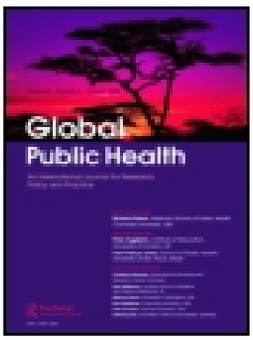

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Pesticide exposure and risk of cardiovascular disease: A systematic review

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ABSTRACT

The increase in pesticide consumption has a negative health impact. Studies point to an association between exposure to pesticides and cardiovascular disease (CVD), one of the leading causes of world mortality. This review synthesize evidence on the association between occupational exposure and environmental contamination by pesticides with CVDs from 1750 references databases (EBSCO, Medline, Science Direct, Scielo, Lilacs and Ovid) without date or language restriction. Selected 24 articles by PRISMA and Downs & Black methodologies, were included from inclusion criteria: original studies (case-control, cohort or cross-sectional design); clear CVD definition and exposure to pesticides; representative sample of the target population. The results show the occupational exposure to pesticides chlorpyrifos, coumafos, carbofuran, ethylene bromide, mancozeb, ziram, metalaxyl, pendimethalin and trifluralin was associated a risk of 1.8 to 3.2 for acute myocardial infarction. Primaphos, fenitrothion, malathion and deltamethrin pesticides were associated with a blood pressure increase. Environmental contamination by tetrachlorodibenzo-p-dioxin was associated with CVD with risk of 1.09 to 2.78 and organochlorine, 1.19 to 4.54; heavy metals, arsenic, trimethylarsine and dimethylarsinic acid with atherosclerosis and systemic arterial hypertension. These findings point to the association between exposure to pesticides and CVD, signaling the importance of greater rigor in the public policy related to pesticides.

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Cardiovascular disease; environmental contamination; farmworker; pesticides; systemic arterial hypertension

Introduction

In recent decades global consumption of pesticides has been rising, reaching 4.6 million tonnes per year. Organochlorine (OC) pesticides and pesticides containing mercury, arsenic and lead, prohibited in some countries, continue to contaminate the environment (Jayaraj et al., 2016). The expansion of the agricultural sector, the introduction of transgenic crops in some countries, with the possibility of inducing resistance to insects and weeds, may be factors related to increased pesticide consumption (Turyk et al., 2009).

Studies indicate association between some pesticides and the risk of developing cancer (Guyton et al., 2015) and chronic diseases, such as diabetes mellitus (Montgomery et al., 2008) and kidney

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disease (Jayasumana, Gunatilake et al., 2015; Jayasumana, Paranagama et al., 2015; Lebov et al., 2016; Lebov et al., 2015). Two literature reviews evaluated exposure to pesticides and development of Cardiovascular Disease (CVD). A non-systematic review pointed increased risk of CVD among exposed farmworkers (Sekhotha et al., 2016). However, the articles evaluated acute cardiovascular effect of pesticides, particular types of pesticides (carbamate, organochlorine and organophosphorus) or had an ecological approach (Sekhotha et al., 2016). In a systematic review with twenty-six articles, eighteen addressed acute, and eight, long-term effects of pesticides on the cardiovascular system. Acute effects observed was a lengthened QT interval, sinus tachycardia and ST segment elevation, while chronic exposure was associated with risk for non-fatal myocardial infaction, arterial peripherical disease and stroke (Wahab et al., 2016). However, there is gap in the knowledge about the chronic effects of pesticides in the development of CVD.

CVD is one of the world's leading causes of death, with 17.5 million deaths in 2014, accounting for 31% of all deaths worldwide, especially in middle and low-income countries (World Health Organization, 2014). Given that pesticides are widely used, and the exposure increases within the food chain (Curl et al., 2015; Hardell et al., 2010), it is important to gain greater understanding about the association between these chemicals, taking into consideration different intensities of exposure and the development of cardiovascular problems. This article presents a summary of evidence on the association between occupational and environmental exposure to pesticides with CVD.

Methods

A systematic review of the literature was performed in the database EBSCO (431 articles), PubMed (269 articles), Science Direct (1000 articles) Scielo (0), Lilacs (0) and Ovid (50 articles) using the following keywords: 'cardiovascular disease' OR 'heart disease' OR 'arterial hypertension' OR 'acute myocardial infarction' OR 'blood pressure', AND 'pesticides' OR 'fungicides' OR 'herbicides' OR 'insecticides', AND 'occupational exposure' OR 'farmworkers' OR 'environmental exposure'. The search was limited to human beings with no restriction to date of publication or language.

This systematic review had the following inclusion criteria: (a) original studies with case–control, cohort or cross-sectional design; (b) representative sample of the target population (c) response rate of at least 60%; (d) clear definition of CVD, or diagnosis of systemic arterial hypertension (SAH) blood pressure (BP) $\geq$ 140/90 mmHg or SAH patients taking medication) or medical diagnosis of acute myocardial infarction (AMI); (e) studies focusing in environmental contamination by persistent organic pollutants (POPs), organochlorine pesticides and arsenic, and exposure to pesticides used in agriculture; (f) well-defined exposure to pesticides, including information on exposure time and type of pesticides or serum levels of chemical compounds.

The review methodology followed the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Moher et al., 2009). The quality of the articles was assessed by seventeen out of the twenty-seven items proposed by Downs and Black (1998) (D&B), which were adapted to evaluate observational studies. The parameters evaluated included: information on sample representativeness, sample size calculation and power of study calculation; clear description of hypotheses, objectives, main outcomes, individuals characteristics, exposure of interest and main findings; appropriation of statistical analyses, adjustment for confounders and demonstration of random variability of the estimates; recruitment of subjects in same time and from the same population; description of lost to follow-up subjects characteristics. When the study did not meet the assessed parameter, a score of zero was assigned; when achieved, a score of one was assigned. Regarding adjustment for confounders, a score of one was given when partially filled and two when it was fulfilled. The score summed a maximum of 18 points. The articles were selected by a pair of evaluators, a third appraiser is requested in case of disagreement.

Results

Considering the titles and abstracts of the 1750 articles retrieved, 116 duplicates, 1541 articles not related with the study subject (ecological study, or outcomes other than CVD, or analysing organochlorine pesticides together with other pollutants, or studies using convenience samples) and 40 articles focusing on literature reviews were excluded. Reading the remained fifty-three articles, other thirty-one were excluded: nineteen because they did not cover the theme of the study, seven owing to methodological problems, such as, non-representative sample and non-characterisation of the exposure, and five because they were not original. Twenty-two articles were selected for this review and a further two were added based on the bibliographical references of the selected articles (Figure 1).

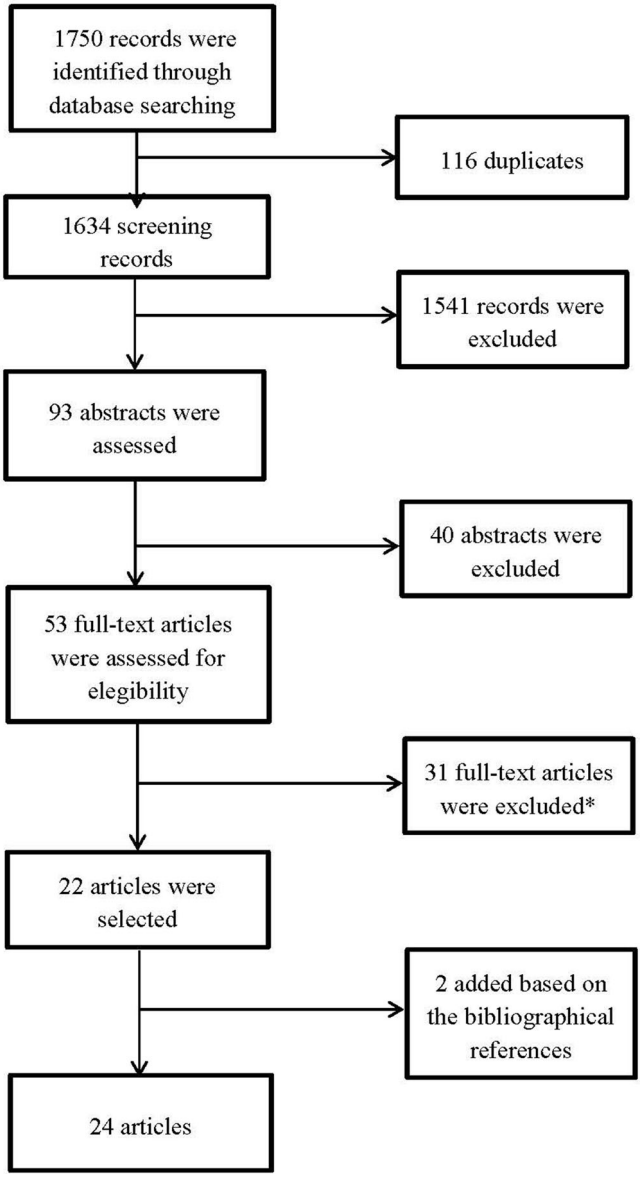

Figure 1. Selection of articles on pesticide exposure and cardiovascular problems in humans. *Articles exclusion: Nineteen articles did not cover the study theme; Two articles: Experimental study and ecologic study Three articles: Review studies Five articles: Not original Two articles: with methodological problems such as, non-representative sample and non-characterization of the exposure.

The articles scores regarding the D&B quality assessment varied between 13 and 18 points. D&B scores were bellow fifteen for five articles (Boers et al., 2012; Cypel & Kang, 2010; Kang et al., 2006; Saldana et al., 2009; Yi et al., 2014), mainly due to the lack of *p*-value and specification of parameters used in the sample size calculation or study power, insufficient assessment of confounding factors (Boers et al., 2012; Yi et al., 2014), lack of description of follow-up losses in cohort studies (Cypel & Kang, 2010; Kang et al., 2006), insufficient detail of exposure and outcome measures (Cypel & Kang, 2010; Saldana et al., 2009; Yi et al., 2014). Five studies had a non-response rate or loss of follow-up of more than 20% (Kang et al., 2006; Saldana et al., 2009; Valera, Ayotte et al., 2013; Valera, Jorgensen, et al., 2013) (Tables 1 and 2).

