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Is dietary pesticide exposure related to semen quality? Positive evidence from men attending a fertility clinic

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Chiu and her colleagues from Harvard School of Public Health and Massachusetts General Hospital present important new data on semen quality in relation to dietary pesticide exposure via fruit and vegetable intake (Chiu *et al.*, 2015). To examine this relationship the authors utilized a novel approach that classifies fruits and vegetables into high versus low-to-moderate pesticide residue groups based on data from the United States Department of Agriculture (USDA) Pesticide Data Program (PDP). Data obtained from a validated food frequency questionnaire (FFQ) combined with USDA PDP yielded individual measures of intake of fruits and vegetables with higher pesticide residues. The authors found that semen quality was reduced among men in the highest quartile of exposure, a finding which could have clinical and public health implications.

Pesticides are designed to be biocides and an extensive literature demonstrates that many of these chemicals adversely impact human reproductive function. It has long been known that occupational exposure to certain pesticides have a devastating effect on semen quality and male fertility. For example plantation workers exposed to the nematocide 1,2-dibromo-3-chloropropne (DBCP) were rendered azoospermic (Whorton *et al.*, 1977). However, studying the subtler effects of non-occupational pesticide exposure on semen quality remains a challenge that is addressed by Chiu and colleagues using a novel method of exposure assessment. Their compelling results justify a discussion of methodological issues and public health implications.

Methodological issues

Interest in the association between pesticide exposure and semen quality is growing rapidly and over 1000 publications in this field have been published during the last 50 years (Fig. 1). This is a diverse literature, heterogeneous in populations, exposures, methods and study results. In light of this literature, we discuss briefly important methodological issues in this study: exposure assessment and timing, population selection, semen analysis methods, sample size and statistical analysis.

The authors have tackled the challenge of estimating exposure by coupling USDA PDP surveillance data with FFQ-based intake of fruits and vegetables. This method has been used to examine associations with other outcomes, but not, to our knowledge, semen parameters. For example, Curl *et al.* recently showed an association between urinary dialkyl phosphate concentrations and estimated dietary organophosphate exposure based on FFQ and USDA PDP pesticide measures (Curl *et al.*, 2015). In a systematic review of environmental and occupational pesticide exposure and semen quality, 15 of the 17 studies included used biomonitoring, while the others used questionnaire data and work histories (Martenies and Perry, 2013). While exposure assessment by human biomonitoring may be the gold standard, high costs, the need to collect and store urine samples and the requirement of a qualified lab limit its utility. Moreover, high analytic costs preclude analysis of multiple samples, and basing exposure assessment on a single spot sample has its own limitation. Assessment of pesticide exposure with the aid of a pesticide residue surveillance program is an alternative method, and the one employed by Chiu and colleagues. This strategy could be especially useful in countries with high exposure to pesticides through diet, such as in Israel, where associations were found between fruit consumption and urinary organophosphate pesticide metabolite concentrations using biomonitoring (Berman *et al.*, 2013).

Timing of exposure is an important consideration in sperm studies, as exposure effects may differ during spermatogenesis (70–75 days). In Chiu *et al.* men completed their FFQ up to 18 months prior to semen collection. The authors examined the question of timing of exposure and found that results were similar in the full cohort and when restricting analysis to men whose semen sample was collected within 1 year of completing the FFQ. Therefore, in this analysis exposure misclassification due to improper timing is unlikely.

Chiu and colleagues recruited male partners from couples presenting to a fertility clinic. The study population contains men with a range of semen quality, selected to some degree by both fertility potential and access to healthcare, limiting generalizability. Additional studies of

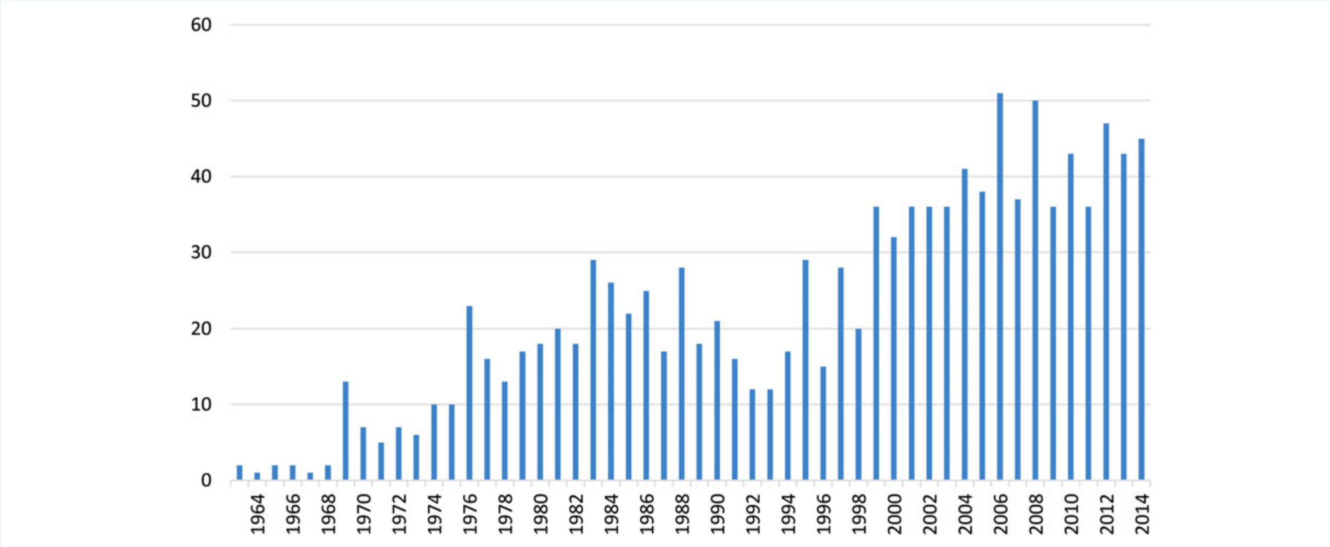

Figure 1 Number of publications per year on '(pesticide) and (semen or sperm)' in PubMed, during 1963–2014 ($N = 1171$).

