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REVIEW ARTICLE

Pesticides: an update of human exposure and toxicity

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Abstract Pesticides are a family of compounds which have brought many benefits to mankind in the agricultural, industrial, and health areas, but their toxicities in both humans and animals have always been a concern. Regardless of acute poisonings which are common for some classes of pesticides like organophosphoruses, the association of chronic and sub-lethal exposure to pesticides with a prevalence of some persistent diseases is going to be a phenomenon to which global attention has been attracted. In this review, incidence of various malignant, neurodegenerative, respiratory, reproductive, developmental, and metabolic diseases in relation to different routes of human exposure to pesticides such as occupational, environmental, residential, parental, maternal, and paternal has been systematically criticized in different categories of pesticide toxicities like carcinogenicity, neurotoxicity, pulmonotoxicity, reproductive toxicity, developmental toxicity, and metabolic toxicity. A huge body of evidence exists on the possible role of pesticide exposures in the elevated incidence of human diseases such as cancers, Alzheimer, Parkinson, amyotrophic lateral sclerosis, asthma, bronchitis, infertility, birth defects, attention deficit hyperactivity disorder, autism, diabetes, and obesity. Most of the disorders are induced by insecticides and herbicides most notably organophosphorus, organochlorines, phenoxyacetic acids, and triazine compounds.

Keywords Pesticide · Toxicity · Chronic disease · Review

Introduction

Pesticides are a large and heterogeneous group of chemicals which have long been used to control and repel pests in different fields. Controlling pests have always been a concern for human life. The literature shows that natural and inorganic chemicals were sporadically used for this purpose, but development of new and potent organic chemical targets has brought pesticides into widespread use during the past century. Human has benefited pesticides in different fields like producing and keeping more and safe agricultural products, repelling home pests, and controlling infectious diseases among which malaria eradication program was a remarkable feature of insecticides' use. Human exposure to pesticides can occur through different routes, including occupations dealing with production, transport, delivery and application of pesticides, residing in the places high in pesticide residue, and circulation and accumulation of pesticides in the food chain. Since pesticides were born as chemicals to be toxic for living organisms, their toxicity for human and the other animal species is inevitable. This issue becomes further apparent in the huge and growing body of epidemiological and experimental evidence on the link between exposure to pesticides and the incidence of

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various health disorders in human beings. Incidence of different human diseases like malignant, neurodegenerative, reproductive, developmental, respiratory, and metabolic diseases in association with exposure to pesticides has frequently become the research topic of numerous studies (Mostafalou and Abdollahi 2012a).

In the previous study, the relation between exposure to pesticides and incidence of different types of human chronic diseases was studied via a systematic review of epidemiological evidence and exploring the involved mechanisms. The results revealed that the largest share was accounted for incidence of cancers and then neurodegenerative, reproductive, and developmental disorders in association with exposure to pesticides (Mostafalou and Abdollahi 2013).

In the current work, diverse toxicities of pesticides within the context of known and prevalent human chronic diseases are updated via a systematic review.

Methodology

Article search

We performed a PubMed search of the literature on the association between pesticide exposure and human diseases. We restricted our search to articles published since 1980. The search used a combination of the following words: pesticides, cancer, bladder cancer, bone tumors, brain tumors, breast cancer, cervical cancer, colorectal cancer, eye cancer, gallbladder cancer, kidney cancer, laryngeal cancer, leukemia, lip cancer, liver cancer, lung cancer, lymphoma, melanoma, mouth cancer, multiple myeloma, neuroblastoma, esophageal cancer, ovarian cancer, pancreatic cancer, soft tissue sarcoma, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, Alzheimer, Parkinson, amyotrophic lateral sclerosis (ALS), asthma, chronic bronchitis, birth defects, infertility, attention deficit hyperactivity disorder (ADHD), autism, developmental delay, diabetes, obesity, and humans. Details of the search are given in Fig. 1.

Article criteria

In order to identify eligible articles, the titles and abstracts and, if needed, the full text of the papers were reviewed. The following characteristics were considered as inclusion criteria for recording articles:

1. Written and published in English
2. Type of study as cross-sectional, case–control, cohort, ecological, and/or meta-analyses
3. Exposure assessment tool as interviews, questionnaires, geographic information system (GIS), job expo-

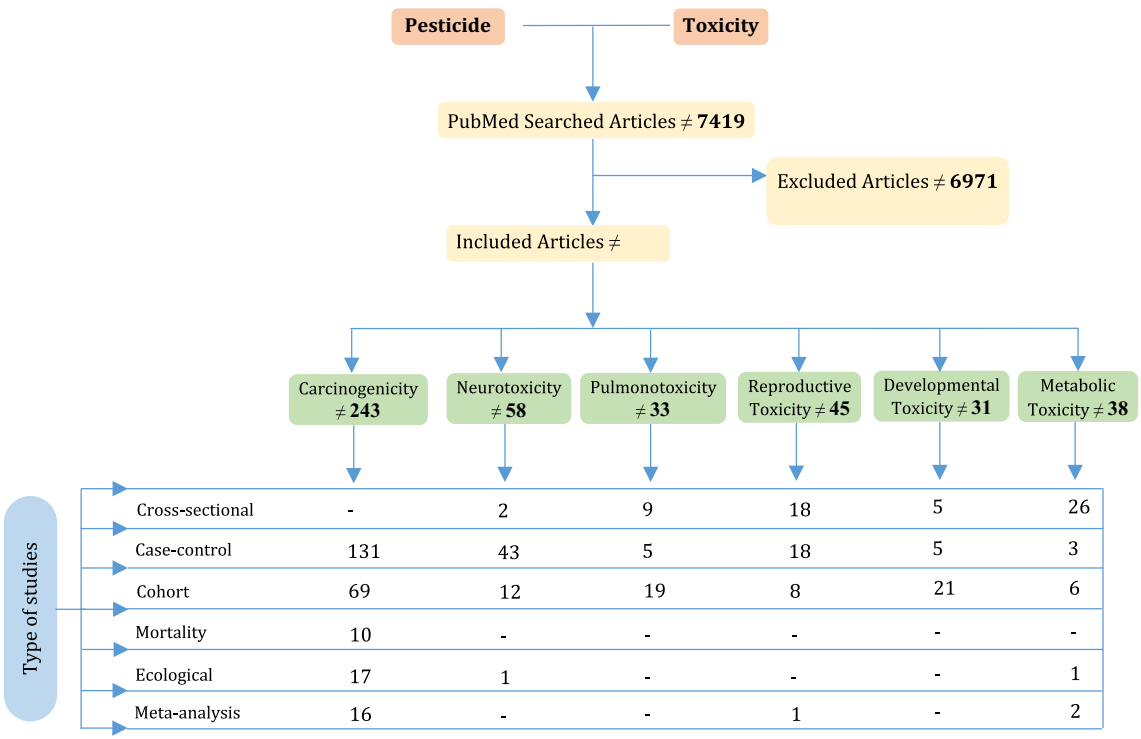

Fig. 1 Flow chart and category of the articles included and excluded in the systematic review

sure matrix (JEM), and/or residue detection in biological samples
4. Reported association of chronic diseases with pesticide exposures

Data extraction

The following information was extracted from eligible papers and presented in the classified tables:

1. Authors
2. Publication date
3. Type of study
4. Number of samples in each study
5. Exposure assessment tool
6. Type of exposure
7. Type of specific pesticide if reported
8. Type of specific disease in each category of toxicity
9. Quantitative risk estimate as the odd ratio (OR), hazard ratio (HR), relative risk or risk ratio (RR), proportional mortality ratio (PMR), standardized mortality ratio (SMR), mortality rate ratio (MRR), and standardized incidence ratio (SIR)
10. Confidence interval for reported risk estimates
11. Significance of the risk as *p* value if reported

Results

The PubMed searches yielded a total of 7419 unique articles. The number of records for each category of toxicity in combination with pesticides was as follows; carcinogenicity 3410, neurotoxicity 1342, pulmonotoxicity 512, reproductive toxicity 833, developmental toxicity 124, metabolic toxicity 1198. After screening the titles, abstracts, and full text of the papers, the irrelevant ones were excluded and the number of remaining articles for reviewing in each category became as follows: carcinogenicity 246, neurotoxicity 58, pulmonotoxicity 33, reproductive toxicity 46, developmental toxicity 31, and metabolic toxicity 38 (Fig. 1).

Disease-based evidence on carcinogenicity of pesticides

The World Health Organization (WHO) defines cancer as a generic term for a large group of neoplastic diseases affecting each part of the body. Cancer is the leading cause of mortality worldwide with almost 8.2 million cancer-related deaths in 2012. In the same year, new cases of cancer were estimated 14 million, which is expected to increase by 70 % over the next two decades. The most common cancer-related deaths are due to lung, liver, stomach, colorectal, breast, and esophageal cancer. Cancer is the result of genetics–environmental interactions, which can be relatively induced under the effect of biological, physical, and chemical exposures (WHO 2015). The association of exposure to different classes of pesticides, including insecticides, herbicides, and fungicides with incidence of cancers has been highlighted during the past half century. Different types of surveys have targeted the link of pesticides with cancers and reported various risk estimates. The number of reports evidencing a positive association between exposure to pesticides and cancer incidence is considerable, and the relevant ones resulted from population-based human studies have been reviewed and classified according to the site of cancer (Table 1).

Tumors of the nervous system

Brain tumors In general, studies concerning the environmental risk factors of brain tumors are separately conducted in children and adults. The link of childhood brain tumors (CBT) with pesticides is mostly studied in the form of parental, maternal, or paternal exposures. Results of a prospective cohort study of cancer in the offspring of agricultural censuses in Norway showed that parental exposure to pesticides is associated with three times higher incidence of CBT especially in children aged under 14 years (Kristensen et al. 1996). The other case–control studies assessing exposure to different classes of pesticides via organized questionnaire-based interviews indicated that incidence of CBT was increased up to 1.3–2 times in children parentally exposed to pesticides (Efird et al. 2003; Greenop et al. 2013; Pogoda and Preston-Martin 1997; Rosso et al. 2008; Shim et al. 2009; van Wijngaarden et al. 2003). Searles Nielsen and colleagues' studies on the role of genetic polymorphisms of *PON1* and *FMO1* in the link between pesticides and CBT implicated that prenatal and postnatal exposures to organophosphorus compounds and perhaps carbamates in people with reduced ability to detoxification were associated with a higher incidence of CBT (Searles Nielsen et al. 2005, 2010). However, there are other studies whose results have been meta-analyzed in some systematic reviews. A meta-analysis of 40 studies found an incidence risk of about times for CBT in children paternally exposed to pesticides (Vinson et al. 2011). In this regard, there is another study, which meta-analyzed the results of 15 studies on the association of CBT with paternal, maternal, and childhood exposures to pesticides and the highest risk estimate of CBT was reported for children whose fathers were exposed to pesticides before conception (Kunkle et al. 2014).

The link of adult brain tumors (ABT) with pesticides has been mostly studied in the populations occupationally dealing with pesticides. Since the disease has a high intrinsic severity, some researchers have reported high mortality ratio as of 200 and 270 due to brain tumors in licensed pesticide users (Blair et al. 1983; Figa-Talamanca et al.

Table 1 Carcinogenicity of pesticides evidenced by diseases

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Childhood brain tumors							
Greenop (2013)	CC	374/1467	Questionnaire	Par.	Home pest control	1.90 (1.08–3.36)	
					Pat. occupation	1.36 (0.66, 2.80)	
Searles Nielsen (2010)	CC	201/285	Interview	Res.	OPs + *PON1* polymorph OPs + *FMO1* polymorph	1.8 (1.1–3.0) 2.7 (1.2–5.9)	
Shim (2009)	CC	526/526	Interview	Par.	Herbicides	1.8 (1.1–3.1)	
Rosso (2008)	CC	318/318	Interview	Par.	During pregnancy After birth	1.6 (1.0, 2.5) 1.8 (1.2, 2.8)	
Searles Nielsen (2005)	CC	66/236	Interview	Par.	+*PON1* polymorph	2.6 (1.2–5.5)	
van Wijngaarden (2003)	CC	322/321	Interview	Pat.	Insecticides Herbicides Fungicides	1.5 (0.9, 2.4) 1.6 (1.0, 2.7) 1.6 (1.0, 2.6)	
Efird (2003)	CC	1218/2223	Interview	Mat.	Pesticide	2	
Pogoda and Preston-Martin (1997)	CC	224/218	Interview	Mat.	Flea/tick pesticides	1.7 (1.1–2.6)	
Kristensen (1996)	Co	323292	Census	Par.	–	3.37 (1.63–6.94)	
Vinson (2011)	MA	40 studies	Before birth	Pat.	–	1.49 (1.23–1.79)	
			After birth	Pat.	–	1.66 (1.11–2.49)	
Kunkle (2014)	MA 15 studies	3 5	Preconception	Pat.	–	2.29 (1.39–3.78)	
			In pregnancy	Pat.	–	1.63 (1.16–2.31)	
		5 7	Agricultural	Mat.	–	1.48 (1.18–1.84)	
			Non-agricultural	Mat.	–	1.36 (1.10–1.68)	
		4 5	Agricultural	Childhood	–	1.35 (1.08–1.70)	
			Non-agricultural	Childhood	–	1.32 (1.04–1.67)	
Adult brain tumors							
Samanic (2008)	CC	657/765	Interview	Occup.	Herbicides (in women)	2.4 (1.4, 4.3)	0.01
Provost (2007)	CC	221/442	Interview-JEM	Occup.	–	2.16 (1.10–4.23)	
Lee (2005)	CC	251/498	Interview	Occup.	Metribuzin Paraquat Bufencarb Chlorpyrifos Coumaphos	3.4 (1.2–9.7) 11.1 (1.2–101) 18.9 (1.9–187) 22.6 (2.7–191) 5.9 (1.1–32)	
Viel (1998)	Ec	89 units	GIS	Occup.	Vineyard pesticides	1.10 (1.03–1.18)	
Rodvall (1996)	CC	192/192	Questionnaire	Occup.	In men	1.8 (0.6–5.1)	
Figa-Talamanca (1993)	Mr	2310	Licensed users	Occup.	In men	SMR: 270 (108.6–556.9)	
Musicco (1988)	CC	240/742	Interview	Occup.	Insecticides, fungicides	2.0	0.006
Blair (1983)	Mr	3827	Licensed users	Occup.	In men	SMR: 200	
Neuroblastoma							
Carozza (2008)	Ec	1078 counties	GIS	Res.	–	1.8 (1.5–2.1)	
Giordano (2006)	Co	168	Applicators	Occup.	–	SMR; 529.2 (144–1368)	
Daniels (2001)	CC	538/538	Interview	Res.	Home used Garden used	1.6 (1.0–2.3) 1.7 (0.9–2.1)	
Feychting (2001)	Co	235635	Census	Pat.	–	2.36 (1.27–4.39)	

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Littorin (1993)	Co	2370	Applicators	Occup.	Insecticides, fungicides	SMR; 2.9 (1.1, 6.2)	
Kristensen (1996)	Co	323292	Census	Par.	–	2.38 (1.03–6.13)	
Esophageal cancer							
Meyer (2011)	CC	5782/5782	Workers	Occup.	–	1.38 (1.26–1.51)	
de Rezende Chrisman (2009)	Ec	11 states	Pesticide sales	Res., Occup.	–	MRR; 2.40 (2.34–2.45)	0.046
Jansson (2006)	CC	356/820	Airborne level	Occup.	–	2.3 (0.9 to 5.7)	
Stomach cancer							
Barry (2012)	Co	53588	Questionnaire	Occup.	Methyl bromide	3.13 (1.25–7.80)	0.02
Mills and Yang (2007)	Nested CC	100/210	Questionnaire	Occup.	2,4-D Chlordane Trifluralin herbicide	1.85 (1.05–3.25) 2.96 (1.48–5.94) 1.69 (0.99–2.89)	
Van Leeuwen (1999)	Ec	40 states	Drinking water	Env.	Atrazine	1.45 (1.20–1.70)	<0.05
Forastiere (1993)	CC	1674/480	Questionnaire	Occup.	–	1.77 (0.75–4.25)	
Colorectal cancer							
Lerro (2015b)	Co	33,484	Interview	Occup.	Acetochlor	1.75 (1.08–2.83)	
Salerno (2014)	Ec	Vercelli	GIS	Gen.	–	2.38 (1,76–2,87)	
Lo (2010)	CC	421/439	Interview	Occup.	Pesticides Insecticides Herbicides	2.6 (1.1–5.9) 3.2 (1.5–6.5) 5.5 (2.4–12.3)	
				Dietary	–	4.6 (1.5–14.6)	
Koutros (2009)	Co	57311	Questionnaire	Occup.	Imazethapyr	2.73 (1.42–5.25)	0.001
Kang (2008)	Co	50127	Questionnaire	Occup.	Trifluralin	1.76 (1.05–2.95)	
van Bemmel (2008)	Co	48378	Questionnaire	Occup.	EPTC	2.09 (1.26–3.47)	<0.01
Lee (2007b)	Co	56813	Questionnaire	Occup.	Chlorpyrifos Aldicarb	2.7 (1.2–6.4) 4.1 (1.3–12.8)	0.008 0.001
Samanic (2006)	Co	41969	Questionnaire	Occup.	Dicamba	3.29 (1.40–7.73)	0.02
Zhong and Rafnsson (1996)	Co	2449	Questionnaire	Occup.	–	2.94 (1.07–6.40)	
Forastiere (1993)	CC	1674/480	Questionnaire	Occup.	–	2.82 (0.75–9.32)	
Liver cancer							
VoPham (2015)	CC	3034/14991	GIS	Gen.	OCs	2.76 (1.58–4.82)	0.0004
de Rezende Chrisman (2009)	Ec	11 states	Pesticide sales	Res., Occup.	–	MRR; 1.49 (1.44–1.54)	
Carozza (2008)	Ec	1078 counties	GIS	Res.	–	3.3 (2.1–5.0)	
Giordano (2006)	Co	168	Applicators	Occup.	–	SMR; 596.3 (204–1365)	
Gallbladder cancer							
Shukla (2001)	CC	30/30	Biliary level	–	HCB DDT	↑ level in cases ↑ level in cases	<0.04 <0.03
Giordano (2006)	Co	168	Applicators	Occup.	–	SMR; 723.8 (129–2279)	
Pancreatic cancer							
Lerro (2015b)	Co	33484	Interview	Occup.	Acetochlor	2.36 (0.98–5.65)	
Antwi (2015)	CC	2092/2353	Questionnaire	Gen.	–	1.21 (1.02–1.44)	
Andreotti (2009)	CC	93/82503	Questionnaire	Occup.	Pendimethalin EPTC herbicide	3.0 (1.3–7.2) 2.56 (1.1–5.4)	0.01 0.01
de Rezende Chrisman (2009)	Ec	11 states	Pesticide sales	Res., Occup.	–	MRR; 2.32 (2.23–2.40)	0.040
Lo (2007)	CC	194/194	Interview	Gen.		2.6 (0.97–7.2)	

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Ji (2001)	CC	484/2095	JEM	Occup.	Pesticides Fungicides Herbicides	1.4 (1.0–2.0) 1.5 (0.3–7.6) 1.6 (0.7–3.4)	0.01
Alguacil (2000)	CC	164/238	JEM	Occup.	Arsenical pesticides Other pesticides	3.4 (0.9–12.0) 3.17 (1.1–9.2)	
Cantor and Silberman (1999)	Mr	9961		Occup.	–	2.71	
Forastiere (1993)	CC	1674/480	Questionnaire	Occup.	–	5.18 (1.55–16.7)	
Alavanja (1990)	Nested CC	22938	Death certificate	Occup.	–	SMR; 133	
Childhood leukemia							
Zhang et al.(2015)	CC	248/111	Urine level	Res.	OPs	1.9 (1.2–3.1)	<0.05
Maryam et al. (2015)	CC	94/94	Interview	Par.	–	4.2 (2.2–7.8)	<0.001
Metayer et al. (2013)	CC	269/333	Dust sample	Res.	Chlorthal	1.57 (0.90–2.73)	0.05
Ding G et al. (2012)	CC	176/180	Urine sample	–	Pyrethroids	2.75 (1.43–5.29)	
Bailey et al. (2011)	CC	388/870	Preconception In pregnancy After birth	Occup.	–	1.19 (0.83–1.69) 1.30 (0.86–1.97) 1.24 (0.93–1.65)	
Soldin et al. (2009)	CC	41/77	Questionnaire	Mat.	Insecticides	↑ risk	0.02
Rull et al. (2009)	CC	213/268	Questionnaire	Res.	Insecticides Herbicides Fungicides	1.5 (0.9–2.4) 1.2 (0.8–1.9) 1.2 (0.7–2.4)	
Carozza (2008)	Ec	1078 counties	GIS	Res.	–	1.2 (1.1–1.3)	
Rudant (2007)	CC	764/1681	Questionnaire	Mat. Pat.	Household use Household use	2.1 (1.7–2.5) 1.5 (1.2–1.8)	
Monge P et al. (2007)	CC	334/579	Interview	Mat.	–	2.2 (1.0–4.8)	
Menegaux et al. (2006)	CC	280/280	Interview	Mat.	–	1.8 (1.2 to 2.8)	
Reynolds et al. (2005)	CC	2189/4335	Questionnaire	Mat.	Metam sodium Dicofol	2.05 (1.01–4.17) 1.83 (1.05–3.22)	
Ma et al. (2002)	CC	162/162	Interview	Mat.	Household use Insecticides	2.8 (1.4–5.7) 2.1 (1.3–3.5)	
Alexander FE et al (2001)	CC	136/266	Questionnaire	Mat.	Baygon/mosquito-cidal	5.14 (1.27–20.85)	0.02
Infante-Rivard et al. (1999)	CC	491/491	Questionnaire	Mat.	Insecticides Herbicides	2.47 (1.43–4.28) 1.84 (1.32–2.57)	
Meinert et al. (1996)	CC	173/175	Questionnaire	Par.	Garden used	2.52 (1.0–6.1)	
Leiss and Savitz (1995)	CC	252/222	Interview	Res.	Household use	1.7 (1.2–2.4)	
Mulder et al. (1994)	CC	14/52	Questionnaire	Res. Pat.	– –	6.0 (0.6–49.3) 3.2 (1.0–10.1)	
Buckley et al (1989)	CC	204/		Pat. job	–	2.7 (1.0–7.0)	0.06
Shu et al. (1988)	CC	309/618		Mat. job	–	3.5 (1.1–11.2)	
Chen (2015)	MA	16 studies		Res.	Indoor pesticides Herbicides	1.47 (1.26–1.72) 1.26 (1.10–1.44)	
Bailey 2014)	MA (13)	8236/14850		Mat.	–	1.01 (0.78–1.30) for ALL 1.94 (1.19–3.18) for AML	
		8169/14201		Pat.	–	1.20 (1.06–1.38) for ALL 0.91 (0.66–1.24) for AML	