Of the twenty-four selected articles, fourteen were cohort studies, nine were cross-sectional and one was a case–control study. Eight studies were conducted in United Sates (U.S.A.), being four related to the Agricultural Health Study (AHS). Canada and Vietnam conducted two studies each, and other studies were from Malaysia, Bangladesh, Taiwan, Spain and France. Seven studies were related to occupational pesticides exposure, and seventeen to environmental exposure to organochlorine pesticides and arsenic. Pesticides were associated with CVD as SAH, hypertensive disorders in pregnancy and pre-eclampsia, AMI, peripheral arterial diseases and cerebrovascular stroke.

Occupational exposure to pesticides

Six of the seven articles evaluating exposure to non-POP pesticides were in exposed workers (Charles et al., 2010; Dayton et al., 2010; Mills et al., 2009; Saldana et al., 2009; Samsuddin et al., 2016; Waggoner et al., 2011) and one was a cohort of individuals hospitalised due to organophosphate poisoning (Hung et al., 2015). Three of four studies conducted with pesticide applicators (AHS) in the states of Iowa and North Carolina (U.S.A.) indicate that exposure to some kinds of pesticides increases the risk of AMI (Dayton et al., 2010; Mills et al., 2009), and hypertensive disorders in pregnancy (Saldana et al., 2009). Ohers studies point a risk for cardiovascular mortality (Charles et al., 2010; Waggoner et al., 2011), arrhythmia (Samsuddin et al., 2016) and increase of BP (Hung et al., 2015) (Table 1).

Some insecticides (organophosphorus and carbamate; Dayton et al., 2010), fungicides (dithiocarbamate and phenylamides; Mills et al., 2009), herbicides (Dayton et al., 2010) and fumigants (Mills et al., 2009) were associated with a risk of 1.5–3.2 for AMI (Dayton et al., 2010; Waggoner et al., 2011). The increase in arterial pressure was observed with exposure to pyrethroid and organophosphorus insecticides (Samsuddin et al., 2016) (Table 1).

The AHS found an increased risk of AMI in women pesticide applicators exposed to insecticides with the following odds ratio (OR) and 95% confidence interval (95%CI): organophosphates chlorpyrifos 2.10 (1.2–3.7), coumaphos 3.20 (1.5–7.0) and carbamate carbofuran 2.50 (1.3–5.0); to herbicides pendimethalin 2.50 (1.2–4.9) and trifluralin 1.80 (1.0–3.1); and the fungicide metalaxyl 2.40 (1.1–5.3); as well as risk of AMI of 1.6 (1.1–2.4) when using at least one of these pesticides (Dayton et al., 2010). Among male applicators, after adjusting for smoking, age and obesity, those who used ethylene dibromide, maneb/mancozeb fungicide and ziram showed an increased risk of 54%, 34%, and 140%, respectively, to infarction mortality, compared with workers who did not use these products (Mills et al., 2009) (Table 1).

Residential exposure to pesticides in the first trimester of pregnancy presented a risk and a 95%CI of 1.27 (1.02–1.60) for gestational hypertension and 1.32 (1.02–1.70) for preeclampsia, while for agricultural exposure the risk was 1.60 (1.05–2.45) and 2.07 (1.34–3.21), respectively (Saldana et al., 2009). A study with pesticide applicators, using it to control mosquitoes, found that exposure to fenitrothion, malathion, pirimiphos-methyl, permethrin, deltamethrin and cyfluthrin pesticides resulted in an increase of 7.5 mmHg (4.7–10.14) in diastolic BP and 6.0 mmHg (2.48–9.69) in systolic BP (Samsuddin et al., 2016) (Table 1).

In Taiwan, the cumulative incidence of arrhythmia, coronary arterial disease and heart failure was higher among a cohort of individuals exposed to acute organophosphorus poisoning when compared to unexposed individuals. Risk among exposed individuals was significant both for arrhythmia

Table 1. Occupational exposure to pesticides associated with cardiovascular disease.

Author/year Country/ Study Design/ Downs and Black	Sample	CVD Outcome/ Exposure	Results Measurement of effect (95%CI)		Adjusted factors	Study Conclusion
Non-fatal and Fatal Acute Myocardial Infarction						
Dayton et al. (2010)	22,425 Women	**Outcome**	**Insecticides**		Age	Six pesticides were with
U.S.A.	Age 17–88 years	AMI	**Organophosphorus and Carbamate**		BMI	positively associated
Iowa and North Carolina	168 Incident non-fatal	Mortality and incidence of non-fatal AMI		OR	Tobacco	AMI in women farmers,
Cross-sectional	PR 100%	**Exposure**	**Chlorpyrifos**	**2.10 (1.2–3.7)**	Smoking	mainly coumaphos, but
D&B -16	Follow-up 69%	Fumigants	**Coumaphos**	**3.20 (1.5–7.0)**	State of residence	no risk was observed
(*p* value not reported; lost follow up not described)	applicator 76% spouses	Fungicides	**Carbofuran**	**2.50 (1.3–5.0)**		among men.
		Herbicides	Terbufos	1.90 (1.0–3.8)		
		Insecticides				
		Carbamates	**Herbicides Phenyl amides**			
		Organophosphates	**Pendimethalin**	**2.50 (1.2–4.9)**		
			Trifluralin	1.80 (1.0–3.1)		
			Fungicide Pheny amides			
			Metalaxyl	**2.40 (1.10–5.3)**		
			At least one of the 6 pesticides	**1.60 (1.1–2.4)**		
			AMI mortality	0.90 (0.7–1.2)		
			Ever use of any pesticide			
Mills et al. (2009)	54,069 Men	**Outcome**	**Fumigants Organobromine**		Age	Having used all 6 to
U.S.A.	476 MI death	AMI mortality		HR	State of origin	pesticides was
Iowa and North Carolina	Age >17 years	Cumulative exposure to pesticides	**Ethylene dibromide**	**1.54 (1.05–2.27)**	Tobacco	associated AMI
Cohort	PR	**Exposure**	**Fungicides**		Smoking	mortality or
D&B -17	Inc. 63%	50 pesticides	**Dithiocarbamate**		BMI	incidence, but not in
(follow-up losses not described)	Mortality 94%	Herbicides	**Dimethyldithiocarbamate**			both. There was no
		Fumicides	**Maneb/mancozeb**	**1.34 (1.01–1.78)**		association between
		Fungicides	**Ziram**	**2.40 (1.49–3.86)**		length of exposure
		Insecticides				pesticides and fatal
		Organophosphates				and non-fatal AMI.
		Pyrethroids				
		Carbamate				
Systemic Arterial Hypertension and Arrhythmia						
Saldana et al. (2009)		**Outcome**	**SAH Pregnancy**	OR	BMI	This study
U.S.A.		SAH in pregnancy	Indirect	1.20 (1.00–1.44)	Parity	suggested an increased risk for

(*Continued*)

Table 1. Continued.

Author/year Country/ Study Design/ Downs and Black	Sample	CVD Outcome/ Exposure	Results Measurement of effect (95%CI)		Adjusted factors	Study Conclusion
Iowa and North Carolina Cross-sectional D&B- 15 (main outcomes and exposure not to be measured clearly, *p* value not reported)	11,274 Age 16–49 years PR 61%	**Exposure to Pesticides:** In the first trimester of the most recent pregnancy	**Residential** **Agriculture** **Pre-eclampsia** Indirect **Residential** **Agriculture** Strat. by gestational DM **SAH** (without DM) **Agriculture** **Pre-eclampsia** (without DM) **Residential**	**1.27 (1.02–1.60)** **1.60 (1.05–2.45)** 1.13 (0.92–1.39) **1.32 (1.02–1.70)** **2.07 (1.34–3.21)** **1.61 (1.04–2.50)** **1.47 (1.12–1.95)**	Age when became pregnant, State of residence Race.	gestational hypertension and preeclampsia in women exposed to pesticides in the first trimester of pregnancy
Samsuddin et al. (2016) Malaysia Case control D&B-18	128 Pesticide applicators (mosquito control) 195 Control PR 79%	**Outcome** Increased LDL Blood pressure (brachial and aortic) mmHg **Exposure** Fenitrothion Malathion Pirimiphos methyl Permethrin Deltamethrin Cyfluthrim	**Exposure to pesticide mix:** **Insecticides** (Organophosphorus, Carbamate and Pyrethroids) **Brachial SBP** **Brachial DBP** **Aortic SBP** **Aortic DBP**	Tobacco Smoking Income Age Lipid profile Pseudo-cholinesterase Paraoxonase **β6.09 (2.48–9.69)** **β7.46 (4.7–10.14)** **β5.67 (2.22–9.13)** **β7.18 (3.02–8.28)**	Chronic exposed to low dose mix-pesticide was possibly at higher risk of oxidative stress modification activities, increase brachial and aortic BP.	
Hung et al. (2015) Taiwan Retrospective cohort NHIRD 2000–2011 D&B-16 (*p* value not reported; follow	7561 OPs Exposed 30,244 Controls PR 97% Cumulative censoring rate 24% (OPs poisoning cohort)	**Outcome** Heart failure Arrhythmia Coronary disease **Exposure** Acute OP poisoning and follow-up until cardiovascular event	overall mortality **Arrhythmia** ≤49/>49 y **Male Exposure** **Without & with Comorbidities** Coronary disease **Age ≤ 49** **With Comorbility**	SRS **1.40 (1.04–1.89)*** **3.16 (2.18–4.59)** **1.33 (1.12–1.59)** * **1.59 (1.33–1.89)** 0.99 (0.85–1.15) **1.94 (1.47–2.54)*** 0.65 (0.54–0.79)*	Age SAH DM Hyperlipidemia COPD	The study shows significant association between acute OP poisoning and cardiovascular disease. Acetylcholine accumulation in nerve endings might be associated with the persistent cardiac injury for patients with OPs poisoning.

