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Review Article

Effects of Pesticides on Male Reproductive Functions

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Abstract

Exposure to pesticides could be one of the contributing cause to the falling sperm counts and rising levels of male infertility. Adverse effects of pesticides in the environment first received widespread attention in the 1960s. However, only recently it has been postulated that long term, low exposure of these chemicals are increasingly linked to human health effects such as immuno-suppression, endocrine disruption, reproductive abnormalities and cancer. This article critically reviewed the epidemiological studies of reproductive toxicity of different pesticides in males. According to previous studies it is shown that exposure to pesticides was significantly associated with sperm levels well below the limit for male fertility. No large-scale studies assessing pesticide exposure and its relationship to infertility have been done. To overcome the difficulties in interpretation and to reach strong conclusions, future studies on human male reproductive effects of different types of pesticides should consider several methodological problems. So, we conclude integrated studies considering many factors are warranted to draw definite conclusion and also in the view of adverse health effects observed to some extent in workers with few pesticides, it is necessary now to find out ecologically sound alternatives to pesticides and also to educate the workers/farmers about the safe use of these pesticides to reduce reproductive health risk associated with exposure.

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Introduction

Scientists studying the impact of man-made chemicals on human health, claim human males will be infertile by the middle of the next century if present industrial trends are maintained. The culprits are the chemicals which have the ability to mimic hormones, particularly the female sex hormone estrogen-are widespread in society and include pesticides (such as DDT), industrial chemicals (such as PCBs), and environmental pollutants such as dioxin and human therapeutics such as anticancer drugs.[1,2] Most, though not all, of the estrogen-mimicking chemicals involve chlorine. Several research studies have indicated that sperm counts have been in decline for decades and scientists say modern lifestyles and contacts with chemicals are a contributing factor.[3]

Exposure to pesticides is just one of the reasons for this decline. Mothers can absorb these chemicals and pass on their destructive properties through the womb to the unborn

child or through breastfeeding to the infant. Although, human is not the unique target which is affected by these agents, many birds and animals in the wild have displayed problems. Birds that refuse to court each other nest or raise their young, female gulls nesting with other females and alligators suffering reproductive problems. Not only have scientists collected evidences that human sperm production has declined over the last half century, but the list of pesticides known to disrupt sperm production or male hormones continue to hamper. So this article aims to review the epidemiological studies of reproductive toxicity induced by different pesticides in males and to suggest possible further research in this field.

Declining Sperm Counts

In 1992, four Danish scientists published a research study suggesting that sperm counts have declined about 50 percent since 1940 worldwide.[4] The study analyzed the results of over 60 studies of sperm counts published between 1938 and 1991 as a statistical analysis that linked results of a large number of independent studies, "meta-analysis".[4] Using a model which assumed that sperm counts changes over time in a linear way, the results of the meta-analysis indicated average sperm counts declined from 113 million to 66 million per ml of semen during the half century (Fig 1).[1] These studies were reported from different countries around the world.

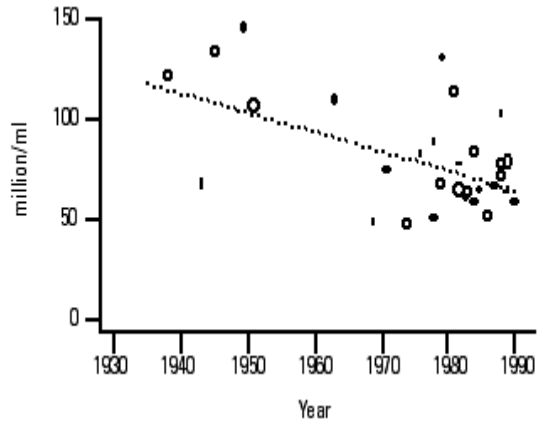

Fig 1: Linear regression of mean sperm density reported in 61 publications (represented by circles whose area is proportional to the logarithm of the number of subjects in study), each weighted according to number of subjects, 1938 to 1990. Data from Carlsen et al.[1]

In this line, three other studies have found similar declines in sperm counts in smaller groups of men. It is found that sperm count among sperm donors had declined about 10 million per ml between 1977 and 1994.[5] Similarly, another study demonstrated that median sperm count among sperm donors had declined about 40 percent in men born in the 1940s in comparison with that born in the late 1960s.[6] It was reported that at a sperm bank, mean sperm counts among donors declined by about two percent per year from 1973 to 1992, for a total decline of 32 percent.[7]

Perhaps of greater concern, these studies found that other measures of sperm quality also showed changes from the normal trend,[8] both the volume of semen produced and the vigor of the sperm declined. Carlsen found that semen volume decreased about 20 percent.[4] In addition, the proportion of men with sperm counts below 20 million per ml tripled.[4] Another study found that both the proportion of abnormal sperm and their mobility decreased during the last 20 years.[5] As well, another study had similar, and just as unsettling results.[7]

