Gooshe, M., Baeeri, M., Navaei-Nigjeh, M., Hassani, S., Jafari, A., Rezayat, S.M., Dehpour, A.R., Mehr, S.E., Abdollahi, M., 2015. Molecular and biochemical evidences on the protective effects of triiodothyronine against phosphine-induced cardiac and mitochondrial toxicity. Life Sci. 139, 30–39.

Abdou, H.M., ElMazoudy, R.H., 2010. Oxidative damage, hyperlipidemia and histological alterations of cardiac and skeletal muscles induced by different doses of diazinon in female rats. J. Hazard. Mater. 182, 273–278.

Adeyinka, A., Pierre, L., 2018. Organophosphates. In: StatPearls. StatPearls Publishing, Treasure Island (FL) 2018 Jan-. 2018 Apr 25.

Akturk, O., Demirin, H., Sutcu, R., Yilmaz, N., Koylu, H., Altuntas, I., 2006. The effects of diazinon on lipid peroxidation and antioxidant enzymes in rat heart and ameliorating role of vitamin E and vitamin C. Cell Biol. Toxicol. 22, 455–461.

Amara, I.B., Soudani, N., Hakim, A., Troudi, A., Zeghal, K.M., Boudawara, T., Zeghal, N., 2013. Protective effects of vitamin E and selenium against dimethoate-induced cardiotoxicity in vivo: biochemical and histological studies. Environ. Toxicol. 28, 630–643.

Anand, S., Singh, S., Nahar Saikia, U., Bhalla, A., Paul Sharma, Y., Singh, D., 2009. Cardiac abnormalities in acute organophosphate poisoning. Clin. Toxicol. 47, 230–235.

Asghari, M.H., Abdollahi, M., de Oliveira, M.R., Nabavi, S.M., 2017. A review of the protective role of melatonin during phosphine-induced cardiotoxicity: focus on mitochondrial dysfunction, oxidative stress and apoptosis. J. Pharm. Pharmacol. 69, 236–243.

Atale, N., Gupta, K., Rani, V., 2014. Protective effect of Syzygium cumini against pesticide-induced cardiotoxicity. Environ. Sci. Pollut. Res. Int. 21, 7956–7972.

Baggish, A.L., Weiner, R.B., Kanayama, G., Hudson, J.I., Lu, M.T., Hoffmann, U., Pope Jr., H.G., 2017. Cardiovascular toxicity of illicit anabolic-androgenic steroid use. Circulation 135, 1991–2002.

Baghaei, A., Solgi, R., Jafari, A., Abdolghaffari, A.H., Golaghaei, A., Asghari, M.H., Baeeri, M., Ostad, S.N., Sharifzadeh, M., Abdollahi, M., 2016. Molecular and biochemical evidence on the protection of cardiomyocytes from phosphine-induced oxidative stress, mitochondrial dysfunction and apoptosis by acetyl-L-carnitine. Environ. Toxicol. Pharmacol. 42, 30–37.

Bar-Meir, E., Schein, O., Eisenkraft, A., Rubinshtein, R., Grubstein, A., Militianu, A., Glikson, M., Cbrn Medical Branch, M.C.I.D.F., 2007. Guidelines for treating cardiac manifestations of organophosphates poisoning with special emphasis on long QT and Torsades De pointes. Crit. Rev. Toxicol. 37, 279–285.

Bas, H., Kalender, Y., 2011. Chlorpyrifos induced cardiotoxicity in rats and the protective role of quercetin and Catechin. GAZI UNIVERSITY J Sci 24, 387–395.

Berardi, R., Caramanti, M., Savini, A., Chiorrini, S., Pierantoni, C., Onofri, A., Ballatore, Z., De Lisa, M., Mazzanti, P., Cascinu, S., 2013. State of the art for cardiotoxicity due to chemotherapy and to targeted therapies: a literature review. Crit. Rev. Oncol. Hematol. 88, 75–86.