up losses not described)	10% (non-OPs poisoning cohort)		**Heart failure** overall mortality **Age ≤ 49**	 0.97 (0.76–1.23) * **2.50 (1.52–4.10)** * *$p < 0.001$		
Cardiovascular Mortality						
Waggoner et al. (2011) U.S.A. Iowa and North Carolina Cohort 1993–2007 D&B- 17 (p value not reported)	Male applicators 57,310 Wives 32,346 Deaths 6,419 PR: 82% Follow-up 100%	**Outcome** Cardiovascular Mortality Exposure **Occupational exposure to pesticides**	**Applicators' wives** CVD SAH/CVD Isch disease Cardiomyopathy **Pesticide applicators** CVD SAH/CVD Isch disease Cardiomyopathy	SMR 0.47 (0.42–0.53)* 0.29 (0.12–59)* 0.45 (0.39–0.52)* 0.48 (0.26–0.83)* 0.54 (0.51–0.56)* 0.52 (0.37–0.70)* 0.52 (0.49–0.55)* 0.69 (0.54–0.87)* p 0.05	Compared with the general population by state, stratified by race, sex and calendar period time	The study shows a low mortality compared with a general American population. The main cause of mortality was lymphohemato poietic cancer. Rates of death from heart disease and other circulatory diseases were both near half the expected rates
Charles et al. (2010) U.S.A. Honolulu Heart Program 1965–1998 Cohort D&B-17 (main outcome measures not reliable)	8006 men Age 45–68 years 4,485 deaths PR:100% Follow-up:100%	**Outcome** Cardiovascular Mortality **Occupational exposure to pesticides** Exposure time score: appropriated level of exposure (0,1,2,3,) multiply by the number of years of exposure, categorised in four levels (0, 1–39, 40–79, >80)	Applicators **Cardiomyopathy** **Exposure time score** Deaths from all causes RR 0 1–39 40–79 >80 Deaths from stroke 0 1–39 40–79 >80	r SMR **1.29 (1.03–1.62)*** 1.00 1.16 (1.01–1.34) 1.48 (0.81–2.70) 1.73 (0.87–3.47) ***p* trend <0.001** 1.00 0.92 (0.58–1.49) 1.48 (0.81–2.70) 3.70 (0.92–14.96) ***p* trend 0.038**	Schooling tobacco smoking, triglycerides, physical activity, alcohol and systolic blood pressure	Occupational exposure to pesticides, metals and solvents during middle age was independently associated with all-cause mortality, cancer and circulatory diseases

Notes: D&B: Downs and Black; PR: Participation rate; CVD: cardiovascular disease; 95%CI: 95% Confidence Interval; RR: relative risk; SMR: standardised mortality ratio; SAH: systemic arterial hypertension; AMI: acute myocardial infarction; HR: hazard ratio; OR: odds ratio; SRS: Subhazard Ratio; COPD: chronic obstructive pulmonary disease; OP: organophosphates; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; DM: diabetes mellitus.
*Linear Regression.

Table 2. Environmental exposure to organochlorines pesticides and heavy metals association with cardiovascular disease.

Author/year Country/ Study design/ Downs and Black	Sample	CVD Outcome Pesticide Exposure	Results Measurement of effect (95%CI)		Adjusted factors	Study Conclusion
Systemic Arterial Hypertension						
	315	**Outcome**	**Insecticides Organochlorines**		**Model 1**	
Valera, Ayotte et al. (2013)	Age ≥ 18 years	SAH	**p-p'DDE**	OR	Age	Some congeners persistent organic pollutants had a positive association with SAH among those most exposed.
Canada	PR 66.7%	**Exposure OC and their metabolites** (8)	Model 1	1.10 (0.92–1.32)	Sex	
Nunavik (Arctic)	Danes 144 41%	p,p′-DDE	**Model 2**	**1,23 (1.06–1.56)**	Glucose	
Cross-sectional		p,p′-DDT	**Model 3**	**1.45 (1.13–1.84)**	Total lipid	
D&B 17		b-CHC	**p-p'-DDT**		Abdominal circumference	The analysis of OC pesticides showed divergent results
(*p* value not reported)		Oxychlordane	Model 1	0.74 (0.65–0.86)	Alcohol consumption	
		Trans-Nonachlor	Model 2	0.79 (0.68–0.93)	Tobacco smoking	
		Cis-Nonachlor	Model 3	0.78 (0.66–0.93)	Physical activity	
		Mirex	**B-CHC**		**Model 2**	
		Plasma measured	Model 1	0.46 (0.36–0.58)	Model 1 + variables + EPA, DHA, % Fatty acids	
			Model 2	0.48 (0.38–0.62)		
			Model 3	0.50 (0.39–0.64)		
			Oxychlordane		**Model 3**	
			Model 1	0.74 (0.65–0.84)	Model 2 + toxic metals (Mercury and lead)	
			Model 2	0.79 (0.69–0.92)		
			Model 3	0.64 (0.52–0.79)		
			Trans-Nonachlor			
			Model 1	0.82 (0.71–0.95)		
			Cis-Nonachlor			
			Model 1	0.85 (0.74–0.98)		
			HCB			
			Model 1	0.74 (0.62–0.89)		
			All 1	*p* 0.05 or <0.00		
Valera, Jorgensen et al. (2013)	1,614	**Outcome**	**Insecticides Organochlorines**		**Model 1**	Most of OC pesticides had no association with SAH, although it differs in age categories
	Age 18–88 years	SAH	Model 1	OR	Age	
Greenland	PR 64.4%	**Exposure OC pesticides** (11)	Aldrin	0.65 (0.47–0.90)	Sex	
Cross-sectional		Serum levels	Mirex	0.77 (0.69–0.86)	**Model 2**	
D&B:18		Aldrin	Alpha chlordane	0.58 (0.37–0.91)	Age	
		Alpha chlordane			Sex	
		Gama chlordane	**Stratified by age**		BMI	
		DDT	**<40 years**		DM	
		DDE	Model 2		Physical activity	
		HCB	Aldrin	0.39 (0.20–0.78)	Tobacco smoking	
		b-HCH	Alpha chlordane	0.38 (0. 19–0.75)		
		Cis-nonachlor	Gama-chlordane	0.10 (0.03–0.38)		

		Trans-nonachlor	**DDT**	**1.42 (1.08–1.85)**	
		Oxyclordane	**≥40 Years**		
		Mirex	Model 1		
			Oxychlordane	0.87 (0.76–0.99)	
			Model 2		
			Mirex	0.80 (0.69–0.93)	
			All	***p* < 0.05**	
Henriquez-Hernandez et al. (2014) Spain ENCA 1998 Cross-sectional D&B-17 (not analyses adjust for different lengths of follow-up of patients)	428 Age ≥ 18 years PR 44.8% Biochemical stage	**Outcome** SAH **Exposure OC pesticides** p,p′-DDE Aldrin Endrin Lindane	**Insecticides Organochlorines**	OR	Sex Age Tobacco smoking BMI Total lipids	Aldrin was negatively associated with increased SBP, suggesting that OC pesticides may induce divergent actions on blood pressure. The findings indicate that the direction of association between SAH and OC may depend on the chemical structure and concentration of compound
			Aldrin	0.28 (0.09–0.92) *p* 0.037		
			p-p′DDE	1.04 (0.90–1.12) *p* 0.622		
Saunders et al. (2014) Guadeloupe French West Indies Cross-sectional 2004–2007 D&B-16 (patients were not recruited over the same period of time; *p* value not reported)	779 pregnant women Age 21–49 years PR 100%	**Outcome** SAH in pregnancy and preeclampsia **Exposure OC Pesticides** Chlordecone plasma levels 1st quartile <0.17 2nd quartile 0.17–0.38 3rd quartile 0.39–0.80 4th quartile >0.80	**SAH in pregnancy**	OR	Maternal place of birth Maternal age Pre-gestational BMI Weight gain during pregnancy Total maternal lipids	The study suggested possible inverse association between chlordecone exposure during the pregnancy with SAH in pregnancy and no association with preeclampsia
			1st quartile	1		
			2nd quartile	0.5 (0.3–1.1)		
			3rd quartile	0.2 (0.1–0.5)		
			4th quartile	0.3 (0.2–0.6)		
			Pre-eclampsia			
			1st quartile	1		
			2nd quartile	1.1 (0.3–2.8)		
			3rd quartile	1.2 (0.4–3.4)		
			4th quartile	1.0 (0.3–3.1)		
Yi et al. (2013) Vietnam Cohort D&B 17 (main outcome measures not used accurate)	114,562 Age <56 ≥60 years Assessed by reported health condition and proximity to Agent Orange and OC serum levels 30% of sample PR 69.8%	**Outcome** Chronic disease **Exposure Herbicides** 2,3,7,8 TCDD 2,4,5-T Agent Orange Reference group Non-exposed or Low exposure (Entered application site) Exposed group Moderate exposure		OR	Age Military rank Tobacco Smoking Schooling Physical activity Alcohol Family income Herbicide use in the past BMI	The exposure index based on proximity shows that the high exposure to Agent Orange was associated with a high prevalence of circulatory diseases: SAH, cerebral infarction and peripheral vasculopathy.
			CVD	**1.86 (1.82–1.91)**		
			SAH	**1.51 (1.48–1.56)**		
			AMI	**1.89 (1.80–1.99)**		
			Angina	**1.71 (1.64–1.79)**		
			Heart failure	**1.92 (1.79–2.06)**		
			Atherosclerosis	**1.90 (1.80–2.01)**		
			PVD	**2.44 (2.33–2.56)**		
			High exposure herbicides			
			CVD			

(*Continued*)

Table 2. Continued.