Several researchers felt Carlsen's results could be a statistical artifact, or caused by changes in sperm counting equipments. A study pointed out that the data used by Carlsen et al. could be analyzed with different statistical models. The three models that seemed to fit the data best showed a 50 percent decline around 1965, but a constant or slightly increasing sperm count in the years since 1970. In summary, there is a controversy in the scientific world about the decline in human sperm count during the past 50 years based on different studies.[9-11]

Causes of decline in sperm counts

Studies of sperm counts over time leave a critical question unanswered. It is important to know what could account for a precipitous decline in sperm production by otherwise healthy men. Carlsen suggested that environmental causes, particularly those toxins that could affect human hormone systems, were likely.[4] Another study developed a more specific hypothesis, and suggested that the decline "is the result of endocrine changes in fetal/ prepubertal life prior to birth or during childhood".[12] In this study, it was hypothesized that this complex system might be disrupted before birth or during childhood by substances acting like natural hormones resulting a permanent impairment of the reproductive system.[12] In particular, it was hypothesized that hormone disruption at a sensitive time of development may block the development of Sertoli cells, cells within the testes that "nurse" sperm cells as they develop. The number of Sertoli cells sets a cap on the number of sperm, which a man is able to produce; therefore, a chemical exposure that blocked

hormone involved with Sertoli cell development would irreversibly limit sperm production.[12]

Sharpe et al. thought that FSH and estrogen are important in determining adult sperm production.[12] Their relevance to sperm production is that FSH in juvenile mammals promotes multiplication of the Sertoli cells. Without enough FSH, fewer Sertoli cells are produced. Levels of FSH are regulated by estrogens; higher levels of estrogen result in lower levels of FSH. Therefore, it was hypothesized that synthetic chemicals acting like estrogen might lower the level of FSH, resulting in fewer Sertoli cells and permanently decrease the sperm production.[12]

A study concerned mother rats that drank water contaminated with two synthetic chemicals, such as octyl phenol and butyl benzyl phethalate, which are known to act like estrogen.[12] The rats used in the study were pregnant or nursing; the study spanned the interval when their male offspring would be developing Sertoli cells. The results fit the mentioned hypothesis perfectly to say that sperm production was reduced (10 to 20 percent) in the offspring of the rats drinking contaminated water and the number of Sertoli cells (as estimated by testes size) was reduced.[12] Furthermore, one should consider that the development and growth of the male reproductive system is obviously a complex process and it is therefore not surprising that synthetic chemicals might affect male fertility in more than one way.

Pesticides linked with Male Infertility

The two chemicals discussed above are found in pesticide products regularly. Octyl phenol and butyl benzyl phthalate are both used as "inert" ingredients, used in most pesticide products to make them more efficient or easier to use. Based on Colborn et al. (Table 1) pesticides are often classified according to the organism specific target, e.g. as fungicides, herbicides, insecticides, nematocides etc.[13]

Chlordecone

In 1975, a worker from a chemical factory visited his family physician for help with persistent headaches, tremors and irritability. Further investigations showed that he and his fellow workers were contaminated with chlordecone, and surprisingly only 25% of workers at the plant had normal sperm counts.[14] The sperm produced by these workers also did not swim like normal sperms. The workers' sperm counts increased over the next five years as medications removed chlordecone from their body tissues.[14]

1,2-Dibromo-3-chloropropane (DBCP)

DBCP was used in the past as a soil fumigant and nematocide on crops; it is no longer used except as an intermediate in chemical synthesis. Its spermatotoxic effects in rats were discovered in the early 60s, but its effects on human spermatogenesis were discovered only in 1977. It was noted that there was paucity of children among the workers in a DBCP plant, after they had started to work in DBCP production.[15] They have also reported in the subsequent study that occupational exposure to DBCP caused a reduction in the sperm concentration in ejaculates from a median 79 million cells/ml in unexposed men to 46 million cells/ml in exposed workers.[16] Potashnik et al. have studied on six workers exposed to DBCP in a pesticide factory, who underwent testicular biopsy and reported complete atrophy of the somniferous epithelium in these exposed workers.[17] Seventeen years follow-up study of 15 workers exposed to DBCP revealed that sperm count recovery was evident within 36 to 45 months in three of the nine azoospermic and in three of the six oligozoospermic men with no improvement thereafter.[18]

Glass et al. reported studies of male DBCP applicators and determined that the effects of the agent were limited to individuals in certain situations, such as applicators involved in irrigation set-up work and in the calibration of equipment. Once released from these situations, the sperm counts of these individuals returned to normal.[19] Later Kahn and Whorton reanalyzed these data and showed that all applicator groups had reduction in sperm counts in a dose related manner and that reversibility was not a certainty.[20] Studies of Y-chromosome non disjunction, DBCP-exposed workers had a higher average YFF frequency compared to non exposed individuals. An agent that increases Y-Chromosomal no disjunction might be anticipated to result in increased pregnancy wastage.[21] In 1997, another study by Multigner et al. showed testicular dysfunction among factory and field workers who were exposed to DBCP.[22] In another study on the male workers involved in manu-