Bers, D.M., Barry, W.H., Despa, S., 2003. Intracellular Na+ regulation in cardiac myocytes. Cardiovasc. Res. 57, 897–912.

Bhaskar, E.M., Moorthy, S., Ganeshwala, G., Abraham, G., 2010. Cardiac conduction disturbance due to prallethrin (pyrethroid) poisoning. J. Med. Toxicol. 6, 27–30.

Bogle, R.G., Theron, P., Brooks, P., Dargan, P.I., Redhead, J., 2006. Aluminium phosphide poisoning. Emerg. Med. J. 23, e3.

Centers for Disease Control and Prevention, 2015. Fourth National Report on Human Exposure to Environmental Chemicals.

Cetin, N., Cetin, E., Eraslan, G., Bilgili, A., 2007. Chlorpyrifos induces cardiac dysfunction in rabbits. Res. Vet. Sci. 82, 405–408.

Chaabane, M., Tir, M., Hamdi, S., Boudawara, O., Jamoussi, K., Boudawara, T., Ghorbel, R.E., Zeghal, N., Soudani, N., 2016. Improvement of heart redox states contributes to the beneficial effects of selenium against Penconazole-induced cardiotoxicity in adult rats. Biol. Trace Elem. Res. 169, 261–270.

Chauhan, M., Dewan, S., Attawar, S., Kamat, S., Kumar, V., 2015. Successful treatment of cardiotoxicity of Aluminium phosphide poisoning with extracorporeal membrane oxygenation (ECMO): a case report. J Pharmacol Clin Toxicol 3, 1056.

Clark, R.D., 2018. Predicting mammalian metabolism and toxicity of pesticides in silico. Pest Manag. Sci. 10 (1002), 4935.

Cominacini, L., Mozzini, C., Garbin, U., Pasini, A., Stranieri, C., Solani, E., Vallerio, P., Tinelli, I.A., Fratta Pasini, A., 2015. Endoplasmic reticulum stress and Nrf2 signaling in cardiovascular diseases. Free Radic. Biol. Med. 88, 233–242.

Dang, Viet D., Kroll, Kevin J., Supowit, Samuel D., Halden, Rolf U., Denslow, Nancy D., 2016. Tissue distribution of organochlorine pesticides in largemouth bass (Micropterus salmoides) from laboratory exposure and a contaminated Lake. Environ. Pollut. 216, 877–883.

Das, Shaon Kumar, 2013. Mode of action of pesticides and the novel trends –A critical review. Int. Res. J. Agricult. Sci. Soil Sci. 3 (11), 393–401.

de la Cerda, E., Navarro-Polanco, R.A., Sanchez-Chapula, J.A., 2002. Modulation of cardiac action potential and underlying ionic currents by the pyrethroid insecticide deltamethrin. Arch. Med. Res. 33, 448–454.

Doroshow, J.H., Locker, G.Y., Myers, C.E., 1980. Enzymatic defenses of the mouse heart against reactive oxygen metabolites: alterations produced by doxorubicin. J Clin Invest 65, 128–135.

Food and Agriculture Organization of the United Nations, 2002. International Code of Conduct on the Distribution and Use of Pesticides.

Ge, We, Zhang, Yingmei, Han, Xuefeng, Ren, Jun, 2010. Cardiac-specific overexpression of catalase attenuates paraquat-induced myocardial geometric and contractile alteration: role of ER stress. Free Radic. Biol. Med. 49 (2), 2068–2077.

Germanakis, I., Tsarouhas, K., Fragkiadaki, P., Tsitsimpikou, C., Goutzourelas, N., Champsas, M.C., Stagos, D., Rentoukas, E., Tsatsakis, A.M., 2013. Oxidative stress and myocardial dysfunction in young rabbits after short term anabolic steroids administration. Food Chem. Toxicol. 61, 101–105.