Author/year Country/ Study design/ Downs and Black	Sample	CVD Outcome Pesticide Exposure	Results Measurement of effect (95%CI)		Adjusted factors	Study Conclusion
		(Present during application or contaminated clothes)		**2.33 (2.24-2.41)***		
		High exposure (Manual application)	**Division of work**			
			High exposure (4 groups)			
			Ref	1		
			CVD	**1.07 (1.02–1.11)***		
			PVD	**1.09 (1.01–1.17)***		
			SAH	**1.02 (0.98–1.06)**		
				***p* 0.45**		
			AMI	**1.10 (1.02–1.19)**		
				***p* 0.02**		
			Angina	1.00 (0.9–1.08)		
				p 0.75		
			Atherosclerosis	1.05 (0.90–1.22)		
				p 0.64 trend**p*<0.00		
Kang et al. (2006)	2977	**Outcome**	Total sample	OR	Age	Vietnamese veterans had a significant high risk for SAH and heart disease after three decades of exposure to phenoxy herbicides.
Vietnam	1499	Chronic disease	CVD	1.09 (0.87–1.38)	Race	
Cohort	Vietnamese veterans	**Exposure**	SAH	1.06 (0.89–1.27)	BMI	
D&B 14 (follow up losses not describe and were not monitored,	1,428	**Herbicides**			Tobacco smoking	
	Non-Vietnamese veterans	TCDD and dioxin	**Herbicides Phenoxyalkonates**		Military rank	
p value not reported;	PR	Serum levels				
statistical analyses were not appropriate and not adjusted for different lengths of follow-up of patient)	Vietnam 73%		**2,4-D/2,4,5-T applicators**			
	Non-Vietnam Veterans 65%		**CVD**	**1.41 (1.06–1.89)**		
			SAH	**1.26 (1.00–1.58)**		
			2,4-D/2,4,5-T applicators			
			Total sample	RR		
			CVD	**1.52 (1.18–1.94)**		
			SAH	**1.32 (1.08–1.61)**		
Chen et al. (2013)	959	**Outcome**	Linear regression		**Model 1**	Show a positive association between past exposure by arsenic and carotid intima-media thickness at follow-up. There is dose–response relationship with MMA at baseline and measured
Bangladesh	Age 26–52 years	Measurement carotid intima-media thickness (μm)	Difference of 1 SD		Sex	
Cohort	PR 97%		**Heavy Metals**		Baseline BMI	
D&B: 18		**Exposure**	**nAs water**		Age	
		Heavy Metals	Model 1	4.0μm (−1.4–9.3)	Tobacco smoking	
				p 0.14	Schooling	

		In As dosage in water Baseline MMA DMA PMI SMI Urine dosage Follow-up	Model 2 **High InAs%** **High MMA%** **High PMI** **Low SMI** At each increment of 1SD of urinary Arsenic concentration **Model 1** **Model 2** At each increment of 10% SD of DMA urinary **MMA%** DMA%	5.1μm (−0.2–10.3) *p* 0.058 **7.5 μm (0.2–14.9)** **2.5 μm (3.3–21.8)** **9.1 μm (0.7–17.5)** **11.9 μm (2.7–21.0)** **11.0μm (0.8–21.1)** ***p* 0.034** **11.7μm (1.8–21.6)** ***p* 0.02** **12.1μm (0.4–23.8)** ***p* 0.042** 6.3μm (−12.8–0.2) *p* 0.057	Age during follow-up carotid measurement Change in urinary arsenic levels between appointments **Model 2** Blood pressure Diabetes mellitus added.	after 7 years with carotid intima-media thickness. The association between basal Ar was higher among those who had high levels of MMA%, InAs and PMI and low urinary SMI
Jones et al. (2011) U.S.A. Cross-sectional D&B:18	4,167 Age ≥ 20 years PR 76%	**Outcome** SAH **Exposure** **Heavy Metals** Total urinary arsenic Arsenic minus AMA DMD	**Heavy Metals** Ar urine AMA DMA DMA **Model 1** 2 quartile 3 quartile 4 quartile **Model 2** 2 quartile 3 quartile 4 quartile	OR 0.98 (0.86–1.11)* 1.03 (0.94–1.14)* 1.11 (0.99–1.24)* 1.06 (0.80–1.41) 1.21 (0.89–1.64) 1.29 (0.93–1.79) ***p* 0.03** 1.05 (0.77–1.42) 1.18 (0.84–1.66) 1.24 (0.84–1.83) ***p* 0.07**	Sex Age BMI Urinary creatinine Serum cotinine **Model 1** Sex Race Urinary creatine Schooling Serum cotinine BMI **Model 2** Urinary creatinine Arsenobetaine added	No association was found with SAH between the low to moderate levels of total arsenic and arsenobetaine, For urinary DMA a small association was found with SAH and it may be stronger in some subgroups
Shiue (2014) U.S.A. Cross-Sectional NHANES 2011/2012	12,000 Age ≥ 20–80 years 9756	**Outcome** SAH **Exposure** 2,5Dichlorophenol 2,4Dichlorophenol	**Heavy Metals**		Age Sex BMI Ethnic origin	Urinary chemical concentration of environmental pollutants such as arsenic was associated with increased blood pressure

(*Continued*)

Table 2. Continued.

Author/year Country/ Study design/ Downs and Black	Sample	CVD Outcome Pesticide Exposure	Results Measurement of effect (95%CI)		Adjusted factors	Study Conclusion
D&B:17 (follow up losses not described)	20–30% Urine collected PR 87.5%	Dichlorophenol Total arsenic Arsenous acid Arsenic acid Arsenobetained Arsenocholine MMA DMA Trimethylarsine Oxide		OR		
			Total arsenic	**1.13(0.99–1.29)** ***p*** **0.06**		
			DMA	**1.42(1.12–1.79)***		
			Trimethylarsine	**2.47(1.27–4.81)*** ***p*** **< 0.05**		
			Sample weight			
Acute Myocardial Infarction and Peripheral Arterial Disease						
Min et al. (2011) U.S.A. Cross-sectional NHANES 1999–2004 D&B 17 (*p* value not reported)	2032 Age ≥ 40 years Subsample OC measured 30%	**Outcome** Peripheral Arterial Disease **Exposure** OC Pesticides Serum dosage p,p -DDE Trans-nonachlor Oxychlordane Dieldrin HCH	**Insecticides Organochlorines** Stratified by BMI ≥ 25	OR	Age Sex Race Schooling Income Tobacco smoking Alcohol consumption DM BMI Cotinine level	The OC plasmatic increased pesticide level was associated with peripheral arterial disease prevalence. Obesity adversely modulates serum levels of OC pesticides and may contributed to atherogenesis.
			p,p-DDE	**1.47 (1.08–1.99)**		
			Trans-nonachlor	**1.68 (1.10–2.56)**		
			Oxychlordane	**1.82 (1.09–3.03)**		
			Dieldrin	**2.36 (1.69–3.31)**		
			Sum of the 5 OCs	**1.19 (1.07–1.33)**		
			< 25 BMI did not present risk of Peripheral Vascular Disease			
			Insecticides Organochlorines			

Mills et al. (2009) U.S.A. Iowa and North Carolina Cohort D&B 17 (follow up losses not described)	32,024 men Age>17 y PR Incidence 63% Mortality 94%	**Outcome** Non-fatal AMI **Exposure** Organochlorine Cumulative exposure to pesticides	Aldrin DDT **Herbicides** **Phenoxyalkonates**	HR **1.20 (1.01–1.43)** **1.24 (1.04–1.46)**	Age State of origin Tobacco smoking BMI	The study concludes that no convincing evidence of the association between OCs and AMI was observed in the chronic use of these chemicals, due to the absence of dose-response and tendency of association in cumulative exposure.
			2,4,5-T	**1.21 (1.03–1.43)**		
Cardiovascular Mortality Kim et al. (2015) U.S.A. Cohort NHANES 1999–2004 D&B 17 (follow up losses not described)	675 elderly OC measured Subsample	**Outcome** CV Mortality **Exposure** OC pesticides measurement tercile	Proportional Cox regression CVD Fat mass <25% T1 T2 **T3** *Risk was not associated with percentage fat above 25%. Elderly with high OC levels: OR 2.9 compared with those with low OC levels (p trend 0.01)	 1 0.26 (0.03–2.37) **4.54 (1.38–15.0)** p trend <0.01	Age Sex Ethnic origin Tobacco smoking Physical activity BMI	OC pesticides were positively associated with CVD mortality in the elderly with low fat mass
Vena et al. (1998) Multicenter IARC Cohort 12 countries 36 cohorts 1939–1992 D&B 16 (follow up losses not described, p value not reported)	26,976 Herbicide applicators or herbicide industry workers 4,160 control workers PR 100% Follow-up-96%	**Outcome** CV Mortality **Exposure** **Herbicides** 2,3,7,8 TCDD/HCD	 **Circulatory Dis.** **Ischemic CVD** CVD	RR **1.51 (1.2–2.0)** **1.67 (1.2–2.3)** 1.54 (0.8–2.9)	Age Sex Country Data started work Length of time of exposure to Chlorophenol, Phenoxy and herbicide	Exposure to TCDD/ HCD increases the risk of ischemic heart disease
Boers et al. (2012) Germany Cohort D&B 15 (follow up losses not described, p value not	2056 men 541 deaths Herbicide industry workers PR 100%	**Outcome** CV Mortality **Exposure** **Herbicides** 2,4,5 TCDD Predictive model of TCDD	Proportional Cox regression **Ischemic Dis.** Ref. (<0.4)	 HR **1.19 (1.08–1.3)** 1	Age Year of follow-up Length of time since first exposure job	Positive association between TCDD plasmatic and ischemic disease

(*Continued*)

Table 2. Continued.