Table 1: Classification of Pesticides

Classification	Pesticides
Herbicides	2,4-D; 2,4,5-T; Alachlor; Amitrole; Atrazine; Metribuzin; Nitrofen; Trifluralin; Paraquat
Fungicides	Benomyl; Hexachlorobenzene; Mancozeb; Maneb; Metiram-complex; Tributyl tin; Zineb; Ziram
Insecticides	β-HCH; Carbaryl; Chlordane; Chlordecone; Dicofol; Dieldrin; DDT and metbolites; Endosulfan; Heptachlor and H-epoxide; Lindane; Methomyl; Methoxychlor; Mirax; Oxychlordane; Synthetic pyrethroids; Toxaphene; Transnonachlor
Nematocides	Aldicarb; DBCP

facturing of DBCP have reported to have a high level of LH and FSH in their serum and a reduced sperm counts.[23]

Carbaryl

Carbaryl is an insecticide used on a variety of crops. Acute (short-term) and chronic (long-term) occupational human exposure to carbaryl has been observed to cause cholinesterase inhibition, and reduced levels of this enzyme in the blood caused neurological effects. Two studies at a carbaryl manufacturing factory have shown that carbaryl exposure affects the quantity and quality of sperm produced by the workers. One study found that frequent exposure of workers to this chemical induced very low sperm counts as compared to a control group of unexposed workers.[24] This result was proved to be significant based on one statistical analysis, but has been criticized because of a second statistical test proving only a closer significance. A second study of the same sperm samples found that the number of sperm abnormalities was increased in workers who were being exposed to carbaryl.[25]

Multiple pesticide exposure

A study conducted by Rope et al. among male workers who were exposed to various mixtures of pesticides such as DDT, BHC, endosulfan; and organophosphorus pesticides i.e. malathion, methyl-parathion, dimethote, monocrotophos, phosphamidon and quinalphos; synthetic pyrethroids such as fenvelrate and cypermethrin during mixing and spraying showed male mediated adverse reproductive outcome such as abortion, stillbirths, neonatal deaths, congenital defects, etc.

It is not possible to say any particular pesticide caused the reproductive toxicity on the basis of these results, as there may be cumulative effects of a number of pesticides.[26] This can be explained based on another study in which an "in culture" bioassay was used to assess the estrogenicity of several estrogenic pesticides such as DDT and chlordecone which cause deleterious reproductive effects. The E-screen test revealed that estrogenic chemicals may act cumulatively; when mixed together they induce estrogenic responses at concentrations lower than those required when each compound is administered separately.[27] Abell et al. studied the testicular function of greenhouse workers exposed to pesticides and reported that male fecundity may be at risk from exposure to pesticides in the manual handling of cultures in green houses.[28]

Dichlorodiphenyltrichloroethane (DDT) and Polychlorinated biphenyls (PCBs)

Studies of males exposed to DDT have found decrements in serum bioavailable testosterone levels,[29] reduced semen volume on ejaculation and reduced sperm counts.[30] In a recent retrospective study, information obtained from 2,033 workers on the reproductive history of the malaria control program workers in the Pacific region revealed an increased risk of birth defects among those most exposed to DDT, without a clear dose response, and a small, non statistically significant, difference in the risk of spontaneous abortion. No change in the sex ratio of newborns was associated with exposure.[31]

PCBs and p, p´-DDE, the most stable metabolite of DDT, are persistent, lipophilic chemicals that are suspected endocrine disruptors. DDT was widely used as an insecticide, whereas PCBs were used in cutting oils, lubricants, and as electrical insulators. In human studies, Bush et al. analyzed 170 semen samples for PCBs and p,p´-DDE from fertile men, men with idiopathic oligospermia, and men after vasectomy.[32] The mean of the total PCBs (sum of all congeners) in the semen samples was 5.8±0.8 ng/g.[33] The authors stated that these concentrations were minimal and consistent with the levels seen in the general population; the semen sample PCB concentrations were of comparable to the concentration of residues in human blood. Bush et al. also stated that in samples with a sperm count less than 20 million cells/ml, there was a significant inverse relationship between sperm motility and the concentration of PCB congeners 153, 138, and 118 (2,4,5,2´,4´,5´- and 2,4,5,2´,3´,4´-hexachlorobiphenyl and 2,4,5,3´,4´-pentachlorobiphenyl) respectively.[33]

