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Environmental and Occupational Pesticide Exposure and Human Sperm Parameters: A Systematic Review

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Abstract

Of continuing concern are the associations between environmental or occupational exposures to pesticides and semen quality parameters. Prior research has indicated that there may be associations between exposure to pesticides of a variety of classes and decreased sperm health. The intent of this review was to summarize the most recent evidence related to pesticide exposures and commonly used semen quality parameters, including concentration, motility and morphology. The recent literature was searched for studies published between January, 2007 and August, 2012 that focused on environmental or occupational pesticide exposures. Included in the review are 17 studies, 15 of which reported significant associations between exposure to pesticides and semen quality indicators. Two studies also investigated the roles genetic polymorphisms may play in the strength or directions of these associations. Specific pesticides targeted for study included dichlorodiphenyltrichloroethane (DDT), hexachlorocyclohexane (HCH), and abamectin. Pyrethroids and organophosphates were analyzed as classes of pesticides rather than as individual compounds, primarily due to the limitations of exposure assessment techniques. Overall, a majority of the studies reported significant associations between pesticide exposure and sperm parameters. A decrease in sperm concentration was the most commonly reported finding among all of the pesticide classes investigated. Decreased motility was also associated with exposures to each of the pesticide classes, although these findings were less frequent across studies. An association between pesticide exposure and sperm morphology was less clear, with only two studies reporting an association. The evidence presented in this review continues to support the hypothesis that exposures to pesticides at environmentally or occupationally relevant levels may be associated with decreased sperm health. Future work in this area should focus on associations between specific pesticides or metabolic products and sperm quality parameters. Analysis of effects of varying genetic characteristics, especially in genes related to pesticide metabolism, also needs further attention.

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Keywords

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1. Introduction

Over the past few decades, several studies have been published indicating a longitudinal decline in sperm quality. A meta-analysis published in 1992 presented evidence that sperm concentrations among men worldwide with no history of infertility had dropped from a mean value of 133×10^6 sperm per milliliter in 1940 to 66×10^6 sperm per milliliter in 1990 (Carlsen et al., 1992). In 2000, Swan et al. published an updated meta-analysis that further supported this finding, showing declines in sperm concentration over time (Swan et al., 2000). More recently published papers continue to build on this body of evidence, with studies focusing on populations from around the globe. For example, decreased semen quality had been found among men in France (Geoffroy-Siraudin et al., 2012), New Zealand (Shine et al., 2008), India (Dama and Rajender, 2012), Tunisia (Feki et al., 2009) and Israel (Haimov-Kochman et al., 2012). In a study on four European populations, evidence indicated there were differences in sperm parameters among men with pregnant partners in different countries within a relatively small geographical region. After controlling for abstinence time, age and season, the study found that sperm concentrations in Danish and French men were significantly lower than in Finnish men (Jorgensen et al., 2001). While genetic differences may play a role in these results, many studies suggest environmental factors as a potential cause of these declines. While semen quality alone is not enough to diagnose male-factor infertility, the assessment of common semen parameters in a laboratory is a relatively easy method for identifying potential semen quality concerns.

Semen quality is often assessed according to guidelines in the World Health Organization [WHO] Laboratory Manual for the Examination and Processing of Human Semen; the most recent edition was published in 2010. The manual describes standardized procedures and scoring criteria for several semen quality measures, including concentration, motility and morphology. WHO also publishes reference values (Cooper et al., 2010) that can be used to dichotomize the status of semen quality or evaluate study populations against a common comparison group. Age and abstinence time are commonly associated with semen volume, sperm concentration and sperm motility (Eskenazi et al., 2003; Magnus et al., 1991).

The spermatogenic process is regulated by the male endocrine system (Dohle et al., 2003), and therefore, semen quality may be particularly sensitive to any pesticides or pesticide metabolites that may mimic male hormones or inflict tissue damage in the testes. A number of pesticides or their metabolites have been implicated as potential endocrine disruptors in human or animal models, including DDT (Kelce et al., 1995; Klotz et al., 1996; Scippo et al., 2004) and pyrethroids (Jin et al., 2011; Tyler et al., 2000). Recent studies have found associations between pesticides or metabolites and levels of reproductive hormones in various populations. Among male floriculture workers in Mexico, for example, increased occupational exposures to organophosphates, measured as dialkylphosphates in urine, were associated with decreased levels of follicle stimulating hormone (FSH), increased levels of testosterone and decreased levels of inhibin B (Blanco-Muñoz et al., 2010). In a study of environmental exposures to pyrethroid pesticides, increasing levels of urinary pyrethroid metabolites were associated with increased FSH and luteinizing hormone (LH) and with decreased inhibin B (Meeker et al., 2009). Organochlorines were shown to be associated with differences in hormone levels in a cohort study of European men (Giwercman et al., 2006). Animal studies have also demonstrated the potential for pesticides to cause testicular damage. Tissue damage in the testes and adverse spermatogenic effects have been seen in rats and mice exposed to cypermethrin (Grewal et al., 2010), malathion (Contreras and Bustos-Obregon, 1999), and parathion (Rodriguez and Bustos-Obregon, 2000).