Author/year Country/ Study design/ Downs and Black	Sample	CVD Outcome Pesticide Exposure	Results Measurement of effect (95%CI)		Adjusted factors	Study Conclusion
reported, confounders partially described)		serum levels – 187 workers	Low (0.4–1.9) Medium (1.9–9.9) **High (≥ 9.9)**	1.02 (0.6–1.8) 1.25 (0.7–2.2) **2.78 (1.6–4.9)**		
Hooiveld et al. (1998) Netherlands Cohort D&B 17 (*p* value not reported)	1,167 549 workers exposed 482 non-Exposed Age 25 ≥ 45 years PR 100% Follow-up 99%	**Outcome** CV Mortality **Exposure** phenoxy herbicides, chlorophenols, and contaminants (2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and other polychlorinated dioxins and furans)	RR CVD Ischemic CVD Comparison between TCDD serum levels Ischemic CVD exposure High Medium	1.4 (0.8–2.5) 1.8 (0.9–3.6) 2.3 (1.0–5.0) 1.5 (0.7–3.6)	Age Year of follow-up and length of time since first exposure / job	The exposure to TCDD was associated a CVD, especially ischemic disease
Consonni et al. (2008) Italy Seveso Cohort 1997–2001 D&B 16 (*p* value not reported, confounders partially described)	278,108 Residents 47,584 deaths Herbicide industrial accident PR 79% Follow up 99%	**Outcome** CV Mortality **Exposure** **Herbicides** TCDD Levels in soil: **Zone A** 15.5- 580.4 Very high contamination **Zone B** 1.7–4.3 High contamination **Zone R** 0.9–1.4 Low contamination	RR **SAH** Zone A Zone B Zone R **AMI** Zone A Zone B Zone R **Ischemic Heart Disease** Zone A Zone B **Zone R** **Zone A** **Circulatory Disease** 0–4 y **5–9 y** 10–14 y 15–19 y > 20 y **Zone A Men** CV circulatory **CVD Ischemic** **Zone R woman**	2.18 (0.90–5.25) 0.72 (0.40–1.31) 1.20 (1.01–1.43) 0.63 (0.28–1.41) 0.86 (0.65–1.12) 0.98 (0.89–1.08) 1.11 (0.53–2.34) 1.06 (0.80–1.42) **1.16 (1.04–1.29)** 1.36 (0.77–2.40) **1.84 (1.09–3.12)** 0.67 (0.28–1.60) 0.59 (0.24–1.42) 0.88 (0.46–1.69) 1.40 (0.97–2.01) **2.48 (1.18–5.22)**	Accident Sex Cohort period and age	For heart disease, accident related stressors might have precipitated death among people with preexisting disease. Circulatory disease mortality was elevated in zone A in the early post accident periods but was lower than expected in the most recent years.

			CVD circulatory	**1.09 (1.03–1.16)**		
Yi et al. (2014)	180, 639	**Outcome**		OR	Age at entry in the cohort	Lack of adjustment for obesity, smoking and alcohol made it difficult to analyse cardiovascular disease
Korea	PR 98.5%	CV Mortality	**SAH**	**1.18 (0.88–1.58)****	Military rank	
Cohort		**Exposure**	Ischemic Dis	0.99 (0.86–1.14)*		
Health Study (KVHS)		**Herbicides**	**Angina**	**2.34 (1.32–4.15)****		
D&B 13		2,3,7,8 TCDD	AMI	0.93 (0.80–1.09)*		
(individuals characteristic and confounders were not clearly described; main outcome measures not reliable)		2,4,5-T Agent Orange		*NS ** p0.003		
Cypel and Kang (2010)	2,872 Vietnamese	**Outcome**	Proportional Cox regression		Ethnic origin	The study shown a positive association between Orang Agent with respiratory disease and cancer.
Vietnam	2,737 Non-Vietnamese	CV Mortality			Military rank	
Cohort	Reported spraying herbicide 662	**Exposure**		HR	Length of military service	
Veteran soldiers	and not 811	**Herbicides**	Circulatory Dis.	1.21(0.93–1.58)	Age when starting follow-up	
D&B 15		2,3,7,8 TCDD	SAH	0.85 (0.19–3.86)		
(follow-up losses not describe and were not monitored, confounders partially described)		2,4,5-T dioxin Agent Orange				

Notes: CVD: cardiovascular disease; PR: participation rate; 95%CI: 95% confidence interval; RR: relative risk; TCDD 2,3,7,8: tetraclorodibenzo-p-dioxin; HCD: hexachlorobenzene; OR: odds ratio; HR: hazard ratio; RR: relative risk; NS: no significant; SAH: systemic arterial hypertension; AMI: acute myocardial infarction; OC: organochlorine; p,p′-DDE: dichloride diphenyl dichloro ethylene; MMA: monomethylarsonic acid; DMA dimethylarsinic acid; PMI: primary metabolite of InAs; SMI: secondary metabolite of InAs; InAs: inorganic arsenic; SD: standard deviation; BMI: body mass index; DM: diabetes mellitus; AMA: arsenobetaine; p,p′-DDT: dichloride diphenyl trichloro ethane; PVD: peripheral vascular disease; b-CHC: hexachlorocyclohexane; b-HCH: beta-hexachlorocyclohexa

(SR1.25 95%CI 1.07–1.39) and for heart failure (SR2.50 95%CI 1.52–4.10) after adjusting for age, sex and comorbidities (Hung et al., 2015) (Table 1).

Two American mortality cohort studies in pesticides exposed workers observed increased risk of death from cardiomyopathy and cerebrovascular stroke (Charles et al., 2010; Waggoner et al., 2011). In the AHS cohort, the standardised mortality ratios (SMR) from heart disease and other circulatory diseases were both near half the expected rates, compared with general population (SMR 0.54 95%CI 0.51–0.56; Dayton et al., 2010). However, when compared the SMR for each cause with all other causes, the cardiomyopathy presented a risk of 1.29 (1.03–1.62; Waggoner et al., 2011). In Honolulu, a cohort study following workers exposed to pesticides between 1964 and 1998 found risk of death due to cerebrovascular stroke of 3.70 (0.92–14.96) among those with longer exposure to pesticides (Charles et al., 2010) (Table 1).

Environmental exposure to organochlorine and others pesticides

Among the eighteen articles assessing organochlorine pesticides, two evaluated pesticides applicators (Mills et al., 2009; Vena et al., 1998), three were on chemical industry workers (Boers et al., 2012; Consonni et al., 2008; Hooiveld et al., 1998), five concerned Vietnamese military personnel (Boers et al., 2012; Cypel & Kang, 2010; Kang et al., 2006; Yi et al., 2013, 2014), eight in general population (Chen et al., 2013; Henriquez-Hernandez et al., 2014; Hooiveld et al., 1998: Jones et al., 2011; Min et al., 2011; Valera, Ayotte et al., 2013; Valera, Jorgensen, et al., 2013), one was on pregnant women (Saunders et al., 2014), one on elderly people (Kim et al., 2015). Seven articles addressed cardiovascular mortality (Boers et al., 2012; Consonni et al., 2008; Hooiveld et al., 1998; Cypel & Kang, 2010; Kim et al., 2015; Vena et al., 1998; Yi et al., 2014) (Table 2).

The studies showed variability in the exposure definition. Some used biological measurement of tetrachlorodibenzo-p-dioxin (TCDD) and arsenic whilst others used exposure indices for each study, based on intensity, time and proximity of the chemical agents. The organochlorine insecticides, such as dichlorodiphenyltrichloroethane (p,p'–DDT) and their metabolites, p,p'– dichlorodiphenyltrichloroethane (p,p'–DDE), hexachlorobenzene (HCB), 2,3,7,8 TCDD or dioxin, herbicides (Agent Orange) and arsenic were positively associated with SAH, peripheral arterial disease, cardiovascular mortality in twelve of the eighteen studies assessed (Boers et al., 2012; Chen et al., 2013; Consonni et al., 2008; Hooiveld et al., 1998; Kang et al., 2006; Kim et al., 2015; Mills et al., 2009; Min et al., 2011; Shiue, 2014; Valera, Ayotte et al., 2013; Vena et al., 1998; Yi et al., 2014).

The risk for CVD among those exposed to Agent Orange ranged from 1.41–2.33 (Kang et al., 2006; Vena et al., 1998; Yi et al., 2013). Specifically for circulatory disease, the risk ranged from 1.09–1.51 (Consonni et al., 2008; Vena et al., 1998), for ischemic disease, ranged from 1.16–2.78 (Boers et al., 2012; Mills et al., 2009; Min et al., 2011; Vena et al., 1998; Yi et al., 2013, 2014), for SAH, was 1.20–1.51 (Kang et al., 2006; Yi et al., 2013) and 1.92 for heart failure (Yi et al., 2013). The organochlorine insecticides increased the risk for SAH in 42% (Valera, Jorgensen, et al., 2013), for peripheral arterial disease the risk ranged from 1.19–2.36 (Min et al., 2011), and for AMI from 1.20 and 1.24 (Mills et al., 2009). The exposure to arsenic was associated with the carotid intima-media thickness increase (Chen et al., 2013) and SAH, with OR 1.42 and 2.47, respectively (Shiue, 2014) (Table 2).

A cross-sectional study with an Arctic population found that serum p,p'–DDE was associated with 1.45 increased risk of SAH (95%CI 1.13–1.84), whereas a protective effect was found for exposure to oxychlordane, beta-HCH and p-p'DDT (Valera, Ayotte et al., 2013). In Greenland, exposure to p,p'–DDT was associated with 42% increased risk of hypertension (1.08–1.85) among those under 39 years old, while a protective effect was observed for aldrin, a-chlordane and g-chlordane (Valera, Jorgensen, et al., 2013). In the Canary Islands, exposure to aldrin and p,p'DDE was not associated with SAH (Henriquez-Hernandez et al., 2014), and chlordecone was not associated with hypertensive disorders in pregnancy and preeclampsia in pregnant women in Guadeloupe (Saunders et al., 2014) (Table 2).

Studies with Vietnam military personnel about exposure to Agent Orange, a defoliant herbicide, extremely toxic, used during the Vietnam War, found risk of 2.33 (95%CI 2.24–2.41) for CVD among those with high exposure (Yi et al., 2013), and risk of 1.41 (95%CI 1.06–1.89) among herbicide applicators (Kang et al., 2006). Those studies used index based on proximity of Agent Orange. Increase in the level serum of TCDD and dioxin showed risk of 51% (Yi et al., 2013) and 26% (Kang et al., 2006) for SAH, respectively (Table 2).

Arsenic has been associated with vascular alteration and SAH (Chen et al., 2013; Jones et al., 2011; Shiue, 2014). Around twenty different forms of arsenic have been identified in nature, the most poisonous being arsenobetaine (AsB), dimethylarsinic acid (DMA), monomethylarsonic acid (MMA), arsenate (As5+) and arsenite (As3+). In U.S.A., the presence of arsenic metabolites in urine, including MMA, DMA and trimethylarsine oxide (arsenic), showed a risk between 1.24–2.47 for SAH (Jones et al., 2011; Shiue, 2014). Chen et al. (2013) found that each standard deviation of urinary arsenic concentration was associated with an 11.7μm increase (95%CI 1.8–21.6) in the thickness of the carotid intima layer after adjustment for sociodemographic characteristics, diabetes mellitus and BP measurement. Similar association was found with urinary arsenic metabolites, whereby for every 10% increase in MMA, carotid thickness increased by 12.1 μm (95%CI 0.4–23.8) (Chen et al., 2013) (Table 2).

