

Key Characteristics of Cardiovascular Toxicants

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BACKGROUND: The concept of chemical agents having properties that confer potential hazard called key characteristics (KCs) was first developed to identify carcinogenic hazards. Identification of KCs of cardiovascular (CV) toxicants could facilitate the systematic assessment of CV hazards and understanding of assay and data gaps associated with current approaches.

OBJECTIVES: We sought to develop a consensus-based synthesis of scientific evidence on the KCs of chemical and nonchemical agents known to cause CV toxicity along with methods to measure them.

METHODS: An expert working group was convened to discuss mechanisms associated with CV toxicity.

RESULTS: The group identified 12 KCs of CV toxicants, defined as exogenous agents that adversely interfere with function of the CV system. The KCs were organized into those primarily affecting cardiac tissue (numbers 1–4 below), the vascular system (5–7), or both (8–12), as follows: 1) impairs regulation of cardiac excitability, 2) impairs cardiac contractility and relaxation, 3) induces cardiomyocyte injury and death, 4) induces proliferation of valve stroma, 5) impacts endothelial and vascular function, 6) alters hemostasis, 7) causes dyslipidemia, 8) impairs mitochondrial function, 9) modifies autonomic nervous system activity, 10) induces oxidative stress, 11) causes inflammation, and 12) alters hormone signaling.

DISCUSSION: These 12 KCs can be used to help identify pharmaceuticals and environmental pollutants as CV toxicants, as well as to better understand the mechanistic underpinnings of their toxicity. For example, evidence exists that fine particulate matter [$PM \leq 2.5 \mu m$ in aerodynamic diameter ($PM_{2.5}$)] air pollution, arsenic, anthracycline drugs, and other exogenous chemicals possess one or more of the described KCs. In conclusion, the KCs could be used to identify potential CV toxicants and to define a set of test methods to evaluate CV toxicity in a more comprehensive and standardized manner than current approaches. <https://doi.org/10.1289/EHP9321>

Introduction

According to the World Health Organization, cardiovascular disease (CVD) is the leading cause of death worldwide, taking 1.7 million lives annually (WHO 2017). Four of five of those deaths are due to myocardial infarction or stroke. Certain environmental pollutants,

such as fine particulate matter [$PM \leq 2.5 \mu m$ in aerodynamic diameter ($PM_{2.5}$)] (Brook et al. 2010, 2016), arsenic (States et al. 2009) and tobacco smoke (Gallucci et al. 2020), are well known to be associated with CVD, but other environmental contaminants, as well as natural toxins, viruses, and other agents, may also be cardiovascular (CV) toxicants.

A systematic approach to identifying chemical hazards was recently developed for carcinogens (Smith et al. 2016), endocrine-disrupting chemicals (La Merrill et al. 2020), and reproductive toxicants (Arzuaga et al. 2019; Luderer et al. 2019) based on the established properties of chemicals known to cause cancer, endocrine disruption, and reproductive toxicity, respectively. These properties, called key characteristics (KCs), have quickly proved useful for the systematic evaluation of the literature on mechanisms by which chemicals induce these toxic effects (Guyton et al. 2018a, 2018b). The KCs are now widely used by various authoritative bodies and regulatory agencies and form the basis for the evaluation of mechanistic data at the International Agency for Research on Cancer (IARC 2019; Samet et al. 2020). Scientists in the pharmaceutical industry have also recognized that the KCs are likely to be useful in the design of a comprehensive set of tests to

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evaluate the potential hazards of novel drug candidates (Fielden et al. 2018; Smith et al. 2020).

Our goal was to develop a consensus on the KCs of chemical and nonchemical agents known to cause CV toxicity and to provide a comprehensive list of tests to be used to evaluate chemicals and other environmental pollutants for CV toxicity. Given that many pharmaceutical drugs have adverse effects on the CV system and because those mechanisms are generally better understood than those of environmental pollutants, we included data from pharmaceuticals in the development of the KCs of CV toxicants. As outlined in Figure 1, we believe there are multiple ways in which these KCs of CV toxicants could be used to enhance current approaches in the clinic and in pharmaceutical development, environmental research, and hazard assessment.

Descriptions of the KCs of CV Toxicants

Experts from various fields related to CV toxicity and chemical regulation convened and identified 12 KCs of CV toxicants using current scientific evidence, such as the earlier work of Laverty et al. (2011), expert knowledge, known examples of CV toxicants, and extensive debate. We acknowledge that these will likely evolve with new scientific discoveries. In considering the differences between acute and chronic effects, as well as between high- and low-dose effects, we concluded that these KCs cover temporal and dose-dependent cardiotoxic mechanisms. We did, however, restrict our task to adult CVD, excluding possible teratogenic effects of environmental pollutants on the developing CV system.

We also identified representative biomarkers, assays, and end points that are most useful for testing each KC using experimental *in vitro/ex vivo* studies and *in vivo* animal models, as well as clinical or epidemiological findings in humans (Table 1). Further, we identified classic examples of CV toxicants for each KC (Table 1) and illustrated how some CV toxicants exhibit multiple KCs, whereas other toxicants may exhibit only one (Tables 2 and 3). We have divided the KCs into those primarily affecting cardiac tissue (numbered 1–4), vascular tissues (5–7), and those which could affect both the heart and vasculature (8–12).

Primarily Cardiac

KC1: impairs regulation of cardiac excitability. Cardiac ion channels play critical roles in generating action potentials (APs) given that the cardiac AP is shaped by a balance of inward and outward currents. In ventricular myocytes, depolarization is initiated by sodium ion (Na^+) channel opening during the AP upstroke, followed by calcium ion (Ca^{2+}) channel opening during the plateau phase. Subsequently, ventricular repolarization is mediated by multiple potassium ion (K^+) channels (Chiamvimonvat et al. 2017; Grandi et al. 2017). Coordinated channel activity is critical to cardiac excitation–contraction coupling, and therefore a disturbance of Na^+/K^+ ion concentrations can lead to cardiac arrhythmias and sudden cardiac death. Classic examples include antiarrhythmic drugs, non-CV drugs that cause QT prolongation (Vlachos et al. 2016), drugs that interfere with $\text{K}_v11.1$ [ether-à-go-go-related gene product (hERG)] potassium channel trafficking (Cubeddu 2016), drugs that cause QRS widening, and tyrosine kinase inhibitors that cause QT prolongation by enhancing inward late Na^+ current during the plateau phase, leading to AP prolongation (Roden 2019). Finally, toxins from diverse organisms have evolved to disrupt the activities of ion channels (Morales-Lázaro et al. 2015): For example, tetrodotoxin and saxitoxin block Na^+ channels, whereas batrachotoxin induces persistent activation of Na^+ channels (Restrepo-Angulo et al. 2010).

Ca^{2+} ions play critical roles in cardiac automaticity, electrical conduction, excitation–transcription coupling and maintenance of vascular tone. Agents that depress Ca^{2+} current can decrease the AP upstroke of the sinoatrial node and slow heart rate and atrioventricular conduction, for example, beta-adrenergic antagonists and L-type Ca^{2+} channel (LTCC) blockers (Abernethy and Schwartz 1999; Olson et al. 2005). Conversely, beta-adrenergic agonists increase the AP upstroke and heart rate (Movsesian 1999).

Alterations in Ca^{2+} ion homeostasis can promote triggered activity including delayed after depolarizations (DADs), under conditions of high intracellular and sarcoplasmic reticulum (SR) Ca^{2+} concentration, as previously reviewed (Bers 2002; Eisner et al. 2017). DADs are observed with excessive catecholamine or digitalis toxicity; digitalis blocks the Na^+/K^+ -ATPase, which elevates intracellular Na^+ concentration and increases Ca^{2+} influx through the sarcolemmal $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) (Rehman

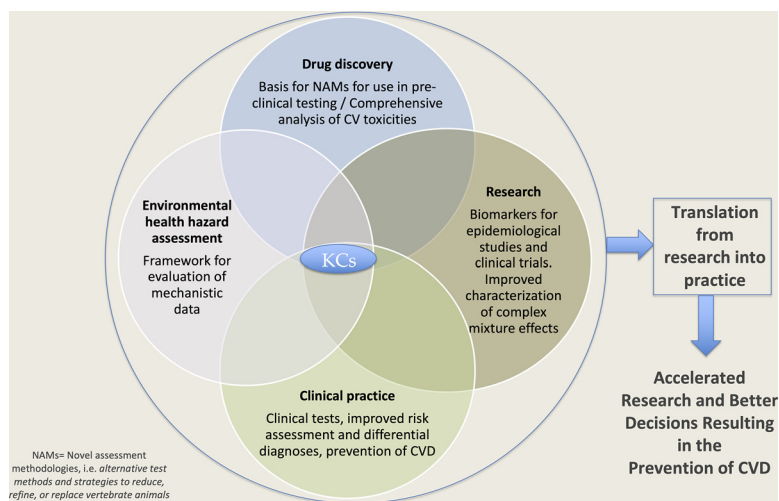


Figure 1. Utility of the key characteristics (KCs) of cardiovascular toxicants in research, drug discovery, hazard assessment, and clinical practice. An illustration of how the KCs could be used in different areas and how translation of the resulting information could lead to accelerated research, inform better regulatory decisions, improve clinical practice, and ultimately prevent CVD. Note: CV, cardiovascular; CVD, cardiovascular disease; NAM, novel assessment methodologies.

Table 1. Key characteristics (KCs) of cardiovascular (CV) toxicants: relevant assays and biomarkers and representative agents.