In the United States, pesticides are evaluated by the US Environmental Protection Agency (US EPA) for their potential human health effects. With the passing of the Food Quality Protection Act (2006), US EPA was charged with evaluating pesticides and other chemicals for endocrine disruption in addition to the standard toxicological data. US EPA has currently evaluated 79 chemicals for their endocrine disrupting properties. However, these endpoints are often difficult to incorporate into risk assessments because the dose response curves are not well understood (WHO, 2011). It is often the case where associations are detected between suspected endocrine disruptors and hormone-related endpoints at low levels of exposure— typically well below the levels of toxicological testing (Reviewed in Vandenberg at al., 2012). More work is needed to discern the relevant levels of exposure to potential endocrine disrupting pesticides and to better elucidate their suspected effects in humans.

An increasing number of human studies in recent years have started to evaluate the potential of pesticides to affect sperm quality, one of many factors related to male-factor infertility. Between 1991 and 2006, 20 studies were published in which the outcomes of interest were common semen quality measures (Perry, 2008). Since 2006, the body of research has grown. This review sought to evaluate the latest studies and build upon evidence previously summarized by Perry in 2008. As with the original body of research, the pesticides and outcomes reported in the studies evaluated here varied, but suggestive trends could be identified. After summarizing and evaluating the weight of evidence, recommendations for future work were also considered.

2. Materials and Methods

2.1 Search Design

Based on previous search criteria used by Perry (2008), literature published between January, 2007 and August, 2012 was searched for relevant articles. The aim of this systematic review was to evaluate the weight of evidence compiled since the publication of the first review on pesticides and their associations with sperm parameters such as concentration, motility or morphology.

2.2 Identification of Studies

Articles were identified and retrieved primarily using PubMed, with secondary searches of Scopus, Web of Science and MEDLINE to ensure the search was comprehensive. Hand search of references of retrieved articles was also performed to confirm completeness. Searches of each database were conducted in a similar matter, using the search terms *sperm, human sperm, semen, human semen* and parameters, semen parameters, sperm parameters, semen quality, motility, morphology or *concentration* in combination with *pesticides, agrochemicals, environmental pesticide exposure*, or *occupational pesticide exposure*. The search parameters included only articles published in English that pertained to original research related to human health outcomes. Animal toxicological studies and systematic reviews were not included.

2.3 Eligibility Criteria

Studies were eligible for inclusion in this review if they were published in English and used data related to human sperm health outcomes. Articles published between January, 2007 and August, 2012 reporting on general or specific pesticide exposures, either occupational or environmental, *and* on associations with semen quality parameters such as concentration, motility, morphology, and sperm count were retrieved and included in the review. Studies that explored persistent organic pollutants (POPs) must have included the organochlorine pesticides dichlorodiphenyltrichloroethane (DDT), or its metabolites, or hexachlorocyclohexane (HCH) to be considered eligible; polychlorinated biphenyls (PCBs) were not included as exposures of interest. Furthermore, articles were included if they explored possible susceptible subpopulations on the basis of genetic characteristics with respect to pesticide exposures and semen quality parameters. While some of the articles included in this paper also reported on alternative sperm characteristics such as DNA integrity, these additional outcomes were considered outside the scope of this review.

3. Results

Twenty-one (21) studies were identified as meeting the search parameters outlined above. Of these 21 studies, 17 were included in this review. Four studies were excluded from the review for one of the following reasons: the study did not assess pesticides as a specific exposure of interest, but rather, evaluated risks based on occupational factors (Vaziri et al., 2011; Tuc et al., 2007); the study did not report any statistical tests between an exposed group and comparison group (Gallegos-Avila et al., 2010); or, the study only presented the results of a stratified analysis and did not report on an overall association between pesticide exposure and sperm parameters (Giwercman et al., 2007).

Of the 17 included studies, two also investigated the effect modification specific genetic polymorphisms may have on the associations between pesticide exposures and sperm parameters (Messaros et al., 2009, Perez-Herrera et al., 2008).

Table 1 summarizes the 17 studies investigating the associations between pesticides and semen quality included in this review, organized by pesticide class. Seven of these studies evaluated occupational exposures to pesticides, whereas the remaining 10 focused on environmental exposures. Most of the studies included in this review evaluated each sperm parameter independently.

