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Association of pesticide exposure with human congenital abnormalities

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ABSTRACT

Human pesticide exposure can occur both occupationally and environmentally during manufacture and after the application of indoor and outdoor pesticides, as well as through consumption via residues in food and water. There is evidence from experimental studies that numerous pesticides, either in isolation or in combination, act as endocrine disruptors, neurodevelopmental toxicants, immunotoxicants, and carcinogens. We reviewed the international literature on this subject for the years between 1990 and 2017. The studies were considered in this review through MEDLINE and WHO resources. Out of the $n = 1817$ studies identified, $n = 94$ were reviewed because they fulfilled criteria of validity and addressed associations of interest. Epidemiological studies have provided limited evidence linking pre- and post-natal exposure to pesticides with cancers in childhood, neurological deficits, fetal death, intrauterine growth restriction, preterm birth, and congenital abnormalities (CAs). In this review, the potential association between pesticide exposure and the appearance of some human CAs (including among others musculoskeletal abnormalities; neural tube defects; urogenital and cardiovascular abnormalities) was investigated. A trend towards a positive association between environmental or occupational exposure to some pesticides and some CAs was detected, but this association remains to be substantiated. Main limitations of the review include inadequate exposure assessment and limited sample size. Adequately powered studies with precise exposure assessments such as biomonitoring, are warranted to clarify with certainty the potential association between pesticide exposure and human CAs.

1. Introduction

According to the Food and Agriculture Organization of the United Nations (FAO), a pesticide is a chemical, biological, or mixture of agents used for the prevention, control, or extermination of pests. Pests including human/animal disease vectors and unwanted species of animals/plants (weeds), cause harm during/interfere with the production, processing, storage, transport or food marketing, agricultural commodities, wood products or animal feedstuffs, or agents administered to animals for controlling pests in or on their bodies (FAO, 2005). Pesticides are extensively tested chemicals. Yet their widespread use estimated to be 2×10^9 kg worldwide annually, continues to raise significant public concerns regarding safety (Grube et al., 2011; Kiely et al., 2004). Human exposure to pesticides can occur environmentally, through consumption via residues in food and water, as well as occupationally, during or after indoor/outdoor application (van den Berg et al., 2012).

Many pesticides act as endocrine disruptors (EDs), neurodevelopmental

Abbreviations: CAs, Congenital abnormalities; CVAs, Cardiovascular abnormalities; DDE, Dichlorodiphenyldichloroethylene; DDT, Dichlorodiphenyltrichloro ethane; EDs, Endocrine disruptors; FSH, Follicle-stimulating hormone; HCB, Hexachlorobenzene; HCH, beta-hexachlorocyclohexane; LH, Luteinizing hormone; MSAs, Musculoskeletal abnormalities; NTDs, Neural tube defects; OCs, Organochlorines; OPs, Organophosphates; UGAs, Urogenital abnormalities; VSD, Ventricular septal defect

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toxicants, immunotoxicants and carcinogens in animals and humans (Bahadar et al., 2015; Blair et al., 2015). The nervous system is particularly susceptible to many pesticides of several distinct chemical classes. A number of studies show that prenatal and early childhood exposure to organophosphates (OPs) is associated with neurodevelopmental effects (Munoz-Quezada et al., 2013). A meta-analysis concluded that low-dose exposures to OPs were linked to reduced psychomotor speed, executive function, visuospatial ability as well as work and visual memory (Ross et al., 2013). Other studies have also associated organochlorines (OCs), OPs and other pesticides with dementias such as Alzheimer's disease, amyotrophic lateral sclerosis, but mainly with Parkinson's disease (Blair et al., 2015; Mostafalou and Abdollahi, 2013).

Other epidemiological studies have linked pesticide exposure to higher risks for chronic health disorders, including infectious diseases. Pesticides dysregulate and disturb immune responses by causing alterations to the normal structure of the immune system. Contaminated breast milk due to maternal exposure revealed pronounced immunological deficiencies and increased risks of infections, mainly meningitis and inner ear infections (World Resources Institute: Pesticides and the Immune System. The Public Health Risks). Furthermore, epidemiological and experimental studies displayed evidence for carcinogenic effects of exposure to pesticides (Petrakis et al., 2017). Some experimental studies support that there is no evidence for pesticide mutagenicity. However, epigenetic mechanisms underlie its association with cancer. Epidemiological studies reported several sites of cancer which were linked to pesticide exposure, including the lungs, the prostate, and the lymphatic and hematopoietic systems (Bonner et al., 2017). Childhood cancer has also been associated with environmental and parental occupational pesticide exposure (World Resources Institute: Pesticides and the Immune System. The Public Health Risks).

Several classes of pesticides such as 1,2-dibromo-3-chloropropane, vinclozolin, and OPs interfere with normal male reproductive system function (Petrakis et al., 2017), leading to reduction and/or inhibition of spermatogenesis; sperm count, viability, density and motility impairment; abnormal sperm morphology; induction of deoxyribonucleic acid damage; seminiferous tubule degeneration; and reduction of epididymis, prostate or seminal vesicle weight. They may also alter the follicle-stimulating hormone (FSH), the luteinizing hormone (LH), and testosterone levels; lower activity/level of antioxidant enzymes in the testes; and inhibit testicular steroidogenesis. Furthermore, dichloro-diphenyl-trichloroethane (DDT) and its metabolites have estrogenic effects on males (Mehrpour et al., 2014). Pesticides and EDs have several biological adverse effects in females as well (Petrakis et al., 2017). Most of them are related to the development of the reproductive system and are specifically attributed to folliculogenesis (Sifakis et al., 2017). The primordial follicles change to primary, pre-antral and antral follicles. Bisphenol A, methotrexate, 2,3,7,8-Tetrachlorodibenzodioxin and phthalates are examples of EDs that can cause toxic effects on the development of follicles, leading to infertility. Bisphenol A has been highly associated with toxicity in the female reproductive system, polycystic ovary syndrome and endometriosis. Several studies correlated bisphenol A with the female reproductive system intoxication (Caserta et al., 2014; Kandaraki et al., 2011; Souter et al., 2013) as a high bisphenol A concentration in plasma or urine has been associated with lower amounts of antral follicle, decreased number of mature and fertilized oocytes, lower peak E2 in response to hyperstimulation with human chorionic gonadotrophin, and increased probability for implantation failure in women undergoing fertility treatments (Caserta et al., 2013; Ehrlich et al., 2012b; Ehrlich et al., 2012a). The toxic effects caused by pesticides and EDs on the human reproductive system have been associated with the dose, frequency and route of exposure as well as with the genotypic characteristics of the exposed individuals (Hernandez et al., 2013). Additionally, human exposure to pesticides has been associated with genetic/epigenetic modifications and chronic diseases (Mostafalou and Abdollahi, 2013), while epidemiological studies have revealed associations of pre- and post-natal exposure to pesticides with fetal death, neurological deficits, childhood cancers, intrauterine growth restriction, preterm birth and birth defects (Weselak et al., 2007).

Congenital abnormalities (CAs) are structural or functional abnormalities (e.g. metabolic disorders) that occur in utero and can be identified prenatally, at birth, or later in life. They consist of a diverse group of disorders attributed to single gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens and micronutrient malnutrition (WHO/CDC/ICBDSR, 2014). Although the majority of CAs cannot be linked to a specific cause, prenatal indoor exposure to pesticides (chlorpyrifos, OPs, vinclozolin etc.) and herbicides (triazines, metolachlor etc.) has been suggested to increase teratogenicity risk (Stillerman et al., 2008) due to the high susceptibility of most fetal systems during certain periods of development (Selevan et al., 2000).