Gilden, R.C., Huffling, K., Sattler, B., 2010. Pesticides and health risks. J. Obstet. Gynecol. Neonatal. Nurs. 39, 103–110.

Green, D.R., Amarante-Mendes, G.P., 1998. The point of no return: mitochondria, caspases, and the commitment to cell death. Results Probl Cell Diff 24, 45–61.

Haglund, K., Dikic, I., 2005. Ubiquitylation and cell signaling. EMBO J. 24, 3353–3359.

Han, J., Zhou, L., Luo, M., Liang, Y., Zhao, W., Wang, P., Zhou, Z., Liu, D., 2017. Nonoccupational exposure to Pyrethroids and risk of coronary heart disease in the Chinese population. Environ Sci Technol 51, 664–670.

Hassani, S., Sepand, M.R., Jafari, A., Jaafari, J., Rezaee, R., Zeinali, M., Tavakoli, F., Razavi-Azarkhiavi, K., 2018. Protective effects of curcumin and vitamin E against chlorpyrifos-induced lung oxidative damage. Hum Exp Toxicol. 34 (6), 668–676.

He, X., Li, C., Wei, D., Wu, J., Shen, L., Wang, T., 2011. Cardiac abnormalities in severe acute dichlorvos poisoning. Crit. Care Med. 39, 1906–1912.

Hennig, B., Petriello, M.C., Gamble, M.V., Surh, Y.J., Kresty, L.A., Frank, N., Rangkadilok, N., Ruchirawat, M., Suk, W.A., 2018. The role of nutrition in influencing mechanisms involved in environmentally mediated diseases. Rev Environ Health 33 (1), 87–97.

Hosseini, M.J., Shaki, F., Ghazi-Khansari, M., Pourahmad, J., 2013. Toxicity of vanadium on isolated rat liver mitochondria: a new mechanistic approach. Metallomics 5, 152–166.

Jalili, S., Farshid, A.A., Heydari, R., Ilkhanipour, M., Salehi, S., 2007a. Histopathological observations on protective effects of vitamin E on endosulfan induced cardiotoxicity in rats. Pak. J. Biol. Sci. 10, 1922–1925.

Kabrawala, V.N., Shah, R.M., Oza, G.G., 1965. Diazinon poisoning. (a study of 25 cases). Indian Pract 18, 711–717.

Kale, M., Rathore, N., John, S., Bhatnagar, D., Nayyar, S.S., Kothari, V., 1999. The protective effect of vitamin E in Pyrethroid-induced oxidative stress in rat tissues. J. Nutr. Environ. Med. 9, 281–287.

Kalender, S., Kalender, Y., Ogutcu, A., Uzunhisarcikli, M., Durak, D., Acikgoz, F., 2004. Endosulfan-induced cardiotoxicity and free radical metabolism in rats: the protective effect of vitamin E. Toxicology 202, 227–235.

Keshk, W.A., Soliman, N.A., Abo El-Noor, M.M., Wahdan, A.A., Shareef, M.M., 2014. Modulatory effects of curcumin on redox status, mitochondrial function, and caspace-3 expression during atrazin-induced toxicity. J. Biochem. Mol. Toxicol. 28, 378–385.

Kiss, Z., Fazekas, T., 1979. Arrhythmias in organophosphate poisonings. Acta Cardiol. 34, 323–330.

Koutroulakis, D., Sifakis, S., Tzatzarakis, M.N., Alegakis, A.K., Theodoropoulou, E., Kavvalakis, M.P., Kappou, D., Tsatsakis, A.M., 2014. Dialkyl phosphates in amniotic fluid as a biomarker of fetal exposure to organophosphates in Crete, Greece; association with fetal growth. Repr Toxicol 46, 98–105.

Lei, Y., Li, X., Yuan, F., Liu, L., Zhang, J., Yang, Y., Zhao, J., Han, Y., Ren, J., Fu, X., 2017. Toll-like receptor 4 ablation rescues against paraquat-triggered myocardial dysfunction: role of ER stress and apoptosis. Environ. Toxicol. 32, 656–668.