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Vinson (2011)	MA	40 CC		Mat.	–	1.48 (1.26–1.75)	
Van Maele-Fabry (2011)	MA	13 CC (1966–2009)		Res., Mat.	–	1.74 (1.37–2.21)	
Turner (2011)	MA	17 CC (1950–2009)		Res.	Pesticides Insecticides Herbicides	1.54 (1.13–2.11) 2.05 (1.80–2.32) 1.61 (1.20–2.16)	
Wigle (2009)	MA	31 CC (1950–2009)		Mat.	Pesticides Insecticides Herbicides	2.09 (1.51–2.88) 2.72 (1.47–5.04) 3.62 (1.28–10.3)	
Adult leukemia							
Baumann Kreuziger (2014)	Co	195	Interview	Occup.	Agent Orange	1.8 (0.7–4.5)	0.24
Bonner (2010)	Co	57310	Questionnaire	Occup.	Terbufos	2.38 (1.35–4.21)	
Miligi (2006)	CC	1925/1232	Questionnaire	Occup.			
Beane Freeman (2005)	Co	23106	Questionnaire	Occup.	Diazinon	3.36 (1.08–10.49)	0.026
Cantor and Silberman (1999)	Mr	9961		Occup.	–	SMR: 3.35	
Ciccone et al. (1993)	CC	67/246	Interview	Occup.	–	4.4 (1.7–11.5)	
Brown (1990)	CC	578/1245	Interview	Occup.	Crotoxyphos Dichlorvos Famphur Pyrethroids Methoxychlor	11.1 (2.2–55.0) 2.0 (1.2–3.5) 2.2 (1.0–5.0) 3.7 (1.3–10.6) 2.2 (1.0–5.0)	
Van Maele-Fabry (2008)	MA	14 studies (1984–2004)		Occup.	–	1.43 (1.05–1.94)	
Van Maele-Fabry (2007)	MA	17 Co (1979–2005)		Occup.	–	1.21 (0.99–1.48)	
Merhi (2007)	MA	13 CC (1990–2005)		–	–	1.35 (0.9–2)	
Hodgkin lymphoma							
Navaranjan (2013)	CC	316/1506	Interview		Insecticides OPs Carcinogen pesticides	1.88 (0.92–3.87) 3.16 (1.02–9.29) 2.47 (1.06–5.75)	
Karunanayake (2012)	CC	316/1506	Interview		Chlorpyrifos	1.19 (1.03–1.37)	
Pahwa (2009)	CC	316/1506	Interview		Dichlorprop	6.35 (1.56–25.92)	
Rudant (2007)	CC	130/1681	questionnaire	Mat.	Household use	4.1 (1.4–11.8)	
Orsi et al. (2007)	CC	824/752	Interview	Occup.	–	2.2 (1.0–4.7)	
van Balen et al. (2006)	CC	591/631	Interview	Occup.	Non-arsenicals	1.8 (1.1 to 2)	
Flower (2004)	Co	17357	Questionnaire	Par.	–	2.56 (1.06–6.14)	
Cerhan (1998)	Mr	88090	Death certificate	Occup.	–	PMR; 1.62 (1.04–2.54)	
Persson (1993)	CC	31/93	Questionnaire	Occup.	Phenoxy herbicides Other pesticides	2.6 (1.4–40) 2.0 (0.05–3.2)	
Non-hodgkin lymphoma							
Nordstrom (1998)	CC	121/484	Interview	Occup.	Insecticides Herbicides Fungicides	2.0 (1.1–3.5) 2.9 (1.4–5.9) 3.8 (1.4–9.9)	
Schinasi (2015)	Co	76493	Questionnaire	Occup.	Insecticides	1.12 (0.95–1.32)	
Coggon (2015)	Co	8036	Questionnaire	Occup.	Phenoxy herbicides	SMR; 1.85 (1.12–2.89)	

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Schinasi and Leon (2014)	MA	44 studies			OPs Carbamates Phenoxy herbicides Lindane	1.6 (1.4–1.9) 1.7 (1.3–2.3) 1.4 (1.2–1.6) 1.6 (1.2–2.2)	
Alavanja (2014)	Co	54,306	Questionnaire	Occup.	Lindane DDT	2.5 (1.4–4.4) 1.7 (1.1–2.6)	0.004 0.02
Balasubramaniam (2013)	CC	390/1383	Interview	Occup.	–	3.1 (1.5–6.2)	<0.01
Karunanayake (2013)	CC	75/321	Questionnaire	Occup.	–	3.08 (1.26–7.53)♂	
Boccolini Pde (2013)	Ec	552 micro-region	GIS	Gen. –	– –	MRR; 2.92 (2.74–3.11)♂ MRR; 3.20 (2.98–3.43)♀	
Bräuner (2012)	Co	57053	Adipose tissue level		DDT cis-nonachlor Oxychlordane	1.35 (1.10–1.66) 1.13 (0.94–1.36) 1.11 (0.89–1.38)	
Pahwa (2012a)	CC	513/1506	Interview	Occup.	Phenoxy herbicide	2.67 (0.90–7.93)	
Viel (2011)	CC	34/34	Serum level	Res.	β-HCH DDT	1.05 (1.00–1.12) 1.20 (1.01–1.45)	
Bonner (2010)	Co	57310	Questionnaire	Occup.	Terbufos	1.94 (1.16–3.22)	
Ruder and Yiin (2011)	Co	2122	Plant workers	Occup.	Pentachlorophenol	SMR; 1.77 (1.03–2.84)	
Eriksson (2008)	CC	910–1016	Questionnaire		Herbicides Phenoxy herbicides Glyphosate Insecticides	1.72 (1.18–2.51) 2.81 (1.27–6.22) 2.26 (1.16–4.40) 1.28 (0.96–1.72)	
Vajdic (2007)	CC	694/694	Questionnaire	Occup.	–	4.23 (1.76–10.16)	
Rudant (2007)	CC	166/1681	Questionnaire	Mat. Pat.	Household use Household use	1.8 (1.3–2.6) 1.7 (1.2–2.6)	
Purdue (2007)	Co	57311	Questionnaire	Occup.	Lindane	2.6 (1.1–6.4)	0.04
Merhi (2007)	MA	13 CC (1990–2005)			–	1.35 (1.2–1.5)	
Chiu (2006)	CC	385/1432	Interview	Gen.	Animal insecticides Crop insecticides Herbicides Fumigants	2.6 (1.0–6.9) 3.0 (1.1–8.2) 2.9 (1.1–7.9) 5.0 (1.7–14.5)	
Miligi (2006)	CC	1925/1232	Questionnaire	Occup.	2,4-D	4.4 (1.1–29.1)	
De Roos (2003)	CC	870/2569	Interview	Gen.	Coumaphos Diazinon Fonofos Chlordane Dieldrin Atrazine Glyphosate	2.4 (1.0–5.8) 1.9 (1.1–3.6) 1.8 (0.9–3.5) 1.5 (0.8–2.6) 1.8 (0.8–3.9) 1.6 (1.1–2.5) 2.1 (1.1–4.0)	
Hardell (2002)	CC	515/1141	Questionnaire		Herbicides Insecticides Fungicides	1.75 (1.26–2.42) 1.43 (1.08–1.87) 3.11 (1.56–6.27)	
Schroeder (2001)	CC	182/	Questionnaire	Occup.	Dieldrin Toxaphene Lindane Atrazine Fungicides	3.7 (1.9–7.0) 3.0 (1.5–6.1) 2.3 (1.3–3.9) 1.7 (1.0–2.8) 1.8 (0.9–3.6)	

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
McDuffie (2001)	CC	517/1506	Interview		Phenoxyherbicides Dicamba Carbamate OPs	1.38 (1.06–1.81) 1.88 (1.32–2.68) 1.92 (1.22–3.04) 1.73 (1.27–2.36)	
Meinert (2000)	CC	234/2588	Interview	Par.	Insecticides	2.6 (1.2–5.7)	0.02
Buckley (2000)	CC	268/268	Interview	Res.	Household use	7.3	0.05
Hardell and Eriksson (1999)	CC	442/884	Interview	Gen.	Herbicides Fungicides	1.6 (1.0–2.5) 3.7 (1.1–13.0)	
Kristensen (1996)	Co	323292	Census	Par.	–	2.47 (1.02–6.15)	
Clavel (1996)	CC	226/425	Interview	Occup.	–	1.7 (1.0–2.6)	
Cantor (1992)	CC	622/1245	Interview	Occup.	Carbaryl Chlordane DDT Diazinon Lindane Malathion	1.7 (0.9–3.1) 1.7 (1.0–2.9) 1.7 (1.2–2.6) 1.5 (0.9–2.5) 2.0 (1.0–3.7) 1.5 (0.8–2.7)	
Zahm (1990)	CC	201/725	Interview	Occup.	2,4-D	1.5 (0.9–2.5)	
Multiple myeloma							
Perrotta (2013)	CC	1959/6192	JEM	Occup.	Garden/nursery use	1.50 (0.9–2.3)	
Kachuri (2013)	CC	342/1357	Questionnaire		Fungicides Probably carcinogenic	1.73 (1.00–3.00) 1.57 (0.96–2.56)	0.04 0.03
Pahwa (2012b)	CC	342/1506	Questionnaire		Carbamate insecticide Captan fungicide Carbaryl	1.90 (1.11–3.27) 2.35 (1.03–5.35) 1.89 (0.98–3.67)	
Perrotta (2012)	CC	277/281	Questionnaire	Occup.	–	1.62 (1.01–2.58)	
Landgren (2009)	Co	57310	Questionnaire	Occup.	Age >50 years	6.8 (5.0–9.3)	
Lope (2008)	Co	2992166	Questionnaire	Occup.	In women	1.29 (0.83–2.00)	
Merhi (2007)	MA	13 CC (1990–2005)	–		–	1.16 (0.99–1.36)	
Cerhan (1998)	Mr	88090	Death certificate	Occup.	–	PMR; 1.17 (0.98–1.40))	
Kristensen (1996)	Co	323292	Census	Par.	–	2.03 (0.51–8.14)	
Bone cancer							
Carozza (2008)	Ec	1078 counties	GIS	Res.	–	2.3 (1.8–2.9)	
Merletti (2006)	CC	96/2632	Interview	Occup.	–	2.33 (1.31–4.13)	
Moore (2005)	CC	196/196	Interview	Par.	–	3.0 (1.1–8.1)	
Holly (1992)	CC	43/193	Interview	Par.	–	6.1 (1.7–21.9)	0.002
Thorpe and Shirmohammadi (2005)	Ec	Maryland	Groundwater	Res.	Metolachlor	2.26 (0.97–5.24)	
Soft tissue sarcoma							
de Rezende Chrisman (2009)	Ec	11 states	Pesticide sales	Res., Occup.	–	MRR; 1.93(1.75–2.12)	0.015
Carozza (2008)	Ec	1078 counties	GIS	Res.	–	1.7 (1.4–2.0)	
Kogevinas (1995)	Nested CC	11/55	Interview	Occup.	Phenoxy herbicides	10.3 (1.2–91)	
Leiss and Savitz (1995)	CC	252/222	Interview	Indoor	Yard treatment	4.1 (1.0–16.0)	
Kidney/renal cancer							
Karami (2008)	CC	1097/1476	Interview	Occup.	–	1.60 (1.00–2.55)	
Carozza (2008)	Ec	1078 counties	GIS	Res.	–	3.3 (1.3–8.3)	
Tsai (2006)	CC	303/575	Interview	Mat.	–	1.41 (0.91–2.20)	Wilms

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Buzio et al. 2003	CC	100/200	Questionnaire	Occup.	+ *GSTM1* polymorph	3.46 (1.12–10.74)	
Buzio (2002)	CC	100/200	Questionnaire	Occup.	–	2.0 (0.8–4.7)	
Hu et al. (2002)	CC	1279/5370	Questionnaire	Occup.	Pesticides Herbicides	4.6 (1.7–12.5) 1.6 (1.3–2.0)	
Fear (1998)	Mr	167703		Pat.	–	PMR; 1.59 (1.18–2.15)	
Kristensen (1996)	Co	323292	Census	Par.	–	8.87 (2.67–29.5)	Wilms
Sharpe (1995)	CC	109/218	Interview	Pat. Mat.	–	3.24 (1.2–9.0) 128.6 (6.4–2,569)	Wilms Wilms
Mellemgaard (1994)	CC	365/396	Interview	Occup.	Insecticides/herbicides	2.2 (0.8–6.3)♂ 5.7 (0.6–58)♀	
Olshan (1993)	CC	200/233	Interview	Mat.	Household pesticide	2.16 (1.24–3.75)	
Forastiere (1993)	CC	1674/480	Questionnaire	Occup.	Olive crop used	3.16 (1.0–12.1)	<0.1
Bladder cancer							
Koutros (2015)	Co	57 310	Questionnaire	Occup.	Imazaquin herbicide Imazethapyr herbicide	1.54 (1.05–2.26) 3.03 (1.46–6.29)	0.005
Amr (2015)	CC	953/881		Occup.	–	1.68 (1.23–2.29)	
Matic (2014)	CC	143/114		Occup.	+ *GSTT1* polymorphism	4.5 (0.9–22.5)	
Sharma (2013)	CC	50/50	Blood level		Total-HCH, DDT	↑ risk	<0.05
Koutros (2009)	Co	57311	Questionnaire	Occup.	Imazethapyr herbicide	2.37 (1.20–4.68)	0.01
Prostate cancer							
Koutros (2013a, b)	CC	776/1444	Interview	Occup.	Malathion + *EHBP1*-SNP Aldrin +*TET2*-SNP	3.43 (1.44–8.15) 3.67 (1.43, 9.41)	0.003 0.006
Karami (2013)	CC	776/1444	Interview	Occup.	Parathion + Vit D gene	3.09 (1.10–8.68)	
Koutros (2013a, b)	Co	54412	Census	Occup.	Fonofos Malathion Terbufos Aldrin	1.63 (1.22–2.17) 1.43 (1.08–1.88) 1.29 (1.02–1.64) 1.49 (1.03–2.18)	0.001 0.04 0.03 0.02
Budnik et al. (2012)	MA	3 studies		Occup.	Methyl bromide	1.21 (0,98–1.49)	0.076
Barry (2011)	CC	776/1444	Interview	Occup.	Fonofos + *CT/TT*-SNP	3.25 (1.78–5.92)	
Cockburn (2011)	CC	173/162	GIS	Res.	Methyl bromide Organochlorines	1.62 (1.02–2.59) 1.64 (1.02–2.63)	
Band (2011)	CC	1516/4994	JEM	Occup.	Dichlone Maneb Ziram Simazine Azinphos-methyl Carbaryl DDT Diazinon Lindane Malathion	1.88 (1.01–3.52) 1.9 (1.09–3.30) 1.83 (1.08–3.10) 1.89 (1.08–3.33) 1.88 (1.06–3.32) 1.73 (1.09–2.74) 1.68 (1.04–2.70) 1.93 (1.21–3.08) 2.02 (1.15–3.55) 1.49 (1.02–2.18)	0.02 0.02 0.03 0.01 0.01 0.01 0.03 0.02 0.03 0.03
Koutros (2011)	CC	776/1444	Interview	Occup.	Terbufos + *MPO*-SNP	3.0 (1.5–6.0)	0.002

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Koutros (2010a, b)	Co	52394	Census	Occup.	Private use Commercial use	1.19 (1.14–1.25) 1.28 (1.00–1.61)	0.002
Multigner (2010)	CC	623/671	Plasma level	Gen.	Chlordecone	1.77 (1.21–2.58)	
Christensen (2010)	Co	47822	Questionnaire	Occup.	Coumaphos	1.65 (1.13–2.38)	0.004
Bonner (2010)	Co	57310	Questionnaire	Occup.	Terbufos	1.21 (0.99–1.47)	
Koutros (2010a, b)	CC	776/1444	Interview	Occup.	Fonofos + 8q24 variants	4.46 (2.17–9.17)	0.002
Parent (2009)	CC	49/183	Interview	Occup.	–	2.3 (1.1–5.1)	
de Rezende Chrisman (2009)	Ec	11 states	Pesticide sales	Res., Occup.	–	MRR; 1.66 (1.63–1.69)	0.019
Chamie (2008)	Co	13144	Veterans	Occup.	Agent Orange	2.19 (1.75–2.75)	
Meyer (2007)	CC	405/392	Interview	Occup.	–	1.6 (1.2–2.2)	
Settimi (2003)	CC	124/659	Interview	Occup.	Organochlorines	2.5 (1.4–4.2)	
Alavanja (2003)	Co	55332	Questionnaire	Occup.	Methyl bromide	3.47 (1.37–8.76)	0.004
Mills and Yang (2003)	Nested CC	222/1110		Occup.	Methyl bromide	1.59 (0.77–3.30)	0.25
MacLennan (2002)	Co	2045	Workers	Occup.	Triazine herbicides	SIR; 394 (128–920)	
Fleming (1999)	Co	33658	Applicators	Occup.	–	SIR; 1.91 (1.72–2.13)	
Cerhan (1998)	Mr	88090	Death certificate	Occup.	–	PMR; 1.26 (1.19–1.33)	
Dich and Wiklund (1998)	Co	20025	Applicators	Occup.	–	SIR; 1.13 (1.02–1.24)	
Forastiere (1993)	CC	1674/480	Questionnaire	Occup.	–	2.13 (0.64–6.49)	
Morrison (1993)	Ret. Co	1148	Acres sprayed	Occup.	Herbicides	2.23 (1.30–3.48)	<0.01
Testicular cancer							
Giannandrea (2011)	CC	50/48	Serum level	Res.	DDE, HCB	3.15 (1.00–9.91)	
Fleming (1999)	Co	33658	Questionnaire	Occup.	–	SIR; 2.48 (1.57–3.72)	
Breast cancer							
Parada (2016)	Mr	633	Blood level	–	DDT	2.72 (1.04–7.13)	
Niehoff (2016)	Co	50884	Interview	Gen.	DDT	1.3 (0.92–1.7)	
Lerro (2015a, b)	Co	30003	Questionnaire	Occup.	OPs	1.20 (1.01–1.43)	
Arrebola (2015)	CC	69/56	Serum level		β-HCH DDE	3.44 (1.30–9.72) 9.65 (1.81–63.33)	<0.1 <0.05
Yang (2015)	CC	75/79	Blood level		β-HCH, PCTA	↑ OCs level	<0.05
			Adipose tissue		β-HCH, DDE, PCTA	↑ OCs level	<0.05
Tang et al (2014a, b)	CC	78/72	Serum level	Diet	DDT	1.95 (0.95–4.00)	
El-Zaemey (2013)	CC	1743/1169	Self-report	Occup.	–	1.43 (1.15, 1.78)	
Boada (2012)	CC	121/103	Serum level		DDD	1.008 (1.001–1.015)	0.024
Ortega Jacome (2010)	CC	110/110	Questionnaire	Res.	–	2.15 (1.22–3.77)	
Teitelbaum (2007)	CC	1508/1556	Interview	Res.	–	1.39 (1.15, 1.68)	
Engel (2005)	Co	30454	Questionnaire	Occup.	2,4,5-TP Captan	2.0 (1.2–3.2) 2.7 (1.7–4.3)	
Charlier (2003)	CC	159/250	Blood level		DDT HCB	5.36 (1.89–15.19) 8.68 (2.83–26.62)	
Mills and Yang (2005)	CC	128/640	Questionnaire	Occup.	–	1.41 (0.66–3.02)	
Duell (2000)	CC	862/790	Interview	Occup.	–	1.8 (1.1–2.8)	
Ovarian cancer							
Lerro (2015a, b)	Co	30003	Questionnaire	Occup.	Diazinon	1.87 (1.02–3.43)	