2. Objective and methods of the review

This review aimed to elucidate the potential association between exposure to pesticides and development of the most prevalent, among others, human CAs according to the National Birth Defects Prevention Network (Parker et al., 2010); namely musculoskeletal abnormalities (MSAs), neural tube defects (NTDs), urogenital abnormalities (UGAs), cardiovascular abnormalities (CVAs), as well as some gastrointestinal, ocular, and facial CAs. Medline was systematically searched up to June 2017 to detect all publications focusing on the topic “Congenital Abnormalities OR Birth defects AND Pesticides AND Human”. Specific CA categories were also searched, applying the following additional literature search strategies:

1. MSAs: pesticide AND (gastroschisis OR hernia OR syndactyly OR craniosynostosis OR polydactyly OR omphalocele OR (limb AND defect); 2. NTDs: pesticide AND (anencephaly OR spina bifida OR “neural tube defects”); 3. UGAs: pesticide AND (hypospadias OR cryptorchidism OR micropenis) pesticide AND urogenital AND (defect OR anomaly); 4. CVAs: pesticide AND (Fallot OR (heart AND defect) OR (valve AND defect) OR (septal AND defect)); 5. Gastrointestinal abnormalities: pesticide AND ((stomach AND defect) OR (intestinal AND defect) OR (gastrointestinal AND (defect OR anomaly OR malformation))) pesticide AND ((esophageal AND atresia) OR (tracheoesophageal AND fistula) OR (rectal AND (atresia OR stenosis)) OR (intestinal AND atresia))); 6. Ocular abnormalities: pesticide AND (anophthalmia OR microphthalmia); 7. Facial abnormalities: pesticide AND cleft.

After excluding duplicates, citations in abstract form, and non-English citations, titles and abstracts of full papers were screened for relevance. Reference lists of selected papers were hand-searched to detect potentially relevant studies. For a study to be relevant, a causative link between human prenatal exposure to a specific pesticide group, substance, or pesticides as a whole and structural CAs had to be considered. Functional defects and chromosomal anomalies were not investigated. In vitro and animal studies were excluded, as well as studies, which did not specifically focus on CAs but rather on other outcomes such as birth weight or fetal death. Studies linking pesticide exposure to fetal death due to CAs were also excluded since the prevalence of fetal loss, rather than the prevalence of CAs was investigated. Studies were further filtered by design to include only original research. A total of 94 epidemiological studies, including case-control, nested case-control, prospective and retrospective cohorts, ecological, and cross-sectional studies were finally selected for review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) methodology (Moher et al., 2009) (Fig. 1).

Selected studies were classified according to CA category based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10 Version: 2016). Studies linking pesticides with more than one CA category or with CAs in general were grouped into an extra category called “all abnormalities”. Categories yielding limited number of studies (gastrointestinal, ocular, facial) were merged

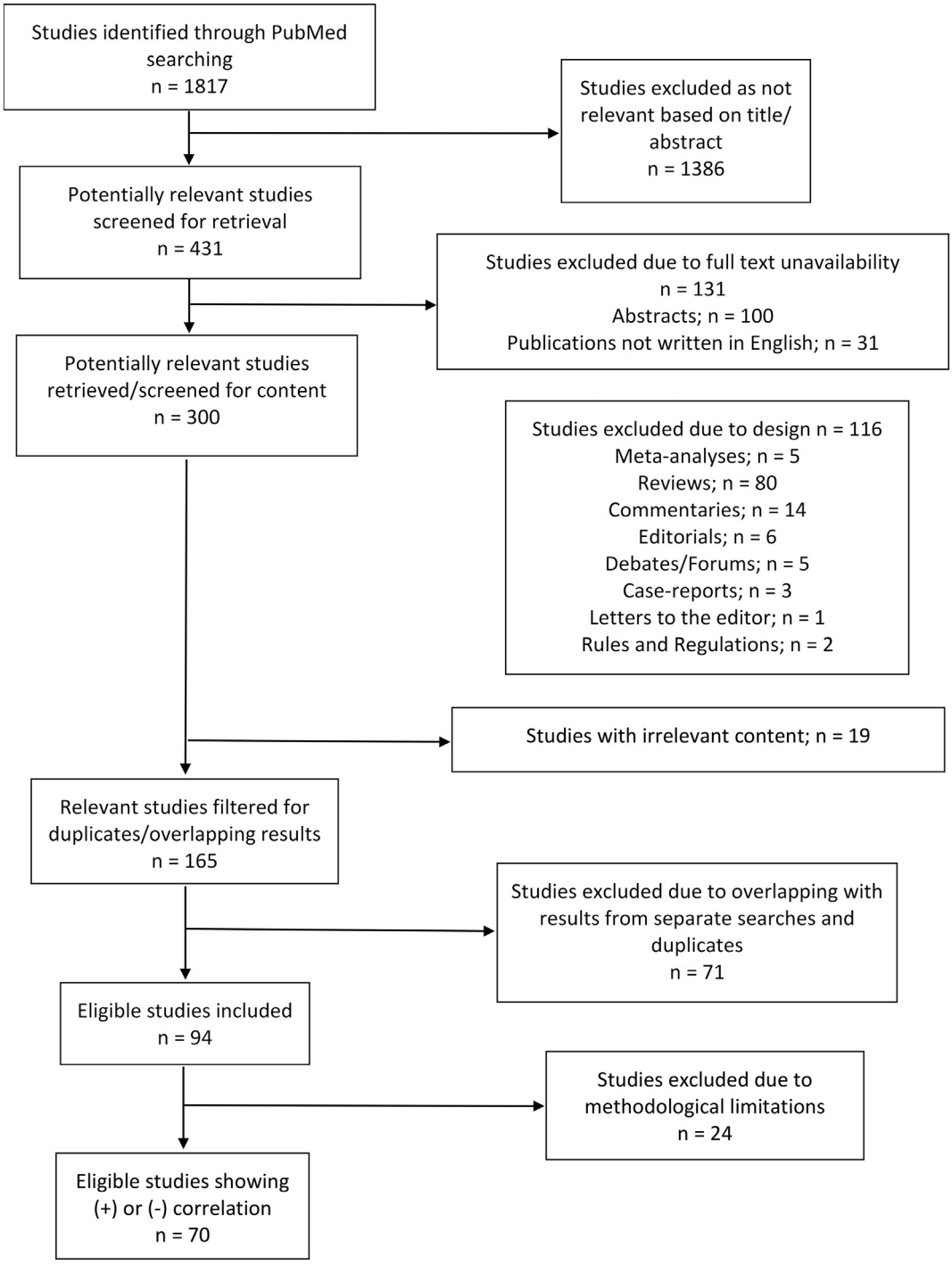

Fig. 1. PRISMA flow chart showing the study selection procedure.

into the "other" category. Most of the studies evaluate parental exposure to pesticides, including maternal/paternal and/or occupational, and/or environmental, and/or home exposure, in relation to the occurrence of CAs of the offspring.

Studies that are based on biomarker-data, are considered the most reliable in comparison to self-reported or other studies, as biomarkers may indicate individual hypersusceptibility to specific chemical exposures and may consequently reveal the appropriate background-knowledge for risk prediction (Grandjean, 1995). Biomarkers refer to events that occur in a biological system, which can be measured and eventually reflect the general state of the organism or severity of influences on it (Grandjean, 1995). It has been previously showed that the self-reported studies or questionnaire-based studies are characterized by measurement errors, which can overshadow potential associations as well as support false-positive correlations. The use of objective biomarkers instead reduced the measurement errors, providing a more accurate approach that enhances reliability (Freedman et al., 2010; Prentice et al., 2009).

3. Pesticides and development of congenital abnormalities

Potential associations of environmental and occupational exposure to pesticides with more than one CA category or with CAs in general ("all abnormalities" category) were investigated in a total of 30 studies.

Table 1
Studies associating environmental/mixed pesticide exposures with congenital malformations.