KC	Relevant assays and biomarkers			Representative chemical and other agents	
	<i>In vitro/ex vivo</i>	Animal	Human	Pharmaceutical	Environmental
<p>Mainly cardiac</p> <p>1. Impairs regulation of cardiac excitability</p>	<p>Patch-clamp recordings in heterologous expression systems, isolated myocytes, or human induced pluripotent stem cell-derived cardiomyocytes (blockade of Na or K ion currents, enhancement of late Na ion current); microelectrode array recordings or optical mapping in <i>ex vivo</i> heart preparation or monolayers of stem cell-derived cardiomyocytes (action potential duration and heterogeneity, conduction velocity), intracellular calcium imaging/measurements.</p>	<p>ECG recordings (QRS duration, QTc intervals), electrophysiologic studies (HV intervals, effective refractory period, and cardiac arrhythmia inducibility), cardiac implantable electronic device interrogation (occurrences of ventricular arrhythmias), development of torsade de pointes ventricular arrhythmias, and sudden cardiac death.</p>	<p>ECG recordings (QRS duration, QTc intervals), electrophysiologic studies (HV intervals, effective refractory period, and cardiac arrhythmia inducibility), cardiac implantable electronic device interrogation (occurrences of ventricular arrhythmias), development of torsade de pointes ventricular arrhythmias, and sudden cardiac death.</p>	<p>Anti-arrhythmic drugs (sotalol, dofetilide, ibutilide, quinidine, procainamide, disopyramide); anti-malarial drug (chloroquine); antibiotics (clarithromycin, erythromycin, azithromycin); tyrosine kinase inhibitors (nilotinib, dasatinib, and sunitinib); antipsychotics (thioridazine, haloperidol); antidepressants (amitriptyline, imipramine, fluoxetine, desipramine, paroxetine); anticonvulsants (felbamate and fosphenytoin); gastric motility drug (cisapride).</p>	<p>Tetrodotoxin, saxitoxin, batrachotoxin, and conotoxin (naturally occurring toxins); lead, alcohol, BPA.</p>
<p>2. Impairs cardiac contractility and relaxation</p>	<p>Contractile measurements via edge detection or sarcomere detection, impedance-based contractility, force transducer, pressure–volume catheter or balloon catheter.</p> <p>Measure the above in isolated cardiomyocytes, stem cell-derived cardiomyocytes, isolated muscle fibers, intact heart preparations.</p>	<p>Pressure–volume catheter; ejection fraction on echocardiography.</p>	<p>Ejection fraction on echocardiography, cardiac CT and MRI; blood pressure and cardiac catheterization.</p>	<p>Glycosides (e.g., digoxin); beta-adrenergic antagonists (e.g., metoprolol, atenolol, carvedilol); calcium sensitizer (e.g., levosimendan); adrenergic agonists (e.g., dobutamine, isoproterenol); haloanesthetics (e.g., halothane, isoflurane); chemotherapeutics (e.g., arsenic trioxide).</p>	<p>Metals (e.g., barium, cadmium, cobalt, lead, nickel); ethanol; BPA.</p>
<p>3. Induces cardiomyocyte injury and death</p>	<p>Cytotoxicity (troponin release, ATP production, nuclear integrity, mitochondrial integrity) in isolated or induced pluripotent stem cell-derived cardiomyocytes; cytochrome complex release, loss of mitochondrial membrane potential.</p>	<p>Cardiac biomarkers (e.g., troponin).</p> <p>Histopathological evaluation (hypertrophy, hyalinization, necrosis, vacuolation, fibrosis).</p>	<p>Cardiac biomarkers (e.g., troponin).</p> <p>Histopathological evaluation (hypertrophy, hyalinization, necrosis, vacuolation, fibrosis).</p>	<p>Anthracyclines (e.g., doxorubicin); sympathomimetics (e.g., isoproterenol); cardiac calcitropes (e.g., milrinone); imatinib mesylate; trastuzumab.</p>	<p>Ethanol, air pollution; diethanolamine; ephedrine; methyl bromide; monochloroacetic acid; 3,3',4',4',5-pentachlorobiphenyl (PCB 126); 2,3,7,8-tetrachlorodibenzodioxin; urethane, cadmium.</p>
<p>4. Induces proliferation of valve stroma</p>	<p><i>In vitro</i> activation of 5HT_{2B} receptors; DNA synthesis induction in cultured interstitial cells from human cardiac valves via 5-HT_{2B} activation; 5-HT_{2B} receptor activation and/or <i>in silico</i> screening incorporated to de-select compounds during drug development.</p>	<p>Valve leaflet fibroplasia and thickening in mice and rats; increased 5-HT levels in whole blood; echocardiogram assessment showing cardiac valve regurgitation.</p>	<p>Valve leaflet fibroplasia and thickening; echocardiogram assessment showing cardiac valve regurgitation.</p>	<p>Fenfluramine, pergolide, cabergoline, ergotamines, MDMA.</p>	<p>None identified.</p>
<p>Mainly vascular</p> <p>5. Impacts endothelial and vascular function</p>	<p>Measurement of binding affinity, functional potency, or expression of vascular receptors and enzymes.</p> <p>Functional effects in isolated vascular tissue preparations segments (human and animal); enzymatic or biochemical effects in endothelial cell culture (e.g., nitric oxide synthase activity, endothelin).</p> <p>Intracellular calcium imaging/measurements.</p>	<p>Blood pressure; regional blood flow measurement (Doppler, ultrasonic transit time, microspheres); vascular resistance determinations.</p>	<p>Blood pressure; cutaneous blood flow assessment (laser Doppler); brachial flow-mediated dilatation; arterial stiffness (pulse wave velocity).</p>	<p>Phenylephrine, sunitinib, sodium nitroprusside, prazosin, minoxidil; calcium channel blockers (e.g., verapamil, nifedipine, diltiazem).</p>	<p>PCBs, BPA, malathion, DDT, air pollution, cigarette smoke, arsenic, cadmium, lead.</p>

Table 1. (Continued.)

KC	Relevant assays and biomarkers			Representative chemical and other agents	
	<i>In vitro/ex vivo</i>	Animal	Human	Pharmaceutical	Environmental
6. Alters hemostasis	Platelet aggregation; platelet activation and function (e.g., surface and cytoplasmic markers and EVs by flow cytometry). Altered coagulation and fibrinolysis (e.g., ACT, PT, APTT; assays of global coagulation; levels of coagulation factors). Endothelial cell anti-aggregation and coagulation function.	Blood cell and platelet counts, MPV; platelet aggregation; platelet activation and function, tail vein bleeding time. Serum antibodies (e.g., anti-PF4 in HIT, lupus anticoagulants). Altered coagulation and fibrinolysis (e.g., ACT, PT, APTT; assays of global coagulation). Vitamin K and vitamin K epoxide levels in serum or plasma (warfarin).	Blood cell and platelet count, MPV; platelet activation and function. Serum antibodies (e.g., anti-PF4 in HIT, lupus anticoagulants). Altered coagulation and fibrinolysis (e.g., ACT, PT, APTT; assays of global coagulation). Vitamin K and vitamin K epoxide levels in serum or plasma (warfarin).	Ibuprofen, quinine, oxalipatin (immune-mediated thrombocytopenia); heparin (HIT); warfarin (interferes with fibrin clot formation by vitamin K deficiency); procainamide, chlorpromazine, and hydralazine (may induce lupus anticoagulants).	Air pollution (PM _{2.5}), arsenic, cadmium.
7. Causes dyslipidemia	Altered gene expression of lipid-related genes and altered synthesis and secretion of VLDL in cultured hepatocytes.	Altered plasma levels of lipids in rodents; altered gene expression of lipid-related genes in liver specimens.	Altered plasma levels of lipids in occupational and epidemiological studies.	Human immunodeficiency virus protease inhibitors; antipsychotic drugs.	PCBs, PFAS, BPA, phthalates, cadmium and lead.
Both cardiac and vascular	Mitochondrial oxygen consumption determination; mitochondrial ROS measurement; mitochondrial Ca ²⁺ imaging; mitochondrial biogenesis, and mitochondrial content determination; mitochondrial membrane polarization measurements; mitochondrial DNA oxidation measurements; ultrastructure imaging. Measurement of the above in isolated cardiomyocytes; submitochondrial preparations; intact heart preparations; human induced pluripotent stem cell-derived cardiomyocytes.	8-OHdG adducts of mitochondrial DNA; mitochondrial oxidative damage (e.g., protein carbonyls and malondialdehyde); histopathological, immunohistochemical, and mitochondrial ultrastructure examination; cardiac contractility–ejection fraction, diastolic relaxation, instrumented LV pressures, QA interval.	Blood mitochondrial DNA methylation; cardiac magnetic resonance.	Chemotherapeutics (e.g., anthracyclines, cisplatin, arsenic trioxide); antiviral compounds (e.g., azidothymidine); anti-diabetics (e.g., rosiglitazone).	Air pollution; metals (e.g., arsenic, mercury, cadmium and lead); diphenylmethane derivatives (e.g., BPA); ethanol, chlorinated hydrocarbons (e.g., PCBs).
8. Impairs mitochondrial function					
9. Modifies autonomic nervous system activity	Measurement of binding affinity or functional potency at autonomic receptors (e.g., alpha and beta-adrenergic; muscarinic subtypes) and transporters (e.g., norepinephrine). Assessment of sympathetic/parasympathetic receptor-mediated function (e.g., cAMP levels, protein phosphorylation) in isolated tissues (heart or vascular tissues). Assess membrane currents/action potentials in isolated neurons/nerves that control CV function. Measure electrical and mechanical activity in co-cultures of cardiomyocytes with parasymphathetic neurons.	Direct measures of sympathetic nerve activity using electrodes or implantable telemetry (membrane currents, action potentials); heart rate variability, baroreflex sensitivity, chemoreceptor sensitivity, with linkage to functional and biochemical measures of CV function (e.g., echocardiography, blood pressure and ECG telemetry, pressure-volume catheter, plasma and urinary catecholamines) in rodents and/or dogs.	Heart rate variability, baroreflex sensitivity, chemoreceptor sensitivity, Valsalva maneuver, isometric handgrip test, deep breathing test, cold pressor test, mental arithmetic, orthostatic test, head-up tilt test, plasma and urinary catecholamines, noradrenaline spillover rate, microneurography (e.g., muscle sympathetic nerve activity), sudomotor function (responses of sweat glands to stimuli), and linkage to measures of CV function (e.g., echocardiography, ECG, blood pressure, and plasma and urinary catecholamines).	Beta-adrenergic agonists (e.g., dobutamine), beta-adrenergic antagonists (atenolol and esmolol), alpha-adrenergic agonists (e.g., clonidine), alpha-adrenergic antagonists (prazosin), muscarinic antagonists (atropine).	Ambient particulate matter air pollution, heavy metals (lead, mercury), cigarette smoke, BPA.

Table 1. (Continued.)

KC	Relevant assays and biomarkers			Representative chemical and other agents	
	<i>In vitro/ex vivo</i>	Animal	Human	Pharmaceutical	Environmental
10. Induces oxidative stress	Increased ROS generation in macrophages, endothelial cells, cardiomyocytes, fibroblasts, human induced pluripotent stem cell-derived cardiomyocytes; increased lipid peroxidation in liposomes.	Increased lipid peroxidation in rats and mice (e.g., malondialdehyde, 8-isoprostanes, hydroxyecosatetraenoates, hydroxyoctadecadienoates); decreased paraoxonase I activity in mice and glutathione peroxidase in rats; oxidative changes in plasma lipoproteins of hyperlipidemic mice resulting in proatherogenic LDL and dysfunctional pro-inflammatory high-density lipoprotein.	Increased lipid peroxidation and decreased paraoxonase I activity in plasma; decreased glutathione peroxidase, decreased superoxide dismutase in blood; Increased NOX in blood.	Anthracyclines.	Air pollution, (PM _{2.5} , ultrafine particles); diesel exhaust; gasoline exhaust; PAHs; arsenic; cadmium; lead; mercury; pesticides (organophosphates); insecticides (carbamates, fenitrothion), tobacco cigarette.
11. Causes inflammation	Analysis of pro-inflammatory gene expression; measurement of cytokine secretion by immune cells (e.g., macrophages); flow cytometry analysis of immune cells; immunofluorescent staining of inflammatory markers; characterization of macrophage polarization; analysis of endothelial cell function.	Analysis of circulating cytokine levels (e.g., IL-1 β , IL-6); flow cytometry analysis of immune cell population in blood and tissues; analysis of inflammatory gene expression in various tissues including aorta; immunostaining of key inflammatory markers in tissues; characterization of macrophage phenotypes within atherosclerotic plaques; calculation of atherosclerotic plaque stability.	Measurement of circulation inflammatory markers (e.g., IL-6, CRP); analysis of immune cells by flow cytometry or other standard methods.	Procainamide (antiarrhythmic); hydralazine (vasodilator); doxorubicin (anthracycline).	PCBs, BPA, arsenic, cadmium, lead, and air pollution (PM _{2.5}).
12. Alters hormone signaling	Altered contractility in isolated cardiomyocytes or intact heart preparations; whole-heart ECG; modifications of intracellular calcium imaging; changes in vascular contractility; changes in SR protein expression, or posttranslational modifications, signal transduction; pharmacological agonist/antagonist studies; adrenal-derived cell lines, increased expression of vascular endothelial growth factor and endothelial nitric oxide synthase in human primary endothelial cells.	Multiple end points in numerous experimental species (including rodents, canine, porcine, primates): ECG recordings, heart rate variability, baroreflex sensitivity, increased blood pressure, in hormone-receptor knockout rodent models; altered responses to ischemia, cardiac transcriptome; changes in fibrosis and extracellular matrix composition.	Multiple end points in epidemiological studies: modifications in blood pressure, hemostasis and vascular resistance; sex-specific lipid profiles, arrhythmia risk, increased hypertrophy, heart failure and dilated cardiomyopathy; altered ECG; increased risk for coronary and peripheral artery disease and atherosclerosis, atrial fibrillation, disturbances in cardiac output and contractility; atherogenic lipid profiles.	Amiodarone; rosiglitazone; testosterone; androgens and anabolic steroids; adrenergic agonists and antagonists; selective estrogen receptor modulators and anti-estrogens; glucocorticoids.	BPA, PCBs, arsenic, cadmium, and lead.