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Koutros (2010a, b)	Co	52394	Census	Occup.	Private use	2.45 (1.12–4.65)	
Donna (1989)	CC		Interview	Occup.	Triazine herbicides	2.7 (1.0–6.9)	
Cervical cancer							
Fleming (1999)	Co	33658	Questionnaire	Occup.	–	SIR; 3.69 (1.84–6.61)	
Eye cancer							
Abdolahi (2013)	CC	198/245	Interview	Pat.	10 years preconception 1 year preconception	1.64 (1.08–2.50) 2.12 (1.25–3.61)	
Carozza (2008)	Ec	1078 counties	GIS	Res.	–	2.6 (1.9–3.5)	
Kristensen (1996)	Co	323292	Census	Par.	–	3.17 (0.93–10.9)	
Laryngeal cancer							
Bravo (1990)	CC	85/170	Interview	Occup.	Insecticides	↑risk	
Lip cancer							
de Rezende Chrisman (2009)	Ec	11 states	Pesticide sales	Res. Occup.	–	MRR; 5.61 (4.88–6.35)	0.01
Rafnsson (2006)	Co	8311	Questionnaire	Occup.	Lindane	1.50 (1.08–2.04)♂ 9.09 (1.02–32.82)♀	
Cerhan (1998)	Mr	88090	Death certificate	Occup.	–	PMR; 1.58 (0.59–4.21)	
Wiklund (1983)	Ret. Co	354228	Questionnaire	Occup.	–	1.83 (1.62–2.05)	
Mouth cancer							
Tarvainen L	Co		JEM	Occup.	–	1.77 (0.85–3.26)	
Lung cancer							
Lerro (2015b)	Co	33484	Interview	Occup.	Acetochlor	1.74 (1.07–2.84)	
Zendehdel et al. (2014)	MA	5 Co		Occup.	Chlorophenols, phenoxyacetic acids	SMR; 1.18 (1.03–1.35)	0.014
Luqman (2014)	CC	400/800	Questionnaire	Occup.	–	5.1 (3.1–8.3)	
Bonner (2010)	Co	57310	Questionnaire	Occup.	Terbufos	1.45 (0.95–2.22)	
Samanic (2006)	Co	41969	Questionnaire	Occup.	Dicamba	2.16 (0.97–4.82)	0.02
Rusiecki (2006)	Co	50193	Questionnaire	Occup.	Metolachlor	2.37 (0.97–5.82)	0.03
Beane Freeman (2005)	Co	23106	Questionnaire	Occup.	Diazinon	2.41 (1.31–4.43)	0.005
Moore (2005)	CC	196/196	Questionnaire	Par.	Household pesticides	3.0 (1.1–8.1)♂	
Lee (2004a, b)	Co	54383	Questionnaire	Occup.	Chlorpyrifos	2.18 (1.31–3.64)	0.002
Alavanja (2004)	Co	57284	Questionnaire	Occup.	Metolachlor Pendimethalin Chlorpyrifos Diazinon	5.0 (1.7–14.9) 4.4 (1.2–15.4) 1.9 (0.9–4.0) 3.2 (1.1–8.9)	0.0002 0.003 0.03 0.04
Pesatori (1994)	Nested CC	65/294	Interview	Occup.	–	2.4 (1.0–5.9)	
Brownson (1993)	CC	429/294	Interview	Occup.	–	2.4 (1.1–5.6)	
Thyroid cancer							
Lerro (2015a, b)	Co	30,003	Questionnaire	Occup.	Malathion	2.04 (1.14–3.63)	
Freeman (2011)	Co	57,310	Questionnaire	Occup.	Atrazine	4.84 (1.31–17.93)	0.08
Lee (2004a, b)	Co	49,980	Questionnaire	Occup.	Alachlor	1.63 (0.42–6.37)	
Pukkala (2009)	Co	15,000,000	Farmers	Occup.	–	SIR; 1.18 (1.07–1.30)	
Skin cancer							
Lerro (2015b)	Co	33,484	Interview	Occup.	Acetochlor	1.61 (0.98–2.66)	

Table 1 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Segatto (2015)	CC	95/96	Interview	Occup.	–	2.03 (1.03–6.89)	
Dennis (2010)	Co	52394	Questionnaire	Occup.	Maneb/mancozeb	2.4 (1.2–4.9)	0.006
					Parathion	2.4 (1.3–4.4)	0.003
					Carbaryl	1.7 (1.1–2.5)	0.013
Mahajan (2007)	Co	21416	Questionnaire	Occup.	Carbaryl (>175 days)	4.11 (1.33–12.75)	0.07
Fortes (2007)	CC	287/299	Interview	Indoor	–	2.18 (1.07–4.43)	0.027

♂: risk found in male, ♀: risk found in female, *MA* meta-analysis, *CC* case–control, *CS* cross-sectional, *Co* cohort, *Ec* ecological, *Mr* mortality, *Ret.* retrospective, *Pros.* prospective, *Occup.* occupational, *Env.* environmental, *Mat.* maternal, *Pat.* paternal, *Par.* parental, *Res.* residential, *Gen.* general, *GIS* geographic information system, *JEM* job exposure matrix, *OR* odd ratio, *RR* relative risk, *HR* hazard ratio, *PMR* proportional mortality ratio, *SMR* standard mortality ratio, *MRR* mortality rate ratio, *SIR* standard incidence ratio, *ALL* acute lymphocytic leukemia, *AML* acute myeloblastic leukemia, *ChE* cholinesterase, *OPs* organophosphoruses, *OCs* organochlorines, *2,4-D* 2,4-dichlorophenoxyacetic acid, *2,4,5-T* 2,4,5-trichlorophenoxyacetic acid, *EPTC* S-ethyl-N,N-dipropylthiocarbamate, *HCB* hexachlorobenzene, *β-HCH* beta-hexachlorocyclohexane, *PCTA* pentachlorothioanisole, *DDT* dichlorodiphenyltrichloroethane, *DDE* dichlorodiphenyldichloroethylene, *DDD* dichlorodiphenyldichloroethane, *GST* glutathione-S-transferase

1993). Furthermore, Viel et al. (1998) reported higher mortality ratio of brain cancer in an ecological model assessment of vineyard pesticide-exposed farmers. Some other case–control studies found an approximately doubled risk of being occupationally exposed to pesticides in cases of brain tumors compared with control. Among these studies, some reported the association of ABT with specified class of pesticides such as herbicides albeit in women (Samanic et al. 2008), and insecticides/fungicides (Musicco et al. 1988), while other evidence of risk of ABT was referred to any class of pesticides (Provost et al. 2007; Rodvall et al. 1996). In this regard, Lee and colleagues' analysis of cases of ABT in comparison with controls revealed elevated odd ratios as 22.6, 18.9, 11.1, 5.9, and 3.4 for participants occupationally exposed to chlorpyrifos, bufencarb, paraquat, coumaphos, and metribuzin, respectively (Lee et al. 2005).

Neuroblastoma Because of the high prevalence of neuroblastoma in infancy and childhood, its association with parental exposure to pesticide has been well studied and the relative risk of about 2.3 reported by two surveys (Feychting et al. 2001; Kristensen et al. 1996). Carozza and colleagues studied the association of childhood cancers in an ecologic analysis of geographic information system (GIS) and reported an OR of 1.8 for the association of residential exposure to pesticides and neuroblastoma in children living in agricultural areas (Carozza et al. 2008). Residential exposure has also been studied in a case–control study of neuroblastoma, and the ORs were resulted as 1.6 and 1.7 for home-used and garden-used pesticides, respectively (Daniels et al. 2001). Furthermore, elevated SMRs due to neuroblastoma were reported by two cohort studies on pesticide applicators (Giordano et al. 2006; Littorin et al. 1993).

Tumors of the digestive system

Esophageal cancer Chrisman and colleagues' ecological study on 11 states in Brazil regarding residential or occupational exposure to pesticides revealed an elevated MRR of 2.4 for esophageal cancer (de Rezende Chrisman et al. 2009). There are also two case–control studies on the association of esophageal cancer with occupational exposure to pesticides among which one assessing the airborne level of pesticides has given an OR of 2.3 (Jansson et al. 2006) and the other death certificate-based study reported an OR of 1.38 (Meyer et al. 2011).

Stomach cancer A study on the link of stomach cancer with occupational exposure to pesticides in a questionnaire-based case–control analysis gave an OR of 1.77 without determining specified pesticides (Forastiere et al. 1993). But other studies in this regard have presented risk estimates of stomach cancer in association with exposure to specified pesticides. An ecological study of 40 ecodistricts in Ontario (Canada) assessed the relation between incidence of stomach cancer and environmental exposure to atrazine measured in drinking water and gave an OR of 1.45 implicated on a significant association (p value <0.05) (Van Leeuwen et al. 1999). Mills and colleagues carried out a nested case–control study on the link of stomach cancer with occupational exposure to different classes of pesticides and found elevated risks regarding 2,4-dichlorophenoxyacetic acid (2,4-D), chlordane, and trifluralin given by ORs of 1.85, 2.96, and 1.69, respectively (Mills and Yang 2007). A significant association of stomach cancer with occupational exposure to methyl bromide was also resulted by a cohort study (Barry et al. 2012).

Colorectal cancer In two separated questionnaire-based case–control studies determining occupational exposure to generally pesticides in cases and controls, the ORs of colorectal cancer were estimated as 2.6 and 2.8. One of these studies calculated the risk estimates of colorectal cancer in association with insecticides and herbicides as well and reported ORs of 3.2 and 5.5, respectively. Further estimate was carried out regarding dietary exposure to pesticides and risk of colorectal cancer represented by an OR of 4.6 (Forastiere et al. 1993; Lo et al. 2010). Among cohort studies analyzing the risk of colorectal cancer in people occupationally exposed to pesticides, apart from one study reporting a tripled incidence ratio (Zhong and Rafnsson 1996), the others estimated the risk regarding specified species of pesticides. Aldicarb, dicamba, imazethapyrc, chlorpyrifos, S-ethyl-N,N-dipropyl thiocarbamate (eptam or EPTC), trifluralin, and acetochlor were the pesticides, arranged in order, for which elevated risk ratios of colorectal cancer reported in occupationally exposed people (Kang et al. 2008; Koutros et al. 2009; Lee et al. 2007b; Lerro et al. 2015b; Samanic et al. 2006; van Bemmel et al. 2008). Recently, Salerno et al. carried out a GIS-based ecological study focusing on the cancer risk among farmers in a province of Italy and reported a double risk of colorectal cancer which may be representative of exposure to pesticides (Salerno et al. 2014).

Liver cancer Ecological analyses on the link of pesticides and incidence of liver cancer were carried out in two separated studies whose results implicated on the elevated OR as 3.3 for residential exposure assessed by GIS on 1078 counties (Carozza et al. 2008) and increased MRR as 1.49 for residential or occupational exposure estimated on the basis of pesticides sale in 11 states (de Rezende Chrisman et al. 2009). Moreover, a high SMR 596.3 due to liver cancer was found in a cohort study conducted on pesticide applicators (Giordano et al. 2006). VoPham et al. compared the cases of liver cancer with matched controls via a GIS-based exposure assessment tool and reported a significant association between exposure to organochlorine pesticides and the incidence of liver cancer given by the OR of 2.76 and a p value of 0.0004 (VoPham et al. 2015).

Gallbladder cancer In a cohort study conducted by Giordano and colleagues on pesticide applicators, a high mortality ratio due to gall bladder cancer was noted with an SMR of 723.8 (Giordano et al. 2006). Further, biliary level of some organochlorine pesticides was measured in a case–control study, and an increased level of hexachlorobenzene (HCB) (p value <0.04) and dichlorodiphenyltrichloroethane (DDT) (p value <0.03) was found in the gall bladder cancer cases in comparison with controls (Shukla et al. 2001).

Pancreatic cancer In 1990, Alavanja and colleagues published the results of cohort mortality and a nested case–control analyses of more than 22000 males. Subjects were enrolled in the life insurance program, and an estimated SMR of 133 due to pancreatic cancer among flour mill workers which were frequently exposed to pesticides (Alavanja et al. 1990). In the same decade, another study found a significantly elevated risk ratio of mortality due to pancreatic cancer among aerial pesticide applicators (Cantor and Silberman 1999). Chrisman and colleagues also reported a high mortality rate ratio of pancreatic cancer in association with per capita sales of pesticides in an ecological study conducted in 11 states of Brazil (de Rezende Chrisman et al. 2009). There are different types of case–control studies on the link between exposure to pesticides and incidence of pancreatic cancer. Regarding occupational exposure to pesticides, an OR of 5.18 was reported for pancreatic cancer by a case–control analysis (Forastiere et al. 1993). ORs including 1.2 and 2.6 were estimated for pancreatic cancer in association with regular exposure to pesticides in two separated case–control studies (Antwi et al. 2015; Lo et al. 2007). Alguacil et al. conducted a case–control study assessing exposure to pesticides via a job exposure matrix (JEM) and estimated a tripled risk of pancreatic cancer in people occupationally exposed to pesticides. In that study, arsenical pesticides were shown to be associated with higher incidence of pancreatic cancer given by OR of 3.4 (Alguacil et al. 2000). Another JEM-based case–control study found significantly elevated ORs including 1.4, 1.5, and 1.6 for pancreatic cancer due to occupational exposure to pesticides, fungicides, and herbicides, respectively (Ji et al. 2001). Occupational exposure to herbicides (EPTC and pendimethalin) was shown to be (p value <0.01) associated with double and triple risks of pancreatic cancer, respectively (Andreotti et al. 2009). Furthermore, an increased relative risk of pancreatic cancer (2.36) in association with occupational exposure to acetochlor herbicide was the finding of the Agricultural Health Study (Lerro et al. 2015b).

Tumors of the hematopoietic system

Leukemia Similar to the brain tumors, studies concerning the link of leukemia with exposure to pesticides are separately designed and conducted with respect to the age of the target population. Regarding childhood leukemia, lots of case–control and other types of epidemiological studies have targeted the association with different routes of exposure, including residential exposure due to indoor or outdoor use of pesticides and parental exposure due to maternal or paternal activities. The results of these studies have been frequently meta-analyzed in various models, and risk of childhood leukemia regarding exposure to pesticides has been estimated. A meta-analysis of 31 case–control studies

published between 1950 and 2009 reported a higher risk of leukemia in children whose mothers dealt with pesticides, insecticides, and herbicides given by ORs of 2.09, 2.72, and 3.62, respectively (Wigle et al. 2009). Another meta-analysis done by Vinson and colleagues on 40 case–control studies assessing maternal exposure to pesticides indicated an elevated OR of 1.48 for leukemia in children (Vinson et al. 2011). Regarding residential exposures, a meta-analysis of 17 case–control studies published between 1950 and 2009 found an elevated ORs including 1.54, 2.05, and 1.61 for incidence of leukemia in children exposed to pesticides, insecticides, and herbicides, respectively (Turner et al. 2011). Further, the results of 16 case–control studies assessing residential exposure in children were meta-analyzed, and 1.4 and 1.2 times elevated risks of childhood leukemia were found in respect to indoor-used pesticides and herbicides (Chen et al. 2015). A meta-analysis of 13 case–control studies published between 1966 and 2009 found an elevated risk estimate of about 1.74 for the link of childhood leukemia with maternal or residential exposure to pesticides (Van Maele-Fabry et al. 2011). Another type of meta-analysis done by Baily and colleagues pooled the results of 13 case–control studies assessing exposure to pesticides in the offspring of parents occupied in the pesticide-related jobs and found associations between childhood AML and maternal exposure, and between childhood ALL and paternal exposure, represented by elevated ORs as 1.9 and 1.2, respectively (Bailey et al. 2014).

Regarding the link of adult leukemia with pesticide exposures, several epidemiological studies have become evident so that their results have been meta-analyzed in different formats. A meta-analysis of 13 case–control studies published between 1990 and 2005 showed that exposure to pesticides and incidence of adult leukemia were associated with an OR of 1.35 (Merhi et al. 2007). Van Maele-Fabry and colleagues meta-analyzed the results of 17 cohort studies published between 1979 and 2005 and found an increased risk estimate (1.2) of leukemia in adults occupationally exposed to pesticides (Van Maele-Fabry et al. 2007). Their another meta-analysis of 14 studies published between 1984 and 2004 revealed 1.4 times higher risk of adult leukemia in association with occupational exposure to pesticides (Van Maele-Fabry et al. 2008). Occupational exposure to crotoxyphos, dichlorvos, famphur, pyrethroids, and methoxychlor was shown to be associated with higher incidence of leukemia in a case–control study (Brown et al. 1990). A high incidence of leukemia was also reported by three separated cohort studies conducted on people occupationally exposed to Agent Orange, terbufos, and diazinon with estimated risks of 1.8, 2.3, and 3.3, respectively (Baumann Kreuziger et al. 2014; Beane Freeman et al. 2005; Bonner et al. 2010). Moreover, Cantor et al. showed that the mortality ratio of leukemia was tripled in people occupationally exposed to pesticides (Cantor and Silberman 1999).

Lymphoma Regarding the tumors of the lymphoid tissues, pesticide exposures have been mostly studied for two main categories of lymphomas, including Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL). Other than one cohort and one mortality studies, 7 case–control analyses have been obtained through this systematic review for HL. The cohort study calculated nearly a triple risk of HL due to parental exposure to pesticides, while the mortality study found a PMR of 1.6 for HL in people occupationally exposed to pesticides (Cerhan et al. 1998; Flower et al. 2004). Among case–control studies, those without determining a specific class of pesticides estimated ORs ranging from 1.8 to 2.2 for HL in association with occupational exposure to pesticides, while the others have reported specified ORs including 1.88, 3.16, 2.47, 4.1, and 2.6 for the link of HL with, respectively, insecticides, organophosphorus compounds, carcinogenic pesticides, household-used pesticides, and phenoxy herbicides, and more specifically, 1.19 and 6.35 for chlorpyrifos and dichlorprop (Karunanayake et al. 2012; Navaranjan et al. 2013; Pahwa et al. 2009; Persson et al. 1993; Rudant et al. 2007).

However, the number of studies targeting the link of NHL and pesticide' exposures is much more than that of HL which may be due to higher prevalence (90 %) of NHL among lymphomas. In this systematic review, a total of 29 studies, including 20 case–control, 8 cohort, and 1 ecological analyses on the link of pesticide exposures with NHL have been collected from which 21 calculated the risk estimate regarding specified classes of pesticides.

Of seven studies not determining the type of pesticides in association with NHL, one cohort study reported RR of 2.47 due to parental exposure and one GIS-based ecological study reported MRRs of 2.9 and 3.2 due to NHL in men and women, respectively (Boccolini Pde et al. 2013; Kristensen et al. 1996). Remaining 5 studies are case–control whose results implicate on the higher incidence of NHL in people exposed to pesticides as given by ORs ranging from 1.7 to 7.3 (Balasubramaniam et al. 2013; Buckley et al. 2000; Clavel et al. 1996; Karunanayake et al. 2013; Rudant et al. 2007; Vajdic et al. 2007).

All of the studies in this systematic analysis, which have estimated the risk of NHL in association with the specified class or type of pesticides, have been designed and conducted in case–control or cohort format composed of different sample numbers. Elevated risk estimates ranging from 1.1 to 3, 1.6 to 2.9, and 1.8 to 3.8 have been reported for NHL in association with exposure to insecticides, herbicides, and fungicides, respectively. Further, five times higher incidence of NHL in people exposed to fumigants has been indicated by Chiu and colleagues (Chiu et al.

2006; Eriksson et al. 2008; Hardell and Eriksson 1999; Hardell et al. 2002; Meinert et al. 2000; Nordstrom et al. 1998; Schinasi et al. 2015; Schroeder et al. 2001).