These three congeners are the major components of Aroclor 1254 and 1260. The magnitude of their effects on motility was large; ranging from 46% to 100%, therefore the maximum of their concentrations the three congeners would produce complete lack of motility. Bush et al. concluded that the relationship between specific PCB congeners and motility is both significant and biologically important.[33] Their findings are intriguing and disturbing because the three congeners that found to be inversely predictive of sperm motility are ubiquitous in the human population.[33] Further evidence of a possible relationship between PCBs and semen quality is presented in a study in rats which suggests that PCB exposure affected the ability of sperm to fertilize eggs.[34]

In a cross-sectional study of 212 male partners of subfertile couples who presented to the Massachusetts General Hospital Andrology Laboratory, Boston, USA their semen sam-

ples were analyzed to determine whether environmental levels of PCBs and p,p'-DDE are associated with altered semen parameters in adult men.[35] Semen parameters were analyzed as both a continuous measure and dichotomized based on World Health Organization reference values for sperm concentration (< 20 million/ml), motility (< 50% motile), and Kruger strict criteria for morphology (< 4% normal).

The comparison group for the dichotomized analysis was men with all the three semen parameters above the reference values. In serum, 57 PCB congeners and p,p'-DDE were measured by congener-specific analysis using gas chromatography with electron capture detection. The results revealed an inverse dose-response relationship between PCB-138 and sperm concentration, motility, and morphology.[35] Whereas, there was limited confirmation of inverse relationships between the sum of PCBs, as well as those PCBs classified as cytochrome P_{450} enzyme inducers, with sperm motility and sperm morphology, and inverse association between p,p'-DDE and sperm motility.[35] The lack of a consistent relationship between semen parameters, individual and grouping congeners of PCB may indicate a difference in spermatotoxicity between congeners.[35]

Lindane

Pages and colleagues in recent study have clearly demonstrated a relatively high level of lindane metabolites in marine environment. Lindane has been directly linked with both reproductive and carcinogenic properties. It is shown that chronic administration of lindane results in endocrine disruption in birds as well as in mammals. Treatment with 1-40 mg of lindane/kg body weight disrupted testicular morphology, decreased spermatogenesis, inhibited testicular steroidogenesis, reduced plasma androgen concentrations and impaired reproductive performances in males.[36]

Endosulfan

A recent study suggests that endosulfan exposure may delay sexual maturity and interfere with hormone synthesis in male children.[37,38]

2,4-Dichlorophenoxy acetic acid (2,4-D)

In a study performed on reproductive functions of 32 male farm sprayers exposed to 2,4-D, and after four days of sexual inactivity the results of their sperm analysis, compared with unexposed workers, showed a significantly high levels of asthenospermia, necrospermia and teratospermia. Over time, asthenospermia and necrospermia diminished but the abnormal spermatozoa (teratospermia) continued.[39]

Table 2: List of pesticide(s) causing male reproductive toxicity.

	pesticide(s)	References
1	Chlordecone	14
2	di-bromochloropropane	15-23
3	Carbaryl	24,25
4	Multiple pesticide exposure	26,28
4	DDT and PCBs	29-35
6	Lindane	36
7	Endosulfan	37,38
8	2,4-dichlorophenoxyacetic acid	39
9	Paraquat	40

Conclusion

Exposure to pesticides lowers sperm levels well below the limit for male fertility. Over 50 currently used pesticides are shown to induce adverse effects on male fertility based on animal or human studies. Although, it is proved that pesticide exposure is associated with infertility, there are not large-scale studies assessing their relationships to human infertility.

To overcome the difficulties in the interpretation and to reach strong conclusions, future studies on the effects different types of pesticides on the human male reproductive system should consider several methodological problems, such as the standardization of analytical procedures with strict quality controls within and between laboratories, adoption of well defined terms of the outcome to be measured, the use of concurrent control subjects, analysis of semen with respect to the time variables, the adoption of standardized criteria for information and motivation of the participants, and exposure assessment.

It is also important to study large cohorts to evaluate, possible effects at different pesticide concentrations, the currently encountered in occupationally exposed populations and to design such studies to characterize the dose-response relation and evaluate change of values over time. This will also enable establishment of a no effect level of the chemical and proper biological limit values.

The question of the indicator of exposure should also be clarified, taking into account that possible indicators such as seminal pesticide concentrations may be more useful in fertility studies than the indicators of recent exposure. It should be underlined that interactions with other occupational and non-occupational exposures must be considered and every possible confounding factor should be controlled. In this respect, integrated studies should be promoted which will evaluate not only seminal and endocrine end points, but also other aspects such as the time of pregnancy and also in the view of adverse health effects observed to some extent in work-

ers/applicators with few pesticides. It is also necessary to find out ecologically sound alternatives to pesticides and to educate the workers / farmers about the safe use of these pesticides to reduce reproductive health risk associated with their exposures.

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