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

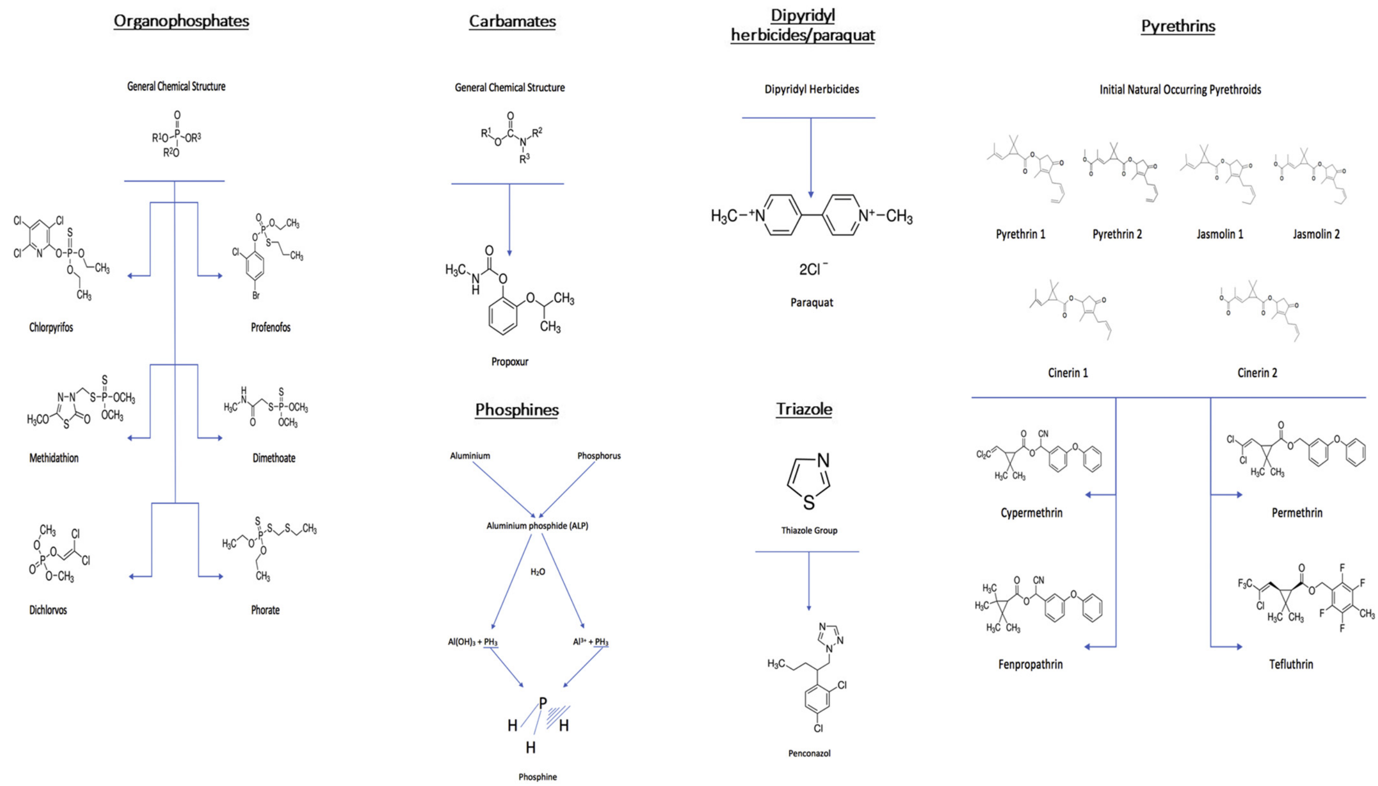

Fig. 1. Chemical structures of main classes of pesticides discussed.

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.