Exposure to organophosphorus and carbamate compounds have been shown to be associated with, respectively, 1.7 and 1.9 times higher incidence of NHL by a case–control analysis, as such results have been calculated by a meta-analysis of 44 studies (McDuffie et al. 2001; Schinasi and Leon 2014). In these classes of insecticides, higher risk estimates of NHL were reported for people exposed to malathion (1.5), diazinon (1.5, 1.9), terbufos (1.9), coumaphos (2.4), fonofos (1.8), and carbaryl (1.7) (Bonner et al. 2010; Cantor et al. 1992; De Roos et al. 2003). Among organochlorine insecticides, elevated risk estimates ranging from 1.6 to 2.6, 1.2 to 1.7, 1.8 to 3.7, and 1.5 to 1.7 have been reported for lindane, DDT, dieldrin, and chlordane, respectively. The risk of NHL has also been calculated in association with exposure to the other organochlorine insecticides, including toxaphene (3.0), oxychlordane (1.1), cis-nonachlor (1.1), and beta-hexachlorocyclohexane (β-HCH) (1.05) (Alavanja et al. 2014; Brauner et al. 2012; Cantor et al. 1992; De Roos et al. 2003; Purdue et al. 2007; Schinasi and Leon 2014; Schroeder et al. 2001; Viel et al. 2011). Ruder and Yiin (2011) have shown higher mortality ratio of NHL in a cohort of plant workers who were occupationally exposed to pentachlorophenol.

The specific link of NHL and herbicides has been mostly evaluated for phenoxy class of herbicides for which elevated ORs ranging from 1.4 to 2.8 have been estimated by three separated case–control studies (Eriksson et al. 2008; McDuffie et al. 2001; Pahwa et al. 2012a). Coggon and colleagues conducted a cohort study on 8036 participants occupied in phenoxy herbicides-manufacturing plants, and the results revealed a high mortality ratio of NHL among workers (Coggon et al. 2015). The ORs as high as 1.5 and 4.4 have also been reported for the risk of NHL in people occupationally exposed to 2,4-dichlorophenoxy acetic acid (2,4-D) by two case–control studies (Miligi et al. 2006; Zahm et al. 1990). The link of NHL with exposure to other specific herbicides including atrazine and glyphosate has also been studied in three case–control studies, and increased ORs ranging from 1.6 to 1.7 and 2.1 to 2.3 have been estimated, respectively (De Roos et al. 2003; Eriksson et al. 2008; Schroeder et al. 2001).

Multiple myeloma Similar to the other malignancies of the hematopoietic system, multiple myeloma has also been the target of epidemiological health studies linking with exposure to pesticides. This review found totally 8 relevant including 4 case–control, 3 cohorts and one mortality studies on the link between incidences of multiple myeloma and exposure to pesticides. Cerhan et al. (1998) reported a PMR of about 1.2 due to multiple myeloma among farmers who had been occupationally exposed to pesticides. The results of two separate cohort studies showed that occupational exposure to pesticides is associated with higher incidences of multiple myeloma as given by risk estimates of 1.3 and 6.8 in women and people aged more than 50, respectively (Landgren et al. 2009; Lope et al. 2008). A cohort of agricultural workers occupationally exposed to pesticides showed a doubled RR of multiple myeloma among their offspring (Kristensen et al. 1996). Two case–control studies conducted by Perrotta and colleagues without determining a specific class of pesticides have given ORs of about 1.5 and 1.6 for the incidences of multiple myeloma in people occupationally dealing with pesticides (Perrotta et al. 2012, 2013). The comparison of cases of multiple myeloma with matching controls regarding prevalence of exposure to specific types of pesticides was made by two separate studies. Their results implicate elevated ORs for fungicides (1.7), probably carcinogenic pesticides (1.6), carbamates (1.9), captan (2.3), and carbaryl (1.9) (Kachuri et al. 2013; Pahwa et al. 2012b). A meta-analysis of 13 case–control studies published between 1990 and 2005 showed an OR of about 1.2 for the risk of multiple myeloma in association with exposure to pesticides (Merhi et al. 2007).

Tumors of the bone and soft tissues

Bone tumors There are two ecological and three case–control studies giving evidence on the link of bone cancer with exposure to pesticides. One of the ecological studies reported the link between residential exposure to pesticides and higher incidence of childhood bone tumors, while another GIS-based ecological study showed an OR of about 2.3 for bone cancers in relation to higher level of metolachlor in groundwater (Carozza et al. 2008; Thorpe and Shirmohammadi 2005). Two separate case–control studies evaluated the Ewing's sarcoma in children and showed its positive association with parental exposure to pesticides with ORs including 3.0 and 6.1 (Holly et al. 1992; Moore et al. 2005). Comparing adult cases of bone sarcoma in adults with matching controls, 2.3 times higher incidence of occupational exposure to pesticides has been found in cases (Merletti et al. 2006).

Soft tissue sarcoma Two ecological and three case–control studies are the results of a systematic review for the link of soft tissue sarcoma with exposure to pesticides. An ecological study assessing the rate of pesticide sales in 11 states of Brazil reported a higher MRR of soft tissue sarcoma in people of states with greater exposure to pesticides (de Rezende Chrisman et al. 2009). The GIS-based ecological study of Carozza and colleagues also indicated that residential exposure to pesticides is associated with 1.7 time higher inci-

dence of soft tissue sarcoma (Carozza et al. 2008). Indoor exposure to pesticides, especially those used for yard treatments, was shown to be 4.1 times higher in people diagnosed with soft tissue sarcoma by a case–control study (Leiss and Savitz 1995). It should be taken into consideration the finding of a nested case–control study estimating an OR of about 10 for the risk of soft tissue sarcoma in association with occupational exposure to phenoxy herbicides (Kogevinas et al. 1995).

Tumors of the urinary system

Kidney cancer A total of 12 including one ecological, one cohort, one mortality and 9 case–control studies have been collected by this systematic analysis regarding the relation between exposure to pesticides and the incidence of renal cancers. An ecological study conducted on health data of children residing in agriculturally intense areas in the USA revealed nearly tripled incidence risk of childhood renal carcinoma in association with residential exposure to pesticides (Carozza et al. 2008). Examining the records of childhood death revealed a PMR of about 1.6 due to kidney cancer in the offspring of fathers who had been occupationally exposed to pesticides (Fear et al. 1998). Furthermore, 8.9 times increment in the RR of Wilm's tumors was noted in a cohort of children whose parents had been exposed to pesticides due to engagement in agricultural activities (Kristensen et al. 1996). Those case–control studies focusing on adults estimated ORs ranging from 1.6 to 5.7 for the risk of kidney cancers in relation to occupational exposure to pesticides, while the others reported ORs between 1.4 and 128.6 for the risk of childhood renal carcinoma including Wilm's tumors in association with parental, paternal, or maternal exposure to pesticides (Buzio et al. 2002; Forastiere et al. 1993; Karami et al. 2008; Mellemgaard et al. 1994; Olshan et al. 1993; Sharpe et al. 1995; Tsai et al. 2006).

Bladder cancer In regard to the association of bladder cancer with pesticide exposures, there have been two cohorts and three case–control studies. Two cohort studies published by Koutros and colleagues in 2009 and 2015 have shown that people occupationally exposed to imazethapyr herbicides were 2.4 and 3 times more prone to be diagnosed with bladder cancer as given by respective p values of 0.01 and 0.005 (Koutros et al. 2009, 2015). An OR of about 1.7 was estimated by a case–control study for the risk of bladder cancer in people who had been occupationally exposed to pesticides (Amr et al. 2015), even though another report has further highlighted such a risk in cases carrying the *GSTT1* polymorphism (Matic et al. 2014). The remaining case–control study has implicated on a significantly higher blood concentration of HCH and DDT in bladder cancer cases when compared to matching controls (Sharma et al. 2013).

Tumors of the male reproductive system

Prostate cancer Since the prevalence of prostate cancer in men is higher than other malignancies, the surveys on its association with exposure to pesticides are sufficiently high. In this review, there have been 25 epidemiological studies on the link of pesticide exposures with incidence of prostate cancer, of which 13 are case–control, 10 are cohort, one is mortality, and one is ecological. The results of ecological and mortality studies implicated on the high mortality ratio of prostate cancer as calculated MRR of 1.7 and PMR of 1.3, respectively (Cerhan et al. 1998; de Rezende Chrisman et al. 2009). There were three cohort studies which linked occupational exposure to pesticides with elevated SIRs for prostate cancer ranging from 1.2 to 1.9 (Dich and Wiklund 1998; Fleming et al. 1999; Koutros et al. 2010a), while the other seven cohort studies estimated the risk in association with specified classes of pesticides. Morrison and colleagues surveyed the prostate cancer mortality in a cohort of pesticide applicators retrospectively and found an increased RR (2.2) in relation to acres sprayed with herbicides (Morrison et al. 1993). Another cohort including workers of a triazine herbicides-manufacturing plant found the prostate cancer incidence and increased SIR of about 390 (MacLennan et al. 2002). Furthermore, a total of 13144 Vietnam War veterans were examined by a cohort study in regard to Agent Orange exposure, and the results showed that twice as many exposed men were identified with prostate cancer (Chamie et al. 2008). Aldrin, malathion, fonofos, terbufos, coumaphos, and methyl bromide are the other pesticides whose association with prostate cancer was studied in different cohorts and increased risk estimated including 1.5, 1.4, 1.6, 1.2, 1.6, and 3.5, respectively (Alavanja et al. 2003; Bonner et al. 2010; Christensen et al. 2010; Koutros et al. 2013b). Similarly, case–control studies estimated the risk of prostate cancer in association with or without specified classes of pesticides, and, respectively, 10 and 3 case–control studies were collected in this review. Elevated ORs including 1.6, 2.1, and 2.3 were reported in three separate case–control studies conducted in cases of prostate cancer and their matched controls in regard to occupational exposure to ever used pesticides (Forastiere et al. 1993; Meyer et al. 2007; Parent et al. 2009). Three separate case–control studies compared the cases of prostate cancer with matching controls and estimated ORs of 1.6 and 2.5 for the risk in association with exposure to organochlorines, and an OR of 1.6 twice for the risk in association with exposure to methyl bromide (Cockburn et al. 2011; Mills and Yang 2003; Settimi et al. 2003). Exposure to malathion, DDT, carbaryl, chlordecone, ziram, dichlone, azinphos, simazine, maneb, diazinon, and lindane was shown to be associated with higher incidence of prostate cancer as evidenced by ORs ranging from 1.5 to 2 by two case–control studies (Band et al. 2011; Multi-

gner et al. 2010). The five remaining case–control studies evaluated the prostate cancer susceptibility against pesticide exposure in people carrying polymorphism of some variants. Elevated ORs including 3, 3.1, 3.2, 3.4, 3.7, and 4.5 have been estimated for the risk of prostate cancer in association with occupational exposure to terbufos in carriers of *MPO*-single nucleotide polymorphism (SNP), parathion in carriers of SNP in genes of vitamin D metabolism, fonofos in carriers of *CT/TT*-SNP, malathion in carriers of *EHBP1*-SNP, aldrin in carriers of *TET2*-SNP, and again fonofos in carriers of 8q24 variants, respectively (Barry et al. 2011; Karami et al. 2013; Koutros et al. 2010b, 2011, 2013a).

Testicular cancer A cohort of licensed pesticide applicators in Florida was evaluated, and a 2.5 times higher SIR was reported for the risk of testicular cancer in relation to occupational exposure to pesticides (Fleming et al. 1999). Giannandrea and colleagues have also measured and compared the serum level of dichlorodiphenyldichloroethylene (DDE) and HCB in cases of testicular cancer with matching controls and observed a significant tripled risk of testicular cancer in association with higher serum levels of mentioned pesticides (Giannandrea et al. 2011).

Tumors of the female reproductive system

Breast cancer Breast cancer is the most prevalent malignancy in female and has been frequently the topic of environmental health studies examining its association with pesticide exposures. In this systematic search, a total of 14 studies including 4 cohort and 10 case–control analyses have been reviewed. The Agricultural Health Study examined a cohort of 30454 farmers' wives prospectively, and breast cancer SIR of 2.0 and 2.7 was calculated for those who had been exposed to 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and captan, respectively (Engel et al. 2005). A cohort of 30003 spouses of pesticide applicators have also been the participants of another Agricultural Health Study whose results implicated on breast cancer RR of 1.2 among women who had personal use of organophosphorus insecticides (Lerro et al. 2015a). Niehoff and colleagues conducted a prospective Sister Study cohort and reported a breast cancer HR of 1.3 in women who had been aged 0–18 years before the ban of DDT in the USA (Niehoff et al. 2016). Furthermore, blood level of DDT was evaluated in relation to women's survival following breast cancer in a prospective cohort study, and an HR of 2.7 was estimated for breast cancer-specific mortality in the highest tertile of blood DDT concentration (Parada et al. 2016). Five separate case–control studies published during 2000 and 2013 showed breast cancer ORs ranging from 1.4 to 2.1 in association with occupational or residential exposure to pesticides (Duell et al. 2000; El-Zaemey et al. 2013; Mills and Yang 2005; Ortega Jacome et al. 2010; Teitelbaum et al. 2007). The other case–control studies measured the blood concentration of organochlorine insecticides in breast cancer cases and their matched controls, and higher concentrations of DDT, DDE, dichlorodiphenyldichloroethane (DDD), β-HCH, and HCB in the blood were shown to be associated with breast cancer ORs of 5.3, 9.6, 1, 3.4, and 8.7, respectively (Arrebola et al. 2015; Boada et al. 2012; Charlier et al. 2003; Tang et al. 2014b). In addition to blood levels, Yang and colleagues reported that there is a positive association between adipose tissue levels of organochlorine insecticides, including DDE, β-HCH, and pentachlorothioanisole (PCTA) with incidence of breast cancer in women (Yang et al. 2015).

Ovarian cancer Updated data on cancer incidence in the Agricultural Health Study revealed an ovarian cancer SIR of 2.4 in association with occupational exposure to pesticides in private sectors (Koutros et al. 2010a). Recently, the results of the Agricultural Health Study with a focus on organophosphorus insecticides have revealed that diazinon use was associated with 1.9 times higher RR of ovarian cancer among spouses of pesticides applicators (Lerro et al. 2015a). In this regard, there is also a case–control study reporting an increased ovarian cancer OR (2.7) in association with occupational exposure to triazine herbicides (Donna et al. 1989).

Cervical cancer There is a cohort study conducted on licensed pesticide applicators in Florida which estimated a cervical cancer SIR of 3.7 in association with exposure to pesticides (Fleming et al. 1999).

Tumors of the head and neck

Eye cancer A GIS-based ecological study conducted by Carozza and colleagues estimated an eye cancer OR of 2.6 in people residing in counties with high density of pesticides (Carozza et al. 2008). In a follow-up of cancer incidence among offspring of parents who had been involved in agricultural activities, a tripled eye cancer RR has been found in association with parental exposure to pesticides (Kristensen et al. 1996). Furthermore, a case–control study focusing on the childhood sporadic bilateral retinoblastoma has found 2.1 and 1.6 times higher risk in children whose fathers had been exposed to pesticides, respectively, 1 year and 10 years before conception (Abdolahi et al. 2013).

Laryngeal cancer Bravo and colleagues have conducted a case–control study and found an increased occurrence of insecticide exposure in cases of laryngeal cancer compared with their matched controls (Bravo et al. 1990).

Lip cancer Association of lip cancer with pesticide exposures has been investigated in an ecological, a mortality, and two cohort studies. Chrisman and colleagues evaluated ecologically the rate of pesticide sales in 11 states and estimated a lip cancer mortality ratio of 5.6 in males who had been residentially or occupationally exposed to pesticides (de Rezende Chrisman et al. 2009). Extracting the causes of death from death certificates of Lowa farmers revealed a PMR of 1.6 due to lip cancer in association with occupational exposure to pesticides (Cerhan et al. 1998). A retrospective cohort study of Swedish agricultural workers presented a decreased risk of most cancers among the study group except lip cancer, which was shown to be greater than the national average by a factor of almost 1.8 (Wiklund 1983). Furthermore, another cohort study carried out on a population engaged in sheep dipping indicated that occupational exposure to lindane increased the risk of lip cancer by 1.5 time in men and by 9 times in women (Rafnsson 2006).

Mouth cancer A study converting the Census occupation to chemical exposures with a JEM-based approach revealed that occupational exposure to pesticides was associated with a mouth cancer SIR of about 1.8 in a cohort of Finns born between 1906 and 1945 (Tarvainen et al. 2008).

Miscellaneous

Lung cancer The link of pesticide exposures with lung cancer incidences has been studied by 11 epidemiological studies of which 7 are cohort and 4 are case–control analyses collected in this review. Occupational exposure to pesticides has been linked to higher incidence of lung cancer by three separated case–control studies estimating ORs including 2.4 and 5.1 (Brownson et al. 1993; Luqman et al. 2014; Pesatori et al. 1994), while the results of another case–control study has implicated on a tripled risk of lung cancer in the sons whose parents had been exposed to household pesticides (Moore et al. 2005). All of cohort studies in this review have determined the incidence of lung cancer in association with specified types of pesticides, as such an elevated risk estimate of 1.7 has been found for occupational use of acetochlor, 1.4 for terbufos, 2.1 for dicamba, 2.4 and 5 for metolachlor, 2.4 and 3.2 for diazinon, 1.9 and 2.2 for chlorpyrifos, and 4.4 for pendimethalin (Alavanja et al. 2004; Beane Freeman et al. 2005; Bonner et al. 2010; Lee et al. 2004a; Lerro et al. 2015b; Rusiecki et al. 2006; Samanic et al. 2006).

Thyroid cancer Searching the role of pesticide exposures in the incidence of thyroid cancer by this review resulted in 4 cohort studies, one of which found a SIR of 1.2 for the risk in farmers who had been occupationally exposed to any kind of pesticides, while the others reported thyroid cancer risk estimates of 1.6, 2, and 4.8 for occupational exposure to alachlor, malathion, and atrazine, respectively (Freeman et al. 2011; Lee et al. 2004b; Lerro et al. 2015a; Pukkala et al. 2009).

Skin cancer Two separate case–control studies estimated skin cancer ORs of 2 and 2.2 in association with occupational use and indoor use of pesticides, respectively (Fortes et al. 2007; Segatto et al. 2015). Occupational exposure to specific classes of pesticides was evaluated in three cohort studies reporting elevated melanoma risk estimates, including 1.6 for acetochlor, 2.4 for maneb, 2.4 for parathion, and 1.7 and 4.1 for carbaryl (Dennis et al. 2010; Lerro et al. 2015b; Mahajan et al. 2007).

Disease-based evidence on neurotoxicity of pesticides

Alzheimer

Alzheimer disease is an increasing age-related neurodegenerative disease which has been shown to be associated with exposure to pesticides. Herein, six studies including three cohort, two case–control, and an ecological studies have been reviewed on the relation between Alzheimer and pesticide exposures (Table 2). The longitudinal and prospective analysis of exposures associated with incidence of Alzheimer diseases by the cohort studies revealed 1.4 and 2.4 times higher risk in people occupationally exposed to any pesticides, while exposure to organophosphorus and organochlorine compounds was shown to increase the risk by 1.5 times. In addition, an Alzheimer RR of about 4.3 in association with exposure to fumigants and defoliants had been previously reported by a cohort study (Baldi et al. 2003b; Hayden et al. 2010; Tyas et al. 2001). A GIS-based ecological study indicated that the prevalence of Alzheimer disease in people living in the areas having higher pesticide usage was two times higher than that of the others (Parron et al. 2011). Two separate case–control studies evaluated pesticide exposures in cases of Alzheimer disease and their matched controls, and the results of the first one indicated an OR of about 1.1 for the risk in relation to pesticides and fertilizers, while the second one showed that the blood level of DDE is positively associated with risk of Alzheimer disease evidenced by an OR of about 4.2 (McDowell et al. 1994; Richardson et al. 2014).