Note: 5-HT, 5-hydroxytryptamine (serotonin); 5-HT_{2B}, 5-HT subtype 2B; ACT, activated clotting time; APTT, activated partial thromboplastin time; ATP, cyclic adenosine monophosphate; CRP, C-reactive protein; CT, computed tomography; DDT, dichlorodiphenyltrichloroethane; ECG, electrocardiogram; EV, extracellular vesicle; HIT, heparin-induced thrombocytopenia; HV interval, conduction time through the distal His-Purkinje tissue measured from the onset of the His-bundle deflection to the earliest ventricular activation; K⁺, potassium ion; LDL, low-density lipoprotein; LV, left ventricular; MDMA, 3,4-methylenedioxymethamphetamine; MPV, mean platelet volume; MRI, magnetic resonance imaging; Na⁺, sodium ion; NOX, nicotinamide adenine dinucleotide phosphate oxidase; PAH, polycyclic aromatic hydrocarbon; PCBs, polychlorinated biphenyls; Pf-4, platelet factor 4; PFAS, per- and poly-fluorinated substances; PM_{2.5}, particulate matter in aerodynamic diameter (fine particulate matter); PT, prothrombin time; QTC, corrected QT interval; ROS, reactive oxygen species; SR, sarcoplasmic reticulum; VLDL, very-low-density lipoprotein.

Table 2. Key characteristics (KCs) of cardiovascular toxicants applied to three established environmental contaminants that are cardiotoxic.

KC	Evidence for each KC for PM _{2.5} air pollution (human–animal– <i>in vitro</i>)	Evidence for each KC for PCBs (human–animal– <i>in vitro</i>)	Evidence for each KC for BPA (human–animal– <i>in vitro</i>)
Mainly cardiac			
1. Impairs regulation of cardiac excitability	—	—	Disrupts intracellular calcium ion homeostasis in excised rat hearts and ventricular myocytes (Posnack et al. 2015; Ramadan et al. 2018; Yan et al. 2011). Directly inhibits multiple voltage-gated calcium channels human cells <i>in vitro</i> and <i>ex vivo</i> in rat aorta (Deutschmann et al. 2013; Feiteiro et al. 2018; Michaela et al. 2014), which are important for nodal cell depolarization, atrioventricular conduction, and the plateau phase of the cardiac action potential. Sinus bradycardia and slowed cardiac electrical conduction observed in experimental models in <i>ex vivo</i> and <i>in vivo</i> studies (Belcher et al. 2015; Patel et al. 2015; Posnack et al. 2014).
2. Impairs cardiac contractility and relaxation	—	—	—
3. Induces cardiomyocyte injury and death	—	—	—
4. Induces proliferation of valve stroma	—	—	—
Mainly vascular			
5. Impacts endothelial and vascular function	Altered vasomotor tone in epidemiological (Dales et al. 2007; Krishnan et al. 2012; Zanobetti et al. 2014) and experimental <i>in vivo</i> (Hansen et al. 2007) and <i>ex vivo</i> (Hansen et al. 2007) studies.	—	—
6. Alters hemostasis	Altered hemostasis in epidemiological (Hajat et al. 2015; Riediker et al. 2004; Viehmann et al. 2015; Zhang et al. 2018), and experimental <i>in vivo</i> studies (Liang et al. 2019; Sun et al. 2008).	—	—
7. Causes dyslipidemia	Induced dyslipidemia in epidemiological (Mathew et al. 2018; McGuinn et al. 2019), and experimental <i>in vivo</i> (Li et al. 2020; Xu et al. 2019b) studies.	Dyslipidemia in humans resulting in increased serum levels of cholesterol and triglycerides (Chase et al. 1982; Penell et al. 2014; Tokunaga and Kataoka 2003). In rodents and zebrafish, PCBs most likely cause dyslipidemia <i>in vivo</i> by altering the regulation of genes related to lipogenesis and lipid catabolism in liver cells (Chapados and Boucher 2017; Li et al. 2019; Wahlang et al. 2013). <i>In vitro</i> , human and mouse hepatocytes exposed to PCBs <i>in vitro</i> have increased triglyceride and total cholesterol concentrations (Boucher et al. 2015; Chen et al. 2020a; Wu et al. 2017).	—
Both cardiac and vascular			
8. Impairs mitochondrial function	—	—	—
9. Modifies autonomic nervous system activity	Altered autonomic nervous system activity in multiple epidemiological (Kirrane et al. 2019; Lee et al. 2014; Mordukhovich et al. 2015; Park et al. 2010; Peters et al. 2015; Pieters et al. 2012), experimental <i>in vivo</i> (Anselme et al. 2007; Bessac and Jordt 2008; Carll et al. 2013; Hazari et al. 2011; Widdicombe	—	Differences in beta-adrenergic receptor expression have been observed in animal models (Belcher et al. 2015) and alterations in heart rate variability have been reported in human subjects (Bae et al. 2012).

Table 2. (Continued.)

KC	Evidence for each KC for PM _{2.5} air pollution (human–animal– <i>in vitro</i>)	Evidence for each KC for PCBs (human–animal– <i>in vitro</i>)	Evidence for each KC for BPA (human–animal– <i>in vitro</i>)
10. Induces oxidative stress	and Lee 2001), and <i>in vitro</i> (Deering-Rice et al. 2011) studies. Induced oxidative stress in epidemiological (Lee et al. 2014; Li et al. 2016; Weichenthal et al. 2016), experimental <i>in vivo</i> (Xu et al. 2019b; Yue et al. 2019), and <i>in vitro</i> lung epithelial (Niu et al. 2020) and dual lung and cardiomyocyte (Gorr et al. 2015) studies.	Altered glutathione metabolism and lipid peroxidation in humans, and <i>in vivo</i> in rats, mice, and crabs (Deng et al. 2019; Feng et al. 2019; Kumar et al. 2014b; Shan et al. 2020; Tremblay-Laganière et al. 2019). Increased ROS production <i>in vitro</i> in human ECs and neutrophil granulocytes (Berntsen et al. 2016; Long et al. 2017; Tang et al. 2017), and in various tissues in pig, mice, hamster, and fish (scup) (Green et al. 2008; Han et al. 2012; Hennig et al. 2002; Long et al. 2020; Majkova et al. 2011; Murati et al. 2017; Schlezinger et al. 2006).	Population-based epidemiological studies have noted associations between BPA exposure, inflammation, and oxidative stress (Kataria et al. 2017; Steffensen et al. 2020; Wang et al. 2019b; Yang et al. 2009).
11. Causes inflammation	Induced inflammation in epidemiological (Altuwayjiri et al. 2021; Liu et al. 2019; Pope et al. 2016; Riediker et al. 2004; Zhang et al. 2020a), experimental <i>in vivo</i> (Bai and Sun 2016; Hadei and Naddafi 2020; Tong 2016), and <i>in vitro</i> lung epithelial (Schwarze et al. 2007) macrophage (Zhao et al. 2016), and dual lung and cardiomyocyte (Gorr et al. 2015) studies.	Increased biomarkers of inflammation, such as ICAM-1 and VCAM-1, in humans (Kumar et al. 2014a). Elevated blood levels and hepatic expression of IL-6 and TNF α in rats and mice after exposure to a PCB mixture (Wahlang et al. 2014; Xu et al. 2019a). <i>In vitro</i> exposure of human monocytes and vascular ECs to PCB 126 induced expression of inflammatory cytokines, including TNF α , monocyte/macrophage chemokine 1f and IL-1 β in the monocytes and up-regulated inflammatory genes, such as IL-6, CRP, ICAM-1, and VCAM-1 in the EC (Milner 1989).	BPA exposure is associated with increased inflammatory makers (Song et al. 2017) and atherosclerosis or coronary artery disease in epidemiological studies (Lind and Lind 2011; Melzer et al. 2012a, 2012b). <i>In utero</i> BPA exposure increases cardiac fibrosis and inflammation in offspring (Belcher et al. 2015; Gear et al. 2017; Rasdi et al. 2020) and impedes recovery after myocardial infarction in adult animals (Patel et al. 2015; Shang et al. 2019). Notably, the effects of BPA on cardiac remodeling and inflammation are significantly attenuated in estrogen receptor- β knockout mice, which further suggests a mechanistic link to BPA's estrogenic activity (Kasneji et al. 2017).
12. Alters hormone signaling	Altered hypothalamus–pituitary–adrenal axis-related stress hormones (Niu et al. 2018), altered thyroid hormone levels during pregnancy (Zhao et al. 2019), and altered insulin and glucose homeostasis (Brook et al. 2016; Zheng et al. 2013), in epidemiological studies. Altered hypothalamus–pituitary–adrenal axis-related stress hormones (Liu et al. 2020), altered renin–angiotensin system signaling (Ghelfi et al. 2010), altered insulin and glucose homeostasis (Xu et al. 2011), altered testosterone synthesis (Yang et al. 2019), and altered PPAR γ signaling (Zheng et al. 2013), in experimental <i>in vivo</i> studies.	Altered circulating thyroid hormone levels in humans, rats, and fish (sea bass) (Collins et al. 1977; Meeker et al. 2007; Schnitzler et al. 2011; Takser et al. 2005). In young non-pregnant women, a clinical indicator of ovarian responsiveness, the FSH:LH ratio, was associated with PCBs (Gallo et al. 2018). In rats, the pituitary content of FSH and LH was increased by PCB-126 exposure (Desaulniers et al. 1999), and rats exposed to a PCB mixture showed increases in uterine weights and uterine ³ H-thymidine labeling (Jansen et al. 1993). <i>In vitro</i> effects on the estrogen receptor have also been observed (Gjernes et al. 2012; Tavorari et al. 2006).	Disruption of intracellular calcium homeostasis is likely mediated through estrogenic effects of BPA, which results in posttranslational modifications of key calcium-handling proteins (Belcher et al. 2012; Gao et al. 2013; Liang et al. 2014).

Note: Details are provided for those KCs that we for cancer treatments and cardiovascular toxicity of the European Society of Cardiology considered to have the strongest evidence for each agent (e.g., a combination of data from human epidemiological/clinical studies and *in vivo* animal studies, as well as *in vitro* studies). —, Other KCs; BPA, Bisphenol A; CRP, C-reactive protein; ECs, endothelial cells; FSH, follicle-stimulating hormone; ICAM-1, intracellular adhesion molecule 1; IL-1 β , interleukin 1 beta; IL-6, interleukin 6; LH, luteinizing hormone; PCBs, polychlorinated biphenyls; PM_{2.5}, particulate matter ≤ 2.5 μm in aerodynamic diameter (fine particulate matter); PPAR γ , peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; TNF α , tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule 1.

and Hai 2021). Beta-adrenergic agonists increase the probability of DADs by stimulating Ca^{2+} current and SR Ca^{2+} uptake. Environmental exposures can also promote Ca^{2+} -mediated arrhythmias and include alcohol consumption (Yan et al. 2018) and bisphenol A (BPA) exposure (Gao et al. 2013; Yan et al. 2011). Arsenic trioxide can increase Ca^{2+} currents and precipitate QT prolongation, torsade de pointes, and sudden cardiac death (Ficker et al. 2004).