Studies	Exposure	Pesticides Tested	General Association	Association	Circulatory-Respiratory/ Association	UGAs/ Association	NTDs/ Association	Clefts/ Association	Exposure Assessment	Study Type/ Sample size	Region	Confounding Factors
(Geschwind et al., 1992)	Environmental	Unspecified	+	+	−	−	+/−	+/−	Hazardous Waste Site Inspection Program database/US Census Dual Independent Map Encoding files	Case-control/ 27,115	New York State (USA)	▪ Maternal age ▪ Maternal race ▪ Maternal education level ▪ Maternal country of residence ▪ Complications during pregnancy/ parity/birth weight gestation length/ sex of the child
(Croen et al., 1997)	Environmental	Unspecified	−	−	+/−	−	+/−	+/−	Interviews/U.S. and California Environmental Protection Agencies' listings on hazardous waste sites	Case-control/ 2119	California (USA)	▪ Infant sex ▪ Maternal age ▪ Maternal race/ethnicity ▪ Maternal education level ▪ Family income ▪ Periconceptional employment status ▪ Alcohol use ▪ Smoking ▪ Vitamin use ▪ Educational attainment of place of residence
(Marshall et al., 1997)	Environmental	Unspecified	−	+/−	−	−	+/−	−	Geocoding (birth certificate data)/distance from waste sites	Case-control/ 16,214	New York State	▪ Maternal age ▪ Maternal race ▪ Maternal education level ▪ Municipality's population density ▪ Number of previous births ▪ Trimester prenatal care initiation Infant sex
(Heeren et al., 2003)	Environmental	OPs, Pesticides, Blue death, Insecticides, Fertilizers	+	+	+	+	+	+	Questionnaires	Case-control/267	Eastern Cape (South Africa)	Not used (Matching was undertaken with respect to age/occupation/type of live stock owned/location)
(Schreinemachers, 2003)	Environmental	Chlorophenoxy pesticides	+	+	+	+/−	+/−	+/−	U.S.D.A. 1992/each county was assigned to either the low- or high-wheat group depending on its percentage of wheat acreage with respect to the median of all selected counties	Ecological	Minnesota/ Montana/ North Dakota/ South Dakota	▪ Maternal age ▪ Maternal education ▪ Marital status/parity ▪ Prenatal care ▪ Previous preterm or SGA birth ▪ Tobacco/alcohol use during pregnancy ▪ Infant sex/time of conception. (Only white singletons included).
(Kennedy et al., 2005)	Therapeutic	Permethrin 1% (for headlice)	−	−	−	+/−	−	−	Questionnaires	Prospective controlled cohort/226	Toronto (Canada)	▪ Matched for age ▪ Smoking status ▪ Alcohol use ▪ Time of call for permethrin information ▪ Trimester of exposure

(*continued on next page*)

Table 1 (*continued*)

Studies	Exposure	Pesticides Tested	General Association	Association	Circulatory-Respiratory/ Association	UGAs/ Association	NTDs/ Association	Clefts/ Association	Exposure Assessment	Study Type/ Sample size	Region	Confounding Factors
(Weselak et al., 2008)	Occupational/ Environmental	All/Unspecified	+	+/−	+	+	+	+	Questionnaires	Case-control/ 3412	Ontario (USA)	■ Pregnancy fever ■ Offspring sex ■ Parity/parental age ■ Education/income/ethnicity/ Maternal caffeine/alcohol consumption during pregnancy/ Parental smoking ■ Maternal medical problems/ pregnancy weight gain Labor ■ Delivery problems ■ Conception season/number of years of recall to the pregnancy years the mother lived on the farm prior to conception
(Winchester et al., 2009)	Environmental	Nitrates, atrazine, other unspecified (surface water)	+	+	+	+	+	+	USGS NAWQA database	Ecological	USA	■ Age/race/ethnicity/residence/ Alcohol consumption/smoking Maternal diabetes ■ Birth year
(de Siqueira et al., 2010)	All	Unspecified	−	−	−	−	−	−	indication of pesticide use by IBGE/Data from National Systematic Survey of Agricultural Production/National Association of Agricultural Defensive Industries	Ecological	Brazil	■ Proportion of pregnant women with a low number of prenatal care visits
(Yang et al., 2012)	All	Unspecified	+	+	+	+	+	+	Questionnaire based interviews	Cross-sectional/ 16,541	Shaanxi (China)	■ Parental education ■ Maternal occupation ■ Family income/residence type
(Yang et al., 2014)	Environmental	461 individual chemicals	−	−	−	−	+	+/−	CEHTP Geocoding Service/California Department of Pesticide Regulation records/ Interviews	Case-control/ 1375	San Joaquin Valley (California)	■ Race/ethnicity/educational level Pre-pregnancy BMI ■ Parity ■ Folic acid supplements ■ Smoking during the month before and the first 2 months of pregnancy/ infant sex
(Cremonese et al., 2014)	Dietary	Unspecified	+	−	+	−	+	−	Agricultural Census Data	Ecological	Brazil	Not used

BBL: Benzyl Benzoate Lotion; BMI: Body Mass Index; CA: Congenital Abnormality; CEHTP: California Environmental Health Tracking Program; IBGE: Brazilian Institute for Geography and Statistics; MITC: Methyl Isothiocyanate; MSAs: Musculoskeletal Abnormalities; NAWQA: National Water Quality Assessment; NTDs: Neural Tube Defects; OCs: Organochlorines; OPs: Organophosphates; OR: Odds Ratio; SGA: Small for Gestational Age; UGAs: Urogenital Abnormalities; USDA: United States Department of Agriculture; USGS: United States Geological Survey; 95% CI: 95% Confidence Interval; +: association detected; −: no association detected; +/−: trend towards association (not statistically significant).

Results on environmental or mixed exposures were inconclusive due to inadequate study design/exposure assessment (Table 1). Most studies evaluating environmental exposure were ecological, assessing pesticide exposure indirectly through national databases of pesticide use, whereas those that were not ecological, used primarily self-report to assess exposure. On the other hand, studies evaluating occupational exposure were case-control with sufficient sample size, thus their design was more reliable. Nevertheless, exposure assessment relied on self-report as well and results should therefore be interpreted with caution. Many studies have reported no increased risk of CAs in offspring residing in areas with pesticide use (de Siqueira et al., 2010; Marshall et al., 1997). Potential association between permethrin/benzyl benzoate lotion during pregnancy for therapeutic reasons (headlice and/or scabies treatment) and CAs was investigated in one study (Kennedy et al., 2005) concluding that no association exists and thus these pesticides are safe. However, the main limitation of this study was the small number of exposed women during the first trimester of pregnancy, when the child is more susceptible to developmental CAs (Kennedy et al., 2005). An exposure-dependent positive link between maternal residence in near toxic waste sites in New York state and CAs and an increased risk for MSAs (OR = 1.2, 95%C = 1.05–1.38) and pesticide exposure was reported (Geschwind et al., 1992) but these results could not be replicated in a following study done in California (Croen et al., 1997). On the other hand, residence in areas with highest wheat acreage increased the risk for circulatory/respiratory and musculoskeletal/integumental abnormalities for combined sexes. A stronger effect was observed for the circulatory subcategory, which excluded heart defects. Infants conceived from April–June had increased chances of having defects from this subcategory (Schreinemachers, 2003). Additional factors contributing to an increase in CAs are maternal pesticide exposure (OR: 2.30, 95% CI: 1.16–4.57) (Yang et al., 2012), exposure to specific pesticides (cyanazine and dicamba (Weselak et al., 2008) or pesticide groups (petroleum derivatives; Anencephaly, hydroxy benzonitrile; Spina Bifida, 2,6-dinitroaniline herbicides, dithiocarbamates-methyl isothiocyanate; Cleft lip) (Yang et al., 2014) and spring conception (Schreinemachers, 2003; Winchester et al., 2009). A case-control study in South Africa (Heeren et al., 2003) linked three exposure types to CAs (plastic containers used for agricultural chemicals storage, particular garden chemicals, and keeping of dipped cattle). Last but not least, an association between per capital consumption of pesticides and CAs was reported in rural but not in urban microregions in Brazil (Cremonese et al., 2014).

Studies examining occupational exposure showed a general trend towards a positive association with CAs (Table 2). Maternal and paternal environmental exposure (Crisostomo and Molina, 2002; Garry et al., 1996; Kristensen et al., 1997) as well as maternal (Kristensen et al., 1997) and paternal occupational exposure (Dimich-Ward et al., 1996; El-Helaly et al., 2011; Salazar-Garcia et al., 2004), residence in areas with high pesticide use (Garry et al., 1996; Garry et al., 2002; Shaw et al., 1999), and spring conception (Garry et al., 1996) emerged as risk factors. Nevertheless, other studies challenge these results. Kristensen et al. (1997) and Shaw et al. (1999) detected an increased risk of specific defects with exposure; no association was detected between parental occupational exposure and CAs in general. Only

Table 2
Studies associating occupational pesticide exposures with congenital malformations.