Li, J., Ichikawa, T., Janicki, J.S., Cui, T., 2009. Targeting the Nrf2 pathway against cardiovascular disease. Expert Opin. Ther. Targets 13, 785–794.

Lopez-Carillo, L., Lopez-Cervantes, M., 1993. Effect of exposure to organophosphate pesticides on serum cholinesterase levels. Arch. Environ. Health 48, 359–363.

Ludomirsky, A., Klein, H.O., Sarelli, P., Becker, B., Hoffman, S., Taitelman, U., Barzilai, J., Lang, R., David, D., DiSegni, E., Kaplinsky, E., 1982. Q-T prolongation and polymorphous ("torsade de pointes") ventricular arrhythmias associated with

organophosphorus insecticide poisoning. Am. J. Cardiol. 49, 1654–1658.
Madeddu, C., Deidda, M., Piras, A., Cadeddu, C., Demurtas, L., Puzzoni, M., Piscopo, G., Scartozzi, M., Mercuro, G., 2016. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med 17 (Suppl. 1), e12–e18 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection.
Mesnage, R., Antoniou, M.N., 2018. Ignoring adjuvant toxicity falsifies the safety profile of commercial pesticides. Front. Public Health 22 (5), 361.
Meyer, A., Seidler, F.J., Aldridge, J.E., Tate, C.A., Cousins, M.M., Slotkin, T.A., 2004. Critical periods for chlorpyrifos-induced developmental neurotoxicity: alterations in adenylyl cyclase signaling in adult rat brain regions after gestational or neonatal exposure. Environ. Health Perspect. 112, 295–301.
Mills, K.T., Blair, A., Freeman, L.E., Sandler, D.P., Hoppin, J.A., 2009. Pesticides and myocardial infarction incidence and mortality among male pesticide applicators in the agricultural health study. Am. J. Epidemiol. 170, 892–900.
Nath, N.S., Bhattacharya, I., Tuck, A.G., Schlipalius, D.I., Ebert, P.R., 2011. Mechanisms of phosphine toxicity. J Toxicol 2011, 494168.
Ozmen, O., 2011. Pathology of Endosulfan. Pesticides in the Modern World - Effects of Pesticides Exposure. InTech Chapter 15.
Paul, V., Rawal, H., 2017. Cardiotoxicity with Itraconazole. BMJ Case Reports 10 (2017:Bcr-2017).
Paul, K.C., Jerrett, M., Ritz, B., 2018. Type 2 diabetes mellitus and Alzheimer's disease: overlapping biologic mechanisms and environmental risk factors. Curr Environ Health Rep. 5 (1), 44–58.
Ramachandra, B., Rachel, O., 2013. A rare case of cardiac and neurotoxicity in acute Lindane poisoning. Int J Pharm Sci Inv 2, 34–35.
Razavi, B.M., Hosseinzadeh, H., Movassaghi, A.R., Imenshahidi, M., Abnous, K., 2013. Protective effect of crocin on diazinon induced cardiotoxicity in rats in subchronic exposure. Chem. Biol. Interact. 203, 547–555.
Razavi, B.M., Hosseinzadeh, H., Imenshahidi, M., Malekian, M., Ramezani, M., Abnous, K., 2015. Evaluation of protein Ubiquitylation in heart tissue of rats exposed to Diazinon (an organophosphate insecticide) and Crocin (an active saffron ingredient): role of HIF-1alpha. Drug Res 65, 561–566.
Roth, A., Zellinger, I., Arad, M., Atsmon, J., 1993. Organophosphates and the heart. Chest 103, 576–582.