Parkinson

Because of approximate similarity between the pathophysiology of Parkinson disease (PD) and toxicity of pesticides, there have been a huge body of epidemiological and experimental evidence on the role of pesticide exposures in the development of PD. Herein, the results of 33 epidemiological human study comprised of 26 case–control, 5 cohort,

Table 2 Neurotoxicity of pesticides evidenced by disease

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Alzheimer							
McDowell (1994)	CC	258/535		Occup.	Pesticides, fertilizers	1.07 (1.18–3.99)	
Tyas (2001)	Co	694	Questionnaire	Occup.	Fumigants, defoliants	4.35 (1.05–17.90)	
Baldi (2003b)	Pros. Co	1507	Questionnaire	Occup.	–	2.39 (1.02–5.63)	
Hayden (2010)	Pros. Co	3084	Questionnaire	Occup.	–	1.42 (1.06–1.91)	0.02
					OPs	1.53 (1.05–2.23)	0.03
					OCs	1.49 (0.99–2.24)	0.06
Parron (2011)	Ec	17,429	GIS	Env.	–	2.10 (1.96–2.25)	<0.001
Richardson (2014)	CC	86/79	Serum level		DDE	4.18 (2.54–5.82)	<0.001
Parkinson							
Baldi (2003a)	CC	84/252	GIS	Gen.	–	2.2 (1.1–4.3)	
Butterfield (1993)	CC	63/68		Env.	Insecticide	5.75	<0.001
					Fumigants	5.25	0.046
					Herbicides	3.22	0.033
Chan (1998)	CC	215/313	Questionnaire	Occup.	Exposed years	1.05 (1.01–1.09)	0.018
Costello (2009)	CC	368/341	GIS	Env.	Maneb, Paraquat	1.75 (1.13–2.73)	
Dick (2007)	CC	959/1989	Questionnaire	Occup.	–	1.41 (1.06–1.88)	
Dutheil (2010)	CC	101/234	Questionnaire	Occup.	OCs	3.50 (0.90–14.5)	
Elbaz (2009)	CC	224/557	Questionnaire	Occup.	–	1.80 (1.1–3.1)	0.01
Firestone (2005)	CC	250/388	Questionnaire	Occup.	–	2.07 (0.67–6.38)	
Fong (2007)	CC	153/155	Questionnaire	Occup.	–	1.69 (1.07–2.65)	
Frigerio (2006)	CC	149/129	Questionnaire	Gen.	–	2.40 (1.1–5.4)	0.04
Gatto (2009)	CC	368/341	Well water use	Env.	Methomyl Chlorpyrifos Propargite	1.67 (1.00–2.78) 1.87 (1.05–3.31) 1.92 (1.15–3.20)	
Gorrel 1998	CC	144/464	Questionnaire	Occup.	Herbicides Insecticides	4.1 (1.37–12.24) 3.55 (1.75–7.18)	
Hancock (2008)	CC	319/296	Questionnaire	Occup.	–	1.61 (1.13–2.29)	
Manthripragada (2010)	CC	351/363	GIS	Gen.	Diazinon Chlorpyrifos	2.2 (1.1–4.5) 2.6 (1.3–5.4)	
Ritz (2009)	CC	324/334	Questionnaire	Occup.	Paraquat, Maneb	2.99 (0.88–1.02)	
Tanner (2009)	CC	519/511	Questionnaire	Occup.	Pesticides 2,4-D	1.9 (1.12–3.21) 2.59 (1.03–6.48)	
Tanner (2011)	CC	110/358	Questionnaire	Occup.	Rotenone Paraquat	2.5 (1.2–3.6) 2.5 (1.4–4.7)	
Wang (2011a)	CC	362/341	Ambient level	Occup.	Ziram, maneb, paraquat	3.09 (1.69–5.64)	
Zorzon (2002)	CC	136/272	Questionnaire	Env. Occup.	–	2.0 (1.1–3.5) 7.7 (1.4–44.1)	0.0237 0.0212
Ascherio (2006)	Pros. Co	143,325	Questionnaire	Occup.	–	1.7 (1.2–2.3)	0.002
Baldi (2003b)	Pros. Co	1507	Questionnaire	Occup.	–	5.63 (1.47–21.58)	
Kamel (2007)	Pros. Co	55,931	Questionnaire	Occup.	–	2.3 (1.2–4.5)	0.009
Kamel (2014)	CC	89/336	Questionnaire	Occup.	Paraquat Rotenone	4.2 (1.5–12) 5.8 (2.3–15)	
Petrovitch (2002)	Pros. Co	7986	Questionnaire	Occup.	–	1.7 (0.8–3.7)	0.006
Richardson (2009)	CC	50/43	Serum level		β-HCH	4.39 (1.67–11.6)	
McCann (1998)	CC	224/310	Questionnaire	Env.	Rural residency	1.8	<0.001
Lee (2012)	CC	357/754	GIS	Env.	Paraquat	1.36 (1.02–1.81)	
Goldman et al. (2012)	CC	87/343	Questionnaire	Occup.	Paraquat Paraquat (GSTT1*0)	1.5 (0.6–3.6) 11.1 (3.0–44.6)	

Table 2 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Steenland (2013)	CS	400	Questionnaire	Occup.	–	2.57 (0.91–7.26)	
Narayan (2013)	CC	357/807	Questionnaire	Res.	Household pesticide OPs Organothiophosphate	1.47 (1.13, 1.92) 1.71 (1.21, 2.41) 1.95 (1.17, 3.23)	
Brouwer (2015)	Pros. Co	5000	JEM	Occup.	–	1.27 (0.86–1.88)	
James and Hall (2015)	CS	332,971	Groundwater level	Env.	1 μg/L pesticides	1.03 (1.02–1.04)	
Moisan (2015)	CC	133/298	Questionnaire	Occup.	–	2.56 (1.31–4.98)	
Amyotrophic lateral sclerosis							
Bonvicini (2010)	CC	41/82	Questionnaire	Occup.	–	3.6 (1.2–10.5)	
Das (2012)	CC	110/240	Questionnaire	Occup.	Pesticides and insecticides	1.61 (1.27–1.99)	0.03
McGuire (1997)	CC	174/348	Questionnaire	Occup.	–	2.0 (1.1–3.5)	
Morahan and Pamphlett (2006)	CC	179/179	Questionnaire	Overall Occup.	Herbicides/pesticides Herbicides/pesticides	1.57 (1.03–2.41) 5.58 (2.07–15.06)	
Pamphlett (2012)	CC	614/778	Questionnaire	Occup.	Herbicides/pesticides	1.77 (1.30–2.39)	
Qureshi (2006)	CC	95/106	Questionnaire	Occup.	–	↑ risk	0.03
Burns (2001)	Co	1517	JEM	Occup.	2,4-D	3.45 (1.1–11.11)	
Deapen and Henderson (1986)	CC	1136	Questionnaire	Occup.	–	2.0 (0.8–5.4)	
Savettieri (1991)	CC	46/92	Interview	Gen.	–	3.0 (0.4–20.3)	
Gunnarsson (1992)	CC	92/372	Questionnaire	Occup.	–	1.1 (0.2–5.3)	
Chancellor (1993)	CC	103/103	Questionnaire	Occup.	–	1.4 (0.6–3.1)	
Weisskopf (2009)	Co	987,229	Questionnaire	Gen.	–	1.48 (0.82–2.67)	0.0004
Kamel (2012)	AHS (Co)	84,739	Questionnaire	Occup.	OCs	1.6 (0.8–3.5)	
Su (2016)	CC	156/128	Blood level	Gen.	OCs, PCBs, BFRs	5.09 (1.85–13.99)	
Beard (2016)	CC	621/958	Questionnaire	War Field	Agent Orange	2.80 (1.44–5.44)	
Burns (2001)	Co	3/40600	Expert Judgment	Occup.	2,4,-D	3.45 (1.10–11.11)	
Furby et al. (2010)	CC	108/122	Questionnaire	Occup.	–	3.04 (1.19–7.75)	
Malek (2014)	CC	66/66	Questionnaire	Occup.	–	6.50 (1.78, 23.77)	
Yu (2014)	CC	66/66	Questionnaire	Occup.	>30 years exposure	6.95 (1.23–39.1)	<0.05

MA meta-analysis, *CC* case–control, *CS* cross-sectional, *Co* cohort, *Ec* ecological, *Mr* mortality, *Ret.* retrospective, *Pros.* prospective, *Occup.* occupational, *Env.* environmental, *Mat.* maternal, *Pat.* paternal, *Par.* parental, *Res.* residential, *Gen.* general, *GIS* geographic information system, *JEM* job exposure matrix, *OR* odd ratio, *RR* relative risk, *HR* hazard ratio, *PMR* proportional mortality ratio, *SMR* standard mortality ratio, *MRR* mortality rate ratio, *SIR* standard incidence ratio, *ChE* cholinesterase, *OPs* organophosphoruses, *OCs* organochlorines, *2,4-D* 2,4-dichlorophenoxyacetic acid, *β-HCH* beta-hexachlorocyclohexane, *DDE* dichlorodiphenyldichloroethylene

and two cross-sectional analyses have been extracted and reviewed (Table 2). The results of a screening test for neurodegenerative diseases conducted in a population-based sample from Costa Rica implicated on a Parkinson OR of about 2.6 in association with occupational exposure to pesticides, while the other cross-sectional analysis measuring the ground water level of some pesticides, including atrazine, simazine, alachlor, and metolachlor reported an increased risk of PD by 3 % for every 1.0 microg/L of pesticide in groundwater (James and Hall 2015; Steenland et al. 2013). All of five cohort studies included in this review prospectively analyzed the risk of PD in different sized samples of population and reported that occupational exposure to pesticides increases the risk of PD up to a range of 1.3–5.6 times (Ascherio et al. 2006; Baldi et al. 2003b; Brouwer et al. 2015; Kamel et al. 2007; Petrovitch et al. 2002). Among case–control studies which compared the cases of PD with their matched controls from the aspect of pesticide exposures, some generally evaluated the risk in relation to ever used pesticides and reported a total of eleven increased ORs ranging from 1.05 to 2.6 (Baldi et al. 2003a; Chan et al. 1998; Dick et al. 2007; Elbaz et al. 2009; Firestone et al. 2005; Fong et al. 2007; Frigerio et al. 2006; Hancock et al. 2008; McCann et al. 1998; Moisan et al. 2015; Zorzon et al. 2002), while the others whose number is also large enough calculated the risk of the disease in association with exposure to specific types of pesticides. In this regard, elevated Parkinson ORs have been reported for the main classes of

pesticides, including two for insecticides (3.5 and 5.7), two for herbicides (3.2 and 4.1), and one for fumigant (5.2), though exposure to organochlorines and organophosphoruses has been shown to increase the risk of PD as given by ORs of 3.5 and 1.7, respectively (Butterfield et al. 1993; Dutheil et al. 2010; Gorell et al. 1998; Narayan et al. 2013). Specifically, environmental and occupational exposure to paraquat has been linked with the most frequently reported Parkinson ORs including 1.4, 1.5, 1.7, 2.5, 3, and 4.2 and then exposure to the maneb (1.7 and 3) and rotenone (2.5 and 5.8) (Costello et al. 2009; Kamel et al. 2014; Ritz et al. 2009; Tanner et al. 2011). Furthermore, a case–control study comparing the cases of PD with their matched controls regarding the ambient level of pesticides at workplace revealed that combined exposure to paraquat, maneb, and ziram was associated with a threefold increase in the risk of Parkinson (Wang et al. 2011a). Environmental exposure to methomyl, chlorpyrifos, and propargite has been compared between cases of PD and the matched controls by a GIS-based analysis of groundwater, and 1.7- to 1.9-fold elevated risks of Parkinson were estimated for usage of contaminated well water with mentioned pesticides (Gatto et al. 2009). Another GIS-based case–control study has shown that residential exposure to chlorpyrifos and diazinon increased the risk of Parkinson by more than two times (Manthripragada et al. 2010). Occupational exposure to the herbicide 2,4-D has been compared between the cases of PD and matched controls, and 2.6 times increased risk of PD in cases was estimated (Tanner et al. 2009). A 4.4 times elevated risk of Parkinson due to exposure to β-HCH was the finding of another case–control study indicating that β-HCH was more often detectable in the blood of PD cases than control (Richardson et al. 2009).

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive disease of the nervous system presented by muscle weakness for which the role of environmental risk factors specially pesticide exposures has been well studied. Herein, 18 studies including 15 case–control and 3 cohort analyses of the possible link between pesticide exposures and the incidence of ALS have been reviewed (Table 2). A cohort study prospectively evaluated the causes of mortality in relation to the exposures and found out an ALS RR of about 1.5 in people having more than 10 years of regular exposure to pesticides (Weisskopf et al. 2009). In addition, a mortality RR of 3.4 was attributed to the ALS among a cohort of male employees in a 2,4-D-manufacturing plant (Burns et al. 2001). A meta-analysis of the Agricultural Health study data taken from a cohort of 84,739 private pesticide applicators revealed that ALS was associated with occupational exposure to pyrethroid, organochlorines, herbicides, and fumigants evidenced by elevated ORs including 1.4, 1.6, 1.6, and 1.8, respectively, (Kamel et al. 2012). Ten case–control studies included in this review reported the link of pesticide exposures with elevated ALS risk estimates ranging from 1.1 to 6.9 (Bonvicini et al. 2010; Chancellor et al. 1993; Deapen and Henderson 1986; Furby et al. 2010; Gunnarsson et al. 1992; Malek et al. 2014; McGuire et al. 1997; Qureshi et al. 2006; Savettieri et al. 1991; Yu et al. 2014). Three separate studies comparing the cases of ALS with controls regarding occupational exposures, estimated higher risk of the disease relevant to the industrial use of herbicides/pesticides (1.8 and 5.6) and insecticides/pesticides (1.6) (Das et al. 2012; Morahan and Pamphlett 2006; Pamphlett 2012). A case–control study of US military veterans has shown that war field exposure to Agent Orange increased the risk of ALS given by OR of 2.8 (Beard et al. 2016). Furthermore, measuring the blood level of organochlorine pesticides in cases of ALS and their controls revealed that cumulative exposure was significantly associated with ALS evidenced giving an OR of about 5.1 (Su et al. 2016).

Disease-based evidence on pulmonotoxicity of pesticides

Asthma

The link of environmental and occupational exposures with asthma has long been discovered, and so the role of pesticide exposures in the etiology of the disease has been well studied in both children and adults. Herein, the results of 18 studies including 7 cross-sectional, 7 cohort, and 4 case–control survey on the relation of pesticide exposures with incidence of asthma have been reviewed (Table 3). Among cross-sectional analyses, two have evaluated the risk of asthma in association with occupational and para-occupational exposure to any kind of pesticides and increased risk of the disease has been found (ORs up to 4.6) (Bener et al. 1999; Salameh et al. 2003), while the other study evaluated death data and found an elevated mortality ratio (3.4) associated with asthma in people occupationally exposed to pesticides (Beard et al. 2003). Three cross-sectional studies have measured the serum levels of dioxin, DDE, and cholinesterase enzyme in the participants and reported higher incidence of asthma in exposure to Agent Orange, DDE, and anticholinesterase insecticides, including organophosphoruses and carbamates as evidenced by ORs of 1.6, 3.7, and 1.9, respectively. Albeit, the reported risk of DDE was estimated in combination with polychlorinated biphenyls (PCBs) and HCB in children exposed after birth (Kang et al. 2006; Karmaus et al. 2001; Ndlovu et al. 2014). Further, an asthma prevalence OR of 1.8 in association with

Table 3 Pulmonotoxicity of pesticides evidenced by disease

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Asthma							
Senthilselvan (1992)	CS	1939		Occup.	Carbamate	1.8 (1.1–3.1)	0.02
Kang (2006)	CS	2927	Serum Dioxin	Occup.	Agent Orange	1.62 (1.28–2.05)	>0.05
Bener (1999)	CS	196		Occup.	–	↑ risk	<0.008
Salameh (2006)	CC	262/110	Interview	Occup.	–	4.98 (1.07–23.28)	0.02
Beard (2003)	CS	3983	Death Data	Occup.	–	3.45 (1.39–7.10)	
Hoppin (2008)	Co	25,814	Questionnaire	Occup.	–	1.46 (1.14–1.87)	
Hoppin (2009)	Co	19,704	Questionnaire	Occup.	Coumaphos	2.34 (1.49–3.70)	
					Heptachlor	2.01 (1.30–3.11)	
					Parathion	2.05 (1.21–3.46)	
					Mix (CCl4/CS2)	2.15 (1.23–3.76)	
					Ethylene dibromide	2.07 (1.02–4.20)	
Sunyer (2005)	Co	468	Cord serum	Mat.	DDE	2.63 (1.19–4.96)	
Sunyer (2006)	Co	462	Cord serum	Mat.	DDE	1.18 (1.01–1.39)	
Karmaus et al. (2001)	CS	343	Blood level	Mat.	DDE	3.71 (1.10–12.56)	
Tagiyeva (2010)	Co	13,971	Questionnaire	Par. job	Biocides/fungicides	1.47 (1.14–1.88)	
Salam (2004)	CC	279/412	Interview	Env.	Pesticides	2.39 (1.17–4.89)	
					Herbicides	4.58 (1.58–5.56)	
Salameh (2003)	CS	3291	Questionnaire	Para-Occup.	–	4.61 (2.06–10.29)	
Meng (2016a, b)	CC	60/60	Indoor dust	Res.	DDE	1.82 (1.00–3.32)	0.04
Meng (2016a, b)	CC	620/218	Pooled serum		DDE	1.02 (1.01–1.03)	0.0004
					α-HCH	1.06 (1.02–1.10)	0.001
Ndlovu et al. (2014)	CS	211	Blood ChE	Occup.	ChE inhibitor	1.93 (1.09–3.44)	
Yi et al. (2014)	Ret. Co	111,726	GIS	Occup.	Agent Orange	1.04 (1.01–1.08)	0.015
Hansen (2014b)	Co	965	Mat. serum	Mat.	HCB	1.92 (1.15, 3.21)	
Exacerbated asthma							
Henneberger (2014)	Co	926	Questionnaire	Occup.	Pendimethalin	2.1 (1.1–4.1)	
					Aldicarb	10.2 (1.9–55)	
Chronic bronchitis							
Hoppin (2007)	Co	20,908	Questionnaire	Occup.	Heptachlor	1.50 (1.19–1.89)	
Salameh (2006)	CC	262/110	Interview	Occup.	–	15.92 (3.50–72.41)	<0.0001
Tual et al. (2013)	Co	14,441	Questionnaire	Occup.	–	1.63	<0.05
Valcin (2007)	Co	21,541 women	Questionnaire	Occup.	Dichlorvos	1.63 (1.01, 2.61)	
					DDT	1.67 (1.13, 2.47)	
					Cyanazine	1.88 (1.00, 3.54)	
					Paraquat	1.91 (1.02, 3.55)	
					Methyl bromide	1.82 (1.02, 3.24)	
Yi et al. (2014)	Ret. Co	111,726	GIS	Occup.	Agent Orange	1.05 (1.02–1.08)	0.015
Wheeze							
Hoppin (2002)	Co	20,468	Questionnaire	Occup.	Parathion	1.5 (1.0–2.2)	
					Atrazine	1.5 (1.2–1.9)	
Hoppin (2006a, b)	Co	89,000	Questionnaire	Occup.	Chlorpyrifos	1.48 (1.0–2.2)	0.02
Hoppin (2006a, b)	Co	2255	Questionnaire	Occup.	Chlorimuron-ethyl	1.62 (1.25, 2.10)	
Salameh (2003)	CS	3291	Questionnaire	Res.	–	2.73 (1.85–4.05)	
Xu (2012)	CS	14,065	Questionnaire	Res.	Household use	1.39 (1.08–1.78)	
Gascon (2014)	Co	405	Mat. serum	Mat.	HCB	1.58 (1.04–2.41)	
					DDE	1.35 (1.07–1.71)	

Table 3 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value
Lower respiratory tract infections (LRTIs)							
Sunyer (2010)	Co	520	Mat. serum	Mat.	DDE	2.40 (1.19–4.83)	
Gascon (2012)	Co	1455	Mat. serum	Mat.	DDE	1.33 (1.08–1.62)	
Gascon (2014)	Co	405	Mat. serum	Mat.	HCB	1.89 (1.10–3.25)	

MA meta-analysis, *CC* case–control, *CS* cross-sectional, *Co* cohort, *Ec* ecological, *Mr* mortality, *Ret.* retrospective, *Pros.* prospective, *Occup.* occupational, *Env.* environmental, *Mat.* maternal, *Pat.* paternal, *Par.* parental, *Res.* residential, *Gen.* general, *GIS* geographic information system, *JEM* job exposure matrix, *OR* odd ratio, *RR* relative risk, *HR* hazard ratio, *ChE* cholinesterase, *OPs* organophosphoruses, *HCB* hexachlorobenzene, *α-HCH* alpha-hexachlorocyclohexane, *DDT* dichlorodiphenyltrichloroethane, *DDE* dichlorodiphenyldichloroethylene

exposure to carbamate insecticides has been previously estimated by a questionnaire-based cross-sectional study (Senthilselvan et al. 1992).

Two separate case–control studies reported asthma ORs of 2.4 and 5 in association with, respectively, environmental and occupational exposure to any kind of pesticides, while 4.6 for environmental exposure to herbicides (Salam et al. 2004; Salameh et al. 2006). Recently, Meng et al. measured and compared the concentration of pesticides in indoor dust and blood samples taken from cases of asthma and controls and published two separate case–control studies reporting higher incidence of asthma in association with exposure to DDE (ORs 1.02 and 1.8) and alpha-hexachlorocyclohexane (α-HCH) (OR of 1.06) (Meng et al. 2016a, b).

Hoppin and colleagues have analyzed data from the Agricultural Health Study and once reported an asthma OR of about 1.5 in female farmers exposed to any pesticide, and once again estimated asthma ORs including 2.3, 2, 2.05, 2.15, and 2.1 in male farmers exposed to coumaphos, heptachlor, parathion, mixed CCl4/CS2, and ethylendibromide, respectively (Hoppin et al. 2008, 2009). In addition, the Agricultural Health Study on a cohort of pesticide applicators with active asthma showed that the symptoms were exacerbated due to occupational exposure to pendimethalin (OR: 2.1) and aldicarb (OR: 10.2) (Henneberger et al. 2014). A cohort of Korean Vietnam veterans have been retrospectively evaluated to determine diseases' prevalence by a GIS-based model assessment of exposure, and an asthma OR of 1.04 was estimated for exposure to Agent Orange (Yi et al. 2014). The link of childhood asthma in association with parental occupation has been evaluated by a birth cohort study, and higher incidence of asthma was found in children whose parents occupationally exposed to biocides/fungicides as given by an OR of 1.5 (Tagiyeva et al. 2010). Measuring the cord serum concentration of DDE taken from two cohorts of offspring and their follow-up by Sunyer and colleagues indicated that prenatal exposure to DDE increased the incidence of childhood asthma as the ORs were estimated to be 1.2 and 2.6 (Sunyer et al. 2006; Sunyer et al. 2005). Moreover, the results of a prospective cohort study measuring the maternal serum concentration of organochlorines with 20-year follow-up revealed that prenatal exposure to HCB was associated with an asthma HR of 1.9 in the offspring (Hansen et al. 2014b).