Studies	Pesticides Tested	General Association	MSAs/ Association	Circulatory-Respiratory/ Association	UGAs/ Association	NTDs/ Association	Clefts/ Association	Other/ Association	Exposure Assessment	Study Type/ Sample size	Region	Confounding Factors
(Restrepo et al., 1990)	Phenoxy herbicides	-	+ / -	+ / -	+ / -	-	+ / -	+	Questionnaire based interviews	Nested case-control/665	Colombia	▪ Consanguinity ▪ Family history of congenital malformation ▪ Diseases during pregnancy ▪ Vaginal bleeding during pregnancy ▪ Mumps during pregnancy ▪ Varicella during pregnancy ▪ Toxoplasmosis ▪ x-ray exposure during pregnancy ▪ Diazepam/ Contraceptive pills/ Pregnancy test with estrogens/ Piperazine/ Vitamins/ Iron/ Other drugs Tobacco smoking/ Alcohol drinking ▪ Exposure to chemicals
(Dimich-Ward et al., 1996)	Chlorophenate wood preservatives	+	+ / -	+ / -	+	+	+ / -	+	Minnesota Department of Agriculture data	Case-control/ 19,675	Minnesota (USA)	▪ Maternal age ▪ Education ▪ smoking/ alcohol consumption ▪ previous miscarriage/earlier births with anomalies
(Garry et al., 1996)	2,4-D, alachlor, atrazine, bentazon, bromoxynil, cyanazine, dicamba, EPTC, imazethapyr, MCPA, metolachlor, trifluralin	+	+	+	+	+	-	+ / -	Cohort of sawmill workers/ Expert raters' estimation	Epidemiological/ 210,723	British Columbia	▪ Not used ▪ Matching by birth year and gender
(Kristensen et al., 1997)	Unspecified	-	+	-	+	+	+ / -	-	Agricultural/ horticultural census information	Cohort/253,768	Norway	▪ Year of birth ▪ Geographical distribution ▪ Maternal age/ parental consanguinity/ birth order maternal chronic disease/ previous stillbirth ▪ Infant sex ▪ Multiple births/ perinatal birth/ preterm delivery/ low birth weight ▪ Animal husbandry ▪ Pesticide purchase/ tractor pesticide spraying equipment/ grain/horticulture farming
(Shaw et al., 1999)	Unspecified	-	+ / -	+ / -	-	+	+ / -	-	Telephone interviews/ Exposure assessed by industrial hygienist	Case-control/ 2,033	California	▪ Maternal periconceptional vitamin use ▪ Smoking ▪ Education/ race/ethnicity
(Garcia et al., 1999)	Unspecified	+	+	+	+	+	+	+	Telephone interviews	Case-control/522	Spain	▪ Age ▪ Smoking/ alcohol consumption/drug use ▪ Medical history/ health of the immediate family/ ▪ Socioeconomic data/ reproductive history including problems during the index pregnancy
(Garry et al., 2002)	14 types of pesticides	+	+	+	+	+	-	+	Telephone interviews/ Questionnaires	Cross-sectional/ 1,532	Minnesota (USA)	▪ Maternal smoking/ alcohol consumption/ age/ chronic diseases (e.g. diabetes and hypertension)/ season of conception
(Salazar-Garcia et al., 2004)	DDT	+	+	+	-	+	+	+	Questionnaire/ Exposure assigned by experts	Nested cross-sectional/ 9,187	Mexico	▪ Parental exposure to other OCs and/or OPs pesticides at the time of pregnancy/ exposure to other chemical substances/ exposure to agricultural pesticides/ ▪ Tobacco/alcohol consumption/ parental age/ socioeconomic status

CAs: Congenital Abnormalities; EPTC: S-Ethyl dipropylcarbamothioate; MCPA: 2-Methyl-4-Chlorophenoxyacetic Acid; MSAs: Musculoskeletal Abnormalities; NTDs: Neural Tube Defects; OPs: Organophosphates; OR: Odds Ratio; UGAs: Urogenital Abnormalities; 95% CI: 95% Confidence Interval; +: association detected; −: no association detected; +/−: trend towards association (not statistically significant).

Restrepo et al. reported increased risk for hemangiomas (Restrepo et al., 1990). Garcia et al. detected a positive association of maternal but not of paternal occupational exposure with CAs (OR of 3.16, 95% CI: 1.11–9.01) that has also been shown by Rappazzo et al. (Garcia et al., 1999; Rappazzo et al., 2016).

Pesticide residues are highest in surface and ground water during the growing seasons (spring and first summer months) (Winchester et al., 2009). Spring conception emerged multiple times as a risk factor for CAs (Garry et al., 1996; Schreinemachers, 2003; Waller et al., 2010; Winchester et al., 2009), resulting in more CAs in rural areas since pesticides are widely used during that season. A recent study however, found not only that spring spike is more pronounced in urban non-agricultural than in other types of counties but also that this lasts longer until fall (McKinnish et al., 2014), which could be attributed to agricultural pesticides contaminating urban water supplies or to the commercial and/or residential pesticide use. Nevertheless, it is also possible that the spring spike is a result of seasonal variations of other environmental pollution types, viral infections, or even use of decongestants.

4. Musculoskeletal abnormalities

MSAs include CAs of the skeletal and muscular system with gastroschisis (1 in 2229 births) and reduction defects of the upper limb (1 in 2869) being the most common (Parker et al., 2010). The literature in the field is limited with only six studies available to date, most of which performed in USA. Nevertheless, most of the studies are case-controlled with adequate sample sizes. Most of the studies detected a positive association between occupational and/or environmental exposure and MSAs (Table 3) (Agopian et al., 2013b; Engel et al., 2000; Kielb et al., 2014; Waller et al., 2010), such as gastroschisis and reduction defects of the upper limb (Lin et al., 1994; Shaw et al., 2014). Risk factors include: maternal exposure (Agopian et al., 2013b; Engel et al., 2000; Waller et al., 2010), maternal co-exposure (Kielb et al., 2014), smaller distance from high pesticide use sites (Waller et al., 2010), spring conception (Waller et al., 2010) and increased maternal age (Agopian et al., 2013b; Kielb et al., 2014). Interestingly two studies showed that increased maternal age is a risk factor specifically for gastroschisis (Agopian et al., 2013b; Kielb et al., 2014). On the contrary, other studies reported younger maternal age as a risk factor. Authors argue whether this is an effect of bioaccumulation, resulting from chronic exposure, or whether it is a result of a pesticide, atrazine in this case, acting as an ED, given that older women have lower first trimester estrogen levels than younger women (WHO/CDC/ICBDSR, 2014). None of these studies, assessed pesticide exposure directly. Distance from residence to pesticide use sites as a proxy for exposure was mostly used. To minimize exposure misclassification, statewide databases were merely used (Agopian et al., 2013b; Lin et al., 1994; Shaw et al., 2014; Waller et al., 2010). Although there is evidence of a positive association between pesticide use and MSAs, more studies are needed to link these CAs to directly assessed pesticide exposure.

5. Neural tube defects

According to World Health Organization, NTDs affect the brain and spinal cord and are among the most common CAs (WHO/CDC/ICBDSR, 2014). Main risk factors include genetic predisposition, reduced pregnancy folate intake and environmental factors such anticonvulsant drugs, maternal obesity and maternal diabetes (Copp et al., 2013).

All studies reported a positive association in newborns. The general trend refers merely to occupational rather than to environmental exposure that was not often assessed (Table 4). Main risk factors include parental occupational exposure to pesticides, with agricultural workers/people living in farms been significantly exposed (Blatter and Roeleveld, 1996; Blatter et al., 2000; Fear et al., 2007; Lacasana et al., 2006; Makelarski et al., 2014). The significance of maternal or paternal environmental/occupational exposure was debated. Maternal exposure to OCs such as endosulfan, DDT and dichloro-diphenyl-dichloroethylene (DDE) was linked to fetal NTDs (Kalra et al., 2016), with mothers delivering affected neonates reported to have 11.3 times greater chances of been exposed to DDE levels above median concentration of controls. Other risk factors are maternal residential proximity to pesticide application, parental pesticide exposure prior/during a periconceptual period of three months and co-exposure (Brender et al., 2010; Makelarski et al., 2014; Wang et al., 2014).

The main limitation in these studies is that they are mostly based on self-report (questionnaires and interviews). Consequently, mis−/partial lack of information on parental exposure is quite likely. As a result, this positive trend should be interpreted with caution, since more studies with better exposure assessment are needed.