fertile (i.e. partners of pregnant women) and/or unselected by fertility (i.e. students or military candidates) populations would extend generalizability. Because Chiu and colleagues provided only limited data on patient selection, and on men who did and did not complete the FFQ, it is difficult to address potential selection bias. In addition, these findings need to be replicated in various populations as effects of dietary pesticide exposure on semen quality might be modified by genetic or phenotypic background (Perez-Herrera *et al.*, 2008).

Since 1980 the World Health Organization (WHO) has published a series of laboratory manuals for semen analysis that define the standards in the field, recommending hemocytometer for determination of sperm concentration (WHO, 2010). Chiu *et al.* used computer-aided sperm analysis (CASA) methods to estimate sperm parameters. Until recently, it was not feasible to accurately measure sperm concentration by CASA because of difficulties in distinguishing spermatozoa from particulate debris. However, advances in technology, particularly in the use of fluorescent DNA stains and tail-detection algorithms, may now allow sperm concentration to be estimated by CASA methods, provided that adequate care is taken in preparing specimens and proper quality-control procedures are followed. In this study, ejaculate volume was measured by graduated pipette, a method that has been shown to underestimate the volume and is not recommended (WHO, 2010). This is important since calculation of total sperm count is based on ejaculate volume and sperm concentration.

The authors gained statistical power despite limited sample size ($N = 155$) by using generalized linear mixed models with random intercepts, to account for within-person correlations between repeated samples. Careful selection of covariates (age, body mass index, smoking, abstinence time, physical activity, total energy intake, history of varicocele and dietary pattern) likely also contributed to the precision of their estimates. Thus, despite the relatively small sample size and exposure assessment limitations, the paper make a convincing case that dietary exposure to pesticides can adversely impact semen quality. While this finding will need to be replicated in other settings and populations, it carries important public health implications.

Public health implications

Male fertility, strongly related to poor semen quality, is of considerable public health importance for several reasons. First, its medical, societal and economic burden is high, as it is a leading cause of unsuccessful attempts to achieve pregnancy and one of the most common medical problems among young men (Winters and Walsh, 2014). Second, it has been suggested as an important marker of male health, predicting both morbidity and mortality (Jensen *et al.*, 2009; Eisenberg *et al.*, 2014a,b). Third, it is sensitive to environmental exposures, including endocrine disrupting chemicals, heat and life-style factors, such as diet (Afeiche *et al.*, 2013; Bergman *et al.*, 2013) or body mass index (Eisenberg *et al.*, 2014a,b). Therefore, it can provide a sensitive marker of the impacts of modern environment on human health (Nordkap *et al.*, 2012).

This paper by Chiu and colleagues contributes to the growing body of evidence that non-occupational exposures, and particularly dietary factors (i.e. meat, fish, dairy, etc.) can impact male fertility (Swan *et al.*, 2007; Gaskins *et al.*, 2012; Afeiche *et al.*, 2014a, b). Several prior studies have examined semen quality in relation to dietary pesticide exposure and/or organic diet (Jensen *et al.*, 1996; Juhler *et al.*, 1999). Several studies have shown that substituting an organic for a conventional diet can reduce exposure to pesticides, at least among children (Lu *et al.*, 2006). Currently, the male partner in couples attending fertility clinic rarely receive assessment or recommendation regarding life-style and dietary factors. Lessons learned from well-conducted studies should be considered when advising men attempting to conceive. In addition, there is clear need for further studies on diet and male fertility, including interventional studies. Such studies can be conducted in a range of settings besides the fertility clinic. One particularly promising, though challenging approach, is to enroll the couple at the time of pregnancy planning and assess the exposure and fecundity of both partners (Louis *et al.*, 2015).

Despite its importance, male infertility is not a major focus of the research community (Louis, 2014). This may be due to increasing population growth in some areas leading to the perception that contraception is the primary public health concern. Moreover, assisted reproductive technology has greatly improved the likelihood of conception despite poor semen quality. However, these techniques are costly, both in resources and health, and there is concern regarding long-term implications of such techniques (Land and Evers, 2003). When fertility is addressed, the male partner is often overlooked; contraception and infertility have been perceived to be primarily female issues, and the root causes of male infertility are not being addressed. These causes might differ along the life course, as male infertility is determined both during fetal development and during adulthood (Juul *et al.*, 2014). As shown by Chiu *et al.*, male fertility studies provide an opportunity not only to better understand the causes of an important public health problem, but more broadly to illustrate effects of the modern environment on human health.

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Conflict of interest

The authors declare they have no actual or potential competing financial interests.

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