An American population-based study with overweight/obesity individuals found association between the serum levels of five organochlorines and peripheral vascular disease OR1.19 (95%CI 1.07–1.33), including p,p'–DDE 1.47 (1.08–1.99), trans-nonachlor 1.68(1.10–2.56), oxychlordane 1.82 (1.09–3.03) and dieldrin 2.36 (1.69–3.31) (Min et al., 2011) (Table 2).

High exposure to Agent Orange presented a risk of 2.44 (95%CI 2.33–2.56) for peripheral vascular disease and 1.89 (95%CI 1.80–1.99) for AMI in a Vietnamese cohort (Yi et al., 2013). The AHS, found around 20% increased risk of nonfatal AMI for pesticide applicators exposed to aldrin, DDT and 2,4,5-T (Mills et al., 2009) (Table 2).

Mortality studies evaluated, except for one article, which evaluated organochlorines, the Agent Orange exposure (Shiue, 2014), four studies point a risk of cardiac ischemic disease (Boers et al., 2012; Consonni et al., 2008; Hooiveld et al., 1998; Vena et al., 1998) but other two did not observe this association (Cypel & Kang, 2010; Yi et al., 2014) (Table 2).

A cohort study found that, among elderly Americans with fat mass lower than 25%, the highest tercile of exposure to organochlorines had four times more risk of cardiovascular mortality (95%CI 1.38–15.0) than those in the lowest tercile (Kim et al., 2015). Among workers in the TCDD producing industry, a multicenter cohort study conducted in twelve countries by the International Agency for Research on Cancer found increased risk of mortality of 51% and 67% for circulatory and ischemic diseases, respectively (Vena et al., 1998). High TCDD serum levels in workers in the Netherlands and Germany was associated with double the mortality risk owing to ischemic heart disease (Boers et al., 2012; Hooiveld et al., 1998). A cohort of herbicides industry workers found that those exposed to areas with higher TCDD contamination due to an accident presented a risk of 2.5 for cardiovascular ischemic disease mortality (Consonni et al., 2008). Two Cohort studies with Vietnamese military exposed to Agent Orange during the Vietnam War, one comparing to non-exposed subjects (Cypel & Kang, 2010) and another considering Agent Orange exposure index (Yi et al., 2014), presented no association with cardiovascular mortality (Cypel & Kang, 2010; Yi et al., 2014) (Table 2).

Discussion

The findings of this review point to CVD risk among those exposed to pesticides (Charles et al., 2010; Dayton et al., 2010; Hung et al., 2015; Mills et al., 2009; Saldana et al., 2009; Samsuddin et al., 2016), organochlorine (Boers et al., 2012; Consonni et al., 2008; Kang et al., 2006; Mills et al., 2009; Min et al., 2011; Valera, Ayotte et al., 2013; Valera, Jorgensen, et al., 2013; Vena et al., 1998; Kim et al., 2015; Yi et al., 2013) and arsenic (Chen et al., 2013; Shiue, 2014). Although pesticide exposure

is greater among agricultural and chemical industry workers, this problem also extends to the general population owing to the contamination of food, soil and water. Exposure is made worse by the fact that some chemicals undergo amplification in the food chain and also remain in human fatty tissue for decades following exposure, as is the case of organochlorine pesticides (Hardell et al., 2010; Jackson et al., 2018). The physicochemical properties of organochlorines, a lipophilic product, when trapped in triacylglycerol lipid droplets, allow bioaccumulation, increase the total organochlorine load, exert inflammatory activity and can negatively influence health (Jackson et al., 2018).

It is possible that some pesticides may be directly involved in CVD genesis, especially in chronic use. The cohort studies with American pesticide applicators were consistent in demonstrating the risk of CVD associated with some pesticides belonging to organophosphorus, carbamate and dithiocarbamate groups, although the type of cardiovascular outcome assessed varied in the different studies (Dayton et al., 2010; Mills et al., 2009; Saldana et al., 2009). The AHS found evidence of significant multichemical exposure (Dayton et al., 2010; Mills et al., 2009; Saldana et al., 2009; Waggoner et al., 2011). This is relevant owing to the fact that cardiovascular toxicity can occur through diverse ways, varying according to the type of chemical.

Widely used in agriculture and in the control of endemic diseases, the organophosphorus (OP) compounds chlorpyrifos, coumaphos, malathion, diazinon (Dayton et al., 2010; Hung et al., 2015), the carbamate carbofuran (Dayton et al., 2010), and the organochlorine pesticide aldrin (Mills et al., 2009) were associated with AMI, SAH, arrhythmia, coronary disease and heart failure. The organophosphorus and carbamates compounds are cholinesterase inhibitors and, in case of acute poisoning, present nicotinic effects on the cardiovascular system, provoking tachycardia and increased BP, due to stimulation of sympathetic nervous system. On the other hand, bradycardia and hypotension occur due to the muscarinic effect (Eddleston et al., 2008). Notwithstanding, their chronic effects are little known. Studies suggest that organophosphorus compounds and the herbicide 2,3,7,8 TCDD have toxic effects on heart muscle fibre (Consonni et al., 2008; Hung et al., 2015).

Some organophosphate compounds, such as diazinon, can lead to the formation of oxidative stress in the cardiovascular system, leading to serious changes in proteins, including accelerated degradation (Razavi et al., 2015), resulting in arrhythmias due to electrolyte disturbances or mechanisms for recovery and healing of damaged myocardium (Georgiadis et al., 2018).

Organophosphorus also act on the human central nervous system, whereby central toxicity may be a common route for the development of CVD in cases of chronic exposure or even through interaction with other classes of chemicals (Crofton, 2008). Experimental study in zebrafish and dieldrin, a organochlorine pesticides, shows the induction of genes modification associated with cardiovascular dysfunction and compromised lysosomal physiology, causing cardiomyocyte injury which is due to altered status of growth, metabolic dysregulation, and lysosomal stress (Slade et al., 2017). The dithiocarbamates, as mancozeb and ziram, its degradation products and metabolites, as ethylene thiourea (ETU) and propylene thiourea, present other toxicity pathway on the cardiovascular system (Crofton, 2008). They might be associated with altered thyroid hormone balance and act as thyroid disrupters, affecting the hypothalamic-pituitary-thyroid axis (Crofton, 2008). Piccoli et al. (2016) show that exposure time to dithiocarbamates, fungicides and herbicides was associated with increased TSH, and lower T4 in agricultural workers.

Cardiovascular mortality was associated with exposure to organochlorines, TCDD and Agent Orange (Boers et al., 2012; Consonni et al., 2008; Hooiveld et al., 1998; Mills et al., 2009; Kim et al., 2015; Vena et al., 1998). The use of organochlorine pesticides (aldrin, chlordane, p,p'–DDT, dieldrin, dioxins, aldrin, furans, heptachlor, HCB and mirex) has been prohibited since the 2001 by the Stockholm Convention. A recent Brazilian study found the presence of organochlorine pesticides (lindane, p,p'–DDT, DDD, alpha-HCH and aldrin) and other pesticides such as trifluralin, alpha-endosulfan, cypermethrin and deltamethrin in the breast milk of nursing mothers living in soybean, maise and cotton growing areas with high pesticide use (Palma et al., 2014). This compunds are stable and persist in the environment for around 30 years.

The mechanisms involved in CVD genesis in cases of chronic exposure to organochlorines have been related to the oestrogenic property of these compounds and their capacity to alter lipid metabolism. Organochlorines bind themselves to lipoproteins, resulting in increased low-density lipoprotein (LDL) serum lipids, leading to chronic inflammation and atherothrombosis which are known CVD risk factors (Kurppa et al., 1984; Ljunggren et al., 2014; Patel et al., 2012; Samsuddin et al., 2016; Teixeira et al., 2015). The presence of organochlorine was identified in fatty tissue of women who had undergone bariatric surgery and a positive association was found with proinflammatory interleukin (IL-6 and IL-10) concentration with cardiovascular risk (Teixeira et al., 2015). In the U.S.A., ecological studies have shown a 20% higher hospitalisation rate of AMI in areas contaminated with POPs, including organochlorine, compared to uncontaminated areas (Sergeev & Carpenter, 2005). In areas of wheat planting and with greater exposure to herbicides, AMI mortality was higher compared to non-wheat areas (Schreinemachers, 2006).

The Cromated Copper Arsenate (CCA) and Ammonia Copper Arsenite (ACA) have been used worldwide as preservatives in wood. ACA contains trivalent arsenic, which is more toxic. These compounds are leached by rain contaminating the environment (Jagels, 1985). Proposal ingested of CCA was associated with refractory ventricular tachycardia and ventricular fibrillation (Hay et al., 2000). Heavy metals such as arsenic, cadmium, lead, mercury and chrome are poisonous but even so they are present in diverse types of agricultural chemical products. Inorganic arsenic has a relatively short half-life, around 2–38 days, and its measurement and their metabolites in urine do not reflect chronic exposure. Exposure of the general population to arsenic occurs through the contamination of drinking water reservoirs, which except when there are specific decontamination interventions, remains stable over time. Among chronically exposed individuals there is a dose–response relationship between arsenic metabolites measured in urine and carotid thickness measurement, this being one of the aspects implied in CVD development (Chen et al., 2013).

The association between exposure to trivalent arsenic (arsenite), the most toxic form of arsenic, and vascular alteration was observed in an experimental study in human umbilical vein. Artherogenesis mechanisms owing to arsenic exposure are little understood. Exposure to arsenite enhances Tumour Necrosis Factor-alpha (TNF-alpha) in the expression of vascular cell adherence molecule 1 (VCAM-1), through Nuclear Factor kappa B (NF-kappa B), Activator Protein 1 (AP1) and growth hormone (GSH), working as inducers of cell proliferation, thus indicating that it is a pathological route for vascular alteration (Tsou et al., 2005).