6. Urogenital abnormalities

Cryptorchidism and hypospadias are the commonest CAs in human males. Based on epidemiological, clinical, biological and experimental evidence, it has been hypothesized that cryptorchidism, hypospadias, testicular cancer, and poor spermatogenesis are signs of a sole developmental disturbance, named testicular dysgenesis syndrome (Skakkebaek et al., 2001). This syndrome is considered the result of embryonal programming/gonadal development disruption during fetal life and may be increasingly common due to adverse environmental influences, mainly exposure to EDs (Skakkebaek et al., 2001; Virtanen et al., 2005). Seasonal trends in the prevalence of hypospadias and cryptorchidism may also support such a link (Mamoulakis et al., 2002; Mamoulakis et al., 2017). A great amount of research has therefore been focused on the effect of environmental factors among others, on male reproductive parameters (Sharpe, 2003). A growing body of toxicology data on animals suggests that exposure to EDs are linked to male reproductive system disorders (Petrakis et al., 2017). Human appears to be less susceptible to many compounds compared to other species but the issue of mixed exposures remains an unresolved problem; each ED may be present in modest concentration but total effect may be additive/multiplicative. Furthermore, the effect of environmental toxicants may be modified by genetic susceptibility.

The relationship between pesticides-UGAs appears to be the most thoroughly explored, with search yielding over 30 studies. The most commonly UGA investigated was hypospadias. It is believed that the “estrogen hypothesis” is crucial to this (Sharpe, 2003). According to this hypothesis, the increase in human male reproductive developmental disorders may have occurred due to increased estrogen exposure in utero (Sharpe and Skakkebaek, 1993). The action of several pesticides as EDs added to the increased interest in this category of CAs (Svechnikov et al., 2010).

No firm conclusions can be generally drawn. It should be stressed that this CA category, apart from being more frequently investigated, it is also the only one extensively explored using biomarkers. This method of exposure assessment, as stated above, is the most reliable since it measures pesticides or metabolites directly in tissues/secretions such as maternal serum (Carmichael et al., 2010; Fernandez et al., 2007; Giordano et al., 2010; Longnecker et al., 2002; Pierik et al., 2007), breast milk (Brucker-Davis et al., 2008; Damgaard et al., 2006), hair (Michalakis et al., 2014), urine (Chevrier et al., 2011), cord blood (Brucker-Davis et al., 2008), and placenta (Fernandez et al., 2007).

Most largest ecological studies did detect a positive association. Nevertheless, it should be noted that such studies are most useful for generating hypotheses rather than assessing true cause-effect relationships at an individual level (Agopian et al., 2013a; Carmichael et al., 2013; Giordano et al., 2010). This limitation was apparent when the positive results of an ecological study in Sicily could not be replicated by a following case-control study conducted by the same authors on the same population (Carbone et al., 2007). Consequently, although a positive trend was found in ecological studies, results were ambiguous in

Table 3
Studies associating pesticides with musculoskeletal malformations.

Studies	Association	Pesticide Tested	CA Tested	Exposure Type	Exposure Assessment	Biomarker Available	Study Type/ Sample size	Region	Confounding Factors
(Lin et al., 1994)	+/−	Unspecified/All	Limb reduction defects	Occupational/ Environmental	Birth Certificates/New York State census of Agriculture data/Industrial hygienist's assessment	No	Case-control/277	New York	▪ Type of county (rural/urban)/ residence in a county with high pesticide use/infant gender/maternal complications during pregnancy
(Engel et al., 2000)	+	Unspecified/All	Limb defects	Occupational	Birth Certificates → Maternal occupation	No	Retrospective cohort/33,972	Washington State	▪ Maternal age/marital status/maternal residence (rural/urban)/birthplace (rural/urban) ▪ Smoking and alcohol use ▪ Prenatal care/parity/maternal race or ethnicity/gestational length/infant sex ▪ Paternal occupation
(Waller et al., 2010)	+	Atrazine/2,4-D (surface waters)	Gastroschisis	Environmental	US Geological Survey Data/ zip coding	Yes	Case-control/ 4421	Washington State	▪ Maternal age ▪ Parity ▪ Tobacco use ▪ Season of conception/log transformed distance from exposure
(Agopian et al., 2013b)	+	Atrazine (crops)	Gastroschisis	Environmental	Registry/Birth Certificates/ US Geological Survey Data	Yes	Case-control/ 9551	Texas	▪ Infant sex ▪ Month of conception ▪ Birth year ▪ Maternal age ▪ Race/ethnicity/education/birthplace/ parity ▪ Smoking
(Kielb et al., 2014)	+	Unspecified/All	Craniosynostosis/ Gastroschisis/ Diaphragmatic hernia/ Transverse limb deficiencies	Occupational	Interviews/Expert raters/ Job exposure matrix	No	Case-control/ 3728	Arkansas/California/ Iowa/Massachusetts/New Jersey/New York/Texas/ Atlanta	▪ Infant sex/maternal age/pre-pregnancy BMI/parity/singleton vs multiple birth/maternal race/ ethnicity/maternal education/folic acid use/maternal smoking and alcohol use
(Shaw et al., 2014)	+/−	22 chemical groups	Gastroschisis	Residential	Interviews/CEHTP Geocoding Service/Public Land Survey Section data/ Pesticide Use Reporting records	No	Case-control/931	San Joaquin Valley of California	▪ Maternal age/race/ethnicity/BMI/ folic acid supplement use/smoking

BMI: Body Mass Index; CAs: Congenital Abnormalities; CEHTP-California Environmental Health Tracking Program; OR: Odds Ratio; 2,4-D: 2,4-Dichlorophenoxyacetic acid; 95% CI: 95% Confidence Interval; +: association detected; −: no association detected; +/−: trend towards association (not statistically significant).

Table 4
Studies associating pesticides with neural tube defects.

Studies	Association	Pesticide Tested	CAs Tested	Exposure Type	Exposure Assessment	Study Type/ Sample Size	Region	Confounding Factors
(Blatter and Roeleveld, 1996)	+/−	Unspecified	Spina bifida	Occupational	Questionnaires/ Interviews	Case Control/ 1446	Sweden	▪ Positive paternal family history of NTDs/use of ovulation stimulating agents
(Blatter et al., 2000)	+/−	Unspecified	Spina Bifida	Occupational	Questionnaires/ Interviews	Case Control/ 4966	Sweden, Spain, and Hungary	▪ Maternal homocysteinaemia/diabetes/ consanguinity/ovulation-stimulating agents/oral contraceptives ▪ Parity ▪ Parental family history of NTDs ▪ Parental alcohol use/smoking
(Lacasana et al., 2006)	+	Unspecified/All	Anencephaly	Occupational	Questionnaires	Case Control/302	State of Mexico, Puebla, Guerrero	▪ Place of delivery/date of childbirth ▪ Federal entity/age ▪ Family income/education/history of congenital malformations in first degree relatives/number of pregnancies/fever in the ARP/adverse reproductive outcomes in previous pregnancies/folate intake/ energy ▪ Tobacco/alcohol/exposure to domestic pesticides and solvents during the ARP/habitual use of wood fires to cook
(Fear et al., 2007)	+	Unspecified/All	All	Occupational	Hospital records	Case Control/ 1388	England	▪ Maternal age ▪ Year of index pregnancy ▪ Infant sex ▪ Multiplicity of birth/number of previous obstetric events
(Brender et al., 2010)	+	Unspecified/All	Anencephaly/Spina bifida	Environmental, Occupational	Interviews/ Questionnaires	Case Control/409	Texas-Mexico border	▪ Single-exposure: Maternal education/smoking/ folate intake. Multiple-exposure: ▪ Other reported pesticide exposures
(Makelarski et al., 2014)	−	Insecticides/ Fungicides/ Herbicides	Unspecified/All	Occupational	Self-reported occupation/Job exposure matrix	Case Control/ 3452	Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Atlanta NBDPS sites (USA)	▪ Maternal age at delivery/race/ethnicity/education/ gravidity/pre-pregnancy BMI/periconceptional smoking/NBDPS site/folate intake/vitamins and/or supplements containing folic acid
(Wang et al., 2014)	+/−	25 OCs	Anencephaly/Spina bifida/Encephalocele	Unspecified	Interview/ Questionnaire/Maternal serum samples	Case Control/238	Shanxi Province of China	▪ Maternal occupation ▪ Age ▪ Educational level ▪ BMI/folic acid supplementation ▪ Active or secondhand smoking/drinking alcohol during the periconceptional period/fever/flu during early pregnancy

ARP: Acute Risk Period; BMI: Body Mass Index; CAs: Congenital Abnormalities; DDT: Dichlorodiphenyltrichloroethane; HCH: hexachlorocyclohexane; NTDs: Neural Tube Defects; OCs: Organochlorines; OR: Odds Ratio; 95% CI: 95% Confidence Interval; +: association detected; −: no association detected; +/−: trend towards association (not statistically significant).