Chronic bronchitis

Regarding the role of pesticide exposures in chronic bronchitis, the results of a case–control plus 4 cohort studies have been reviewed (Table 3). The comparison of occupational exposure to pesticides between cases and controls resulted in a significantly elevated OR of 15.9 for chronic bronchitis (Salameh et al. 2006). Besides, findings from the French AGRICAN cohort study has shown that pesticide poisoning and pesticide exposures among potato farmers were significantly associated with risk of chronic bronchitis (OR 1.6) (Tual et al. 2013). The other three cohort studies determined the risk of chronic bronchitis in association with specified types of pesticides, as a chronic bronchitis OR of 1.5 was estimated for heptachlor usage by pesticide applicators involved in the Agricultural Health Study (Hoppin et al. 2007). Such a risk of chronic bronchitis has also been found by the Agricultural Health Study on non-smoking farm women who had been exposed to dichlorvos, DDT, methyl bromide, cyanazine, and paraquat with respective ORs including 1.6, 1.7, 1.8, 1.9, and 1.9 (Valcin et al. 2007). Further, exposure of a cohort of Korean Vietnam veterans to Agent Orange was shown to be significantly associated with increased risk of chronic bronchitis with estimated OR of 1.05 (Yi et al. 2014).

Wheeze

Wheeze as a typical symptom of the most respiratory disorders has also been the focus of environmental health studies assessing its risk in relation to pesticide exposures. In this regard, the results of two cross-sectional plus 4 cohort studies have been presented in this review (Table 3). Two questionnaire-based cross-sectional analyses have indicated

that residential exposure to pesticides increased the risk of wheeze in children with ORs of 1.4 and 2.7 (Salameh et al. 2003; Xu et al. 2012). Hoppin and colleagues made three separated analyses on data from the Agricultural Health Study and reported that occupational exposure to parathion, atrazine, chlorpyrifos, and chlorimuron-ethyl were associated with increased incidence of wheeze with ORs ranging from 1.5 to 1.6 (Hoppin et al. 2002, 2006a, b). Measurement of maternal serum concentration of persistent organic pollutants (POPs) in a cohort study indicated that incidence of wheeze in the offspring prenatally exposed to DDE and HCB was increased with respective ORs including 1.3 and 1.8 (Gascon et al. 2014).

Low respiratory tract infections (LRTIs)

LRTIs in relation to pesticide exposures have been studied in three separate cohorts of children whose mothers' serum concentration of organochlorines was measured (Table 3), and the results implicated on elevated risk of LRTIs in association with prenatal exposure to DDE (ORs 1.3 and 2.4) and HCB (OR 1.9) (Gascon et al. 2012, 2014; Sunyer et al. 2010).

Disease-based evidence on reproductive toxicity of pesticides

Infertility

There are various types of reproductive disorders in both males and females which may be resulted in infertility or not. Infertility has been defined as the inability to reproduce naturally and has been well studied in relation to the environmental risk factors such as pesticides. The search for the link of human infertility with pesticide exposures has brought totally 9 relevant studies, including two cross-sectional, five case–control, and two cohort analyses in this review (Table 4). One of the cross-sectional studies has measured the level of organochlorines in cord blood of the couples enrolled in a French birth cohort (PELAGIE) and concluded that the time-to-pregnancy increased in association with higher serum concentrations of DDE (Chevrier et al. 2013). The other study is questionnaire based and reported early abortion ORs of 1.4 and 1.5 in the women exposed to phenoxy and atrazine herbicides before conception, while such an exposure to glyphosate and thiocarbamates in women resulted in late abortion ORs of 1.7 and 1.8 (Arbuckle et al. 2001).

There have been two questionnaire-based case–control studies, one of which calculated an infertility OR of about 3 in females occupationally exposed to any kind of pesticides, while increased ORs of 3.3 and 27 were estimated by the other study for female infertility in association with occupational exposure to fungicides and herbicides, respectively (Greenlee et al. 2003; Smith et al. 1997). Two case–control studies published in 2013 compared the blood level of organochlorines between cases of infertile women with controls and cases of endometriosis with controls and reported significantly higher incidence of infertility in association with DDE exposure, while elevated endometriosis ORs of 1.3 and 1.5 were estimated for respective exposure to HCH and mirex (Bastos et al. 2013; Upson et al. 2013). Cases of infertile men were also compared with controls regarding semen concentration of organochlorines, and significantly elevated risk of infertility as well as lower sperm count and motility has been found in association with higher levels of HCH and DDT in the semen (Pant et al. 2007).

Furthermore, there is an infertility-targeted cohort study measuring the maternal serum concentration of DDT and DDE, which has shown increased time-to-pregnancy in daughters of women exposed to DDT (Cohn et al. 2003). Increased time-to-pregnancy in women living in the glyphosate condensed areas has also been reported by a cohort study applying a GIS approach for assessing the exposure to the pesticide in Colombian regions (Sanin et al. 2009).

Low quality of semen

Some characteristics of the semen are critical determinants of male fertility, and lowered quality of the semen has been studied in association with exposure to pesticides (Mehrpour et al. 2014). Herein, a total of 14 studies including 8 cross-sectional, 5 case–control, and one cohort analyses on the role of pesticide exposure in the lowered quality of the semen have been reviewed (Table 4). Blood concentration of organochlorines was measured in two cross-sectional and one case–control studies, and their results implicated on the lowered quality of the semen characterized by decreased sperm count and motility, decreased volume of ejaculation, oligozoospermia, asthenozoospermia, and Yq deletion in association with exposure to DDE, DDT, and HCH for different values (Aneck-Hahn et al. 2007; Khan et al. 2010; Messaros et al. 2009). The incidence of oligozoospermia, asthenozoospermia, and teratospermia in association with occupational exposure to any used pesticides has also been reported by a questionnaire-based case–control study (De Fleurian et al. 2009). In association with organophosphorus and pyrethroid insecticides, different studies have measured their blood or urine concentration in human and linked their exposure to lowered sperm count and motility, increased sperm DNA damage, and disrupted volume and pH of the semen (Meeker et al. 2009; Perry et al. 2007, 2011; Recio-Vega et al. 2008; Yucra et al. 2008). In addition to DNA damage and low quality of the

Table 4 Reproductive toxicity of pesticides evidenced by disease

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value	Found risk
Infertility								
Bastos (2013)	CC	15/21	Blood level	–	DDE	69 %	0.001	Infertility♀
Arbuckle (2001)	CS	2110	Questionnaire	Mat.	2,4-D & 2,4,5-T	1.5 (1.1–2.1)		Early abortion
					Triazines	1.4 (1.0–2.0)		Early abortion
					Glyphosate	1.7 (1.0–2.9)		Late abortion
					Thiocarbamate	1.8 (1.1–3.0)		Late abortion
Pant (2007)	CC	50/50	Semen level	–	HCH, DDT	–	<0.05	Infertility
						–	<0.05	↓ sperm count ↓ sperm motility
Greenlee (2003)	CC	322/322	Interview	Occup.	Herbicides	27 (1.9–380)		
					Fungicides	3.3 (0.8–13)		
Upson (2013)	CC	248/538	Serum level		HCH Mirex	1.3 (0.8–2.4) 1.5 (1.0–2.2)		Endometriosis
Sanin (2009)	Co	2592	GIS	Res.	Glyphosate	0.15 (0.12–0.18)		↑ TTP
Smith (1997)	CC	281/216	Questionnaire	Occup.		3.02 (1.10–8.29)		
Cohn (2003)	Co	289	Serum level	Mat.	DDT	32 %		↑ TTP
Chevrier (2013)	CS	3421	Cord blood		DDE	–		↑ TTP
Semen disquality								
Swan (2003)	CC	50/36	Urine sample	–	Arachlor	30 (4.3–210)		↓ sperm count, ↓ Sperm motility, ↓ sperm morphology
					Diazinon	16.7 (2.8–98)		
					Atrazine	11.3 (1.3–98.9)		
Aneck-Hahn (2007)	CS	311	Blood level	–	DDE	−0.02	0.001	↓ Sperm motility
						−0.0003	0.02	↓ Ejaculate volume
						1.001	0.03	Oligozoospermia
						1.001	0.02	Asthenozoospermia
Celik-Ozenci (2012)	CS	40	Blood level	Occup.	Abamectin	–		↓ Sperm motility ↓ Sperm maturity
De Fleurian (2009)	CC	314/88	Questionnaire	Occup.		3.6 (0.8–15.8)		Oligospermia, asthenospermia, or teratospermia
Perry (2007)	CS	17	Urine level	Occup.	Pyrethroids, OPs	–		↓ sperm count
Perry (2011)	CC	94/95	Urine level		OPs	1.30 (1.02–1.65)		↓ sperm count ↓ Sperm motility
Ji et al (2011)	CS	240	Blood level		Pyrethroids	−0.27 0.27	<0.001 <0.001	↓ sperm count ↑ sperm DNA damage
Recio-Vega (2008)	Co	52	Urine level	Occup.	OPs	–		↓ sperm count
Khan (2010)	CC	50/50	Blood level	–	HCH	–		↓ sperm count Yq deletion

Table 4 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value	Found risk
Meeker JD et al. (2008)	CS	207	Blood level	–	Pyrethroids	–		↓ sperm count ↓ sperm motility ↑ sperm DNA damage
Messaros (2009)	CS	336	Blood level	–	DDE, DDT	–		↓ sperm count ↓ sperm motility ↑ sperm morphology
Miranda-Contreras (2013)	CS	100	Blood level (ChE activity)	–	OPs, carbamates	–		↑ sperm DNA damage ↓ sperm parameters ↑ FSH, LH
Xia et al. (2008)	CC	376	Urine level	–	Pyrethroids	2.04 (1.02–4.09)	0.027	↓ sperm count
Yucra (2008)	CS	62	Urine level	Occup.	OPs	–		↓ semen volume ↑ semen pH
Birth defects								
Gemmill (2013)	Co	442	GIS	Mat.	Methyl bromide	−113.1 g −0.85 cm −0.33 cm		↓ birth weight ↓birth length Head circumference
Sathyanarayana (2010)	Co	2246	Questionnaire	Mat.	Carbaryl	−82 (−132, −31)		↓ birth weight
Burdorf (2011)	Co	8880	JEM	Mat.	–	2.42 (1.10–5.34)		↓ birth weight
Brender (2010)	CC	184/225	Interview	Mat.	–	2 (1.2–3.1)		Neural tube defects
Brucker-Davis (2008)	CC	56/69	Colostrum	Mat.	DDE			Cryptorchidism
Chevrier C ET AL. 2011	Co	579	Urine level	Mat.	Atrazine	1.5 (1.0–2.2) 1.7 (1.0–2.7)		↓ fetal growth Head circumference
de Siqueira (2010)	Ec	26 states	Pesticide use	Par.	–	–	0.045 0.004	↓ birth weight congenital abnormality
Dugas (2010)	CC	471/490	Interview	Mat.	Insecticides	1.8 (1.06–3.11)		Hypospadias
Perera (2003)	CS	263	Plasma level	Mat.	Chlorpyrifos	–	0.01 0.003	↓ birth weight ↓ birth length
Ren (2011)	CC	80/50	Placental level	Mat.	DDT α-HCH	5.19 (1.70–15.82) 3.89 (1.26–11.97		Neural tube defects
Rocheleau (2009)	MA	9 studies	JEM	Mat.	–	1.36 (1.04–1.77)		Hypospadias
				Pat.	–	1.19 (1.00–1.41)		
Whyatt (2004)	CS	314	Cord blood		Chlorpyrifos/diazinon	–	<0.05	↓ birth weight ↓ birth length
Waller (2010)	CC	805/3616	Surface water	Mat.	Atrazine	1.6 (1.10–2.34)	0.014	Gastroschisis
Michalakis (2014)	CS	29	Hair sample	Par.	DDT HCH DMP	–	0.009 0.037 0.071	Hypospadias
Kielb et al. (2014)	CC	871/2857	JEM	Mat.	–	1.88 (1.16–3.05)		Gastroschisis

Table 4 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value	Found risk
Makelarski (2014)	CC	502/2950	JEM	Mat.	Insecticides + Herbicides	2.1 (1.0–4.1)		Spina Bifida
Jørgensen (2014)	Co	600000	JEM	Mat.	–	1.31 (1.21–1.53)		Cryptorchidism
Carmichael (2013)	CC	690/2195	GIS	Mat.	Aldicarb Dimethoate Phorate	2.69 (1.04–6.96) 2.45 (1.36–4.39) 2.76 (1.19-6.44)		Hypospadias
Changed sex ratio and maturation and hormones								
Tiido (2005)	CS	149	Blood level	Occup.	DDE	1.6 (0.8–2.5)	<0.001	Yq fraction
Tiido (2006)	CS	547	Blood level	Res.	DDE	–	<0.001	Yq fraction
Den Hond (2011)	CS	1679	Blood level	–	HCBDDE	–		Pubertal staging (men)
Meeker (2009)	CS	161	Blood level		Pyrethroids	–	<0.05 <0.03 <0.09	↑ FSH ↓ inhibin B ↓ testosterone
Meeker (2006)	CS	268	Blood level		Chlorpyrifos Carbaryl Naphthalene	–		↓ testosterone, FAI and LH

♂: risk found in male, ♀: risk found in female, *MA* meta-analysis, *CC* case–control, *CS* cross-sectional, *Co* cohort, *Ec* ecological, *Mr* mortality, *Ret.* retrospective, *Pros.* prospective, *Occup.* occupational, *Env.* environmental, *Mat.* maternal, *Pat.* paternal, *Par.* parental, *Res.* residential, *Gen.* general, *GIS* geographic information system, *JEM* job exposure matrix, *OR* odd ratio, *RR* relative risk, *HR* hazard ratio, *ChE* cholinesterase, *OPs* organophosphoruses, *DMP* dimethyl phosphate, *2,4-D* 2,4-dichlorophenoxyacetic acid, *2,4,5-T* 2,4,5-trichlorophenoxyacetic acid, *HCB* hexachlorobenzene, *α-HCH* alpha-hexachlorocyclohexane, *DDT* dichlorodiphenyltrichloroethane, *DDE* dichlorodiphenyldichloroethylene, *FAI* free androgen index, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone

sperm, increased levels of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have been reported by a cross-sectional study assessing the exposure via the enzymatic activity of acetylcholinesterase and butyrylcholinesterase in the blood (Miranda-Contreras et al. 2013). Swan and colleagues compared cases having low sperm count, motility, and morphology with controls regarding biomarkers of pesticide exposure and found that arachlor, diazinon, and atrazine were more often detectable in the urine of cases than that of controls with respective ORs including 30, 16.7, and 11.3 (Swan et al. 2003). Lowered sperm motility and maturity have also been found in people occupationally exposed to abamectin (Celik-Ozenci et al. 2012).

Birth defects

Birth defects, also known as congenital disorders or anomalies, have different types, e.g., low birth weight and length, cryptorchidism, hypospadias, neural tube defect, spina bifida, gastroschisis, and head circumference, and a substance inducing birth defects is called teratogen. There has been remarkable evidence on the teratogenicity of pesticides in human of which 18 relevant studies including 3 cross-sectional, 8 case–control, 5 cohort, and one ecological have been presented in this review (Table 4). Association of low birth weight with maternal exposure to pesticides, regardless of the type, with an OR of 2.4 has been reported by a JEM-based cohort study (Burdorf et al. 2011). Further, a questionnaire-based analysis of a cohort in the Agricultural Health Study indicated that maternal exposure to carbaryl lowered the birth weight as given by an OR of −82 g (Sathyanarayana et al. 2010). Such a risk plus lower birth length have been linked to maternal exposure to chlorpyrifos and diazinon by two separate cross-sectional studies (Perera et al. 2003; Whyatt et al. 2004). In addition to lower birth weight and length, head circumference has been reported by two cohort studies examining the offspring whose mothers were exposed to atrazine and methyl bromide (Chevrier et al. 2013; Gemmill et al. 2013). In this regard, an ecological study conducted in 26 states of Brazil revealed that there are significant correlations between pesticide use in the agriculture and low birth weight as well as congenital abnormality (de Siqueira et al. 2010).

The risk of neural tube defect has been shown to be doubled due to maternal exposure to pesticides by a questionnaire-based case–control study, while another study comparing the cases with controls regarding the placental level of organochlorines reported that maternal exposure to DDT and α-HCH

is associated with neural tube defect with respective ORs 5.2 and 3.9 (Brender et al. 2010; Ren et al. 2011). Moreover, an almost doubled risk of spina bifida has been estimated for maternal exposure to insecticides and herbicides by a JEM-based case–control study (Makelarski et al. 2014).

A cryptorchidism HR of 1.3 has been estimated by a JEM-based cohort study among the sons of mothers engaged in horticulture and farming (Jorgensen et al. 2014). Further, comparing the cases with controls regarding maternal exposure to organochlorines indicated that DDE had been more often detectable in the colostrum of mothers whose son suffered from cryptorchidism (Brucker-Davis et al. 2008).

Elevated hypospadias OR (1.8) in association with maternal exposure to insecticides was estimated by a questionnaire-based case–control study (Dugas et al. 2010). In addition, the results of a GIS-based case–control study showed that maternal exposure to aldicarb, dimethoate, and phorate increased the risk of hypospadias with respective ORs of 2.7, 2.4, and 2.8 (Carmichael et al. 2013). Michalakis and colleagues have evaluated parental exposure to organochlorines and organophosphates by measuring their level in the hair samples and concluded that chronic exposure of parents to DDT, HCH, and organophosphoruses was associated with higher incidence of hypospadias in the offspring (Michalakis et al. 2014). There has also been a meta-analysis of 9 studies whose results gave elevated hypospadias ORs of 1.4 and 1.2 in the boys whose, respectively, mothers and fathers had been occupied in the jobs dealing with pesticides (Rocheleau et al. 2009).

Gastroschisis, another type of birth defect, has also been linked to prenatal exposure to pesticides by a JEM-based case–control study estimating an OR of about 1.9 (Jorgensen et al. 2014). Further, Waller and colleagues reported that the incidence of gastroschisis increased in the offspring whose mothers were residing in the areas with high concentration of atrazine in the surface water (Waller et al. 2010).

Changed sex ratio, maturation, and hormones

There is sporadic evidence on pesticide-induced sexual dysfunction, some of which relevant to the reproduction have been presented in this review (Table 4). Tiido and colleagues conducted two separate cross-sectional studies examining pesticide exposure via their blood level measurement and concluded that exposure to DDE was significantly associated with the Y-chromosome fraction in human sperm (Tiido et al. 2005, 2006). Higher concentration of DDE and HCB in the blood samples was shown to link with disruption of pubertal staging in men (Den Hond et al. 2011). Regarding sexual hormone alteration, two separate cross-sectional studies carried out by Meeker and colleagues reported an increased level of FSH accompanying a decreased level of inhibin B, testosterone, LH, and free androgen index (FAI) in association with exposure to pyrethroids, chlorpyrifos, carbaryl, and naphthalene (Meeker et al. 2006, 2009).

Disease-based evidence on developmental toxicity of pesticides

Attention deficit hyperactivity disorder (ADHD)

ADHD is a neurodevelopmental disorder manifested by behavioral problems such as attention difficulty, hyperactivity, troubled relationship, and lowered self-esteem. There has been recently ongoing evidence on the role of environmental risk factors such as pesticide exposure in the incidence of ADHD, as such 11 epidemiological studies published during the last decade have been reviewed here. They include 4 cross-sectional, 6 cohort, and a case–control analyses on the link of ADHD with exposure to pesticides (Table 5). Elevated ORs of 1.5 and 5.1 for ADHD have been linked with organophosphoruses by two cross-sectional studies examining the exposure via urine and blood samples (Bouchard et al. 2010; Suarez-Lopez et al. 2013). Comparing the cases of ADHD with control regarding exposure to organophosphoruses indicated that the biomarkers of organophosphoruses were 2–3 times more detectable in the urine sample of the cases than that of controls (Yu et al. 2016). Furthermore, a cohort study measuring the biomarkers of organophosphoruses in the urine samples of the mothers revealed an OR of 1.3 for the risk of ADHD in association with maternal exposure to organophosphoruses (Marks et al. 2010). Another cohort study measuring the urine concentration of organophosphoruses indicated that maternal exposure to chlorpyrifos increased the risk of ADHD in boys and attention deficit (AD) in girls with respective ORs 5.5 and 5.8 (Fortenberry et al. 2014). The link between prenatal exposure to chlorpyrifos and higher incidence of ADHD with a risk estimate of 6.5 was resulted from a cohort study examining the exposure via blood level measurement of the pesticides (Rauh et al. 2006).