KC2: impairs cardiac contractility and relaxation. The opening of LTCCs allows Ca^{2+} entry, which triggers SR Ca^{2+} release via ryanodine receptors (RyR2), leading to crossbridge formation between actin and myosin molecules. Cardiac relaxation requires a decline in intracellular Ca^{2+} concentration through the SR Ca^{2+} adenosine triphosphate (ATP)ase (SERCA) and the NCX. Drugs or xenobiotics that alter the LTCC, RyR2, SERCA, or NCX can significantly affect cardiac contractility. Beta-adrenergic agonists increase cAMP-dependent protein kinase A, leading to the phosphorylation of the LTCC and phospholamban (PLB). Phosphorylation of PLB releases the inhibition on SERCA and increases SR Ca^{2+} uptake and SR Ca^{2+} load. Therefore, beta-adrenergic agonist stimulation of LTCCs and SR Ca^{2+} uptake significantly increases cardiac contractility; the opposite effects occur with beta-adrenergic blockers (Movsesian 1999). Ca^{2+} channel blockers can significantly decrease cardiac contractility and may precipitate heart failure in patients with reduced left ventricular function. For example, diltiazem and verapamil exhibit negative inotropic effects that can worsen heart failure to a greater extent than the dihydropyridine Ca^{2+} channel blockers (e.g., nifedipine) because the negative inotropic effects are not offset by vasodilation (Elliott and Ram 2011). Drugs that may cause or exacerbate heart failure have been summarized in a recent scientific statement from the American Heart Association (Page et al. 2016). Exposure to cadmium may modulate intracellular Ca^{2+} concentration (Thévenod and Lee 2013), and high levels are associated with future heart failure (Borné et al. 2015).

In contrast to our current knowledge regarding agents or drugs that directly affect cardiac inotropy, there is a significant paucity in our understanding for drugs or xenobiotics that may alter cardiac lusitropy, the rate of cardiac relaxation. Experimental studies demonstrate that several drugs may improve left ventricular diastolic function; for example, JTV519 reduces SR Ca^{2+} leak and SES0400 inhibits the NCX entry mode. However, clinical data are not currently available for these drugs (Tschöpe et al. 2017).

KC3: induces cardiomyocyte injury and death. Cardiomyocytes, although critical for both myocardial contraction and electrical conduction, are thought to have little, if any, regenerative capacity. Hence, the injury or death of cardiomyocytes can have progressive, debilitating, and lethal consequences. Morphological changes to cardiomyocytes include hypertrophy, hyalinization, or vacuolation (Berridge et al. 2016). Hypertrophy is often a response to increased work and may be generalized or regional. Hyalinization generally represents hypercontraction of the cell, condensation of the cytoplasm, and fragmentation of the myofibrillar contractile apparatus. Vacuolation may represent swelling of cellular organelles (e.g., mitochondria), dilation of the SR, or lipid accumulation. Cardiomyocyte cell death is usually a lytic event, with the release of cellular contents prompting a mixed inflammatory cell response and repair by fibrosis (Clements et al. 2010; Kong et al. 2014). Although apoptosis may be observed *in vitro*, it is difficult to demonstrate *in vivo*.

Anthracyclines, such as doxorubicin, are well-established CV toxicants, as are many other cancer chemotherapeutics (Bhagat and Kleinerman 2020; Herrmann 2020; Jain et al. 2017; Octavia et al. 2012; Shan et al. 1996). Clinical presentations for these toxicities include arrhythmias and decreased contractile function.

Increased serum troponins are often important precedent biomarkers that indicate cardiomyocyte injury (Taggart et al. 2021). Endogenous and synthetic catecholamines are also well recognized CV toxicants at high levels of exposure, and direct and indirect cardiomyocyte injury are important mediators of systolic dysfunction, such as in methamphetamine-associated cardiomyopathy (Reddy et al. 2020). Intraperitoneal administration of the short-acting sympathomimetic drug, isoproterenol, to rodents induces a dose-related cardiomyocyte necrosis (Clements et al. 2010). Myocardial degeneration, characterized as diffuse cardiomyocyte degeneration and necrosis, with varying levels of inflammatory cell infiltrate and fibrosis, has been observed with a number of industrial chemicals in rodent studies conducted by the National Toxicology Program (Jokinen et al. 2005). Cardiomyocyte injury was generally dose progressive and occurred in studies from 6–13 wk in length. Tested chemicals have included monochloroacetic acid (used in the synthesis of herbicides and other organic compounds), 3,3'-4,4'-tetrachloroazoxybenzene (a dioxin-like compound), diethanolamine (used in the synthesis of a variety of chemicals), and urethane (used in a variety of industrial processes). Exposure to cadmium has also been associated with apoptosis and cell death in a mouse fibroblast cell line *in vitro* (Biagioli et al. 2008).

KC4: induces proliferation of valve stroma. A novel mechanism of cardiotoxicity was discovered with fenfluramine, a 5-hydroxytryptamine (5-HT; serotonin) agonist used to treat obesity, which inadvertently targets 5-HT subtype 2B (5-HT_{2B}) receptors on heart valves (Fitzgerald et al. 2000) (Table 3). An activation can induce pathological proliferation of valve leaflet stroma myofibroblasts, leading to abnormalities in leaflet structure and subsequent valvular heart disease (Elangbam 2010; Reid et al. 2013; Taylor et al. 2007), with plaques containing proliferative myofibroblasts in an abundant extracellular matrix (ECM) and lymphocytic infiltrations (Connolly et al. 2009; Steffee et al. 1999; Volmar and Hutchins 2001). This mechanism of cardiotoxicity was recapitulated in mice and rats following administration of 5-HT (Elangbam et al. 2008).

Pharmaceutical drugs associated with similar valvular pathology related to activation of 5-HT_{2B} receptors include ergot alkaloids (e.g., methysergide, ergotamine), designer drugs [e.g., 3,4-methylenedioxymethamphetamine (MDMA, or Ecstasy)], anorexigens (e.g., fenfluramine, dexfluramine), and dopamine agonists (e.g., pergolide, cabergoline) [reviewed by Elangbam (2010)]. Fenfluramine was withdrawn from the market because of a high incidence of drug-induced valvular heart disease (Roth 2007; Rothman et al. 2000), and candidate drugs are now routinely screened for 5-HT_{2B} agonist activity before progressing to clinical trials (Reid et al. 2013). We currently are not aware of any environmental agents that possess this KC.

Primarily Vascular

KC5: impacts endothelial and vascular function. Blood vessels are composed of endothelial cells (ECs), smooth muscle cells (SMCs), and adventitia (fibroblasts and connective tissue). The ECs have surface receptors and intracellular pathways [e.g., nitric oxide (NO), endothelin] that maintain critical functions, such as organ blood flow and the transcellular transport of nutrients and lipids (Alexander et al. 2021). Endothelial dysfunction—characterized by its hallmark feature of impaired vasodilation, among other changes (e.g., loss of vascular integrity, increased expression of adhesion molecules, pro-atherogenic phenotype, up-regulation of cytokine production)—is linked to inflammation, increased vascular permeability, a pro-thrombotic phenotype, and atherosclerotic disease (Mundi et al. 2018). The ECM, a structural scaffold for ECs that regulates ECs and SMCs through

Table 3. Key characteristics (KCs) of cardiovascular toxicants applied to two classic cardiotoxic drugs and the chemotherapeutic agent arsenic trioxide.

KC	Evidence for each KC for doxorubicin (human–animal– <i>in vitro</i>)	Evidence for each KC for fenfluramine (human–animal– <i>in vitro</i>)	Evidence for each KC for arsenic trioxide (human–animal– <i>in vitro</i>)
Mainly cardiac			
1. Impairs regulation of cardiac excitability	QTc prolongation in humans and monkeys unrelated to potassium channel (hERG) inhibition (Engwall et al. 2021; Nousiainen et al. 1999).	—	QTc prolongation in humans with animal and <i>in vitro</i> evidence of potassium channel (hERG) inhibition (Alexandre et al. 2018; Dennis et al. 2007).
2. Impairs cardiac contractility and relaxation	Alters calcium homeostasis by inducing calcium leakage from the sarcoplasmic reticulum (Nebigil and Désaubry 2018).	—	Clinically relevant concentrations of arsenic trioxide causes intracellular calcium overload from damaged mitochondria (Varga et al. 2015).
3. Induces cardiomyocyte injury and death	Induces cardiomyocyte apoptosis, necrosis, necroptosis, and autophagy in cardiac cells and mice, which lead to injury and cell death (Ma et al. 2020).	—	Induces cardiomyocyte apoptosis and death in animal and cell culture models (Varga et al. 2015).
4. Induces proliferation of valve stroma	—	<i>In vitro</i> activation of 5-HT _{2B} receptors; dose-dependent valve leaflet fibroplasia and thickening in mice, rats, and humans; development of valvular cardiac disease in clinical studies (Elangbam et al. 2008; Elangbam 2010; Fitzgerald et al. 2000; Reid et al. 2013; Roth 2007; Rothman et al. 2000; Taylor et al. 2007).	—
Mainly vascular			
5. Impacts endothelial and vascular function	—	—	—
6. Alters hemostasis	—	—	—
7. Causes dyslipidemia	—	—	—
Both cardiac and vascular			
8. Impairs mitochondrial function	Promotes mitochondrial fission, inhibits mitochondrial fusion, and impairs mitochondrial function in several ways, including decreasing the oxygen consumption rate and altering mitochondrial membrane potential (Osataphan et al. 2020).	—	Pro-apoptotic effect of arsenic trioxide in ventricular cardiomyocytes shown to be associated with Parkin-dependent ubiquitin proteasome activation and loss of mitochondrial membrane potential (Varga et al. 2015).
9. Modifies autonomic nervous system activity	—	—	—
10. Induces oxidative stress	Induces ROS and decreases superoxide dismutase-2 in cardiac tissues (Osataphan et al. 2020).	—	—
11. Causes inflammation	Induces markers of inflammation <i>in vivo</i> , as reviewed by Prathumap et al. (2020).	—	Chronic environmental exposures are associated with elevated circulating inflammatory markers in humans (Cosselman et al. 2015; Wu et al. 2014). Leads to vascular inflammation, endothelial dysfunction and atherosclerosis development in animals (Cosselman et al. 2015; States et al. 2009).
12. Alters hormone signaling	—	—	—

Note: Details are provided for those KCs that we for cancer treatments and cardiovascular toxicity of the European Society of Cardiology considered to have the strongest evidence for each agent (e.g., a combination of data from human epidemiological/clinical studies, *in vivo* animal studies and *in vitro* studies). —, Other KCs; 5-HT_{2B}, 5-HT subtype 2B; hERG, ether-à-go-go-related gene; QTc, corrected QT interval; ROS, reactive oxygen species; RyR2, ryanodine receptors.

integrins, undergoes increased or abnormal ECM protein expression and collagen deposition in vascular disease or injury, which in turn may modify normal EC and SMC function (González-Santiago et al. 2002). Vascular SMCs contain a variety of extracellular receptors and intracellular pathways that regulate the contraction of the vascular wall and modulate the diameter of the blood vessel lumen (Brozovich et al. 2016; Tykocki et al. 2017). Vascular SMC activity is modified by extrinsic (e.g., neural, endocrine) and intrinsic factors (e.g., endothelial and muscle cell metabolites, myogenic mechanisms). Vascular contraction is linked tightly to intracellular calcium fluctuations that activate the actin–myosin complex and drive SMC shortening (Fan et al. 2019). The vasculature is an important target for amlodipine and

other voltage-sensitive LTCC blockers used for the treatment of hypertension (Luo et al. 2019). Vascular dysfunction contributes to various CV disease processes, including hypertension, atherosclerosis, coronary vasospasm, and myocardial infarction (Thygesen et al. 2018).