Table 5
Studies associating environmental/mixed pesticide exposure with urogenital abnormalities.

Studies	Association	Pesticide Tested	CAs Tested	Exposure Type	Exposure Assessment	Study Type/Sample Size	Confounding Factors
(Sharpe and Skakkebaek, 1993)	+/−	Diethylstilbestrol (DES)	Cryptorchidism Hypospadias	Environmental Pharmacological	Unspecified	Collection of Epidemiological Studies	■ Pregnancy ■ Endogenous estrogen levels ■ Use of synthetics ■ Diet source of oestrogens ■ Exposure to environmental oestrogenic chemicals ■ Maternal Age
(Garcia-Rodriguez et al., 1996)	+	Unspecified/All	Cryptorchidism	Environmental	Use of 4-point scale in each municipality, according to total surface area under cultivation and predominant crops.	Ecological	■ Population of municipality cases and controls/age
(Skakkebaek et al., 2001)	+/−	Unspecified/All	Testicular dysgenesis syndrome	Environmental/ Occupational	Unspecified	Collection of Epidemiological Studies	■ Embryonal programming and gonadal development during fetal life. ■ Fertility ■ Parental exposure
(Mamoulakis et al., 2002)	+	Unspecified/All	Cryptorchidism	Environmental	Three major pediatric center databases in Athens (Aghia Sophia Children's Hospital, Aglaia Kyriakou Children's Hospital and Pentelis Children's Hospital	Retrospective epidemiological study/208,912 live-born boys	■ Seasonality by month of birth ■ Maternal hCG profiles ■ Low environmental temperature ■ Daylight length
(Bianca et al., 2003)	+	Unspecified/All	Hypospadias	Unspecified/All	Towns with intense industrial (Augusta) and agricultural (Vittoria) activity compared to a commercial one (Catania)	Ecological	■ Parental age ■ Gestational age ■ Parity/number of previous spontaneous abortions ■ Mode of delivery ■ Birth weight ■ Paternal occupation/paternal educational level
(Sharpe, 2003)	+	Oestrogens and oestrogenic chemicals	Testis cancer, cryptorchidism, hypospadias, low sperm counts	Environmental Pharmacological	Unspecified Interviews/Questionnaire	Collection of Epidemiological Studies	■ Maternal Age ■ Low birth weight (Intra-uterine growth retardation) ■ First pregnancy ■ Impaired androgen production/action in fetal life ■ Exposure during pregnancy
(Virtanen et al., 2005)	+	9 compounds	Testicular dysgenesis syndrome	Environmental/ Occupational	The Turku University Central Hospital data GLOBOCAN 2000	Collection of clinical and epidemiological findings and biological and experimental studies	■ Karyotype ■ Gestational age ■ Birth weight ■ Parental exposure
(Meyer et al., 2006)	+/−	38 compounds	Hypospadias	Environmental	Interviews/NASS data/Arkansas agricultural databases/usage guidelines published by University of Arkansas Cooperative Extension Service and the Southern Integrated Pest Management Center	Case-control/1081	■ Pregnancy ■ Month when prenatal care began/number of previous births ■ Exposure metric representing total pesticide use ■ Maternal age ■ Maternal race/paternal education ■ Gestational age at birth ■ Maternal pregnancy smoking/pregnancy weight gain

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Table 5 (*continued*)

Studies	Association	Pesticide Tested	CAs Tested	Exposure Type	Exposure Assessment	Study Type/Sample Size	Confounding Factors
(Carbone et al., 2007)	+/−	Unspecified/All	Hypospadias/ Cryptorchidism	Environmental/ Occupational	Interviews/Job exposure matrix	Case-control/293	▪ Birth weight ▪ Parental age/educational level ▪ Parity ▪ Contraceptives' types used prior to pregnancy/parental genital tract pathologies/anti-abortion drugs use during pregnancy/smoking/alcohol consumption
(Brouwers et al., 2007)	+/−	Unspecified/All	Hypospadias	Unspecified/All	Mailed questionnaires	Case-control/834	▪ Educational level/parental native country/+23 unspecified risk factors assessed
(Dugas et al., 2010)	+/−	Unspecified/All	Hypospadias	Environmental	Questionnaire-based telephone interviews	Case-control/961	▪ Maternal smoking ▪ Maternal age ▪ Parental income ▪ Birth weight ▪ Previous stillbirth ▪ Folate intake during first 3 months of pregnancy
(Giordano et al., 2010)	+	HCB/DDE	Hypospadias	Occupational/ Dietary	Interviews/Job exposure matrix/ Questionnaires	Case-control/58	▪ Maternal age/breastfeeding duration ▪ Percent of lipids in the serum
(Carmichael et al., 2013)	+	292 chemicals	Hypospadias	Environmental	Residence geocoding/Pesticide Use Reporting records	Case- control/2885	▪ Maternal race/ethnicity ▪ Maternal age ▪ Infant birth year
(Agopian et al., 2013a)	+	Atrazine	All	Residential	US Geological Survey Data/AgroTrak surveys/Census of Agriculture and National Agriculture Statistics Service	Case- control/32,866	▪ Season of conception ▪ Birth year ▪ Maternal age ▪ Race/ethnicity/education ▪ History of previous live births ▪ Birthplace ▪ Smoking
(Kalfa et al., 2015)	+	All EDCs	Hypospadias	Environmental/ Occupational	Job history questionnaire completed by mothers.	Case- control/219 newborns	▪ Job-exposure matrix ▪ Gestational age ▪ Neonatal and parental data were collected at birth (personal characteristics, maternal lifestyle, and medical history)
(Mamoulakis et al., 2017)	+	Unspecified/All	Hypospadias	Environmental	Data on the population at risk were collected from the Hellenic Statistical Authority	Case-control/542	▪ Intrauterine life: i) air temperature; ii) rainfall amount; iii) sunshine duration

CAs: Congenital Abnormalities; DDE: Dichlorodiphenyldichloroethylene; DDT: p,p'-Dichlorodiphenyltrichloroethane; EDs: Endocrine Disruptors; HCB: Hexachlorobenzene; HCH: Hexachlorocyclohexane; NASS: National Agricultural Statistics Service; OPs: Organophosphates; OR: Odds Ratio; RR: Relative Risk; VSDs: Ventricular Septal Defects; 95% CI: 95% Confidence Interval; +: association detected; -: no association detected; +/−: trend towards association (not statistically significant).

Table 6
Studies associating pesticides with the use of biomarkers with urogenital abnormalities.