3.1 Studies Reporting No Association

Two of the 17 studies included in this review reported no significant associations between pesticides and semen parameters. Both of these studies looked at non-specific occupational pesticide exposures determined by self-report or job exposure classification. One paper examined the relationship between occupational exposures, as determined by participant questionnaire, and altered semen. The researchers found suggestive odds of occupational exposure to pesticides (Odds Ratio [OR]=3.6, 95% Confidence Interval [CI]: 0.8-15.8) among men with altered semen, but the association failed to reach statistical significance (de Fleurian et al., 2009). A second paper reported no association between occupational exposures to pesticides and sperm characteristics among men working on a banana plantation. There were no significant differences in sperm parameters between the 20 workers who were routinely exposed to pesticides, as determined by job function, and the 20 workers identified as non-exposed controls (Multigner et al., 2008).

3.2 Studies Reporting an Association between Pesticides and Sperm Parameters

Fifteen (15) studies summarized in this review reported at least one significant association between a pesticide exposure and a sperm parameter. Both studies exploring genetic susceptibilities found associations specific to a particular genotype. Sperm concentration (or sperm count) was the most commonly reported semen parameter associated with pesticide exposure, and this was true across all pesticide classes investigated. Although less frequent, associations were reported between exposures to pyrethroids, organochlorines, organophosphates and abamectin and sperm motility. Patterns related to morphology were less consistent, with only two studies reporting associations: one with exposure to DDT and one with exposure to organophosphates.

Studies reporting associations included case-control and cross-sectional designs, with sample sizes ranging from 18 men in a pilot study (Perry et al., 2007) to 402 men seeking evaluations for infertility in France (de Fleurian et al., 2009). All but two of the studies reporting an association between pesticides and semen parameters relied on biomonitoring to assess or confirm environmental or occupational exposures; only in the studies by Hossain et al. (2010) and Perez-Herrera et al. (2008) was exposure assessment conducted by questionnaire and work history alone.

Associations were reported for a variety of pesticide classes. Among the 15 studies reporting associations, three (3) studies found significant results for pyrethroid pesticides (Ji et al., 2011; Meeker et al., 2008; Xia et al., 2008). Relationships between the persistent organic pollutants (POPs) DDT and HCH and sperm characteristics were found in five studies (Aneck-Hahn et al., 2007; Haugen et al., 2011; Khan et al., 2010; Messaros et al., 2009; Pant et al., 2007). Organophosphates (OP) were shown to be associated with lowered sperm parameters in six of the studies (Hossain et al., 2010; Perez-Herrera et al., 2008; Perry et al., 2007, 2011; Recio-Vega et al., 2008; Yucra et al., 2008). One study found an association between the pesticide abamectin and decreased sperm motility (Celik-Ozenci et al., 2012).

4. Discussion

As originally reported by Perry (2008), 20 studies published between 1991 and 2006 investigated the relationship between pesticide exposures and outcomes related to individual semen parameters. Thirteen of these original studies reported significant findings. In the seven years following this initial review, an additional 17 studies have been published. Fifteen of these studies reported positive findings for associations between pesticide exposures and semen parameters. The most recent literature also includes two studies pertaining to potentially susceptible subpopulations on the basis of genetic polymorphisms. Based on the increased volume of papers published in the last seven years, it is evident that there is much interest in this area of research. Organophosphates were the class of pesticides most frequently investigated among the studies presented here, followed by organochlorines and then pyrethroids. For pyrethroids and organophosphates, non-specific metabolites were most frequently studied, and associations were found with semen concentration. DDT and HCH were both associated with semen concentration as well. Although they were reported less frequently than semen concentration, associations between each of the pesticide classes (pyrethroids, organochlorines and organophosphates) and sperm motility were also found. Specific aspects of these associations and how they contribute to the weight of evidence are discussed further below.

4.1 Weight of evidence

4.1.1 Pyrethroids—Pyrethroid pesticides were evaluated for their associations with semen parameters in four of the studies reviewed here, of which two found an association between the metabolite 3- phenoxybenzoic acid (3-PBA) and lower sperm concentration (Ji et al., 2011; Xia et al., 2008). 3-PBA is a metabolite common to several pyrethroid pesticides, including permethrin, fenvalerate and cypermethrin. Meeker et al. (2008) found significantly higher odds of lower sperm concentration for men with high total urinary *cis*- and *trans*-3-(2,2,dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (CDCCA and TDCCA), two metabolites common to a few pyrethroid pesticides, including permethrin, cypermethrin and cyfluthrin (Sudakin, 2006). The fourth study (Perry et al., 2007) also found a suggestive association between pesticide exposure and lower sperm concentration for the metabolites 3-PBA and TDCCA. These consistent results are not definitive, but suggest that exposure to pyrethroids at environmentally relevant levels may somehow impact semen concentration.