Chronic exposure to arsenic is associated with hypertension due to vascular injury and endothelial dysfunction (Ellsworth 2015; Stea et al. 2014). Exposure to polychlorinated biphenyls (PCBs) has been linked to increased blood pressure (Goncharov et al. 2011), and may occur via increased aldosterone biosynthesis (Goncharov et al. 2011; Perkins et al. 2016). NO, which is physiologically produced in ECs, plays a critical role in CV function and the deregulation of NO contributes to many CVDs

(Vanhoutte et al. 2017). PCBs have been shown to impair endothelium-mediated vasodilation (EVD) of rat aortic rings *ex vivo* (Helyar et al. 2009), suggesting reduced NO synthase (NOS) activity. The organophosphate pesticide malathion impairs EVD in rats (de Carvalho et al. 2014), and other pesticides, such as dichlorodiphenyltrichloroethane, have been linked to hypertension in humans (Lind et al. 2014). Arsenic and cadmium exposures have been linked to reduced NOS activity in ECs *in vitro* (Majumder et al. 2008; Pi et al. 2000), impaired endothelial function and hypertension in experimental animals (Pinheiro Júnior et al. 2020), and depressed NO production in humans (Pi et al. 2000). Chemicals and metals, such as arsenic, that increase endothelial and smooth muscle nicotinamide adenine dinucleotide phosphate (i.e., NADPH) oxidase catalyze superoxide generation and decrease NO availability as a result of the formation of vaso-toxic peroxynitrite (Al Ghouleh et al. 2011; Barchowsky et al. 1999).

KC6: alters hemostasis. Hemostasis is mainly primed to prevent blood loss and involves circulating platelets, coagulation proteins, and vascular ECs. Loss of, or interference with, any of these components can cause either anticoagulant or procoagulant actions that lead to either blood loss or thrombosis, microangiopathies, and organ ischemia. Immune responses to xenobiotics can target platelet or protein activation or clearance, as well as endothelial antithrombotic activity.

Chemotherapy-induced thrombocytopenia is a frequent side-effect of myelosuppressive cancer therapy (Weycker et al. 2019). Multiple drugs are implicated in immune-mediated thrombocytopenia (Curtis 2014) (Table 1). In heparin-induced thrombocytopenia (HIT), antibodies are formed against a heparin/protein (usually platelet factor 4) complex that activates platelets and aggregation (Evans and Gomes 2017; Greinacher et al. 2017). Drug-induced thrombotic thrombocytopenic purpura, a rare and life-threatening thrombotic microangiopathy (Joly et al. 2017), is caused by quinine, cyclosporine, and tacrolimus (Al-Nouri et al. 2015) through antibody generation and direct EC toxicity (Lian 2005; Veyradier and Meyer 2005). In addition, certain classes of drugs modulate platelet procoagulant and endothelial anticoagulant function through mechanisms that include prostaglandin synthesis inhibition, interference with platelet agonist-receptors interactions, and interference with calcium translocation (Abrams 2006). Exogenous chemicals could interfere with fibrin clot formation in several ways. For example, warfarin promotes vitamin K deficiency (Berry et al. 2000; Chua and Friedenber 1998). Recently, a class of new oral anticoagulants has emerged to treat thromboembolic diseases. They are selective for one specific coagulation factor, either thrombin (e.g., dabigatran) or factor Xa (e.g., rivaroxaban, apixaban, edoxaban) (Almarshad et al. 2018). Procainamide, chlorpromazine, and hydralazine may induce lupus anticoagulants, which are antibodies that interfere with the protein C system regulating thrombosis (Bertolaccini et al. 2004). Thrombosis associated with exposure to PM_{2.5} air pollution may involve platelet activation and the promotion of circulating toxic microvesicles (Robertson and Miller 2018). Cadmium exposure has been reported to increase plasminogen activation inhibitor-1 generation in a human vascular EC line (Hara et al. 2021).

KC7: causes dyslipidemia. Low-density lipoprotein (LDL)-cholesterol is necessary for atherosclerosis development, where deposits of LDL-cholesterol in plaque accumulate in the intima layer of blood vessels and trigger chronic vascular inflammation. LDL-cholesterol is increased either by dietary overfeeding, increased synthesis and output from the liver, or by an increased uptake from the intestine/change in bile acids and enterohepatic circulation (Lorenzatti and Toth 2020). A number of drugs reduce LDL-cholesterol and include statins and cholestyramine (López-

Miranda and Pedro-Botet 2021), but other drugs might increase cholesterol as an adverse effect, such as some antiretroviral drugs (e.g., human immunodeficiency virus protease inhibitors) (Distler et al. 2001) and some antipsychotic drugs (Meyer and Koro 2004; Rummel-Kluge et al. 2010). A number of environmental contaminants, such as PCBs and pesticides (Aminov et al. 2014; Goncharov et al. 2008; Lind et al. 2004; Penell et al. 2014) and phthalates (Olsén et al. 2012) have also been associated with increased levels of LDL-cholesterol and triglycerides. In addition, some metals, such as cadmium (Zhou et al. 2016) and lead (Xu et al. 2017), have also been linked to dyslipidemia. Proposed mechanisms leading to dyslipidemia are reduced β -oxidation and increased lipid biosynthesis in the liver (Li et al. 2019; Wahlang et al. 2013; Wan et al. 2012), altered synthesis and secretion of very-low-density lipoprotein (Boucher et al. 2015), increased intestinal lipid absorption and chylomicron secretion (Abumrad and Davidson 2012), and increased activity of fatty acid translocase (FAT/CD36) and lipoprotein lipase (Wan et al. 2012). Furthermore, dioxins, PCBs, BPA, and per- and poly-fluorinated substances have been associated with atherosclerosis in humans (Lind et al. 2017; Melzer et al. 2012a) and in mice (Kim et al. 2014) and with increased prevalence of CVD (Huang et al. 2018; Lang et al. 2008).

Both Cardiac and Vascular

KC8: impairs mitochondrial function. Mitochondria generate energy in the form of ATP and also play vital roles in Ca²⁺ homeostasis, apoptosis regulation, intracellular redox potential regulation, and heat production, among other roles (Westermann 2010). In cardiac cells, mitochondria are highly abundant and needed for the synthesis of ATP as well as to synthesize different metabolites such as succinyl-coenzyme A, an essential signaling molecule in protein lysine succinylation, and malate, which plays a significant role in energy homeostasis (Frezza 2017).

Impairment of cardiac mitochondrial function—as demonstrated by lower energy metabolism, increased reactive oxygen species (ROS) generation, altered Ca²⁺ handling, and apoptosis—can be induced by environmental chemical exposure or by commonly prescribed drugs. Arsenic exposure can induce mitochondrial DNA damage, decrease the activity of mitochondrial complexes I–IV, decrease ATP levels, alter membrane permeability, increase ROS levels, and induce apoptosis (Pace et al. 2017). The increased ROS production triggered by arsenic is most likely via the inhibition of mitochondrial complexes I and III (Pace et al. 2017). Similarly, the environmental pollutant methylmercury may impair mitochondrial function by inhibiting mitochondrial complexes, resulting in increased ROS production and inhibiting the citric acid cycle in the mitochondria (Jia et al. 2015). Several prescribed drugs induce mitochondrial dysfunction that is linked to their CV toxicity (Varga et al. 2015). Anthracyclines can exert significant damage to the heart by impairing mitochondrial biogenesis and cause mitochondrial dysfunction by increasing iron accumulation, resulting in increased ROS production (Henriksen 2018). Rosiglitazone impairs mitochondrial biogenesis by inhibiting peroxisome proliferator-activated receptor (PPAR)-coactivator-1 and azidothymidine inhibits the enzyme needed for mitochondrial DNA replication, mitochondrial DNA polymerase- γ (Varga et al. 2015). Nitrogen dioxide, a component in diesel exhaust, has been shown in rats to produce impairment in endothelial function by means of mitochondrial dysfunction (Karoui et al. 2020), and exposure to PM_{2.5} air pollution has been shown to induce vascular fibrosis in rats by mitochondrial down-regulation (Ning et al. 2020). Cadmium has been linked to mitochondrial dysfunction in a human cell line (Xu et al. 2021).

KC9: modifies autonomic nervous system activity. The autonomic nervous system (ANS) consists of counter-balancing sympathetic (SNS) and parasympathetic (PNS) nervous systems (Chen et al. 2014) that maintain homeostatic control of CV function. Activation of the SNS by endogenous chemicals could promote arrhythmia by increasing AP firing in pacemaker cells, leading to increased heart rate and atrioventricular conduction velocity and by modulating atrial and ventricular repolarization (Lederer 2017; Shen and Zipes 2014). By contrast, agents that activate the PNS decrease AP firing, reducing heart rate and atrioventricular conduction velocity, and reduce the effective refractory period, mainly in the atria (Lederer 2017; Shen and Zipes 2014). Agents that block SNS activity may also impair cardiac systolic and diastolic function and disrupt vascular smooth muscle tone by altering intracellular Ca^{2+} levels (Boulpaep 2017).

Sympathomimetic drugs mimic increased sympathetic activity by activating beta-adrenergic receptors in the heart and are often used to treat acute heart failure (Tariq and Aronow 2015). Sympatholytic drugs, on the other hand, block sympathetic neurotransmission at the peripheral organ level or in the central nervous system and decrease blood pressure (Becker 2012). Anticholinergics (i.e., muscarinic antagonists) block PNS transmission and cause tachycardia (Andersson et al. 2011). Importantly, a shift toward increased SNS tone, via sympathetic activation or parasympathetic withdrawal, increases CV morbidity and mortality (Brook et al. 2010). Environmental exposure to $\text{PM}_{2.5}$ air pollution has been linked with increased cardiac sympathetic tone, decreased heart rate variability, and the attendant increased risk of ischemic heart disease and heart failure (Brook et al. 2010). These effects of $\text{PM}_{2.5}$ air pollution likely involve ANS reflexes, including the activation of respiratory sensory mechanisms and altered baroreceptor responsiveness (Perez et al. 2015).

KC10: induces oxidative stress. In atherosclerosis, the interplay between pro- and anti-oxidant factors in the blood vessels may determine the degree of ROS generation and plaque formation (Dubois-Deruy et al. 2020). These oxidative effects can derive from direct redox chemistry given that some CV toxicants (e.g., $\text{PM}_{2.5}$) have a high content of redox-active chemicals, or from the exacerbation of endogenous sources of ROS. ROS originate from all the main cell types present in atherosclerotic lesions, including ECs, macrophages, SMCs, and cardiac cells. Enhanced ROS production could be due to the activation of nicotinamide adenine dinucleotide phosphate oxidase (NOX), which has been shown to be an important source of vascular ROS (Ying et al. 2009). Enhanced ROS could also be due to activation of endogenous pro-oxidative pathways, such as the lipoxygenase pathways (Lin et al. 2019; Yin et al. 2013), which enable enzymatically mediated oxidation of polyunsaturated fatty acids and amplification of lipid peroxidation cascades, through xanthine oxidase, through the induction of mitochondrial dysfunction (Yin et al. 2019), or through the inactivation of antioxidant extracellular and intracellular defense pathways, such as enzymatic inhibition of antioxidant enzyme paraoxonase 1 (PON1) (Lin et al. 2019; Yin et al. 2013), glutathione peroxidase, and superoxide dismutase (SOD) (Delfino et al. 2009).