Studies	Association	Pesticide Tested	CAs Tested	Exposure Type	Biomarker Assessment	Study Type/Sample Size	Confounding Factors Examined
(Longnecker et al., 2002)	+/−	DDE	Hypospadias/ Cryptorchidism/ Polythelia	Environmental	Maternal serum	Nested case-control/ 1137	▪ Season of birth ▪ Mother's age ▪ Parity ▪ Socioeconomic index ▪ BMI before pregnancy ▪ Pregnancy weight gain ▪ Pregnancy smoking ▪ Hyperemesis gravidarum ▪ Hypertension ▪ Age at menarche ▪ Infertility history ▪ Menstrual cycle irregularity pregnancy estrogen ▪ Progesterone use ▪ Method of delivery ▪ Serum sodium level ▪ Preterm birth ▪ Birth weight/IUGR ▪ Gestational age
(Bhatia et al., 2005)	+/−	DDT/DDE	Hypospadias/ Cryptorchidism	Environmental	Maternal serum	Nested case-control/ 428	▪ Cholesterol/Triglyceride level ▪ Maternal race ▪ Maternal age ▪ Pre-pregnancy BMI ▪ Parity ▪ Maternal ethnicity ▪ Maternal place of birth ▪ Maternal occupation before pregnancy ▪ Birth weight ▪ Gestational age ▪ Date of blood draw ▪ Season of birth
(Damgaard et al., 2006)	+	27 OCs	Cryptorchidism	Environmental	Breast milk	Case-control/130	Unspecified/Not used (Lipid content in milk, maternal age, maternal BMI, parity, and smoking habits were matched between the 2 groups)
(Fernandez et al., 2007)	+	16 OCs	Hypospadias/ Cryptorchidism	Unspecified/All	Placenta tissue	Nested case-control/ 164	▪ Maternal age ▪ Birth weight
(Pierik et al., 2007)	+/−	HCE/HCB/β-HCCH	Cryptorchidism	Unspecified/All	Maternal serum	Nested case-control/ 783	▪ Race ▪ Season of birth ▪ Mother's age ▪ Parity ▪ Socioeconomic index ▪ Pre-pregnancy ▪ Pregnancy weight gain ▪ Pregnancy smoking ▪ Hyperemesis gravidarum ▪ Gestational hypertension ▪ Age at menarche ▪ Infertility history ▪ Menstrual cycle irregularity ▪ Pregnancy estrogen/ progesterone use ▪ Method of delivery ▪ Preterm birth ▪ Birth weight ▪ Intrauterine Growth Retardation ▪ Gestational age
(Brucker-Davis et al., 2008)	+/−	DDE	Cryptorchidism	Unspecified/All	Cord blood/ Colostrum	Case-control/378	▪ Gestational age ▪ Birth-weight ▪ Maternal pre-pregnancy BMI ▪ Maternal age ▪ Parity ▪ Season of birth ▪ Paternal history of cryptorchidism ▪ Town of birth

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Table 6 (*continued*)

Studies	Association	Pesticide Tested	CAs Tested	Exposure Type	Biomarker Assessment	Study Type/Sample Size	Confounding Factors Examined
(Carmichael et al., 2010)	+/−	9 persistent pesticides	Hypospadias	Environmental	Maternal serum	Nested case-control/48	▪ Maternal race ▪ Maternal ethnicity ▪ Maternal education level ▪ Maternal age ▪ Number of previous live births ▪ Time elapsed between blood collection and AFP analysis ▪ Time elapsed between AFP analysis and storage in serum bank at −70 °C
(Giordano et al., 2010)	+	HCB/DDE	Hypospadias	Occupational/ Dietary	Maternal serum	Case-control/58	▪ Maternal age ▪ Breastfeeding duration ▪ Serum lipid concentration
(Chevrier et al., 2011)	−	Triazine and chloroacetanilide herbicides	Hypospadias/ Undescended testis/ Micropenis	Environmental	Maternal urine	Nested case-control/ 715 (malformation and control subgroups)	▪ Folic acid intake during the 3 months before enrollment ▪ Early pregnancy maternal fever ▪ Child's sex ▪ Parity ▪ Pre-pregnancy BMI ▪ Maternal exposure to solvents ▪ Gestational age at birth ▪ Year of enrollment ▪ Residence district ▪ Maternal age ▪ Maternal education level ▪ Maternal smoking status ▪ Maternal alcohol consumption ▪ Maternal hypertention ▪ Season of conception
(Trabert et al., 2012)	+/−	Trans-nonachlor, Oxychlordane	Hypospadias/ Cryptorchidism	Environmental	Maternal serum	Nested case-control/ 971	▪ Total PCBs/p,p´-DDE ▪ Triglycerides/cholesterol ▪ Race/maternal age/history of previous live birth ▪ Season of birth ▪ Socioeconomic index ▪ Pregnancy smoking ▪ Gestational hypertension/ hyperemesis gravidarum/ infertility history/menstrual cycle irregularity ▪ Pregnancy estrogen/ progesterone use/age at menarche/pregnancy weight gain
(Michalakis et al., 2014)	+	OCs/OPs	Hypospadias	Environmental	Parental & Offspring Hair and Blood	Retrospective cohort/ 29 (children) + 49 (parents)	Unspecified/Not used

AFP: a-Fetoprotein, BMI: Body Mass Index; DDE: Dichlorodiphenyldichloroethylene; DDT: p,p'-dichlorodiphenyltrichloroethane; HCB: Hexachlorobenzene; HCH: Hexachlorocyclohexane; HCE: Heptachlor Epoxide; OCs: Organochlorines; OPs: Organophosphates; OR: Odds Ratio; PCBs: Polychlorinated Biphenyls; UGBD- urogenital birth defects, β-HCCH– β-hexachlorocyclohexane; 95% CI: 95% Confidence Interval; +: association detected; −: no association detected; +/−: trend towards association (not statistically significant).

observational studies, which have an inherently more reliable design for assessing environmental and occupational exposures and no conclusions could be drawn in studies with better exposure assessment using biomarkers or with a larger exposure (occupational exposure).

Concerning environmental or mixed exposures (i.e., exposure to more than one pesticide or unspecified exposure) using biomarkers (Table 5), a positive trend towards an association was observed, largely supported by ecological studies reviewed (Bianca et al., 2003; Garcia-Rodriguez et al., 1996). Ecological studies aside, results were ambiguous; with three studies supporting a positive association (Agopian et al., 2013a; Carmichael et al., 2013; Giordano et al., 2010) and four studies negating it (Brouwers et al., 2007; Carbone et al., 2007; Dugas et al., 2010; Meyer et al., 2006). The primary risk factor was maternal exposure (Agopian et al., 2013a; Giordano et al., 2010). A large case-control study reported increased risk for mothers having a medium-low/medium exposure but no association was detected in the highly exposed group (Agopian et al., 2013a). There are studies, however, supporting that parental and paternal exposure do not increase the risk of UGAs (Brouwers et al., 2007; Carbone et al., 2007). Meyer et al. examined 38 different compounds, finding a positive association only for diclofop-methyl (Meyer et al., 2006), while Carmichael et al. examined 292 chemicals finding a positive association for only a few of them (Carmichael et al., 2014). Last but not least, a French cohort study of 300 children focusing on hypospadias showed that fetal exposure to pesticides in pregnancies resulting in hypospadiac births was about 9% with 78% of exposures occurring around the period of genital differentiation during the first trimester of pregnancy (Kalfa et al., 2015).

Studies assessing individual-level exposure using pesticide biomarkers (Bhatia et al., 2005; Brucker-Davis et al., 2008; Carmichael et al., 2010; Chevrier et al., 2011; Damgaard et al., 2006; Fernandez

Table 7
Studies associating occupational pesticide exposure with urogenital abnormalities.

Studies	Association	Pesticide Tested	CAs Tested	Exposure Assessment	Study Type/Sample Size	Confounding Factors
(Weidner et al., 1998)	+	Unspecified/All	Hypospadias/Cryptorchidism	Tax authority information sheets (indicating employee's working place)	Register-based case-control/30,795	▪ Birth year/birth weight/gestational age/parity/twin birth ▪ Maternal history of stillbirth ▪ Parental age/nationality/professional status ▪ Maternal occupation/occurrence of the same malformation in an older brother
(Andersen et al., 2008)	+	200 compounds	All	Questionnaire-assisted interview/ governmental risk assessment/employer's interview	Cohort/113	Birth weight/birth length/gestational age/age at examination/IUGR/smoking during pregnancy
(Gaspari et al., 2011)	+	Unspecified/All	Hypospadias/Cryptorchidism/Micropenis/ Disorders of sexual differentiation	Questionnaire	Nested case-control/ 115	▪ Time to pregnancy ▪ Parity ▪ Weeks of gestation/birth weight/folic acid supplements Contraceptive pill use/smoking/alcohol intake during pregnancy
(Rocheleau et al., 2011)	−	Unspecified/All	Hypospadias	Interview/Job exposure matrix (only low exposures assessed)	Case-control/2143	▪ Maternal age ▪ Parity ▪ History of miscarriage/singleton/multiple pregnancy ▪ Gestational age/birth weight of the index infant ▪ Maternal alcohol/smoking/folic acid supplement use ▪ Pre-pregnancy BMI/race/income category ▪ Parental education/parental birthplace outside the US/ language of the interview
(Jorgensen et al., 2014)	+	Unspecified/All	Cryptorchidism	Employment Classification Module from Statistics Denmark	Cohort/ > 600,000	▪ Birth year/maternal and paternal age ▪ Maternal parity status ▪ Geographical region at birth

BMI: Body Mass Index; CAs: Congenital Abnormalities; HR: Hazard Ratio; OR: Odds Ratio; UGAs: Urogenital Abnormalities; 95% CI: Confidence Interval; +: association detected; −: no association detected; +/−: trend towards association (not statistically significant).