The majority of the articles had good scores using D&B criteria. The studies that obtained low scores were due to loss of follow-up and lack of description of follow-up losses (Cypel & Kang, 2010; Kang et al., 2006). Deficiency of precise definition of outcome and exposure, as well as only assessing age as a confounding factor for CVD may affect the associations (Boers et al., 2012; Cypel & Kang 2010; Yi et al., 2014).

This review suggests that some pesticides of the organophosphorus, carbamate, dithiocarbamate and pyrethoid chemical groups, used extensively in agricultural production and/or control of endemic diseases, may be involved in CVD genesis in chronically exposed individuals. It also points out that POP- organochlorines, TCDD and arsenic, although not currently authorised for agricultural use, may still be impacting the development of CVD. This occurs due to the long persistence of POPs in the soil or in the human fatty tissue and to the use of arsenic, until recently, in wood processing.

Although male exposure to pesticides is well recognised, women also have significant exposure at work, cleaning clothes and areas with pesticide dust and thru environmental contamination.

CVD is an important public health problem due to its frequency and high mortality rate worldwide. Pesticides exposure is, directly or indirectly, present in the everyday lives of individuals. This study contributes to summarise the evidences of occupational and environmental pesticide exposure risk for the development of CVD, extending knowledge beyond well known risk factors such as tobacco smoking, alcohol and obesity.

These findings point to the importance of greater rigour in the public policy related to pesticides, which in addition to cardiovascular risk are associated with serious health events such as cancer, endocrine and neurological disorders. Future studies should characterise pesticide exposure in greater depth, specifying different forms of exposure, intensity and duration, so as to be able to assess the effects of specific chemical types and also the effects of multiple chemical exposure. In order to improve study comparability, it is also necessary to standardise the characterisation of cardiovascular outcomes, serum pesticides measurement and to conduct robust analyses, which include adjustment for confounding factors.

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References

Boers, D., Portengen, L., Turner, W. E., Bueno-de-Mesquita, H. B., Heederik, D., & Vermeulen, R. (2012). Plasma dioxin levels and cause-specific mortality in an occupational cohort of workers exposed to chlorophenoxy herbicides, chlorophenols and contaminants. *Occupational and Environmental Medicine*, *69*(2), 113–118. https://doi.org/10.1136/oem.2010.060426

Charles, L. E., Burchfiel, C. M., Fekedulegn, D., Gu, J. K., Petrovitch, H., Sanderson, W. T., Masaki, K., Rodriguez, B. L., Andrew, M. E., & Ross, G. W. (2010). Occupational exposure to pesticides, metals, and solvents: The impact on mortality rates in the Honolulu Heart Program. *Work*, *37*(2), 205–215. https://doi.org/10.3233/WOR-2010-1071

Chen, Y., Wu, F., Graziano, J. H., Parvez, F., Liu, M., Paul, R. R., Shaheen, I., Sarwar, G., Ahmed, A., Islam, T., Slavkovich, V., Rundek, T., Demmer, R. T., Desvarieux, M., & Ahsan, H. (2013). Arsenic exposure from drinking water, arsenic methylation capacity, and carotid intima-media thickness in Bangladesh. *American Journal of Epidemiology*, *178*(3), 372–381. https://doi.org/10.1093/aje/kwt001

Consonni, D., Pastori, A. C., Zocchetti, C., Sindaco, R., Cavalieri, L. D., Rubagotti, M., & Bertazzi, P. A. (2008). Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-Up. *American Journal of Epidemiology*, *167*(7), 847–858. https://doi.org/10.1093/aje/kwm371

Crofton, K. M. (2008). Thyroid disrupting chemicals: Mechanisms and mixtures. *International Journal of Andrology*, *31*(2), 209–223. https://doi.org/10.1111/j.1365-2605.2007.00857.x

Curl, C. L., Beresford, S. A. A., Fenske, R. A., Fitzpatrick, A. L., Lu, C., Nettleton, J. A., & Kaufman, J. D. (2015). Estimating pesticide exposure from dietary intake and organic food choices: The multi-ethnic study of atherosclerosis (MESA). *Environment Health Perspect*, *123*(5), 475–483. https://doi.org/10.1289/ehp.1408197

Cypel, Y., & Kang, H. (2010). Mortality patterns of army chemical corps veterans who were occupationally exposed to herbicides in Vietnam. *Annals of Epidemiology*, *20*(5), 339–346. https://doi.org/10.1016/j.annepidem.2010.02.003

Dayton, S. B., Sandler, D. P., Blair, A., Alavanja, M., Beane Freeman, L. E., & Hoppin, J. A. (2010). Pesticide use and myocardial infarction incidence among farm women in the agricultural health study. *Journal of Occupational and Environmental Medicine*, *52*(7), 693–697. https://doi.org/10.1097/JOM.0b013e3181e66d25

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health*, *52*(6), 377–384. https://doi.org/10.1136/jech.52.6.377

Eddleston, M., Buckley, N. A., Eyer, P., & Dawson, A. H. (2008). Management of acute organophosphorus pesticide poisoning. *The Lancet*, *371*, 597–607. https://doi.org/10.1016/S0140-6736(07)61202-1

Georgiadis, N., Tsarouhas, K., Tsitsimpikou, C., Vardavas, A., Rezaee, R., Germanakis, I., Tsatsakis, A., Stagos, D., & Kouretas, D. (2018). Pesticides and cardiotoxicity. Where do we stand? *Toxicology and Applied Pharmacology*, *353*, 1–14. https://doi.org/10.1016/j.taap.2018.06.004

Guyton, K. Z., Loomis, D., Grosse, Y., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Scoccianti, C., Matoock, H., & Straif, K. (2015). Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. *The Lancet Oncology*, *16*(5), 490–491. https://doi.org/10.1016/S1470-2045(15)70134-8

Hardell, S., Tilander, H., Welfinger-Smith, G., Burger, J., & Carpenter, D. O. (2010). Levels of polychlorinated biphenyls (PCBs) and three organochlorine pesticides in fish from the Aleutian Islands of Alaska. *PLoS One*, *5*(8), e12396. https://doi.org/10.1371/journal.pone.0012396

Hay, E., Derazon, H., Eisenberg, Y., & Natalia, B. (2000). Suicide by ingestion of a CCA wood preservative. *Journal of Emergence Medicine*, *19*(2), 159–163. https://doi.org/10.1016/s07364679(00)00202-x

Henriquez-Hernandez, L. A., Luzardo, O. P., Zumbado, M., Camacho, M., Serra-Majem, L., Alvarez-Leon, E. E., & Boada, L. D. (2014). Blood pressure in relation to contamination by polychlorobiphenyls and organochlorine pesticides: Results from a population-based study in the Canary Islands (Spain). *Environmental Research*, *135*, 48–54. https://doi.org/10.1016/j.envres.2014.05.036

Hooiveld, M., Heederik, D. J., Kogevinas, M., Boffetta, P., Needham, L. L., Patterson, D. G., & Mesquita, H. B. B. (1998). Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. *American Journal of Epidemiology*, *147*(9), 891–901. https://doi.org/10.1093/oxfordjournals.aje.a009543. http://aje.oxfordjournals.org/.

Hung, D. Z., Yang, H. J., Li, Y. F., Lin, C. L., Chang, S. Y., Sung, F. C., & Tai, S. C. (2015). The long-term effects of Organophosphates poisoning as a risk Factor of CVDs: A nationwide population-based cohort study. *PloS One*, *10*(9), e0137632. https://doi.org/10.1371/journal.pone.0137632

Jackson, E., Shoemaker, R., Larian, L., & Cassis, L. (2018). Adipose tissue as a site of toxin accumulation. *Comprehensive Physiology*, *7*(4), 1085–1135. https://doi.org/10.1002/cphy.c160038

Jagels, R. (1985). Health hazards of natural and introduced chemical components of boatbuilding woods. *American Journal of Industrial Medicine*, *8*(3), 241–251. https://doi.org/10.1002/ajim.4700080309

Jayaraj, R., Megha, P., & Sreedev, P. (2016). Organochlorine pesticides, their toxic effects on living organisms and their fate in the environment. *Interdisciplinary Toxicology*, *9*(3–4), 90–100. https://doi.org/10.1515/intox-2016-0012

Jayasumana, C., Gunatilake, S., & Siribaddana, S. (2015). Simultaneous exposure to multiple heavy metals and glyphosate may contribute to Sri Lankan agricultural nephropathy. *BMC Nephrology*, *16*(103), 1–8. https://doi.org/10.1186/s12882-015-0109-2

Jayasumana, C., Paranagama, P., Agampodi, S., Wijewardane, C., Gunatilake, S., & Siribaddana, S. (2015). Drinking well water and occupational exposure to herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka. *Environmental Health: A Global Access Science Source*, *14*, 6. https://doi.org/10.1186/1476-069X-14-6. http://www.ehjournal.net/content/14/1/6.