Saquib, Q., Attia, S.M., Siddiqui, M.A., Aboul-Soud, M.A., Al-Khedhairy, A.A., Giesy, J.P., Musarrat, J., 2012. Phorate-induced oxidative stress, DNA damage and transcriptional activation of p53 and caspase genes in male Wistar rats. Toxicol. Appl. Pharmacol. 259, 54–65.
Sauviat, M.P., Pages, N., 2002. Cardiotoxicity of lindane, a gamma isomer of hexachlorocyclohexane. J Soc Biol 196, 339–348.
Sawyer, Douglas B., Peng, Xuyang, Chen, Billy, Pentassuglia, Laura, Lim, Chee Chew, 2010. Mechanisms of anthracycline cardiac injury: can we identify strategies for cardio-protection? Prog. Cardiovasc. Dis. 53, 105–113.
Scheme, W.P.E., Team, W.H.O.C.S., 2005. Safety of Pyrethroid for Public Health Use.
Shiyovich, A., Matot, R., Elyagon, S., Liel-Cohen, N., Rosman, Y., Shrot, S., Kassirer, M., Katz, A., Etzion, Y., 2018. QT prolongation as an isolated long-term cardiac manifestation of Dichlorvos organophosphate poisoning in rats. Cardiovasc. Toxicol. 18, 24–32.
Sirenko, O., Grimm, F.A., Ryan, K.R., Iwata, Y., Chiu, W.A., Parham, F., Wignall, J.A., Anson, B., Cromwell, E.F., Behl, M., Rusyn, I., Tice, R.T., 2017. In vitro cardiotoxicity assessment of environmental chemicals using an organotypic human induced pluripotent stem cell-derived model. Toxicol. Appl. Pharmacol. 322, 60–74.
Solgi, R., Baghaei, A., Golaghaei, A., Hasani, S., Baeeri, M., Navaei, M., Ostad, S.N., Hosseini, R., Abdollahi, M., 2015. Electrophysiological and molecular mechanisms of protection by iron sucrose against phosphine-induced cardiotoxicity: a time course study. Toxicol. Mech. Methods 25, 249–257.
Spencer, C.I., Yuill, K.H., Borg, J.J., Hancox, J.C., Kozlowski, R.Z., 2001. Actions of pyrethroid insecticides on sodium currents, action potentials, and contractile rhythm in isolated mammalian ventricular myocytes and perfused hearts. The J Pharmacol Exp Ther 298, 1067–1082.
Summers, L.A., 1980. The Bipyridinium Herbicides. Academic Press, New York, NY.
Trainer, V.L., McPhee, J.C., Boutelet-Bochan, H., Baker, C., Scheuer, T., Babin, D., Demoute, J.P., Guedin, D., Catterall, W.A., 1997. High affinity binding of pyrethroids to the alpha subunit of brain sodium channels. Mol. Pharmacol. 51, 651–657.
Tsatsakis, A.M., Aguridakis, P., Michalodimitrakis, M.N., Tsakalov, A.K., Alegakis, A.K., Koumantakis, E., Troulakis, G., 1996a. Experiences with acute organophosphate poisonings in Crete. Vet. Hum. Toxicol. 38, 101–107.
Tsatsakis, A.M., Tsakalof, A.K., Siatitsas, Y., Michalodimitrakis, E.N., 1996b. Acute poisoning with carbamate pesticides: the Cretan experience. Sci. Justice 36, 35–39.
Tsatsakis, A.M., Docea, A.O., Tsitsimpikou, C., 2016. New challenges in risk assessment of chemicals when simulating real exposure scenarios; simultaneous multi-chemicals' low dose exposure. Food Chem. Toxicol. 96, 174–176.
United Nations Environment Programme, 2005. Ridding the World of POPs: A Guide to the Stockholm Convention on Persistent Organic Pollutants.
Vadhana, M.S., Nasuti, C., Gabbianelli, R., 2010. Purine bases oxidation and repair following permethrin insecticide treatment in rat heart cells. Cardiovasc. Toxicol. 10, 199–207.