4.1.2 Organochlorines—Results from studies reporting on organochlorines were fairly consistent among studies, with a few exceptions. Aneck-Hahn et al. (2007) found an increased risk of oligospermia (sperm concentrations below 20 million sperm per milliliter of ejaculate) with increasing levels of *p,p'*- DDE and an increased risk of asthenozoospermia (low total sperm motility grades) with increasing levels of *p,p'*-DDT and *p,p'*-DDE. In a cross-sectional study by Haugen et al. (2011), semen parameters were evaluated with respect to blood serum levels of *p,p'*-DDE for two groups of men: one group living below the Arctic Circle and one group living above. The study found significantly higher levels of *p,p'*-DDE among men living below the Arctic Circle compared to the group living above. Contrary to the other studies in this review, higher levels of *p,p'*-DDE were correlated with higher semen concentration (r=0.25, p=0.03) among men living in the northern region of Norway

(Haugen et al., 2011). Serum concentrations of *p,p'*-DDE and *p,p'*- DDT were combined by Messaros et al. (2009) to evaluate their associations with semen parameters: high sum *p,p'*-DDE and *p,p'*-DDT concentrations increased the odds of low sperm concentration, low sperm motility and abnormal morphology. In a study comparing 50 infertile men to 50 fertile men, *p,p'*-DDE and *p,p'*-DDD in seminal plasma were both associated with decreased sperm counts in infertile men (Pant et al., 2007). The evidence presented in these studies supports the hypothesis that exposure to DDT may be associated with decreased semen parameters, but future research should seek to strengthen the evidence for particular metabolites.

Two studies found in this review evaluated associations between HCH and semen parameters. Associations between HCH and semen parameters were seen in men classified as infertile, but the relationships were inconsistent. While Khan et al. (2010) reported an association between two HCH isomers (α-HCH and β-HCH) and increased sperm counts among infertile men, Pant et al. (2007) found an association between two HCH isomers (β-HCH and γ-HCH) and decreased sperm count and motility among infertile men. When stratifying by semen classification however, Khan et al. (2010) found associations between γ-HCH and decreased sperm counts among asthenospermic men (low motility scores) and between β-HCH and total HCH and decreased sperm counts among oligo-asthenospermic men (low sperm count and low motility scores). Both studies determined exposure by assaying seminal fluid for HCH isomers, and both studies used the same sample sizes (50 fertile and 50 infertile men) taken from a population in Lucknow, India. The total HCH concentration measured in the semen of infertile men in the Pant et al. (2007) study, however, appears to be lower than the concentration reported for infertile men by Khan et al. (2010) (93μg/L versus 500μg/L, respectively). The two studies also used different case definitions when defining their infertile subject groups. Khan et al. (2010) based infertility on sperm concentration and motility whereas Pant et al. (2007) defined infertile men as those with partners who had not conceived after a year of regular unprotected intercourse, making comparisons between the two studies more difficult. Only one other study, published in 2004, has explored the association between HCH and semen parameters. This study found levels of seminal HCH were higher in men classified as infertile compared to fertile controls (Pant et al., 2004). This discrepancy in results suggests that more study into the associations between seminal HCH levels and semen parameters is warranted.

4.1.3 Organophosphates—Organophosphates were the most frequently studied pesticide class among the papers reviewed here: all six studies included in the review reported significant associations between OPs and a semen parameter. In a study on farmers in Malaysia, Hossain et al. (2010) found higher risk for abnormal semen parameters for exposed men compared to unexposed men. Two studies found associations between higher OP exposure and decreased sperm concentration (Perry et al., 2007, 2011). OP exposure was also found to be significantly associated with decreased sample volume (Recio-Vega et al., 2008; Yucra et al., 2008) and decreased sperm count (Recio-Vega et al., 2008).

Two of the organophosphate studies (Perry et al., 2007; 2011) identified associations with specific OP metabolites. Diethylthiophosphate (DETP) was shown to be associated with decreased sperm concentration (Perry et al., 2007). Men were 1.3 times more likely to be classified with semen parameters below the population median for every 1μg/mL increase in urinary dimethylphosphate (DMP) in a study among environmentally exposed men in China (Perry et al., 2011). It is important to note that the metabolites of interest in these studies are non-specific to the OP class of pesticides and could represent a number of different parent compounds. Future studies should incorporate biomonitoring for particular OP pesticide metabolites when available and appropriate (e.g., assaying biological samples for 3,5,6-trichloro-2-pyridinol [TCPy] to measure exposure to chlorpyrifos). Despite a lack of specificity for particular pesticides, the studies in this review support evidence compiled earlier (Perry, 2008) indicating that OP pesticides may be associated with declines semen quality.