Jones, M. R., Tellez-Plaza, M., Sharrett, A. R., Guallar, E., & Navas-Acien, A. (2011). Urine arsenic and hypertension in US adults: The 2003–2008 National Health and Nutrition Examination Survey. *Epidemiology*, *22*(2), 153–161. https://doi.org/10.1097/EDE.0b013e318207fdf2

Kang, H. K., Dalager, N. A., Needham, L. L., Patterson, D. G., Lees, P. S., Yates, K., & Matannoski, G. M. (2006). Health status of Army Chemical Corps Vietnam veterans who sprayed defoliant in Vietnam. *American Journal of Industrial Medicine*, *49*(11), 875–884. https://doi.org/10.1002/ajim.20385

Kim, S. A., Kim, K.-S., Lee, Y.-M., Jacobs, D. R., & Lee, D.-H. (2015). Associations of organochlorine pesticides and polychlorinated biphenyls with total, cardiovascular, and cancer mortality in elders with differing fat mass. *Environmental Research*, *138*, 1–7. https://doi.org/10.1016/j.envres.2015.01.021

Kurppa, K., Hietanen, E., Klockars, M., Partinen, M., Rantanen, J., Rönnemaa, T., & Viikari, J. (1984). Chemical exposures at work and cardiovascular morbidity. Atherosclerosis, ischemic heart disease, hypertension, cardiomyopathy and arrhythmias. *Scandinavian Journal of Work, Environment & Health*, *10*(6), 381–388. https://doi.org/10.5271/sjweh.2316

Lebov, J. F., Engel, L. S., Richardson, D., Hogan, S. L., Hoppin, J. A., & Sandler, D. P. (2016). Pesticide use and risk of end-stage renal disease among licensed pesticide applicators in the agricultural health study. *Occupational and Environmental Medicine*, *73*(1), 3–12. https://doi.org/10.1136/oemed-2014-102615

Lebov, J. F., Engel, L. S., Richardson, D., Hogan, S. L., Sandler, D. P., & Hoppin, J. A. (2015). Pesticide exposure and end-stage renal disease risk among wives of pesticide applicators in the agricultural health study. *Environmental Research*, *143*(Pt A), 198–210. https://doi.org/10.1136/oemed-2014-102615

Ljunggren, S. A., Helmfrid, I., Salihovic, S., Bavel, B., Wingren, G., Lindahl, M., & Karlsson, H. (2014). Persistent organic pollutants distribution in lipoprotein fractions in relation to cardiovascular disease and cancer. *Environment International*, *65*, 93–99. https://doi.org/10.1016/j.envint.2013.12.017

Mills, K. T., Blair, A., Freeman, L. E., Sandler, D. P., & Hoppin, J. A. (2009). Pesticides and myocardial infarction incidence and mortality among male pesticide applicators in the agricultural health study. *American Journal of Epidemiology*, *170*(7), 892–900. https://doi.org/10.1093/aje/kwp214

Min, J. Y., Cho, J. S., Lee, K. J., Park, J. B., Park, S. G., Kim, J. Y., & Min, K. B. (2011). Potential role for organochlorine pesticides in the prevalence of peripheral arterial diseases in obese persons: Results from the National Health and Nutrition Examination Survey 1999–2004. *Atherosclerosis*, *218*(1), 200–206. https://doi.org/10.1016/j.atherosclerosis.2011.04.044

Moher, D. L. A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed1000097

Montgomery, M. P., Kamel, F., Saldana, M. T., Alavanja, M. C. R., & Sandler, D. P. (2008). Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural health study, 1993–2003. *American Journal of Epidemiology*, *167*(10), 1235–1246. https://doi.org/10.1093/aje/kwn028

Palma, D. A. C., Lourencetti, C., Uecker, M. E., Mello, P. R. B., Pignatia, W. A., & Dores, E. F. G. C. (2014). Simultaneous determination of different classes of pesticides in breast milk by solid-phase dispersion and GC/ECD. *Journal of Brazilian Chemuical Society*, *25*(8), 1419–1430. https://doi.org/10.5935/0103-5053.20140124

Patel, C. J., Cullen, M. R., Ioannidis, J. P., & Butte, A. J. (2012). Systematic evaluation of environmental factors: Persistent pollutants and nutrients correlated with serum lipid levels. *International Journal of Epidemiology*, *41*(3), 828–843. https://doi.org/10.1093/ije/dys003

Piccoli, C., Cremonese, C., Koifman, R. J., Koifman, S., & Freire, C. (2016). Pesticide exposure and thyroid function in an agricultural population in Brazil. *Environmental Research*, *151*, 389–398. https://doi.org/10.1016/j.envres.2016.08.011

Razavi, B. M., Hosseinzadeh, H., Imenshahidi, M., Malekian, M., Ramezani, M., & Abnous, K. (2015). Evaluation of protein Ubiquitylation in heart tissue of rats exposed to Diazinon (an organophosphate insecticide) and Crocin (an active saffron ingredient): Role of HIF1 alpha. *Drug Research*, *65*, 561–566. https://doi.org/10.1055/s-0034-1384533

Saldana, T. M., Basso, O., Baird, D. D., Hoppin, J. A., Weinberg, C. R., Blair, A., Alavanja, M. C. R., & Snadler, D. P. (2009). Pesticide exposure and hypertensive disorders during pregnancy. *Environmental Health Perspectives*, *117*(9), 1393–1396. https://doi.org/10.1289/ehp.0900672

Samsuddin, N., Rampal, K. G., Ismail, N. H., Abdullah, N. Z., & Nasreen, H. E. (2016). Pesticides exposure and cardiovascular hemodynamic parameters among male workers involved in mosquito control in East Coast of Malaysia. *American Journal of Hypertension*, *29*(2), 226–233. https://doi.org/10.1093/ajh/hpv093

Saunders, L., Kadhel, P., Costet, N., Rouget, F., Monfort, C., Thome, J. P., Guldner, L., Cordier, S., & Multigner, L. (2014). Hypertensive disorders of pregnancy and gestational diabetes mellitus among French Caribbean women chronically exposed to chlordecone. *Environment International*, *68*, 171–176. https://doi.org/10.1016/j.envint.2014.03.024

Schreinemachers, D. M. (2006). Mortality from ischemic heart disease and diabetes mellitus (type 2) in four U.S. Wheat-producing states: A hypothesis-generating study. *Environmental Health Perspectives*, *114*(2), 186–193. https://doi.org/10.1186/1476-069X-9-11

Sekhotha, M. M., Monyeki, K. D., & Sibuyi, M. E. (2016). Exposure to agrochemicals and cardiovascular disease: A review. *International Journal of Environmental Research and Public Health*, *13*(2), 229, 1–12. https://doi.org/10.3390/ijerph13020229

Sergeev, A. V., & Carpenter, D. O. (2005). Hospitalization rates for coronary heart disease in relation to residence near areas contaminated with persistent organic pollutants and other pollutants. *Environmental Health Perspectives*, *113*(6), 756–761. https://doi.org/10.1289/ehp.7595

Shiue, I. (2014). Higher urinary heavy metal, phthalate, and arsenic but not parabens concentrations in people with high blood pressure, U.S. NHANES, 2011–2012. *International Journal of Environmental Research and Public Health*, *11*(6), 5989–5999. https://doi.org/10.3390/ijerph110605989

Slade, L., Cowie, A., Martyniuk, C. J., Kienesberger, P. C., & Pulinilkunnil, T. (2017). Dieldrin augments mTOR signaling and regulates genes associated with cardiovascular disease in the adult zebrafish heart (Danio rerio). *Journal of Pharmacology and Experimental Therapeutics*, *361*(3), 375–385. https://doi.org/10.1124/jpet.116.239806

Teixeira, D., Pestana, D., Santos, C., Correia-Sá, L., Marques, C., Norberto, S., Meireles, M., Faria, A., Silva, R., Faria, G., Sá, C., Freitas, P., Taveira-Gomes, A., Domingues, V., Delerue-Matos, C., Calhau, C., & Monteiro, R. (2015). Inflammatory and cardiometabolic risk on obesity: Role of environmental xenoestrogens. *The Journal of Clinical Endocrinology & Metabolism*, *100*(5), 1792–1801. https://doi.org/10.1210/jc.2014-4136

Tsou, T.-C., Yeh, S. C., Tsai, E.-M., Tsai, F.-Y., Chao, H.-R., & Chang, L. W. (2005). Arsenite enhances tumor necrosis factor-alpha-induced expression of vascular cell adhesion molecule-1. *Toxicology and Applied Pharmacology*, *209*(1), 10–18. https://doi.org/10.1016/j.taap.2005.03.006

Turyk, M., Anderson, H., Knobeloch, L., Imm, P., & Persky, V. (2009). Organochlorine exposure and incidence of diabetes in a cohort of great lakes sport fish consumers. *Environmental Health Perspectives*, *117*(7), 1076–1082. https://doi.org/10.1289/ehp.0800281

Valera, B., Ayotte, P., Poirier, P., & Dewailly, E. (2013). Associations between plasma persistent organic pollutant levels and blood pressure in Inuit adults from Nunavik. *Environment International*, *59*, 282–289. https://doi.org/10.1016/j.envint.2013.06.019

Valera, B., Jorgensen, M. E., Jeppesen, C., & Bjerregaard, P. (2013). Exposure to persistent organic pollutants and risk of hypertension among Inuit from Greenland. *Environmental Research*, *122*, 65–73. https://doi.org/10.1016/j.envres.2012.12.006

Vena, J., Boffetta, P., Becher, H., Benn, T., Bueno-de-Mesquita, H. B., Coggon, D., Colin, D., Flesch-Janys, D., Green, L., Kauppinen, T., Littorin, M., Lynge, E., Mathews, J. D., Neuberger, M., Pearce, N., Pesatori, A. C., Saracci, R., Steenland, K., & Kogevinas, M. (1998). Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. *Environmental Health Perspectives*, *106*(Suppl 2), 645–653. https://doi.org/10.1289/ehp.98106645

Waggoner, J. K., Kullman, G. J., Henneberger, P. K., Umbach, D. M., Blair, A., Alavanja, M. C., Kamel, F., Lynch, C. F., Knott, C., London, S. J., Hines, C. J., Thomas, K. W., Sandler, D. P., Lubin, J. H., Beane Freeman, L. E., & Hoppin, J. A. (2011). Mortality in the agricultural health study, 1993–2007. *American Journal of Epidemiology*, *173*(1), 71–83. https://doi.org/10.1093/aje/kwq323

Wahab, A., Hod, R., Ismail, N. H., & Omar, N. (2016). The effect of pesticide exposure on cardiovascular system: A systematic review. *International Journal of Community Medicine and Public Health*, *3*(1), 1–10. https://doi.org/10.18203/2394-6040.ijcmph20151542

World Health Organization. (2014). *Global status report on non communicable diseases, a report about health*. Retrieved November 28, 2016, from http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf

Yi, S. W., Ohrr, H., Hong, J. S., & Yi, J. J. (2013). Agent Orange exposure and prevalence of self-reported diseases in Korean Vietnam veterans. *Journal of Preventive Medicine and Public Health-Yebang Uihakhoe chi*, *46*(5), 213–225. https://doi.org/10.3961/jpmph.2013.46.5.213

Yi, S. W., Ryu, S. Y., Ohrr, H., & Hong, J. S. (2014). Agent Orange exposure and risk of death in Korean Vietnam veterans: Korean Veterans Health Study. *International Journal of Epidemiology*, *43*(6), 1825–1834. https://doi.org/10.1093/ije/dyu183