Vadhana, D., Saravanaperumal, S.A., Carloni, M., Nasuti, C., Gabbianelli, R., 2013. Early life permethrin treatment leads to long-term cardiotoxicity. Chemosphere 93, 1029–1034.
Vasilaki, F., Tsitsimpikou, C., Tsarouhas, K., Germanakis, I., Tzardi, M., Kavvalakis, M., Ozcagli, E., Kouretas, D., Tsatsakis, A.M., 2016. Cardiotoxicity in rabbits after long-term nandrolone decanoate administration. Toxicol. Lett. 241, 143–151.
Velmurugan, G., Venkatesh Babu, D.D., Ramasamy, S., 2013. Prolonged monocrotophos intake induces cardiac oxidative stress and myocardial damage in rats. Toxicology 307, 103–108.
Vijaya Padma, V., Poornima, P., Prakash, C., Bhavani, R., 2013. Oral treatment with gallic acid and quercetin alleviates lindane-induced cardiotoxicity in rats. Can. J. Physiol. Pharmacol. 91, 134–140.
Wang, Q., Yang, L., Hua, Y., Nair, S., Xu, X., Ren, J., 2014. AMP-activated protein kinase deficiency rescues Paraquat-induced cardiac contractile dysfunction through an autophagy dependent mechanism. Toxicol. Sci. 142 (1), 6–20.
Wang, S., Zhu, X., Xiong, L., Zhang, Y., Ren, J., 2016. Toll-like receptor 4 knockout alleviates paraquat-induced cardiomyocyte contractile dysfunction through an autophagy-dependent mechanism. Toxicol. Lett. 22 (257), 11–22.
Wang, S., Zhu, X., Xiong, L., Ren, J., 2017. Ablation of Akt2 prevents paraquat-induced myocardial mitochondrial injury and contractile dysfunction: role of Nrf2. Toxicol. Lett. 269, 1–4.
Wolthuis, O.L., Meeter, E., 1968. Cardiac failure in the rat caused by diisopropyl fluorophosphate (DFP). Eur. J. Pharmacol. 2, 387–392.
Yan, D., Zhang, Y., Liu, L., Shi, N., Yan, H., 2018. Pesticide exposure and risk of Parkinson's disease: dose-response meta-analysis of observational studies. Regul. Toxicol. Pharmacol. 96 (3), 57–63.
Yavuz, T., Altuntas, I., Delibas, N., Yildirim, B., Candir, O., Cora, A., Karahan, N., Ibrisim, E., Kutsal, A., 2004. Cardiotoxicity in rats induced by methidathion and ameliorating effect of vitamins E and C. Hum Exp Toxicol 23, 323–329.
You, H., Kim, G., Kim, Y., Chun, Y., Park, J., Chung, M.H., Kim, M., 2000. Increased 8-hydroxyguanine formation and endonuclease activity for its repair in ischemic-reperfused hearts of rats. J. Mol. Cell. Cardiol. 32, 1053–1059.
Zafiropoulos, A., Tsarouhas, K., Tsitsimpikou, C., Fragkiadaki, P., Germanakis, I., Tsardi, M., Maravgakis, G., Goutzourelas, N., Vasilaki, F., Kouretas, D., Hayes, A., Tsatsakis, A., 2014. Cardiotoxicity in rabbits after a low-level exposure to diazinon, propoxur, and chlorpyrifos. Hum Exp Toxicol 33, 1241–1252.
Zaki, N., 2012. Evaluation of Profenofos intoxication in white rats. Forests. Nat. Sci. 10, 67–77.
Zamorano, J.L., Lancellotti, P., Rodriguez Muñoz, D., Aboyans, V., Asteggiano, R., Galderisi, M., Habib, G., Lenihan, D.J., Lip, G.Y.H., Lyon, A.R., Lopez Fernandez, T., Mohty, D., Piepoli, M.F., Tamargo, J., Torbicki, A., 2016. ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for practice guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur. Heart J. 37 (36), 2768–2801.