4.1.4 Other pesticides and non-specific pesticide exposures—Abamectin was evaluated as an exposure of interest in one study of occupationally exposed farmworkers in Antalya, Turkey. Abamectin is a pesticide consisting of a mix of compounds called avermectins. These avermectins are fermentation products of the soil bacterium Streptomyces avermitilis and have been used as acaricides and nematicides (Burg et al., 1979). In this one study, men exposed to the pesticide had significantly lower sperm motility and higher semen volume compared to unexposed controls (Celik-Ozenci et al., 2012). Animal models have shown abamectin to be deleterious to sperm count and motility (Celik-Ozenci et al., 2011) and to reduce fertility in rats (Elbetieha and Da'as, 2003). These findings suggest additional investigation of abamectin is warranted.

4.2 Identification of Genetic Susceptibilities

Two studies were identified that evaluated genetic susceptibilities to impacts on semen quality as a result of occupational or environmental pesticide exposure (Messaros et al., 2009; Perez-Herrera et al., 2008). Genes for three different proteins involved in the metabolism of pesticides were evaluated as potential effect modifiers. Polymorphisms in genes related to a cytochrome P-450 enzyme (CYP1A1) and to glutathione-S-tranferases (GSTM1, GSTT1 and GSTP1) were evaluated by Messaros et al. (2009) for effects on DDT-DDE exposure. The study found the null GSTT1 genotype increased the odds of decreased sperm motility compared to men with the GSTT1 genotype intact. The highest odds of decreased sperm motility were seen among men with the GSTT1 null genotype and high DDE-DDT exposures. The authors also found evidence of a protective effect for low sperm morphology among men with increasing numbers of variant alleles in the CYP gene for both low and high DDE-DDT exposures. In the second paper, Perez-Herrera et al. (2008) examined the modifying effects of polymorphisms in the PON1 gene that codes for paraoxonase, an enzyme involved in OP deactivation. An interaction was found between pesticide exposure in the three months prior to sampling and the 192RR genotype on sperm viability. This modification effect was not seen when investigating exposures at the time of sampling. These results suggest that differences in pesticide metabolism among individuals may affect susceptibilities to sperm abnormalities as a result of exposure. Evidence also suggests that timing of exposure is an important consideration when evaluating these associations. These genes and others related to pesticide metabolism should be further studied to more clearly identify genetic subpopulations at higher risk for impacts on sperm quality due to pesticide exposure.

4.3 Sample size

The overall sample sizes of the studies investigating pesticides and semen parameters have grown in the six years since the original review was published. Sample sizes in this collection of literature range from 18 men analyzed in a pilot study (Perry et al., 2007) to 402 men recruited from a fertility clinic (de Fleurian · The median sample size was 152 and the mean was 172.5. Even with the growing number of study subjects, none of the studies reported on the statistical power of their study designs. This may not be a major concern, however, because a majority of the studies included in this review reported at least one significant finding. Design of future studies should seek to ensure that study power is optimized.

4.4 Methods of exposure assessment

Five studies in this review relied on survey data or work history to conduct exposure assessments. Of the two studies reporting no association, both relied on self-reported exposures in their analyses (de Fleurian et al., 2009; Multigner et al., 2008). One study assessed non-specific occupational exposures through survey questions designed to elicit information on risk factors for impaired semen parameters; the questionnaire collected dichotomous data on non-specific occupational pesticide exposures (de Fleurian et al., 2009). The other study, which involved banana plantation workers, collected information from participants about their pesticide use, distinguishing between occupational and other exposures (Multigner et al., 2008). Two studies reporting a significant finding (Hossain et al., 2010; Perez-Herrera et al., 2008) used survey questions and work history to conduct exposure assessment. Hossain et al. (2010) identified two groups of study participants, exposed and unexposed, on the basis of whether or not they had a history of occupational pesticide exposure. Perez-Herrera et al. (2008) also utilized survey data to compile occupational exposures to pesticides and constructed two exposure profiles: one at the time of sampling and one for the three months prior.