In vitro and *in vivo* animal evidence support the ROS-inducing actions of CV toxicants, including various metals such as lead and arsenic (Balali-Mood et al. 2021) and polycyclic aromatic hydrocarbons (PAHs) (Låg et al. 2020). Some commonly used drugs, such as anthracyclines, are known CV toxicants and have been shown to induce ROS production in cardiac, endothelial, and fibroblast cells (Nebigil and Désaubry 2018). Studies have shown that arsenic exposure induces NOX2 expression/activity, which increases ROS in several CV cell types and depletes cardiac glutathione and increases oxidized glutathione levels

(Alamolhodaie et al. 2015; Waghe et al. 2015). Interaction with glutathione and the depletion of SOD, catalase, and glutathione peroxidase—all enzymes involved in the regulation of oxidative stress—have been shown to contribute to cadmium-induced endothelial dysfunction (Almenara et al. 2020). Acrolein depletes glutathione and causes ROS-mediated suppression of glutathione S-transferase activity in CV tissues (Henning et al. 2017). Human studies also support the pro-oxidative effects of CV toxicants $\text{PM}_{2.5}$ (Delfino et al. 2009; Lin et al. 2019) and tobacco cigarette smoke (Zhou et al. 2000) via the inhibition of the antioxidant enzymes PON1, glutathione peroxidase, SOD, and catalase.

KC11: causes inflammation. Exposure to many chemicals, including PCBs and BPA, has been associated with elevated levels of inflammatory markers and the increased risk of atherosclerosis or CV disease in humans (Table 1). Unresolved acute inflammation can lead to the development of chronic inflammation, which is a well-known mediator of some common and important CVDs, such as atherosclerosis (Hansson 2017; Libby 2002). Chronic inflammation has also been associated with cardiac arrhythmia (Lewek et al. 2014). Animal studies have confirmed that exposure to dioxin-like PCBs increases systemic inflammation and accelerates atherosclerosis in mouse models, probably by activation of aryl hydrocarbon receptor (AhR) or nuclear factor kappa-light-chain-enhancer of activated B cells (i.e., NF- κ B) signaling (Petriello et al. 2018; Wang et al. 2019a). BPA exposure can increase macrophage foam cell formation and atherosclerosis in hyperlipidemic mouse models (Sui et al. 2014, 2018). In addition to activating estrogen receptors (ERs), BPA is also a ligand for human pregnane X receptor that may contribute its atherogenic effects (Sui et al. 2012, 2014). Epidemiological studies have associated arsenic (States et al. 2009) and certain heavy metals, including lead (Boskabady et al. 2018), with elevated levels of inflammatory markers and CV disease. Chronic exposure to arsenic can also lead to vascular inflammation, endothelial dysfunction, and increased atherosclerosis in animal models (States et al. 2009).

$\text{PM}_{2.5}$ in air has been consistently associated with increased atherosclerotic risk and inflammation and is considered one of their main mechanisms (Bai and Sun 2016). $\text{PM}_{2.5}$ exposure can dysregulate inflammatory pathways in the lung and induce secretion of inflammatory factors into the circulation, leading to enhanced EC activation and vascular inflammation. $\text{PM}_{2.5}$ exposure can also affect macrophage polarization, resulting in increased pro-inflammatory M1 macrophages, but decreased anti-inflammatory M2 macrophages (Zhao et al. 2016). In addition, cadmium exposure has been associated with a pro-inflammatory state in rats (Kumar et al. 2021).

KC12: alters hormone signaling. Membrane and intracellular hormone receptors (e.g., G-protein coupled receptors, receptor tyrosine kinases, and nuclear receptors) are expressed throughout the CV system and regulate numerous critical CV functions. PPAR-gamma (PPAR γ) agonists have been linked to increased risks for heart failure and ischemic heart disease in diabetic patients (Kaul et al. 2010; Nissen and Wolski 2007; Wallach et al. 2020). The mechanisms of the adverse CV effects of rosiglitazone are related to its PPAR γ -agonist dependent-induction of atherogenic lipid profiles and renal-mediated changes in fluid balance that increases intravascular blood volume (Wallach et al. 2020). Excessive thyroid hormone receptor activation activity is associated with atrial fibrillation and disturbances in cardiac output, contractility, blood pressure, hemostasis, and vascular resistance (Osuna et al. 2017). Amiodarone, an iodine-rich Class 3 antiarrhythmic drug, can cause hyperthyroidism, which causes hemodynamic changes that lead to heart failure and dilated cardiomyopathy (Macchia and Feingold 2000).

Increased exposure to PCBs is associated with CV diseases, including hypertension (Donat-Vargas et al. 2015; Lind and Lind 2012). Potential mechanisms of PCB action include increased activation of the AhR and dysregulation of the renin–angiotensin–aldosterone system (RAAS) (Kraugerud et al. 2010; Li and Lin 2007; Lin et al. 2006; Perkins et al. 2016). CV toxicity associated with BPA, such as hypertension (Han and Hong 2016; Rancière et al. 2015), is mediated by signaling via nuclear receptors ER α , ER β , and membrane associated ERs (La Merrill et al. 2020). Exposure to BPA has also been associated with increased risk for coronary and peripheral artery disease in humans (Lind and Lind 2011; Melzer et al. 2012b; Shankar et al. 2012) and a mouse model (Sui et al. 2014). Experimental animal studies have also identified sex-specific mechanisms of BPA actions in the heart that cause pro-arrhythmic changes in excitation–contraction coupling (Gao and Wang 2014; Zhang et al. 2020b).

Measuring the KCs of CV Toxicants

Table 1, which is based on the expertise of the authors, summarizes established assays and other methods to evaluate the 12 different KCs *in vitro*, in animal models, and in humans; see also a summary of evaluation methods by Berridge et al. (2013). From these summaries, it is evident that *a*) although some assays used *in vitro* (e.g., cytotoxicity assays, quantitative polymerase chain reaction) are high-throughput and, therefore, suited to serve as screening for multiple chemicals, such high-throughput assays are not available for most KCs (Villeneuve et al. 2019); *b*) there are usually fewer end points that can be measured in humans, and those are most often not high-throughput; and *c*) in some cases, the output of the assays and end points used *in vitro* and in animals are not easily translated into the output of the biomarkers used in humans.

Regarding KC1 (cardiac excitability), robust *in vitro* functional assays and end points (e.g., half maximal inhibitory concentration values) are available to determine altered Na⁺ or K⁺ channel function (Mathie et al. 2021; Sigg et al. 2010); in nonrodent animal models and humans, the fast sodium and hERG channels are linked directly to ventricular depolarization (e.g., QRS interval) and repolarization (e.g., QT interval), respectively (Baldrick 2021; Edwards and Louch 2017; Strauss et al. 2021). The evaluation of intracellular Ca²⁺ concentrations in humans is not currently feasible in clinical practice (Bruton et al. 2020). For KC2 (contractility and relaxation), ultrasound of the heart is a very commonly used technique both in animal models and in humans (Lindsey et al. 2018; Wang et al. 2018). Cardiomyocyte injury and death for KC3 can be evaluated *in vitro* and in animals in several ways. Cardiac troponins are a very useful and rather high-throughput biomarker in humans regarding myocardial infarction (Taggart et al. 2021), but a good assay to evaluate apoptosis is needed in the clinical setting (Mohamad Kamal et al. 2020). Echocardiography, cardiac magnetic resonance imaging, and myocardial perfusion scan can, however, provide evaluation of overall cardiac function and areas of myocardial injury (Makavos et al. 2021; Sivapackiam et al. 2020; Sreenivasan et al. 2021). Regarding the proliferation of valve stroma for KC4, a high-throughput assay is available for *in vitro* use (Reid et al. 2013), and echocardiographic imaging in humans is routinely performed to evaluate valvular heart disease (Jain et al. 2021). Endothelial and vascular function for KC5 can be assessed with isolated blood vessels obtained from animals [medium-throughput (Knox et al. 2019)] and human donors [low-throughput (Virdis and Taddei 2016)]. It could be studied in humans *in vivo* by flow-mediated vasodilation (Tremblay and Pyke 2018), but this technique is only reliable in younger subjects (Lind 2006).

Mitochondrial function for KC8 can be measured well *in vitro* (Koklesova et al. 2021), but is difficult to directly evaluate in humans (Pelletier-Galarneau et al. 2021). There are several techniques (e.g., heart rate variability) to measure ANS activity (Nolte et al. 2017) and understand sympathetic and parasympathetic involvement for KC9 that are relatively easy to apply in humans (Cygankiewicz and Zareba 2013) but more challenging in animal models. Measurements of biomarkers related to hemostasis (KC6) (Adelborg et al. 2021; Lind et al. 2011), dyslipidemia (KC7) (Lind 2019; van Wijk et al. 2009), oxidative stress (KC10) (Kumar et al. 2014b; Tejchman et al. 2021), inflammation (KC11) (Friedman and Shorey 2019; Kumar et al. 2014a; Libby 2002), and hormone signaling (KC12) (Penell et al. 2021; Svobodová and Cajthaml 2010) are readily achievable in both experimental models and humans.

We therefore conclude that there is an unmet need for a systematic improvement of the nonclinical assays, biomarkers, and physical tests used to evaluate all of the KCs. There is also a need to standardize nonclinical tests to assure data quality and reproducibility, as well as their value for translation to human investigations. Hence, the systematic and comprehensive identification of the KCs and the available end points presented herein will help to prioritize the development of improved methods to evaluate potential CV toxicants both experimentally and in humans. Ideally, qualified biomarkers could be used to advance public health by assisting regulatory decision-making (FDA 2019).

Examples of How the KCs May Produce CV Dysfunction and Disease

Figure 2 illustrates how the KCs may contribute to the pathogenesis of acute and chronic injury to the heart (Figure 2A) and blood vessels (Figure 2B). Note that multiple KCs may contribute at different locations in the CV system to produce short- or long-term injury and eventually disease. Below and in Tables 2 and 3 we detail how the KCs can be used to generate a holistic picture of how environmental pollutants and drugs that are established CV toxicants can cause CV toxicity. We also describe how the KCs can contribute to understanding the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These examples further illustrate how evidence for each KC can be organized and evaluated using the published literature.

Fine PM air pollution

Exposure to ambient PM in air pollution increases CVD risk. Although exposures to coarse (2.5–10 μ m in aerodynamic diameter) and ultrafine (\leq 0.1 μ m in aerodynamic diameter) PM have both been linked to adverse effects, the evidence is strongest for PM_{2.5} regarding incident CVD (Brook et al. 2010; Newby et al. 2015). Because the lung is the initial organ of contact upon inhalation, most CV effects ascribed to PM_{2.5} are likely secondary to the interaction of PM with lung tissue, with less evidence for direct effects of PM components on CV tissue (Brook et al. 2010). These early effects and initiating KCs include 1) oxidative stress (KC10) and 2) inflammation (KC11) that may originate from lung injury and 3) modulation of cardiac autonomic tone (KC9), potentially stemming from activation of lung sensory afferents (Thompson et al. 2019). PM_{2.5} also demonstrates well-documented effects on at least four other KCs (5, 6, 7, and 12), see Table 2. Figure 3 shows how these KCs are interconnected and may work in concert to produce CV toxicity from PM_{2.5} air pollution.

