Abstract

Cardiovascular diseases are among the most significant causes of mortality in humans. Chemical substances toxicity and risk for human health are regulated at a European level through a well-developed regulatory network, but cardiotoxicity is not described as a separate hazard class. Currently, when assessing chemicals toxicity, cardiac effects if monitored and detected in animal studies, mainly on the tissue level, are considered by the authorities, but cardiotoxicity, as such, is not described as a separate hazard class of chemical substances through the available regulations, both at a European level and world-wide. Therefore, chemicals other than pharmaceutical agents are recognised to be cardiotoxic after having exerted such deleterious effects on humans, based on epidemiological studies.

We investigated the published literature in order to conduct an in-depth review of the cardiac pathology and function impairment due to exposure to different group of chemicals, such as pesticides and anthracyclines based on both animal and human data. Then we evaluated two important echocardiographic indices, namely ejection fraction and fractional shortening, in the literature concerning anthracycline administration to rats as the reference laboratory animal model. Finally, we performed an in-depth review analysis of several biomarkers reported to be altered in animal models after anthracyclines administration in order to investigate which of them could potentially be used as biochemical criteria in a weight of evidence approach in conjunction to the echocardiography indices and the histopathology findings.

The majority of human data on cardiotoxicity of pesticides (organophosphates, organothiophosphates, organochlorines, carbamates, pyrethroids, dipyridyl herbicides, triazoles and triazines), comes 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 remodelling and histopathological findings, such as haemorrhage, vacuolisation, signs of apoptosis and degeneration. Our research 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 pesticides. In addition, the underlying mechanisms of the adverse outcomes are investigated in correlation with the mode of action of the various pesticides was reviewed. More than 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.

Anthracyclines are used in cancer chemotherapy (e.g., leukaemia, lymphomas, stomach, uterine, ovarian, bladder and lung cancers) and they are isolated from *Streptomyces* bacterium. Clinically, the most important anthracyclines are doxorubicin, daunorubicin, epirubicin and idarubicin. Anthracyclines, are considered as well-established cardiotoxic compounds causing myocardial suppression. Cardiotoxicity in terms of impairment of cardiac function is largely diagnosed by echocardiography and based on objective metrics of cardiac function. In our research, we focused on the evaluation of two important echocardiographic indices, namely ejection fraction (EF) and fractional shortening (FS), in the literature concerning anthracycline administration to rats as the reference laboratory animal model. The normal and suppressed values of the two main echocardiographic indices discussed, %EF and %FS, respectively, have been identified. Reported baseline (normal) %EF values in rats vary (55%-96.5%). In 78.2% of the studies reviewed, normal values range from 70 to 90%. High %EF values (>90%) are reported in 14% of the studies. In contrast, normal %FS values present even higher variability (25%-84.2%). The majority (66.7%) of the values, though, are reported to be within the range of 40 and 60%. The suppressed %EF values reported from rats after anthracycline administration vary from 31% to 91%. EF values 50-80% are reported in 72.3% of the studies reviewed. Suppression of the %EF due to anthracycline administration varies from 10 to 40% compared to the normal values in more than two thirds of the studies reviewed (71.7%). On the other hand, suppressed %FS values ranging from 14% to 71.8%, present a more narrow distribution (%FS values 20-50% in 84.6% of the studies).

We performed an in-depth review analysis of several biomarkers reported altered in animal models after anthracyclines administration in order to investigate which of them could potentially be used as biochemical criteria in a weight of evidence approach. The statistical analysis of the cardiac enzymes mainly, but of the biomarkers of oxidative stress, reveal a similar pattern from healthy rats to rats with cardiotoxic manifestations due to anthracycline exposure known to be relevant to humans.

All these published data suggest clearly that there is a need to establish regulatory criteria for assessing cardiotoxicity as an inherent property of a chemical substance well in advance and characterize the risk of exposure to such chemicals through a well-developed regulatory network based on animal models, as it is the case for other human health hazard classes. Regulatory

established criteria will enable international organizations to early identify cardiotoxic effects and classify chemicals in order to avoid long-term cardiovascular complications.

Classification should be based on:

a. Anatomical and histopathological criteria,

b. Echocardiographic criteria (e.g. LVEF, LVFS), and/or other cardiac imaging modalities (e.g. MRI) and

c. Biochemical criteria, of generic nature (e.g. circulating oxidative stress mark-ers), of more specific nature (e.g. oxidative stress markers of the cardiac tissue) and heart specific biomarkers (e.g. cardiac enzymes).