For the remaining 13 studies, analytical detection of pesticides or metabolites in biological matrices served as a primary method of exposure assessment or as a confirmation of exposure status. Compounds were detected in blood serum (Aneck-Hahn et al., 2007; Celik-Ozenci et al., 2012; Haugen et al., 2011; Messaros et al., 2009), urine (Ji et al., 2011; Meeker et al., 2008; Perry et al., 2007, 2011; Recio-Vega et al., 2008; Xia et al., 2008; Yucra et al., 2008), and seminal fluid (Khan et al., 2010; Pant et al., 2007) using a variety of extraction techniques and instrumentation. These biomarkers allowed for more detailed statistical analyses beyond dichotomous exposure status. For example, in some studies, pesticide exposure was analyzed continuously to examine dose-response relationships between exposures and sperm parameters and in others, potential covariates or confounders could be controlled.

Detailed analyses detecting several different pesticide metabolites will be vital in future studies, as evidence suggests that metabolites of pesticide compounds may behave differently with respect to their endocrine-like activities and their impacts on the spermatogenic process. For example, previous work has suggested that different DDT metabolites may possess varying endocrine disrupting properties. Research has shown that *p,p'*-DDE acts as an androgen antagonist and interferes with the male reproductive system in mice (Kelce et al., 1995). In a recombinant model using human estrogen receptor (hERα), androgen receptor (hAR) and progesterone receptor (hPR), *p,p'*-DDD and *o,p*-DDD showed affinities for hAR; when compared to the dihydrotestosterone (DHT) control ligand, the relative binding affinities (RBA) were 0.333% and 0.294%, respectively (Scippo et al., 2004). Additionally, *in vitro* study results showed two pyrethroid metabolites, 3-PBA and DCCA, both elicited anti-estrogenic responses in recombinant yeast expressing human sex hormone receptors; however, 3-phenoxybenzyl alcohol, an intermediate metabolite and metabolic precursor to 3-PBA, produced estrogenic and anti-androgenic effects (Tyler et al, 2000). These potential differences in the activities of pesticide metabolites warrant detailed, precise exposure assessment to more thoroughly assess associations between pesticide exposures and semen health parameters. Studies should continue to isolate particular pesticides and pesticide metabolites whenever possible and assess individual associations with semen parameters.

Many exposure assessments related to organophosphate pesticides are conducted by measuring non-specific metabolites called dialkylphosphates (DAPs). These compounds cannot be attributed to an original parent compound (Bravo et al., 2004), and therefore are not indicative of any one OP pesticide. In addition to being metabolic products, DAPs are found in the environment and in food as degradation products of organophosphate pesticides. The use of DAPs as a biomarker for OP exposures has been criticized due to the inability to distinguish exposures to parent compounds from exposures to pre-formed DAPs (Krieger et al., 2012; Sudakin and Stone, 2011). Several studies have indicated that intake of preformed DAPs may account for a significant portion of urinary DAP concentrations (Bouvier et al., 2006; Lu et al., 2005, Zhang et al., 2008). Assuming that exposure to preformed degradation products has the same impact on spermatogenesis as exposure to parent compounds needs more empirical support. Whenever possible, researchers should attempt to assess and control for intake of preformed DAPs in the diets of study subjects. Regardless of these limitations, however, urinary pesticide metabolite analyses continue to be used extensively in biomonitoring studies due to their relatively low costs compared to more parent compound analyses, and their utility for interpreting health effects needs further scrutiny.

As was true in the studies reviewed previously, timing of exposure was not well considered in most of the studies presented here; only a few accounted for timing in their exposure assessments. For instance, Perez-Herrera et al. (2008) conducted an exposure assessment by surveying agricultural workers and constructing two exposure profiles: one indicating exposures during the month of sample collection and one indicating exposures in the three months prior to sampling to account for a full spermatogenesis cycle, which typically lasts between 42 and 76 days (Wein et al., 2012). A significant inverse association between OP exposure and sperm viability was reported for men with the PON1 RR genotype who had been exposed in the three months prior to sampling (Perez-Herrera et al., 2008). This same association was not significant for the same genotypic group for exposures at the time of sampling. Because the mechanisms underlying links between pesticides and sperm parameters are not well understood, detailed exposure assessments that specify time-specific exposure windows can better determine when exposures are most critical to the spermatogenic process. Single point estimates are unlikely to accurately reflect cumulative exposures to pesticides, particularly when they are rapidly metabolized.

4.5 Outcomes of Interest

World Health Organization (WHO) criteria for semen parameters are commonly referenced throughout the papers evaluated here. Most of the studies used procedures published by WHO (1992, 1999) for collection, preparation and analysis of semen samples. Among the studies reviewed here, most reported on the three most common semen quality parameters: concentration, motility and morphology. In order to better evaluate a range of impacts, future studies should consider including other sperm health indices, including seminal volume, sperm vitality, DNA damage and fragmentation, and chromosomal abnormalities.