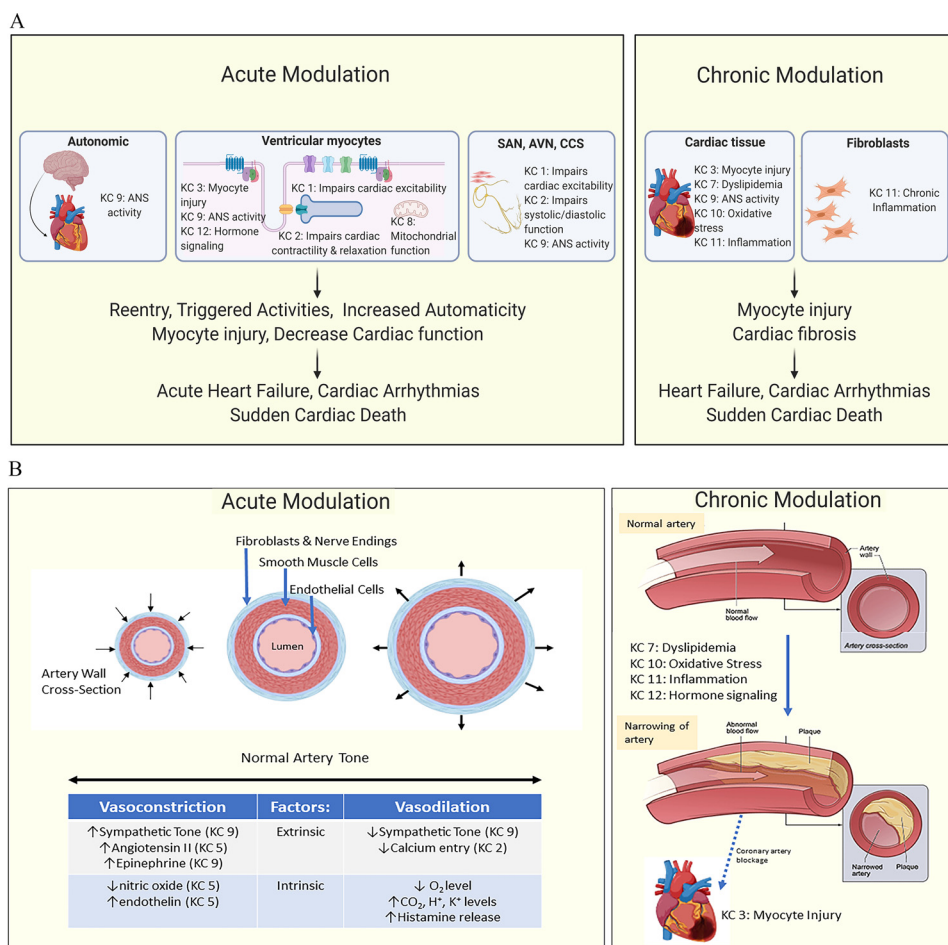


Figure 2. Key characteristics (KCs) associated with cardiac and vascular dysfunction. A summary of how different KCs of cardiovascular toxicant could affect (A) the heart and (B) the vasculature in both the acute and chronic setting. Some of the detailed mechanisms are given, as well as some clinical end points. Note: ANS, autonomic nervous system; AVN, avascular necrosis; CCS, cardiac conduction system; CO₂, carbon dioxide; H⁺, hydrogen ion; K⁺, potassium ion; O₂, oxygen; SAN, sinoatrial node.

Polychlorinated biphenyls (PCBs)

There are 209 different PCBs congeners of varying biological activity. Some of these are found in the circulation of almost all humans (Salihovic et al. 2012). The majority of experimental studies use dioxin-like PCBs or a PCB mixture that induces biological effects by binding to the AhR. In humans, high background exposure to PCBs has been linked to CV disease processes (Ha et al. 2007) that may increase CV-related mortality (Li et al. 2015), including carotid and coronary atherosclerosis (Lind et al. 2012) and systolic dysfunction (Sjöberg Lind et al. 2013) leading to stroke (Lee et al. 2012), myocardial infarctions (Bergkvist et al. 2015, 2016), and clinical heart failure (Akhane et al. 2018; Åkesson et al. 2019). There is strong evidence for at least four KCs (7, 10, 11, and 12) being involved in these CV effects of PCBs (Table 2).

Bisphenol A

The ER agonist BPA is ubiquitous in both the environment and clinical setting, and human exposure is nearly continuous, with biomonitoring studies detecting BPA in >90% of the population (Calafat et al. 2005, 2008, 2009; Vandenberg et al. 2010). Population-based epidemiological studies have noted associations between BPA exposure, inflammation, and oxidative stress markers (Kataria et al. 2017; Steffensen et al. 2020; Wang et al. 2019b; Yang et al. 2009), which can contribute to endothelial

dysfunction and the development of hypertension in adults and children (Bae et al. 2017; Han and Hong 2016; Ramadan et al. 2020; Warembourg et al. 2019). In a randomized trial, the consumption of canned beverages with a BPA-liner resulted in higher urinary BPA concentrations and an acute increase in blood pressure (Bae and Hong 2015). Given its estrogenic properties (Khan et al. 2021), some biological effects of BPA on the CV system are likely mediated by endocrine disruption (KC12), but BPA may also exert its biological effects through multiple other KCs (e.g., KCs 1, 9, 10, and 11), see Table 2.

Doxorubicin, an anthracycline

Anthracycline chemotherapy regimens are widely used to treat breast cancer, lymphomas, and childhood solid tumors (McGowan et al. 2017; Nebigil and Désaubry 2018). Doxorubicin was one of the first anthracyclines to be used in clinical practice, but other analogs are also used (McGowan et al. 2017). A significant clinical safety issue associated with doxorubicin and other anthracyclines is the development of dilated cardiomyopathy and heart failure, which increase the mortality of cancer survivors (Gilchrist et al. 2019). The incidence of heart failure is dose dependent and can occur early after initiation of treatment (within 1 y) or emerge decades after cumulative exposure (Zamorano et al. 2016). As illustrated in Figure 4, there is strong evidence, documented in Table 3, that multiple KCs (2, 3, 8, 10,

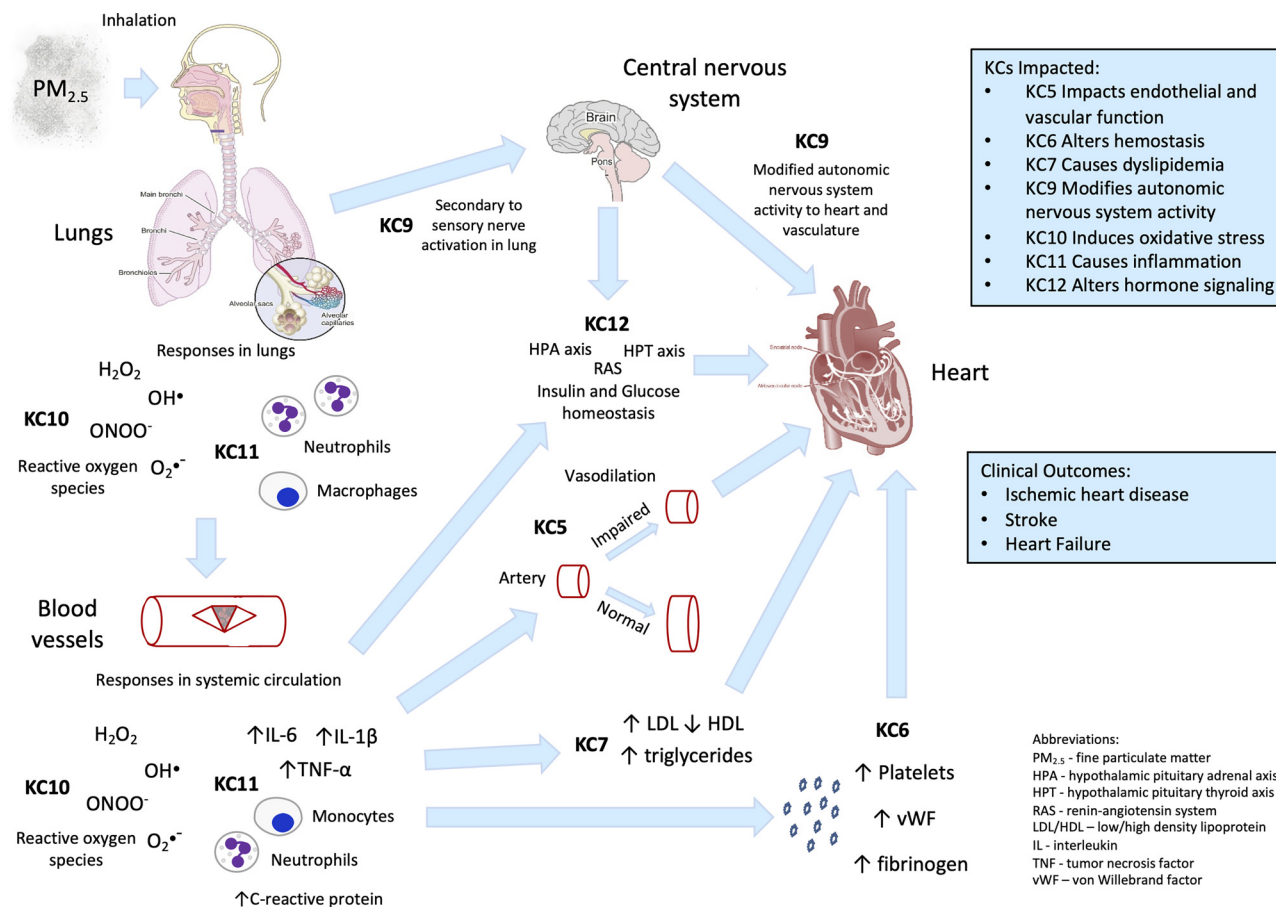


Figure 3. Key characteristics (KCs) associated with PM_{2.5} toxicity. A summary of how different KCs of fine particulate air pollution (PM_{2.5}) could affect the heart and the vasculature. Some of the detailed mechanisms are given, as well as some clinical end points. Note: H₂O₂, hydrogen peroxide; OH[•], hydroxide; O₂^{•-}, reactive oxygen species; ONOO⁻, peroxyntirite; PM_{2.5}, particulate matter ≤2.5 μm in aerodynamic diameter (fine particulate matter).

and 11) contribute either directly or act together to cause cardiac dysfunction or failure (Mele et al. 2016; Minotti et al. 2004).

Arsenic

Arsenic is a unique example of a CV toxicant that is both an approved human therapeutic and an environmental contaminant. Arsenic exhibits multiple KCs, depending on dose and type of exposure. Acute lethality results from mitochondrial collapse in many tissues, including blood vessels and the myocardium (KC8). Arsenic trioxide is also used to treat leukemia and as an adjuvant in treating some solid tumors, but it is considered among the most hazardous anticancer drugs for increasing cardiac QTc prolongation and risk of torsade de pointes arrhythmias, potentially through direct inhibition of hERG current (Drolet et al. 2004) and altered channel expression (KC1) (Alexandre et al. 2018; Dennis et al. 2007). Arsenic trioxide also exhibits KCs 2, 8, and 10 (Varga et al. 2015). In contrast to the toxicities from arsenic therapies, chronic environmental arsenic exposure is closely associated with increased risk of coronary heart disease at exposures of <100 μg/L in drinking water (Moon et al. 2018; Wu et al. 2014) and occlusive peripheral vascular disease at higher exposure levels (Newman et al. 2016). Chronic exposure from contaminated drinking water was linked to ventricular wall thickness and hypertrophy in young adults (Pichler et al. 2019). There is well-documented evidence that chronic environmental arsenic exposure exhibits KCs 5, 6, 7, 10, and 11 (Cosselman et al. 2015; Moon et al. 2018; Straub et al. 2008, 2009; Wu et al. 2014).