Table 8
Studies associating pesticides with heart and other malformations.

Studies	Association	Pesticide Tested	CAs Tested	Exposure Type	Exposure Assessment	Study Type/ Sample Size	Region	Confounding Factors
(Loffredo et al., 2001)	+ and +/−	Unspecified	Great Arteries Transposition/Laterality and looping defects/Non-TGA cardiac outflow tract anomalies/Endocardial cushion defects/Left-sided obstructive lesions/Pulmonic stenosis/ VSDs/Atrial septal defects	Environmental	Interviews, Questionnaires	Case Control/837	Maryland/District of Columbia/adjacent counties of northern Virginia	▪ Race/socioeconomic status ▪ Maternal age ▪ Maternal smoking/alcohol use/ family history of heart defects/ maternal diabetes/maternal solvent exposures ▪ Paternal pesticide exposures
(Agopian et al., 2013c)	+	Atrazine (crops)	Choanal atresia/stenosis	Environmental	Registry/US Geological Survey Data	Case-control/ 4000	Texas	▪ Infant sex ▪ Season of conception/birth year ▪ Maternal age/race/ethnicity/ education/smoking status
(Carmichael et al., 2014)	+ and +/−	461 individual chemicals and 62 physicochemical groupings	Heterotaxia/Tetralogy of Fallot/D-transposition of the great arteries/Hypoplastic left heart syndrome/Coarctation of the aorta/ Pulmonary valve stenosis/Perimembranous VSD/Atrial septal defect secundum	Environmental	Interviews/ Questionnaires/Pesticide use report records/ Geocoding	Case-control/ 1354	San Joaquin Valley (California)	▪ Maternal race/ethnicity/ education/age ▪ Folic acid supplements use/ alcohol/smoking during the month before and the first two months of pregnancy
(Rocheleau et al., 2015)	+ and +/−	Fungicides/Insecticides/ Herbicides	Congenital heart defects	Occupational	Expert-guided task-exposure matrix/self-reported job history details	Case-control/ 6316	USA	▪ Maternal age ▪ Parental race/ethnicity/birth outside the US/education/income ▪ Pre-pregnancy BMI/folic acid intake/smoking/alcohol use ▪ Parity ▪ Pre-pregnancy diabetes/the NBDPS site/first-degree family history of CVAs ▪ Multiple pregnancy/gestational diabetes in the index pregnancy

EUROCAT: European Surveillance of Congenital Anomalies; TGA: Transposition of Great Arteries; CVAs: Cardiovascular Abnormalities; 95% CI: 95% Confidence Interval; +: association detected; -: no association detected; +/−: trend towards association (not statistically significant).

et al., 2007; Giordano et al., 2010; Longnecker et al., 2002; Michalakis et al., 2014; Pierik et al., 2007; Trabert et al., 2012) yielded conflicting results (Table 6). Most of them failed to detect an association (Bhatia et al., 2005; Brucker-Davis et al., 2008; Carmichael et al., 2010; Chevrier et al., 2011; Longnecker et al., 2002; Pierik et al., 2007; Toft et al., 2016; Trabert et al., 2012) while some of them directly linked UGAs risk with DDE and/or DDT (Bhatia et al., 2005; Brucker-Davis et al., 2008; Longnecker et al., 2002). Some others detected just a positive association (Damgaard et al., 2006; Fernandez et al., 2007; Giordano et al., 2010; Michalakis et al., 2014). Four studies linked hypospadias/cryptorchidism with specific pesticides including mirex/lindane (Fernandez et al., 2007), hexachlorobenzene (Giordano et al., 2010), DDT and its metabolites (Longnecker et al., 2002), as well as OPs/OCs (Michalakis et al., 2014). Increased concentrations of eight substances (p,p´-DDE, p,p´-DDT, β-HCH, hexachlorobenzene (HCB), α-endosulfan, cis-heptachloroepoxide, dieldrin, oxychlordane) were measured in cases of cryptorchid boys in another study (Damgaard et al., 2006). Finally, significantly increased levels of OCs and OPs in cryptorchid boys and their parents compared to occupationally exposed adults were reported (Damgaard et al., 2006).

Occupational exposure results assessed without using biomarkers differed (Table 7). More than half of the studies reported maternal occupational exposure as a risk factor for UGAs (Andersen et al., 2008; Gaspari et al., 2011; Jorgensen et al., 2014; Weidner et al., 1998). It should be noted, that one study negating positive association with mild hypospadiac cases included only low exposure cases (Rocheleau et al., 2011), possibly compromising final outcome. Paternal was not as strongly associated as maternal occupational exposure with UGAs.

7. Cardiovascular abnormalities

CVAs constitute a major proportion of clinically significant CAs and are an important component of pediatric cardiovascular disease, with an estimated prevalence of 6 to 9 per 1000 live births (Botto et al., 2001; Hoffman et al., 2004), and with VSD being the most common (Bjornard et al., 2013; Botto et al., 2001). During the first year of life, CVAs are the leading cause of death from CAs (Yang et al., 2006). The prevalence of some CVAs, especially mild types, is increasing, while the prevalence of other types has remained stable (Botto et al., 2001; Yang et al., 2006). Despite the frequency of these CAs, the literature on their association with pesticides is limited. Only four studies were identified from 1990 till mid-2015 (Agopian et al., 2013b; Carmichael et al., 2014; Loffredo et al., 2001; Rocheleau et al., 2015). They all presented adequate study designs and moderate sample sizes. However, their main limitation was that exposure assessment was based on self-report in all cases.

A general positive association between CVAs (heart abnormalities only) and pesticide use was observed (Table 8) (Carmichael et al., 2014; Loffredo et al., 2001; Rocheleau et al., 2015). Residential proximity to specific chemicals (Carmichael et al., 2014) and exposure to certain types of pesticides (Loffredo et al., 2001; Rocheleau et al., 2015) were found to be associated with specific CVAs. A dose-response relationship was detected between one-time exposure, monthly exposure, and no exposure but not for once a week and a few times per week exposure (Loffredo et al., 2001).

A positive association between transposition of great arteries and herbicides/rodenticides (Loffredo et al., 2001), other CVAs and insecticides, herbicides and fungicides (Rocheleau et al., 2015) as well as with specific chemicals rather than chemical groups was reported (Carmichael et al., 2014). Such associations include pulmonary valve stenosis-bipyridylium/organophosphorus, perimembranous ventricular septal defects (VSD)-avermectin, coarctation of the aorta-pyridazinone, atrial septal defect secundum-dichlorophenoxy acid or ester and Fallot's tetralogy/hypoplastic left heart syndrome-neonicotinoids.

8. Other defects

The remaining studies were classified into this category. Overall, the results of these studies were inadequate to draw conclusions for these categories of CAs and thus they were not further analyzed.

9. Conclusions

The association between CAs and pesticides remains uncertain, regardless of the type. A trend suggestive of a positive association was detected for MSAs, NTDs, and CVAs, but no firm conclusions could be drawn. Pesticides are a very diverse group of compounds with multiple modes of action. Assuming that few selective active ingredients contribute to CAs, their actions may be masked in studies examining them in conjunction with other innocuous chemicals, resulting in an ambiguous picture. The main limitation of the studies was poor exposure assessment, since many of them relied solely on self-report and only studies associating pesticides with UGAs utilized biomarkers extensively. Use of specific biomarkers of exposure in mothers may be preferable for detecting such associations between exposure and possible teratogenic effects; an issue that should be addressed in future studies. Investigation of potential associations between specific CAs with specific active ingredients of occupational or daily used chemicals might prove to be more promising in the long run.

Conflict of interests

The authors declare that there are no conflicts of interest from any funding sources.

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