4.6 Treatment of Covariates

Most studies included in this review assessed a variety of combinations of the common covariates related to semen quality, including age, abstinence time, body mass index (BMI), smoking status, race (when appropriate), and alcohol use when conducting statistical analyses. Depending on the extent of the exposure assessment and biomonitoring efforts, some studies included a number of covariates in their adjusted models. For example, Yucra et al. (2008) controlled for methylated OP metabolites to determine the associations between ethylated OP metabolites and semen parameters. Messaros et al., (2009) controlled for a variety of other environmental exposures, including other organochlorine pesticides and polychlorinated biphenyls.

Risk factors shown in other studies to be associated with decreased semen quality include: more advanced age (Sartorius and Nieschlag, 2010); smoking behavior (Ramlau-Hansen et al., 2007); exposure to trace metals such as lead (Fatima et al., 2010); higher levels of dietary fat intake (Attaman et al., 2012); exposure to endocrine disruptors such as bisphenol-A (Li et al., 2011) or polybrominated diphenyl ethers (PBDEs) (Abdelouahab et al., 2011); and, exposure to non-pesticide organochlorine compounds, including polychlorinated biphenyls (PCBs) (Dallinga et al., 2002). To the extent possible, these risk factors should be considered in future studies, and potential effect modifiers should be further explored.

5. Conclusions

Because positive study findings are more likely to be published than null or negative findings, the studies included in this review may not be representative of all research findings (Dickersin, 1990). However, evidence presented in this paper continues to support the hypothesis that exposure to pesticides at both occupationally and environmentally relevant levels may have associations with decreased sperm quality parameters, particularly sperm concentration. Pesticides from a number of classes were reported to be associated with decreased semen quality. A majority of these studies used biomonitoring to assess or confirm both occupational and environmental pesticide exposures. Impacted semen quality parameters included concentration, motility and morphology, with decreased semen concentration being the most commonly reported finding. As was the case in the original review article, the studies presented here to do not strongly indicate any one particular pesticide that may have deleterious effects on semen. Because most of the studies evaluated non-specific metabolites, the associations found were more often for classes of pesticides rather than specific parent compounds. The exception to this is was for the organochlorines and abamectin. Many pesticide metabolites can exist as environmental degradation products or as the result of the body's metabolism of parent pesticide compounds. Non-specific biomonitoring cannot distinguish between these two different sources; therefore, evaluating health effects due to parent compound exposures can be uncertain. Methods to detect preformed degradation products should be pursued, as well as methods to detect specific metabolites whenever possible in order to more directly associate differences in sperm parameters with individual pesticide exposures. Biomonitoring may also help to better control for other potentially correlated exposures, such as PCBs. Survey and questionnaire data can be used to identify specific pesticides of interest, but their use would likely be limited to occupational settings where specific pesticides are known. Future studies should also continue to use genotyping to identify susceptible subpopulations; differences in pesticide metabolism may play a key role in how these exposures affect spermatogenesis.

Manuscript Abbreviations

AMB	Abamectin
CDCCA	*cis*-3-(2,2,dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
CI	95% confidence interval
CYP	Cytochrome P-450 enzymes
DAP	Dialkylphosphate
DCCA	3-(2,2,dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
DDT	Dichlorodiphenyltrichloroethane
DETP	Diethylthiophosphate
DMP	Dimethylphosphate
FSH	Follicle Stimulating Hormone
GST	Glutathione-S-transferase
hAR	Human androgen receptor
hERα	Human estrogen receptor
hPR	Human progesterone receptor
HCH	Hexachlorocyclohexane
LH	Luteinizing Hormone
OP	Organophosphate
OR	Odds Ratio
P	Pyrethroids

3PBA	3-Phenoxybenzoic acid
PON1	paraoxonase
POP	Persistent Organic Pollutants
***p,p'*-DDD**	1,1-dichloro-2,2-bis(p-chlorophenyl)-ethane
***p,p'*-DDE**	1,1-dichloro-2,2-bis (*p*-chlorophenyl-ethylene)
***p,p'*-DDT**	1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethylene
r	Pearson's coefficient
TCPy	3,5,6-trichloro-2-pyridinol
TDCCA	*trans*-3-(2,2,dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid

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Table 1

Summary of studies investigating environmental or occupational exposures to pesticides and associations with semen quality