Lead

Epidemiological studies have linked lead exposure with CVD mortality and persistent hypertension, as reviewed by Lamas et al. (2021) and Navas-Acien (2021). There is evidence that lead exhibits KCs 1, 2, 5, 7, 8, 10, 11, and 12. Occupational exposure modulated cardiac conduction (KC1) (Kietucki et al. 2017) and acute exposure altered cardiac excitability in isolated guinea pig hearts (Ferreira de Mattos et al. 2017). Exposure of rats to low concentrations exerted direct positive inotropic and lusitropic effects on contractile function (KC2) and increased ventricular systolic pressure (Silva et al. 2015). Occupational exposure induced electrocardiogram disturbances, possibly related to decreased RyR1 expression (Xie et al. 2019). Lead replaces calcium in cellular signaling and may cause hypertension by inhibiting the calmodulin-dependent synthesis of NO (KC5) (Vaziri 2008). Lead exposures have also been linked to dyslipidemia (KC7) (Dudka et al. 2014; Xu et al. 2017). Altered cardiac mitochondrial activity (KC8), including increased oxidant and malondialdehyde generation, was associated with lead exposure in animals (Basha et al. 2012; Davuljigari and Gottipolu 2020; Roshan et al. 2011). Lead-exposed male workers had dysfunctional ANS activity (KC9), manifest as a significant decrease of R-R interval variation during deep breathing (Teruya et al. 1991) and chronic exposure in rats caused sympathovagal imbalance and reduced baroreflex sensitivity (Shvachiy et al. 2020; Simões et al. 2017). Lead can increase oxidative stress (KC10) by altering cardiac mitochondrial activity (KC8) (Basha et al. 2012; Davuljigari and Gottipolu 2020; Roshan et al. 2011) and

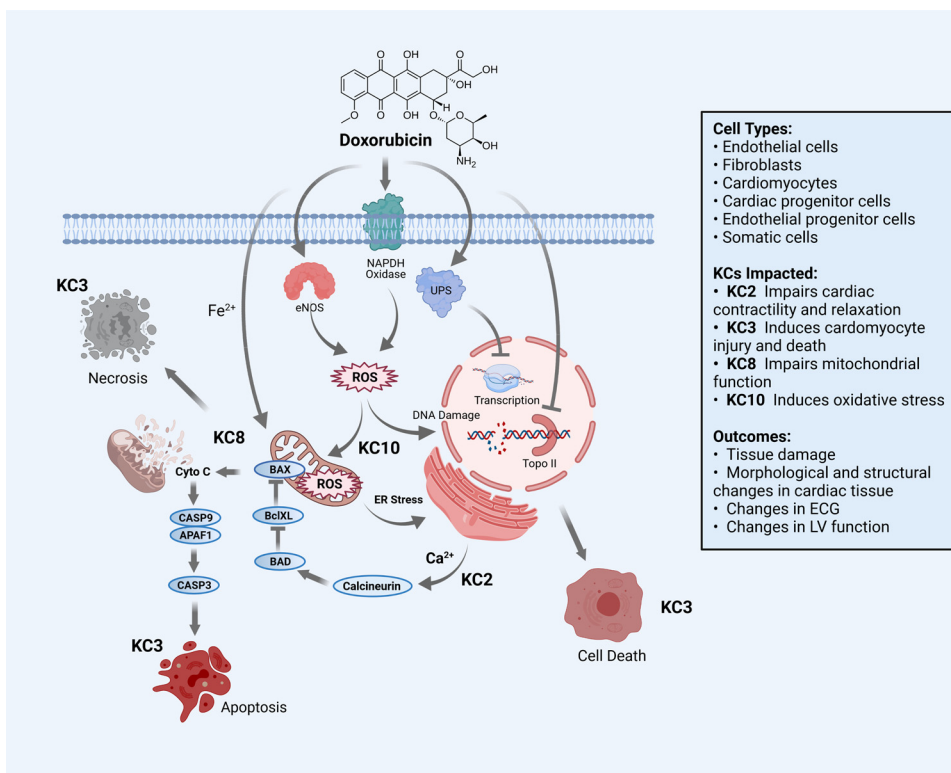


Figure 4. Key characteristics (KCs) associated with doxorubicin cardiotoxicity. A summary of how different KCs of doxorubicin could affect the heart and the vasculature. Some detailed mechanisms are given, as well as some clinical outcomes. Note: APAF1, apoptotic protease activating factor 1; Bad, Bcl-2-associated agonist of cell death; Bax, Bcl-associated X; BclXL, B-cell lymphoma-extra large; Ca^{2+} calcium ion; CASP3, caspase 3; CASP9, caspase 9; CytoC, cytochrome complex; ECG, electrocardiogram; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; Fe^{2+} , iron ion; LV, left ventricular; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; Topo II, topoisomerase II; UPS, ubiquitin-proteasome system.

inhibiting glutathione synthesis and SOD (Navas-Acien 2021). The resulting increase in oxidants can increase lipid peroxidation and reduce NO (KC5) levels, leading to endothelial dysfunction and atherosclerosis (Navas-Acien 2021). Epidemiological studies have associated lead with elevated inflammatory markers (KC11) (Boskabady et al. 2018). Finally, lead-induced blood pressure elevation may be mediated by stimulation of the renin-angiotensin system (KC12) (Fiorim et al. 2011; Simões et al. 2011).

SARS-CoV-2

The KC approach for CV toxicants above was developed based on data from chemical agents, but this approach can also be applied to nonchemical agents such as SARS-CoV-2, the infectious agent responsible for the current pandemic of coronavirus disease starting in 2019 (COVID-19). Indeed, CV toxicity has emerged as a serious complication of SARS-CoV-2 infection, presenting with acute myocardial injury in 10–15% of patients (defined by elevated troponin levels) (Cheng and Leedy 2020). Numerous hypotheses as to how SARS-CoV-2 might cause or mediate CV toxicity have emerged, and the KCs can serve as a useful organizing framework for systematically mapping the mechanistic evidence. At present, data in humans suggest that SARS-CoV-2 exhibits multiple KCs given that it has been reported to induce inflammation (KC11), induce vasodilation and hypotension through alterations in the RAAS (KC12) (Chen et al. 2020b; Garvin et al. 2020), increase SNS activity (KC9), alter hemostasis giving rise to thrombosis (KC6), and induce myocyte injury (KC3) that can result in lethal cardiac arrhythmias (Cheng and Leedy 2020; Xiong et al. 2020; Zheng et al. 2020). Moreover, the KCs, along with the biomarkers and assays listed in Table 1, provide a systematic roadmap for ongoing and future

experimental studies to evaluate SARS-CoV-2 with respect to end points of known relevance to established mechanisms of toxicity to the heart and vasculature.

Discussion

Regulatory agencies consider a broad range of health end points when determining if a drug or an exogenous chemical poses a hazard. Given the importance of CVD as a major health burden on society, it is critical to identify potential environmental CVD hazards and reduce exposure to them. Like the KCs for other organ systems, the 12 KCs described here will help these agencies better evaluate hazards and risks to human health by facilitating the systematic assessment of the mechanistic data (Figure 1). In the area of clinical practice, the KCs can help to target improvements in assays, biomarkers, and physiological tests used for risk assessment and differential diagnoses. For toxicologists, the KCs provide a potential framework to facilitate a holistic approach to studies of the potential effects of both pharmaceutical drugs and environmental chemicals on CV toxicity through *in vitro* screening, *in vivo* characterization, and human data. Further, the identification of KCs and knowledge of the methods to evaluate them will inform the development of high-throughput assays and *in silico* screens that could be used to expedite acquisition of information regarding potential CV toxicity (Blanchette et al. 2019; Burnett et al. 2021; Sirenko et al. 2017). The KC framework also enables study of the CV effects of mixtures comprising chemicals that exhibit different KCs, as was recently described for studies of the carcinogenic effects of mixtures (Rider et al. 2021).

Development of the 12 KCs described herein benefited substantially from experience with pharmaceutical drugs, by taking

advantage of knowledge collected over decades of drug development and intensive research on adverse effects of pharmaceuticals. We have applied this list of KCs to both pharmaceutical agents and environmental pollutants to illustrate the utility of this approach for both classes of chemicals. However, not all possible mechanisms whereby a chemical could cause CV toxicity may be covered by these 12 KCs, and it is likely that as knowledge in the field of CV toxicity advances, more KCs could be added in the future. For example, emerging evidence suggests that exposure to PM in air pollution impacts the human gut microbiome, resulting in an altered intestinal redox lipidome that may contribute to CV and gastrointestinal diseases (Feng et al. 2020). However, further elucidation is needed to determine whether this represents a characteristic of CV toxicants, as well as whether it is sufficiently distinct from other KCs, such as KC7.

The examples of SARS-CoV-2 and air pollution show that the KCs also could be used for nonchemical agents and mixtures, respectively, and not just individual chemicals. Other such examples include food items, such as foods high in saturated fat (Saluja et al. 2021) and sweetened beverages that have been linked to CVD (Kim et al. 2020), radiation therapy that could give rise to a great number of myocardial pathologies ranging from fibrosis to ischemic disease (Burke et al. 2020), and the well-known endocarditis induced by Streptococcal infections (Chamat-Hedemand et al. 2020). Because food items are a mixture of naturally occurring and synthetic chemicals, the KC approach could be used to investigate which components of the food may possess CV toxicant properties.

It also should be emphasized that a KC is akin to an umbrella under which many different detailed pathophysiological events take place. These events and their underlying molecular mechanisms are understood to varying degrees. For some KCs, such as effects on the Na⁺/K⁺ ion channels and the valvular stroma, the critical mechanisms are known at the molecular and cellular levels, but for KCs such as inflammation and oxidative stress, much knowledge on basic pathophysiology is yet to be uncovered in detail. The KC approach represents a systematic way to not only define the pathophysiological events involved in CV toxicity but also to identify and address gaps in the mechanistic understanding of how exogenous chemicals could harm the heart or vasculature.

Some environmental pollutants, such as PCBs, arsenic, and dioxins, have been linked to both CVD (Li et al. 2015; Lind et al. 2019) and cancer (Lauby-Secretan et al. 2016). The identification of KCs for the major organ systems, or health conditions, could facilitate identification of important mechanisms whereby chemicals could affect multiple different organ systems. Thus, if a KC were found to be linked to impairments in several organ systems or pathological processes, such as cancer development, the need to develop high-throughput testing assays for this KC would be of higher priority. In a similar manner, although our focus was on CV toxicity in adults in this commentary, KCs relevant to the developing organ systems, including the CV system, and associated health conditions could be developed in the future.

In conclusion, the identification of KCs for CV toxicants facilitates, in an objective and systematic fashion, the further understanding of CV effects of exogenous chemicals, chemical mixtures, and other agents, both in drug development as well as for environmental pollutants. When coupled to the development of high-throughput assays, new candidate drugs, novel marketplace chemicals, as well as existing agents to which the population is exposed, could be screened for specific unwanted characteristics. Thus, the systematic use of KCs may serve as a powerful tool to prevent and mitigate CV toxicity.

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