In association with pyrethroids, there is a cross-sectional study measuring their biomarkers in the urine and calculated an ADHD risk estimate of 2.4 in relation to exposure to pyrethroids (Wagner-Schuman et al. 2015).

Three separate cohort studies evaluated the cord blood concentration of organochlorines and found a higher incidence of ADHD complications such as irritability and behavioral problems in association with prenatal exposure to DDE (Sagiv et al. 2008, 2010; Sioen et al. 2013). In addition, higher concentration of trichlorophenol has been detected in the urine samples taken from children having ADHD for which an OR of 1.8 has been estimated by a cross-sectional study (Xu et al. 2011).

Table 5 Developmental toxicity of pesticides evidenced by diseases

Study	Type of study	Sample no.	Exposure assessment	Exposure	Associated target	OR/RR/HR (95 % CI)	*p* value	Found disorder related to
ADHD								
Wagner-Schuman (2015)	CS	687	Urine level		Pyrethroid	2.42 (1.06–5.57)		
Bouchard (2010)	CS	1139	Urine level		OPs	1.55 (1.14–2.10)		
Yu (2016)	CC	97/110	Urine level		OPs	Two-threefold	<0.05	
Marks (2010)	Co	323	Urine level	Mat.	OPs	1.3 (0.4–2.1)		
Rauh (2006)	Co	254	Plasma	Mat.	Chlorpyrifos	6.50 (1.09–38.69)		
Suarez-Lopez (2013)	CS	307	Blood ChE	–	OPs (boys)	5.14 (0.84–31.48)		Neurodevelopment
Sioen (2013)	Co	270	Cord blood	Mat.	DDE	9.95 (1.37–72.35)♀	0.023	Behavioral
Sagiv (2010)	Co	607	Cord blood	Mat.	DDE	1.8		
Sagiv (2008)	Co	788	Cord blood	Mat.	DDE	↑ risk	0.03	Irritability
Fortenberry (2014)	Co	187	Urine level	Mat.	Chlorpyrifos	5.55 (−0.19, 11.3)♂ 5.81 (−0.75, 12.4)♀	0.06 0.08	ADHD AD
Xu (2011)	CS	2546	Urine level		Trichlorophenol	1.77 (1.18–2.66)	0.006	
Autism								
Eskenazi (2007)	Co	531	Urine level	Mat.	OPs	–3.5 (–6.6–0.5)		Mental
Braun (2014)	Co	175	Blood, urine	Mat.	Chlordane	4.1 (0.8–7.3)		
Cheslack-Postava (2013)	CC	75/75	Serum	Mat.	DDE	1.79 (0.52–6.21)	0.36	
Roberts (2007)	CC	465/6975	GIS	Mat.	OCs	6.1 (2.4–15.3)		
Keil (2014)	CC	407/262	Interview	Mat.	Imidacloprid	1.3 (0.78–2.2)		
Shelton (2014)	CC	486/316	Questionnaire	Mat. (3rd) Mat. (2nd) Mat. (3rd)	OPs Chlorpyrifos Pyrethroids	2.0 (1.1–3.6) 3.3 (1.5–7.4) 1.87 (1.02–3.43)		
Developmental Delay								
Andersen (2015)	Co	133	Interview	Mat.	–			Neurobehavioral
Bosma (2000)	Co	830	Questionnaire	Occup.	–	2.02 (1.27–3.20)		Cognitive
Ribas-Fitó (2003)	Co	92	Cord blood	Mat.	p,p′-DDE	−3.5 −4.01		Mental Psychomotor scale
Viel et al. (2015)	Co	428	Urine level	–	Pyrethroids		<0.01	Verbal Memory
Zhang (2014)	Co	249	Urine level	Mat.	OPs	−1.78 (−2.12, −1.45		Neurobehavioral
Bouchard et al. (2011)	Co	329	Urine level	Mat.	OPs (DAP)	−5.6 (−9.0, −2.2)	<0.01	IQ
Engel (2011)	Co	404	Urine level	Mat.	OPs			Cognitive
Engel (2007)	Co	311	Urine level	Mat.	Malathion	2.4 (1.55–3.24)		Abnormal reflexes
Young (2005)	Co	381	Urine level	Mat.	OPs (DAP)	4.9 (1.5–16.1)		Abnormal reflexes
Horton (2012)	Co	725	Cord blood	Mat.	Chlorpyrifos	−1.71 (−3.75 to 0.32)		Working memory
Rauh (2011)	Co	265	Cord blood	Mat.	Chlorpyrifos	1.4 2.8	0.064 0.001	Full-scale IQ Working memory

Table 5 continued

Study	Type of study	Sample no.	Exposure assessment	Exposure	Associated target	OR/RR/HR (95 % CI)	*p* value	Found disorder related to
Harari (2010)	CS	87	Interview	Mat.	–	−7.1 (−12.5, −1.6) 5.32 (1.03–27.62) 6.62 (1.02–42.93)	<0.05 <0.05 <0.05	Motor speed Motor coordination Visual memory
Torres-Sánchez (2013)	Co	203	Serum	Mat.	DDE	−1.37 (−2.56 to 0.19 –0.80 (−1.52 to 0.08)	<0.05 <0.05	Cognitive index Memory
Dallaire (2012)	Co	153	Cord blood	Mat.	Chlordecone	−0.19 (−0.35,−0.03) 1.25 (1.07–1.45)	0.02 0.002	Cognitive Motor
			Breast milk	Mat.	Chlordecone	−0.14 (−0.29, −0.01)	0.07	Cognitive

♂: risk found in male, ♀: risk found in female, *MA* meta-analysis, *CC* case–control, *CS* cross-sectional, *Co* cohort, *Ec* ecological, *Mr* mortality, *Ret.* retrospective, *Pros.* prospective, *Occup.* occupational, *Env.* environmental, *Mat.* maternal, *Pat.* paternal, *Par.* parental, *Res.* residential, *Gen.* general, *GIS* geographic information system, *JEM* job exposure matrix, *OR* odd ratio, *RR* relative risk, *HR* hazard ratio, *ChE* cholinesterase, *OPs* organophosphoruses, *DDE* dichlorodiphenyldichloroethylene, *DAP* dialkyl phosphate, *ADHD* attention deficit hyperactivity disorder, *AD* attention deficit, *IQ* intelligence quotient

Autism

Autism has also been recently studied in relation to pesticide exposures for which 6 relevant studies, including two cohorts and 4 case–control analyses, all implicating on maternal exposures, have been brought in this review (Table 5). A GIS-based case–control study reported an autism OR of 6.1 in association with organochlorines, as such a risk with estimated ORs including 1.8 and 4.1 has been, respectively, reported for DDE and chlordane by two blood-measuring studies, one of which was case–control and the other one was cohort (Braun et al. 2014; Cheslack-Postava et al. 2013; Roberts et al. 2007).

Urine sample analysis for biomarkers of organophosphoruses was performed in a cohort of young Mexican–American children, and the results implicated on decreased mental development indices (beta −3.5 points per tenfold increase in prenatal biomarkers of organophosphoruses) at 24 months of age (Eskenazi et al. 2007). In addition, the Childhood Autism Risks from Genetics and Environment (CHARGE) study compared the cases with control regarding residential proximity to agricultural pesticides during pregnancy and reported that exposure to organophosphoruses and pyrethroids during the third trimester and chlorpyrifos during the second trimester of pregnancy was associated with increased risk of autism (ORs ranging from 1.9 to 3.3) in the offspring (Shelton et al. 2014). An autism OR of 1.3 in association with maternal exposure to imidacloprid has also been found by a questionnaire-based case–control study (Keil et al. 2014).

Developmental delay

Developmental impairments, manifested by different features such as cognitive, memory, verbal, visual, behavioral, and motor dysfunctions, have been evaluated in association with pesticide exposures by 14 epidemiological studies, including 13 cohorts as well as one cross-sectional analyses brought in this review (Table 5). The results of a questionnaire-based cross-sectional study implicated on impaired motor speed, motor coordination, and visual memory in association with maternal exposure to any kind of pesticides (Harari et al. 2010). Maternal and occupational exposures to ever used pesticide have also been shown to link with, respectively, neurobehavioral deficits and cognitive dysfunction by two separate cohort studies (Andersen et al. 2015; Bosma et al. 2000). All of the remaining 10 cohort studies have evaluated the risk of developmental impairments in association with maternal exposure to specified classes of pesticides measured in biological samples. Urine sample analysis was performed for detecting biomarkers of organophosphoruses as well as malathion itself by five cohort studies whose results implicated on reduced neurobehavioral development, cognitive development, and intelligence quotient (IQ) as well as increased abnormal reflexes in children having maternal exposure to the mentioned pesticides (Bouchard et al. 2010; Engel et al. 2007, 2011; Young et al. 2005; Zhang et al. 2014). Furthermore, maternal exposure to chlorpyrifos, measured by cord blood analysis in two separate cohort studies, was shown to be associated with lower

working memory and full-scale IQ in childhood (Horton et al. 2012; Rauh et al. 2011).

Regarding developmental impairments in relation to organochlorines, there are two cohort studies on maternal exposure to DDE which has been linked with reduced mental and psychomotor scale, general cognitive index, and memory function (Ribas-Fito et al. 2003; Torres-Sanchez et al. 2013). There is another cohort study analyzing cord blood and breast milk samples and reported both decreased cognitive and motor development due to prenatal and decreased cognitive development due to postnatal exposure to chlordecone (Dallaire et al. 2012).

Disease-based evidence on metabolic toxicity of pesticides

Diabetes

Diabetes has become epidemic because of its prevalent risk factors, including Western diet and physical inactivity in the modern life, though the environmental risk factors, particularly pesticide exposures, have also been linked to its development (Bahadar et al. 2014; Mostafalou and Abdollahi 2012c). Herein, a total of 28 studies including 19 cross-sectional, three case–control, five cohort, and an ecological analyses of the link between human exposure to various pesticides and incidence of diabetes have been reviewed (Table 6). Except one questionnaire-based cross-sectional study estimating gestational diabetes OR of 2.2 in association with occupational exposure to any kind of pesticides (Saldana et al. 2007), the other studies reported the risk of diabetes in relation to specified classes of pesticides. The cross-sectional association of the serum concentration of organochlorines with diabetes and insulin resistance was investigated using data resulted from the National Health and Examination Survey 1999–2002, and adjusted ORs for diabetes and insulin resistance were estimated as 37.7 and 7.5, respectively (Lee et al. 2006, 2007a). Recently, a meta-analysis of 22 studies on the link of exposure to pesticides with incidence of human diabetes resulted in a risk estimate of about 1.7 for organochlorines (Evangelou et al. 2016). Among organochlorines specifically associated with diabetes, the highest number of evidence belongs to the DDE given 11 elevated diabetes risk estimates ranging from 1.3 to 12.7 in 7 cross-sectional, 2 case–control, and 2 cohort studies examining the exposure via blood sample analysis (Airaksinen et al. 2011; Codru et al. 2007; Cox et al. 2007; Lee et al. 2011a; Philibert et al. 2009; Rignell-Hydbom et al. 2007, 2009; Son et al. 2010; Turyk et al. 2009a, b; Ukropec et al. 2010). Furthermore, there has been a published meta-analysis of 18 studies evaluating the incidence of diabetes in relation to DDE, and a significant elevated risk estimate of 1.3 has been analyzed (Tang et al. 2014a). The other organochlorines for which elevated diabetes risk estimates have been found include DDT with 5 reported ORs ranging from 1.9 to 10.6, HCB with five reported ORs ranging from 2.8 to 6.8, trans-nonachlor with 5 reported ORs ranging from 2.2 to 8.1, oxychlordane with four reported ORs ranging from 2 to 6, heptachlor with three reported ORs ranging from 1.7 to 3.1, β-HCH with two reported ORs including 2.1 and 8.2, mirex with two reported ORs including 2.1 and 3.7, aldrin with an OR of 1.5, dieldrin with an OR of 2, chlordane with an OR of 1.6, and alachlor with an OR of 1.3 (Airaksinen et al. 2011; Codru et al. 2007; Cox et al. 2007; Everett et al. 2007; Gasull et al. 2012; Kim et al. 2014; Lee et al. 2010, 2011a; Montgomery et al. 2008; Patel et al. 2010; Son et al. 2010; Starling et al. 2014; Ukropec et al. 2010; Wu et al. 2013). Moreover, a cross-sectional association of occupational exposure to pentachlorophenol with hyperglycemia manifested by fasting blood glucose higher than 100 mg/dl has been found in retired workers of a pentachlorophenol-manufacturing plant (Chang et al. 2012).

Regarding organophosphoruses, there is a questionnaire-based cross-sectional study reporting that occupational exposure to organophosphorus insecticides is significantly associated with hyperglycemia (Malekirad et al. 2013). Parathion, phorate, fonofos, and trichlorfon are organophosphorus insecticides for which, respectively, elevated risk estimates including 1.6, 1.6, 1.6, and 2.6 have been calculated by two separate questionnaire-based cohort studies (Montgomery et al. 2008; Starling et al. 2014).

Occupational exposure to pyrethroids has also been evaluated by two questionnaire-based cross-sectional studies, one of which reported significantly elevated diabetes OR of 1.5, while the other estimated an OR of 18.5 in association with a 5.6 % increase in HbA1c (Hansen et al. 2014a; Wang et al. 2011b).

A cohort study conducted by Montgomery and colleagues indicated that occupational exposure to the herbicide cyanazine is significantly associated with increased risk of diabetes given by an OR of about 1.4 (Montgomery et al. 2008). Occupational exposure to the phenoxy herbicides has also been linked with elevated incidence of diabetes with an estimated HR of 1.6 by a questionnaire-based cohort study (Starling et al. 2014). Furthermore, association of diabetes with exposure to Agent Orange was revealed by a cross-sectional and an ecological study estimating respective ORs of 2.7 and 1.04 among Korean Vietnam veterans (Kim et al. 2003; Yi et al. 2014).

Table 6 Metabolic toxicity of pesticides evidenced by diseases

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value	Found risk
Diabetes								
Lee (2006)	CS	2016	Serum level	–	OCs	37.7 (7.8–182)	<0.001	
Kim (2003)	CS	1378	Military record	–	Agent Orange	2.69		
Yi et al. (2014)	Ec	111726	GIS	Occup.	Agent Orange	1.04 (1.01–1.07)		
Kim (2014)	CS	50	VAT/SAT	–	DDT	9.0 (1.3–62.9)	0.02	
Son (2010)	CC	40/40	Serum	–	Oxychlordane Trans-nonachlor Heptachlor epoxide Hexachloroben-zene β-HCH Mirex DDE DDT	6.0 (1.3–517.4) 8.1 (1.2–53.5) 3.1 (0.8–12.1) 6.1 (1.0–36.6) 8.2 (1.3–53.4) 3.7 (0.9–15.8) 12.7 (1.9–83.7) 10.6 (1.3–84.9)	<0.01 0.02 0.05 0.03 0.02 0.08 <0.01 0.02	
Wang (2011b)	CS	3080	Questionnaire	Occup.	Pyrethroids	1.48 (1.23–1.77)	<0.001	
Chang (2012)	CS	1167	Retired workers	Occup.	Pentachlorophe-nol	7.22 (4.04–12.90)		↑FBG
Malekirad (2013)	CS	374	Questionnaire	Occup.	OPs	–	<0.001	↑FBG
Hansen (2014a)	CS	208	Questionnaire	Occup.	Pyrethroids	18.5 (5.5–62.5)		↑HbA1c
Starling (2014)	Co	13,637	Interview	Occup.	Fonofos Phorate Parathion Dieldrin 2,4,5-T/2,4,5-TP	1.56 (1.11–2.19) 1.57 (1.14–2.16) 1.61 (1.05–2.46) 1.99 (1.12–3.54) 1.59 (1.00–2.51)		
Patel (2010)	CS	503–3318	EWAS	–	Heptachlor epoxide	1.7	<0.001	
Lee (2010)	Nested CC	90/90	Serum level	–	trans-Nonachlor Oxychlordane Mirex	4.8 (1.7–13.7) 2.0 (0.8–5.0) 2.1 (0.8–5.5)	0.06	
Montgomery (2008)	Co	33,457	Questionnaire	Occup. (>100 days)	Aldrin Chlordane Heptachlor Trichlorfon Alachlor Cyanazine	1.51 (0.88–2.58) 1.63 (0.93–2.86) 1.94 (1.02–3.69) 2.47 (1.10–5.56) 1.31 (1.11–1.55) 1.38 (1.10–1.72)	0.08 0.05 0.02 0.02 0.001 0.004	
Lee (2007a)	CS	749	Serum level	–	OCs	7.5 (2.3–23.9)	<0.01	↑HOMA-IR
Saldana (2007)	CS	11,273	Questionnaire	Occup.	–	2.2 (1.5–3.3)		Gestational
Airaksinen (2011)	CS	1988	Serum level	–	Oxychlordane trans-Nonachlor DDE	2.08 (1.18–3.69) 2.24 (1.25–4.03) 1.75 (0.96–3.19)		T2DM
Philibert (2009)	CS	101	Serum level	–	DDE	6.1 (1.4–27.3)		
Ukropec (2010)	CS	2047	Serum level	–	DDE DDT	1.86 (1.17–2.95) 2.48 (1.77–3.48)		
Gasull (2012)	CS	886	Serum level	–	HCB	2.8		
Rignell-Hydbom (2007)	CS	543	Serum level	–	DDE	1.3 (1.1–1.6)		
Everett (2007)	CS	1830	Serum level	–	DDT	2.69 (1.35–5.36)		
Cox (2007)	CS	1303	Serum level	–	Oxychlordane trans-Nonachlor DDE DDT β-HCH	3.1 (1.1–9.1) 2.9 (1.3–6.4) 2.6 (1.2–5.8) 1.9 (1.0–3.7) 2.1 (1.0–4.3)		

Table 6 continued

Study	Type of study	No. of samples	Exposure assessment	Exposure	Target pesticide	OR/RR/HR (95 % CI)	*p* value	Found risk
Codru (2007)	CS	352	Serum level	–	DDE HCB	6.2 (1.8–21.9) 6.8 (2.3–20.3)		
Turyk (2009a)	CS	503	Serum level	–	DDE	3.6	0.009	
Lee (2011a, b)	Co	725	Serum level	–	trans-Nonachlor, DDE, HCB	3.4 (1.0–11.7)	0.03	
Turyk (2009b)	Co	471	Serum level	–	p,p′-DDE	7.1 (1.6–31.9)		
Wu (2013)	Co	1095	Serum level	–	HCB	3.1 (1.3–7.7)		
(Rignell-Hydbom 2009)	Nested CC	39/39	Serum level	–	DDE	5.5 (1.2–25.0)		T2DM
Tang (2014a, b)	MA	18 studies	–	–	DDE	1.33 (1.15–1.54)	0.0007	
Evangelou (2016)	MA	22 studies	–	–	OCs	1.68 (1.37, 2.07)	8×10^{-7}	
Obesity								
Bachelet (2011)	CS	1055	Serum level	–	DDE	1.39 (1.13–1.70)		↑BMI
Jakszyn (2009)	CS	953	Serum level	–	DDE, β-HCH, HCB			↑BMI
Lee (2006)	CS	2016	Serum level	–	OCs		<0.01	↑BMI
Lee (2012)	CS	970	Serum level	–	DDE DDE HCB trans-Nonachlor	1.7 (0.9–3.1)♀ 2.6 (1.1–5.7)♂ 3.4 (1.6–7.5)♂ 2.5 (1.1–5.6)♂	<0.05 <0.01 <0.01 0.04	
Dirinck (2011)	CS	145	Serum level	–	β-HCH		<0.001 <0.05	↑BMI ↑HOMA-IR
Ibarluzea (2011)	CS	1259	Serum level	–	HCB, β-HCH		<0.001	
Lee (2011a, b)	Co	5115	Serum level	–	DDE, DDT		0.05	
Glynn (2003)	CS	205	Serum level	–	DDE β-HCH HCB	3.9 (1.3–6.6) 3.8 (2.1–5.6) 1.1 (0.5–2.3)		

♂: risk found in male, ♀: risk found in female, *MA* meta-analysis, *CC* case–control, *CS* cross-sectional, *Co* cohort, *Ec* ecological, *Mr* mortality, *Ret*. retrospective, *Pros*. prospective, *Occup*. occupational, *Env.* environmental, *Mat.* maternal, *Pat.* paternal, *Par*. parental, *Res*. residential, *Gen*. general, *GIS* geographic information system, *JEM* job exposure matrix, *OR* odd ratio, *RR* relative risk, *HR* hazard ratio, *EWAS* environment-wide association study, *OPs* organophosphoruses, *OCs* organochlorines, *2,4-D* 2,4-dichlorophenoxyacetic acid, *2,4,5-T* 2,4,5-trichlorophenoxyacetic acid, *HCB* hexachlorobenzene, *β-HCH* beta-hexachlorocyclohexane, *DDT* dichlorodiphenyltrichloroethane, *DDE* dichlorodiphenyldichloroethylene, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *FBG* fasting blood glucose, *HbA1c* Hemoglobin A1c, *HOMA-IR* homeostatic model assessment—insulin resistance, *T2DM* type 2 diabetes mellitus, *BMI* body mass index

Obesity

Obesity, a condition involving excessive body fat, may not be categorized alone as a disease, but increases the risk of other serious health problems, and recent environmental health studies have shown that obesity may have other risk factors than excess calorie intake and physical inactivity. Exposure to pesticides especially those categorized as persistent organic pollutants has been linked to increased incidence of obesity by epidemiological studies, some of which including 7 cross-sectional and a cohort analyses have been reviewed in this study (Table 6). All of these studies have evaluated exposure to different organochlorine via blood sample analysis of participants, and higher risk of obesity, manifested by increased body mass index (BMI), has been linked with DDE, DDT, HCB, β-HCH, trans-nonachlor, and oxychlordane exposure (Bachelet et al. 2011; Dirinck et al. 2011; Glynn et al. 2003; Ibarluzea et al. 2011; Jakszyn et al. 2009; Lee et al. 2006, 2011b, 2012).

Discussion and conclusion

Our systematic review of 43 human diseases divided into six broad groups of toxicities in association with exposure to pesticides shows that recorded evidence belongs to the, in order from the highest to the lowest, carcinogenicity, neurotoxicity, reproductive toxicity, metabolic toxicity, pulmonotoxicity, and developmental toxicity of pesticides (Fig. 2). Further, carcinogenicity is considered as the most reported toxicity studied in relation to each class of

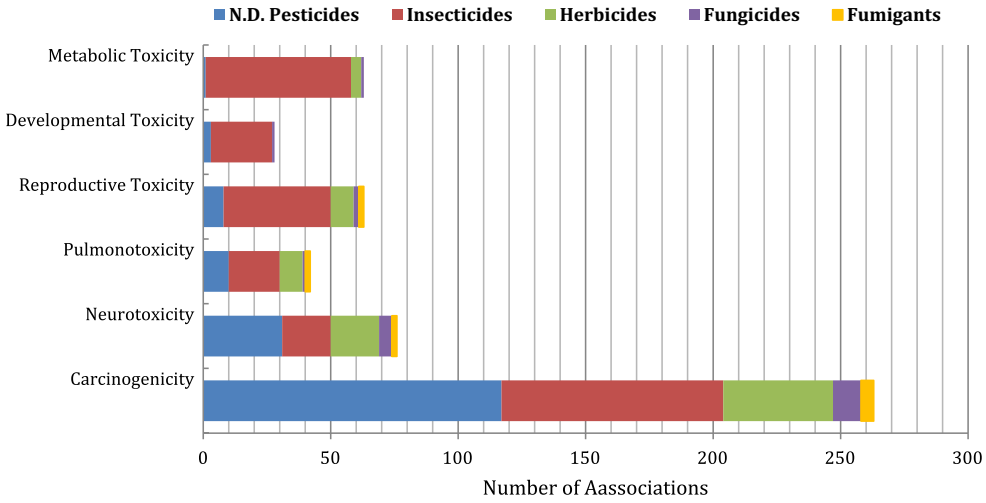

Fig. 2 Schematic diagram showing the weight of evidence on the toxicities of pesticides. *ND* not determined

pesticides, including insecticides, herbicides, fungicides, and fumigants (Fig. 3).

The link of cancer incidence with human exposure to pesticides has been presented based on 28 cites of cancers divided into nine body organ systems among which the most studied associations are related to the malignancies of the hematopoietic system notably leukemia and lymphoma. Brain tumors, prostate cancer, breast cancer, colorectal cancer, pancreatic cancer, and lung cancer have then the most prevalent evidence in association with exposure to pesticides. Among studies focusing on the link of cancers with specified class of pesticides, insecticides have been located in the first place, followed by herbicides, fungicides, and fumigants (Table 7). It should be noted that insecticides and herbicides are generally considered as the most used pesticides which may explain the differences in the rate of their association with cancer incidences (Mostafalou et al. 2013). In the same way, the differences in the prevalence of cancers can exemplify the different degrees of correlation between pesticide exposures and incidence of each site of cancers. Nevertheless, the body of evidence on this link is so huge that the role of pesticides in cancer development cannot be doubted. In addition to epidemiological evidences, such a confirmation can also be derived from experimental studies investigating the mechanisms by which carcinogenicity of pesticides is mediated.

As known, heritable changes in the genes controlling cell cycle, via genetic or epigenetic mechanisms, are responsible for cancer initiation by chemical carcinogens. During the past half century, the progress of molecular biology techniques has made it possible to largely investigate carcinogenicity of widely used chemicals, particularly pesticides. Various pathways leading to genetic or epigenetic alterations of the cell have been explored regarding pesticides tested ex vivo, in vitro, in vivo, and in human. Since genetic damages at the level of both DNA and chromosomes are considered as likely mechanisms of carcinogenicity, the huge body of evidence on genotoxicity of pesticides brought a global concern on carcinogenesis of these chemicals on which human life has become so dependent (Mostafalou and Abdollahi 2012b; Shadnia et al. 2005). In addition to genetic toxicity, epigenetic alterations, including the methylation and acetylation of DNA and its accompanying proteins, histon, have been shown to be induced by some classes of pesticides specially those categorized as endocrine disruptors (Maqbool et al. 2016).

Neurotoxicity has been ordered as the second ranked toxicity of pesticides according to the associations brought in this review, which have been derived from evidence related to the link of pesticides with just three neurodegenerative diseases including Alzheimer, Parkinson, and ALS (Table 8). In comparison with the other toxicities, this can be indicative of a high susceptibility to the neurotoxicity of pesticides, though the incidence of age-related neurodegenerative diseases including Alzheimer and Parkinson itself has been increased, somewhat, due to elevated life expectancy of human in today's world. It should be noted that the primary mechanism of toxicity for the main groups of pesticides, particularly insecticides such as organochlorines, organophosphoruses, and carbamates, is through targeting components of the nervous system (Abdollahi and Karami-Mohajeri 2012; Karami-Mohajeri et al. 2014). However, evidence on the neurotoxicity of pesticides specifically brought in this review shows that the risk of insecticides is somehow similar to that of herbicides among which the most frequently reported evidences are related to the link of paraquat and Parkinson disease. Perhaps, such

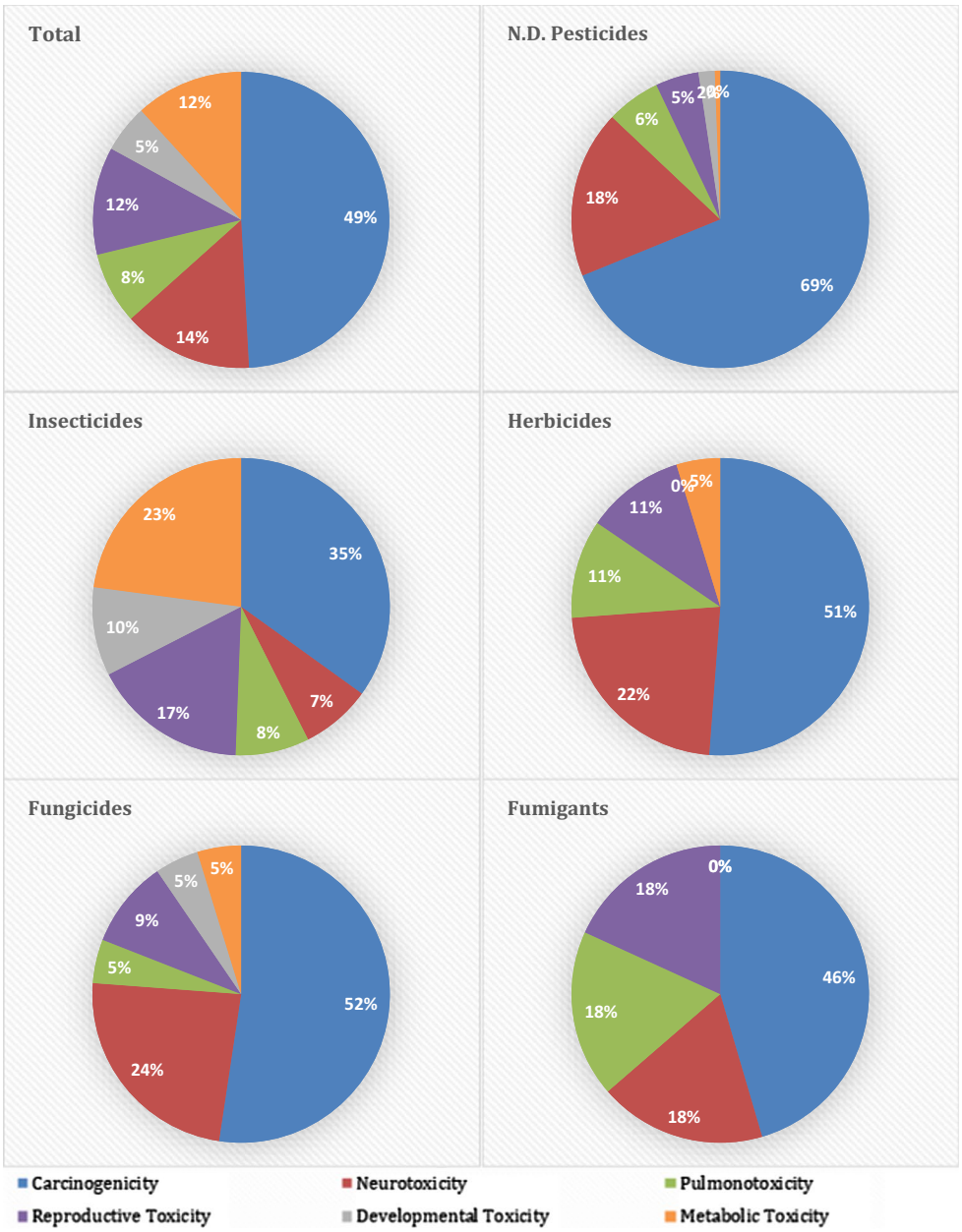

Fig. 3 Schematic charts showing the percent of toxicities attributed to each category of pesticides. *ND* not determined

inspirations to search the link of paraquat with Parkinson by environmental health scientists originate from the use of this herbicide as a drug to induce Parkinson disease in experimental investigating models. In fact, paraquat acts through overproduction of reactive oxygen species which is held in common with toxicity of many other pesticides, and this can give a clue to trace the role of such pesticides in Parkinson disease.

Reproductive and metabolic toxicities have been ordered as the next prevalent toxicities of pesticides in both of which insecticides have adopted the most associations. In these toxicities, the highest share is allocated to the organochlorine insecticides whose physicochemical properties such as high lipid solubility and crossing biological membranes made environmental health scientist much suspicious to their disrupting effects on endocrine and reproductive systems (Table 8). In addition, their dioxin-like biological effect on the nuclear receptors, particularly aryl hydrocarbon receptors, which are involved in the metabolic pathways, has provided enough stimulation to search the role of organochlorine insecticides in the metabolism at cellular or the whole organism level. Although most of the organochlorine insecticides have been widely banned, their ability to persist in the environment for a long period of time made environmentalists to continue their research on the health problems associated with human exposure. For example, lots of evidence on the metabolic disrupting effects of persistent organochlorine

Table 7 Association of cancer incidence with different classes of pesticides

Cancers of	Association with			
	Any pesticide (no.)	Targeted class of pesticides (no.)	Chemical class of pesticides (no.)	Single pesticides
Nervous system	19	Insecticides (1) Herbicides (1) Fungicides (1)	OPs (1) Carbamates (1)	Chlorpyrifos, bufenacarb, paraquat, coumaphos, metribuzin
Digestive system	19	Insecticides (1) Herbicides (2) Fungicides (1)	OCs (1)	Atrazine, 2,4-D, chlordane, trifluralin, methyl bromide Aldicarb, dicamba, imazethapyrc, chlorpyrifos, S-ethyl-N,N-dipropyl, thiocarbamate, trifluralin, acetochlor, HCB, DDT, arsenicals, EPTC, pendimethalin, acetochlor
Hematopoietic system	30	Insecticides (4) Herbicides (5) Fungicides (2) Fumigants (1)	OPs (2) Carbamates (2) OCs (1) Pyrethroids (1) Phenoxy (3)	Crotoxyphos, dichlorvos, famphur, methoxychlor, terbufos, diazinon, Agent Orange, chlorpyrifos, dichlorprop, malathion, diazinon, terbufos, coumaphos, fonofos, carbaryl, lindane, DDT, dieldrin, chlordane, toxaphene, oxychlordane, cis-nonachlor, β-HCH, pentachlorophenol, atrazine, glyphosate, 2,4-D, captan, carbaryl
Bone and soft tissues	7	–	Phenoxyacetic acid (1)	Metolachlor
Urinary system	12	–		Imazethapyr, HCH, DDT
Male reproductive	9	Herbicides (1)	OCs (2) Triazines (1)	Agent Orange, aldrin, malathion (2), fonofos (2), terbufos (2), coumaphos, methyl bromide (3), DDT, carbaryl, chlordecone, ziram, dichlone, azinphos, simazine, maneb, diazinon, parathion, DDE, HCB
Female reproductive	7	–	OPs (1) Triazines (1)	2,4,5-T, captan, DDT (3), DDE (2), DDD, β-HCH (2), HCB, PCTA, diazinon
Head & neck	7	Insecticides (1)	–	Lindane
Lung cancer	4	–	–	Acetochlor, terbufos, dicamba, metolachlor, diazinon, chlorpyrifos, pendimethalin
Thyroid cancer	1	–	–	Alachlor, malathion, atrazine
Skin cancer	2	–	–	Acetochlor, maneb, parathion, carbaryl

OPs organophosphoruses, *OCs* organochlorines, *2,4-D* 2,4-dichlorophenoxyacetic acid, *2,4,5-T* 2,4,5-trichlorophenoxyacetic acid, *EPTC* S-ethyl-N,N-dipropylthiocarbamate, *HCB* hexachlorobenzene, *HCH* hexachlorocyclohexane, *PCTA* pentachlorothioanisole, *DDT* dichlorodiphenyltrichloroethane, *DDE* dichlorodiphenyldichloroethylene, *DDD* dichlorodiphenyldichloroethane

insecticides within the context of insulin resistance such as diabetes and obesity have been gathered during the past two decades in which there was no extensive use of these chemicals formally (Karami-Mohajeri and Abdollahi 2011). These metabolic effects of organochlorine insecticides have been attributed to their ability to easily cross through biological membranes and accumulate in adipose tissues which can lead to the inflammation in insulin-responsive tissues (Mostafalou 2016). Furthermore, there is lots of experimental evidence on the role of organophosphorus insecticides in disrupted metabolism of glucose in both insulin-secreting and insulin-responsive tissues which

Table 8 Association of non-cancerous human toxicities with different classes of pesticides

Disease	Association with			
	Any pesticide (no.)	Targeted class of pesticides (no.)	Chemical class of pesticides (no.)	Single pesticides
Alzheimer	3	Herbicides (1) Fumigants (1)	OPs (1) OCs (1)	DDE
Parkinson	17	Insecticides (2) Herbicides (2) Fungicides (1)	OPs (1) OCs (1)	Atrazine, simazine, alachlor, metolachlor, paraquat (7), maneb (3), rotenone (2), ziram, methomyl, chlorpyrifos (2), propargite, diazinon, 2,4-D, β-HCH
ALS	11	Insecticides (1) Herbicides (2) Fumigants (1)	OCs (2) Pyrethroids (1)	2,4-D, Agent Orange
Asthma	6	Herbicides (1) Fumigants (1)	OPs (1) Carbamates (2)	Agent Orange (2), DDE (2), coumaphos, heptachlor, parathion, CCL4/CS2, ethylendibromide, pendimethalin, aldicarb, HCB
Chronic bronchitis	2	–	–	Heptachlor, dichlorvos, DDT, methyl bromide, cyanazine, paraquat, Agent Orange
Wheeze	2	–	–	Parathion, atrazine, chlorpyrifos, chlorimuron-ethyl, DDE, HCB
LRTIs		–	–	DDE (2), HCB
Infertility	1	Herbicides (1) Fumigants (1)	Phenoxyacetic acid (1)	DDE (3), atrazine, glyphosate (2), thiocarbamates, HCH (2), mirex, DDT (2)
Low quality of semen	1	–	OPs (5) Carbamates (1) Pyrethroids (2)	DDT, DDE, HCH, arachlor, diazinon, atrazine, abamectin
Birth defects	6	Insecticides (2) Herbicides (1)	OPs (1)	Carbaryl, chlorpyrifos, diazinon, atrazine (2), methyl bromide, DDT (2), HCH (2), DDE, aldicarb, dimethoate, phorate,
Changed sex functions	–	–	Pyrethroids (1)	DDE (2), HCB, chlorpyrifos, carbaryl, naphthalene
ADHD	–	–	OPs (5) Pyrethroids (1)	Chlorpyrifos, DDE (3), trichlorophenol
Autism	–	–	OCs (1) OPs (2) Pyrethroids (1)	DDE, chlordane, chlorpyrifos, imidacloprid
Developmental delay	3	–	OPs (1)	Malathion, chlorpyrifos, DDE (2), chlordecone
Diabetes	1	–	OCs (3) OPs (1) Pyrethroids (1) Phenoxyacetic acid (1)	DDE (12), DDT (5), HCB (5), trans-nonachlor (5), oxychlordane (4), heptachlor (3), β-HCH (2), mirex (2), aldrin, dieldrin, chlordane, alachlor, pentachlorophenol, parathion, phorate, fonofos, trichlorfon, cyanazine, Agent Orange (2)
Obesity	–	–	–	DDE, DDT, HCB, β-HCH, trans-nonachlor, oxychlordane

The number of associations is brought in the parentheses

OPs organophosphoruses, *OCs* organochlorines, *2,4-D* 2,4-dichlorophenoxyacetic acid, *2,4,5-T* 2,4,5-trichlorophenoxyacetic acid, *HCB* hexachlorobenzene, *β-HCH* beta-hexachlorocyclohexane, *DDT* dichlorodiphenyltrichloroethane, *DDE* dichlorodiphenyldichloroethylene, *DDD* dichlorodiphenyldichloroethane

have been implicated in prediabetic effects of this chemical class of pesticides (Jamshidi et al. 2009; Mostafalou et al. 2012b; Nili-Ahmadabadi et al. 2013; Pakzad et al. 2013; Rahimi and Abdollahi 2007; Teimouri et al. 2006; Pournourmohammadi et al. 2005).

Polmunotoxicity exhibited by diseases such as asthma and chronic bronchitis in association with occupational and environmental exposures has a long history of evidence, and pesticide exposure in this case had a similar pattern. But the association of pesticide exposures with childhood respiratory problems such as asthma and low respiratory tract infections has been recently much considered in regard to maternal or parental exposure to pesticides.

In this context, it should be noted that the link of pesticide exposures with developmental toxicity manifested by ADHD, autism, and developmental delays has been recently evidenced in the population studies concerning maternal or paternal exposure to pesticides in children. Although the lifetime of such an issue is almost short, a remarkable amount of studies have been conducted on the role of parental exposure to pesticides in developmental deficits presented in children. In this regard, most of the associations have been attributed to insecticides particularly organophosphoruses which have been widely used during the last few decades. The proven neural and oxidative stress-induced toxicities of organophosphoruses (Abdollahi et al. 2004a; Akhgari et al. 2003; Bayrami et al. 2012; Ranjbar et al. 2002) have inspired toxicologist to investigate the role of parental exposures in developmental and neuro-developmental disorders such as ADHD and autism, which have recently become prevalent in children, and positive associations have been traced for such risks.

Taken together, going through the mechanistic evidence on the toxicity of pesticides in association with human health disorders clears some common mechanisms, including oxidative stress, mitochondrial dysfunction, inflammatory responses, immune dysregulation, and endocrine disruption (Abdollahi et al. 2004b; Karami-Mohajeri and Abdollahi 2013; Mokarizadeh et al. 2015). In this way, induction of oxidative stress has been much highlighted in the studies focusing on the protective role of antioxidants such as cysteine and selenium against toxic effects of pesticides so that antioxidant therapy has been proposed and investigated for management of pesticide poisoning in human (Fakhri-Bafghi et al. 2016; Mostafalou et al. 2012a; Shadnia et al. 2011). Unveiling the link of oxidative stress with aging and age-related diseases, and inflammation with obesity and metabolic disorders is instances for ongoing exploration on the role of theses mechanisms in rising human diseases (Abdollahi et al. 2014). Given that these mechanisms and the others are gradually scrutinized in the pathology of newly focused diseases, it would be important that future studies pursue the current state of the science on the toxicity of pesticides with systematic approaches coordinated with new discoveries in the modality of human diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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