First Author (Year)	Study Population	Country of Study	Results
			Pyrethroids
Ji (2011)	240 men recruited from a medical university hospital	China	Significant correlation between 3-PBA levels in urine and decreased sperm concentration (β= −0.27, 95%CI: −0.41to −0.12)
Meeker (2008)	207 men recruited from an infertility clinic	USA	Significant association between TDCCA and decreased motility when controlling for CDCCA. Men with the highest total DCCA urine concentrations had higher odds of low sperm concentrations. (OR=2.66, 95%CI: 1.07-6.92).
Xia (2008)	376 infertile men	China	Men in the highest quartile of 3-PBA urine concentration had higher odds of low sperm concentration.
			Organochlorines
Aneck-Hahn (2007)	311 men living in a malaria-endemic region	South Africa	Higher *p,p*'-DDE concentrations were associated with decreased sperm concentration and higher *p,p*'-DDT and *p,p*'-DDE concentrations were associated with decreased motility.
Haugen (2011)	207 men: 114 living below and 93 living above the Arctic Circle	Norway	Significant correlation between *p,p*'-DDE and higher sperm concentration (r=0.25, p=0.03) for men living above the Arctic Circle in Norway.
Khan (2010)	100 men recruited from an infertility clinic: 50 fertile and 50 infertile	India	Significant association between α-HCH and β-HCH and increased sperm count among infertile males. Significant associations between and γ-HCH and decreased sperm counts for asthenospermic men and between β-HCH and total HCH and decreased sperm counts for oligo-asthenospermic men.
Messaros (2009)	336 men recruited from infertility clinics	USA	Men with high total DDT-DDE exposures had higher odds of low sperm concentration, low motility and low morphology. The risk of low motility due to DDT exposure was increased among men with a GSTT1 null genotype. Evidence suggests a protective effect of increasing numbers of variant alleles in the CYP1A gene against abnormal morphology.
Pant (2007)	100 men: 50 fertile men and 50 infertile men	India	Among infertile men, β-HCH, γ-HCH, *p,p*'-DDE and *p,p*'-DDD were associated with decreased sperm counts. γ-HCH was associated with decreased motility.
			Organophosphates
Hossain (2010)	152 farmers: 62 with a history of exposure to pesticides	Malaysia	Men with occupational pesticide exposures had higher risks for lower semen volume, lower concentration, higher abnormal morphology and decreased sperm motility.
Perez-Herrera (2008)	54 agricultural workers	Mexico	For men with the 192RR genotype of the PON1Q192R gene, there was a significant negative association between OP exposure three months before sampling and decreased sperm viability.

First Author (Year)	Study Population	Country of Study	Results
Perry (2007)	18 environmentally exposed men	China	Concentration was significantly lower among men with higher levels of urinary DETP. Suggestive, but not significant, association between high pesticide exposure and lower sperm concentration.
Perry (2011)	189 men: 94 cases and 95 controls	China	Men with sperm concentration and total motility below the population median had higher levels of urinary DMP compared to controls.
Recio-Vega (2008)	52 men: 17 non-occupationally exposed men, 16 agricultural workers and 19 OP sprayers	Mexico	Exposure to OPs was associated with decreased semen volume and decreased sperm count for men in the highest exposure group (OP sprayers).
Yucra (2008)	62 men: 31 exposed (OP sprayers) and 31 non-exposed	Peru	Ethylated OP metabolites in urine were significantly associated with decreased semen volume.
			Other/Non-Specific Pesticides
Celik-Ozenci (2012)	40 men: 20 farmworkers and 20 non-exposed men	Turkey	ABM exposed men had significantly decreased sperm motility and increased semen volume compared to men in the unexposed control group.
de Fleurian (2009)	402 men recruited from an infertility clinic	France	Suggestive, but not significant, association between non-specific occupational pesticide exposure and altered semen (adjusted OR= 3.6, 95%CI: 0.8-15.8, adjusted p=0.087).
Multigner (2008)	87 men: 42 exposed banana plantation workers and 45 controls	Guadeloupe	No statistically significant associations between non-specific occupational pesticide exposures and semen parameters.

AMB= Abamectin CDCCA= cis-3-(2,2,dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid CI= 95% confidence interval CYP= Cytochrome P-450 enzymes DCCA= 3-(2,2,dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid DDT= Dichlorodiphenyltrichloroethane DETP= Diethylthiophosphate DMP= Dimethylphosphate GST= Glutathione-S-transferase HCH= Hexachlorocyclohexane OP= Organophosphate OR= Odds Ratio P= Pyrethroids 3PBA= 3-Phenoxybenzoic acid PON1= paraoxonase POP= Persistent Organic Pollutants *p,p*'-DDD= 1,1-dichloro- 2,2-bis(p-chlorophenyl)-ethane *p,p*'-DDE= 1,1-dichloro-2,2-bis (p-chlorophenyl-ethylene) *p,p*'-DDT= 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethylene r= Pearson's coefficient TDCCA= trans-3-(2,2,dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid