The influence of occupational exposure on male reproductive function

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Abstract
Recently, many studies have found a decrease in semen quality which has increased the focus on male reproductive health. Occupational hazards are by far the best documented in reproductive epidemiological research. Generally, occupational exposures have been divided into physical exposures (heat and radiation), chemical exposures (solvents and pesticides), psychological exposures (distress), exposure to metals and welding. The recent and/or most important epidemiological studies exploring the effect of occupational exposures on semen quality and fecundity, the ability to conceive, are reviewed. The evidence for an adverse effect on male reproduction of several occupational and environmental exposures and toxicants, such as heat, ionizing radiation, inorganic lead, dibromochloropropane, ethylene dibromide, some ethylene glycol ethers, carbon disulfide and welding operations, is strongly supported in well-designed epidemiological studies. For other agents, the association is only suspected or suggested and needs further evaluation before conclusions can be drawn. It is also important to bear in mind that many workers in the non-Western world still are exposed to substances that are banned in the Western world, sometimes in high concentrations.

Key words Males; occupational exposure; reproductive health; semen quality.

Introduction
Male reproductive health has been in focus after the meta-analysis by Carlsen et al. in 1992 [1] which reported a significant decline in sperm concentration from 1940 to 1990. The importance of the possible decline in semen quality lies partly in its possible link with other problems of male reproductive organs, such as a widespread rise in the incidence of testicular cancer [2], and a suggested increase in hypospadias and cryptorchidism in some geographical areas [3,4]. A hypothesis has suggested the existence of a pathogenetic link, the testicular dysgenesis syndrome (TDS) [5]. TDS may be a result of genetic as well as environmental factors causing poor testicular development. Endocrine disruption due to environmental agents with oestrogenic [6] and/or antiandrogenic [7] effects has been suggested to be responsible for these parallel changes but the human evidence is currently not convincing.

Male reproduction can also be measured as the biological fecundity defined as the probability of a couple to conceive in a menstrual cycle. Time taken to conceive [time to pregnancy (TTP)] has proven a valuable tool in occupational epidemiology [8,9]. It is easy to obtain information about and well recalled in groups that deliberately discontinue contraception to have a child [10,11]. Fecundity is the biological ability of a couple to conceive which may be affected both by female and male factors. Several studies have shown that sperm concentration and morphology are correlated to the TTP of a couple [12–15].

Despite the possible effects of endocrine disruptors, considering environmental risk to male reproduction, physical and chemical hazards encountered at the workplace during adulthood are the best documented in epidemiological research. The potential strong effects of occupational exposures were highlighted in 1977 by the discovery of severe damage to spermatogenesis by a specific pesticide, dibromochloropropane (DBCP) [16]. Generally, occupational exposures have been divided into physical (heat and radiation), chemical (solvents and pesticides) and psychological (distress). In addition, we will study the effects of metals and welding. The effects of these factors have already been extensively reviewed [17–20] and, therefore, this review will focus on newly published studies and discuss problems in studies of reproductive health.

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Methodology

The review is based on searches in the scientific literature in the standard databases (Medline, Toxline and em base) covering the period 1990–2005. Reviews covering earlier periods are included. Only epidemiological studies are cited and the main emphasis has been on devoted studies with some exposure quantification, not just comparing job title or self-reported occupational exposures among infertility clients and controls.

Measurement of TTP

TTP measures how long a couple takes to conceive. The TTP distribution in a population describes its fertility. It is a functional measure, the final common path of a large number of biological mechanisms in both sexes; its use is complementary to more mechanistic research on the biological processes necessary for fertility and studies of specific medical conditions [8,9]. Information about TTP is easy to obtain [10,11], and it has proven useful in descriptive epidemiology to identify risk factors. Since the unit of study is the couple, covariates relating to both partners are required.

TTP can be studied by use of either a prospective or retrospective design [21]. Prospective studies recruit couples at the start of their attempt, that is, couples who are prepared to undertake regular testing and to be followed up. These studies are therefore able to obtain detailed, timed information on key biological events. The drawback is the need for highly motivated participants, which might cause response bias and planning bias. These drawbacks may adversely impact external validity to a degree that cannot be empirically evaluated, so that the findings may be difficult to generalize to all couples. A key advantage of the retrospective design is that it is possible to achieve a sample that is representative of the target population, with the consequent benefit of high external validity, which is particularly important for descriptive studies. If studies are well designed, conducted and analysed, most of the theoretical problems can be avoided or minimized in practice, especially if information is collected on accidental pregnancies, phases of infertility not leading to a pregnancy and ongoing attempts [21]. Studies of time trends and spatial differences are susceptible to bias that may be difficult to control [22], although information on accidental pregnancies can be useful here [23]. The main drawback of retrospective studies is that it is not possible to obtain detailed time-specific information about behaviour and risk factors.

It is important to obtain information about the potential confounding factors affecting both partners: parental age, caffeine and alcohol intake and smoking, timing of sexual intercourse, recent use of oral contraceptives and occupational exposures. In addition, numerous biases may operate when analysing TTP: recall bias, infertility treatment bias, truncation bias, behavioural bias, planning bias. They have all previously been discussed [9,24,25].

Measurement of semen quality

Semen quality is an ill-defined term that refers to one or more of several semen characteristics that can be measured in a fresh ejaculate. Semen volume (ml), sperm concentration (millions/ml), percentage of motile sperms, percentage of sperms with normal morphology and the calculated total sperm count (concentration × volume, millions) are by far the most important factors for male fecundity. There is considerable variability between technicians when counting morphology and motility [26]. Measurement of sperm chromatin structure after in situ denaturation by flow cytometric methods provides a rather stable indicator of semen quality that predicts TTP independently of the conventional semen characteristics [27].

Many factors have to be taken into account when analysing sperm concentration. It varies greatly between individuals [28]: there is a 10-fold difference between the 10th and the 90th percentile of the distribution in fertile men [29]. Sperm concentration is also subject to a great deal of within-subject biological variation over time. Furthermore, many population characteristics may influence semen quality: sexual activity and period of abstinence, occupation, age, medication and diseases, nutrition, smoking habits, stress and season at delivery of the sample. In addition, the mode of semen collection and analysis is very important, as there is large intra- and inter-technician variability.

Most occupational semen studies have been cross-sectional comparing semen quality between exposed and unexposed workers. The participation rate seldom exceeds 40–60%, and is even lower among controls. This may introduce selection bias since unexposed controls are more likely to participate if they suspect fertility problems. Self-volunteers are often better educated [30] or men with doubts about their own fertility and consequently eager to participate to obtain information on their own health status. It is therefore important to obtain information about their motivation for participation and about non-participants so the selection process can be described. It is preferable to study men recruited with the same procedures and from whom information about the above factors is present and semen analysis is standardized. Feasible biological indicators for female fecundity suitable for large-scale studies remain to be developed.

Exposure assessment

Exposure assessment is a crucial part of occupational epidemiology. Often, information about exposure is based on job title, self-reported questionnaire data or
employment and quality of semen [42]. In these two
studies of infertility clients seemed to support earlier cir-
cumspective has proved the most informative [31]. It seems
evident that an integrated measure of exposure during
the last few months preceding the semen sample is of
interest, reflecting the ~10 weeks that human spermato-
and spermiogenesis take to complete (see below). Life-
long cumulative exposure may also be of importance if an
exposure has permanent effects on endocrine or testicu-
lar tissue (as with stem cell toxicants) or if toxicants are
highly biopersistent as with some halogenated organic
compounds. Assessment of past exposure for individuals
or groups of workers may utilize records of hygiene meas-
urements or biological monitoring data. Few attempts
have been made to design prospective studies of semen
quality with repeated measures of exposure after entry
into a new job or in occupations with seasonal exposures
[32–34]. Considering the potential for selection bias in
cross-sectional semen studies, longitudinal studies with
adequate exposure assessment are of interest but have
proven difficult to carry out in practice.

**Mechanisms and site of actions**

The spermatogenic cycle spans 72 days in humans and
can be disrupted by toxicants at any stage of cell differ-
entiation, giving rise to reduced sperm counts, morpho-
logically abnormal sperm, impaired stability of sperm
chromatin or sperm DNA damage [35]. Toxins accumu-
lating in the epididymis, prostate, vesicular seminalis or
semen fluid may impair normal progressive sperm mo-
tility [36]. The neuroendocrine control of spermatogen-
esis can be disrupted by actions on the testis (secretion
of androgens from Leydig cells or Inhibin B from Sertoli
cells [37]) or the central nervous system (gonadotrophin-
releasing hormone released from the hypothalamus or
gonadotrophins from the pituitary). Toxins that disrupt
the stem cells are likely to cause delayed, long-lasting and
possibly permanent effects, while actions on the later
stages most likely result in transient effects. Experimental
research has established highly specific site of actions of
various chemicals.

**Welding and metals**

Twenty years ago, two independent Danish case-referent
studies of infertility clients seemed to support earlier cir-
cumstantial evidence (by Beikufner and Langhof [38],
Zimmermann [39] and Hanke [40]) that welding carries
an increased risk of delayed time to conception [41] and
reduced quantity and quality of semen [42]. In these two
studies, the risk estimate for delay of conception was 1.4
(95% CI = 1.1–1.8) and for reduced semen quality 2.0
(95% CI = 1.2–3.5), but findings were not entirely consis-
tent when considering various types of welding expo-

ures and outcomes.

These case-referent studies formed the basis for stud-
ies of male fertility in cohorts of metalworkers. While one
cross-sectional study of mild steelworkers demonstrated
a welding fume exposure-related deterioration of several
semen characteristics [43], another cross-sectional study
addressing, in particular, welding of stainless steel did not
demonstrate any associations [44]. There is little support
for the hypothesis that exposure to hexavalent chromium
and nickel conferred by welding of stainless steel is re-
lated to reduced fecundity [45–47], while additional
studies of mild steel welders clearly indicated increased
risk for infertility [48] and reduced fertility rate [49].

In the mid-1990s, a comprehensive follow-up study of
couples who discontinued contraception to become preg-
nant for the first time did not reveal any evidence for a
relation between welding and impaired semen quality
[50] or delayed TTP [51]. These apparent inconsisten-
cies may be due to reduction of exposure levels in more
recent times, but lacking evidence for plausible mech-

anism adds to continuing uncertainty with respect to
the causal inferences. The risk seems not to be related
to exposure to the strongly carcinogenic and mutagenic
hexavalent chromium [45–47]. Welders are exposed to
rather high levels of extremely low-frequency electromag-
netic radiation, but this exposure is not a likely cause
[52], and exposure to radiant heat is probably only of
importance in uncommon and highly specialized weld-
ing operations [53]. There is some evidence that spouses
of male stainless steel welders have increased risk of
early and later embryonal loss, but findings in a strong
follow-up design [54] have not been corroborated in
studies using other designs [55].

The new evidence suggest that metal welding is not as
damaging to male reproduction as previously suggested,
probably because the exposure levels in the Western
world has decreased. Some specialized workers may
however still perform special tasks (e.g. stainless steel
welding) which may damage their reproduction.

**Inorganic lead**

The male reproductive toxicity of lead has been known
for a long time. During the past 20 years, several occu-
pational cross-sectional studies have linked exposure to
inorganic lead with reduced sperm count [34,56–59] and
other semen characteristics [60], but the literature is not
entirely consistent [61]. Reasons for disparate results in
these cross-sectional semen studies may include different
exposure levels, insufficient exposure contrast and selec-
tion bias in studies with low participation rates [62]. The
evidence in humans is supported by compelling evidence
in mice, rabbits and some rat strains [63], but the question about mechanisms and lowest observed adverse effect level remains open. An international European study points to a threshold around 45 µg/dl lead in blood below which effects on sperm counts seem unlikely [34,64]. These findings are consistent with studies of delayed TTP which do not indicate effects in the lower exposure range below 50 µg/dl [64]. A study of TTP in male lead workers [65] demonstrated a clear exposure–response relation between current blood lead level and time taken to conceive. Studies from recent years have shown that lead may interfere with the reorganization and tight packaging of sperm DNA during spermatogenesis by competition with zinc- on protamine-binding sites. If reduced stability of the sperm head chromatin is a major mechanism for reproductive toxicity of lead, it may be hard to identify in studies relying on conventional semen characteristics. There is indeed limited evidence that chromatin structure abnormalities are related to lead exposures in the lower range of blood lead values in men with high concentrations of lead within spermatozoa [34]. Lead is probably interfering with male reproductive function by actions at several sites and levels. While most studies point to a no-adverse effect level of some 40–50 µg/dl in blood, new studies using more refined and advanced measures of male reproductive function may challenge this prevailing view.

There is evidence of an adverse effect of inorganic lead on male reproduction and fecundity. In addition, several studies in rats and mice have demonstrated testicular toxicity of a number of other metals including cadmium, mercury, boron, manganese and hexavalent chromium but human data are sparse [63,66–68].

Physical exposures

Heat and sedentary body posture

The testes are located outside the body to keep temperature below the core temperature, and it is well known that internal heating as in fever and external heating for short periods of time may result in a dramatic but temporary decrease of sperm count and other aspects of semen quality after a delay of some 6–8 weeks [69]. In the occupational setting, a few cross-sectional studies among foundry workers, ceramics workers and bakers have indicated reduced sperm counts in exposed men [70], but cross-sectional findings in rather small study groups that have not been corroborated in independent studies must be considered as circumstantial. In a longitudinal study of a group of specialized welders, several semen characteristics declined significantly compared with pre-exposure basic levels and increased to these levels some weeks after discontinuation of exposure [53]. It is now well documented that the sedentary work position is associated with an increased scrotal temperature. Men sitting at work for 8 h a day have on average 0.7°C increased scrotal temperature during the day in comparison with employees with <8 h in the sedentary body position [71]. Although an increase of scrotal temperature of this order of magnitude might be sufficient to impair spermatogenesis, reduced sperm count seems not related to sedentary work [72,73], but male taxi drivers from Rome had a decreased number of morphological normal sperms [74], indicating that it may be car vibration causing the adverse effects. Likewise, it has been speculated that tight underwear could increase testicular temperature and a few studies have reported reduced sperm count related to the use of tight underwear and trousers.

There is no doubt that heat may affect male reproduction but whether heat exposures in current workplaces are of this magnitude is undetermined. The effect of sedentary work needs to be further explored.

Radiation

Testicular tissue is highly sensitive to ionizing radiation. A radiation dose in the range of 0.15 Gy may temporarily reduce sperm counts, while 2 Gy may result in long-lasting or permanent azoospermia [75]. An occupational exposure limit of 15 mSv/year has been adopted in several countries, and if this limit is not exceeded, testicular effects are unlikely. Apparent testicular effects of high-frequency electromagnetic radiation (HHF; 300 kHz–300 000 MHz including radar exposure and microwaves) that have been observed in earlier studies may result from testicular heating. So far, no consistent evidence indicates that non-ionizing radiation interferes with male reproductive function unless the amount of energy is sufficient to disrupt testicular temperature regulation.

Chemical exposures

Solvents

Organic solvents have a wide range of applications in all branches of industry. Workers have often encountered high exposure levels because of the high volatility of several organic hydrocarbons. Many studies of adverse reproductive outcomes (spontaneous abortions, congenital defects and childhood cancers) among workers exposed to organic solvents have been conducted. Often the exposure assessment is limited and workers exposed to solvents are compared to unexposed workers. Because exposure to solvents is common in many occupational settings and often involves several compounds, it is difficult to study the effect of a single compound. The evidence of exposure to single compounds available from occupational studies on effects on male reproductive health is therefore more limited.

Glycol ethers [in particular 2-ethoxyethanol (2-EE) and 2-methoxyethanol (2-ME)] are an important group
of organic solvents widely used as, for example, constituents of paint, glue, dyes and thinners and printing ink and have generally been considered safe because of their low volatility, though absorption through skin is possible. Exposed painters, chemical industry workers, metal casters and semiconductor industry workers have all been reported to have some decrease in semen quality [31,76,77]. Infertile men were more likely to work with solvents and had detectable amounts of ethoxyacetic acid in urine than healthy controls, although infertile men working with solvents did not have poorer semen quality than other infertile men [78]. 2-EE and 2-ME are therefore classified by the European Union as toxic to reproduction and dermal contact should be avoided.

Carbon disulphide is mainly used in the manufacture of viscose rayon fibres, in the production of carbon tetrachloride and in analytical chemistry. Exposure to carbon disulphide has been reported to cause decreased libido and loss of potency [79–81]. The results regarding the serum concentrations of reproductive hormones are conflicting [80–86]. In high concentrations, it has been shown to affect semen quality, whereas low exposures have shown no effects on semen quality among exposed workers [79,82,85].

Acetone is used in glues, rubber cement and varnishes. Among 25 workers in a reinforced plastic production plant exposed to styrene and acetone, sperm morphology and motility was reduced compared to controls recruited from an infertility clinic [87]. It is impossible to separate the exposure, and the choice of control group was inappropriate. Longitudinal studies of newly hired workers in the reinforced plastics industry provide limited evidence for effects on human semen quality [32]. A European multi-centre study did not observe effects on TTP in men exposed to styrene in various industries in several European countries [88].

Trichloroethylene (TCE) and tetrachloroethylene (PER) are used as degreasers. PER has been widely used in the dry-cleaning industry and has been found to affect reproduction of female workers. Eskenazi [89] found an effect on sperm motility and morphology among exposed male workers. In addition, the TTP among their wives was prolonged [90]. Other studies reported no effect on reproductive function [91–93]. PER has widely been replaced by TCE in dry-cleaning industry, which is assumed to be less toxic to reproductive function.

The effect of some compounds has only received limited interest; 2-bromopropane used as a substitute for Freon decreased semen quality among six out of eight male South Korean workers [94]. Likewise, trinitrotoluene is used in production of explosives and workers have been found to have decreased sperm motility and morphology [95].

In conclusion, the available data suggest that a number of solvents used in industries can affect male reproductive function (2-EE, 2-ME, 2-bromopropane, carbon disulphide), while the evidence for others is more limited.

Pesticides

Much of the research about reproductive health among occupationally exposed workers was prompted by the discovery of the testicular toxicity of DBCP among agricultural workers or workers in a pesticide factory. Workers experienced a wide range of negative reproductive effect ranging from azoospermia and oligospermia, damage of germinal epithelium, genetic alterations in the sperm, reduced fertility to increased risk of spontaneous abortions among wives [96–98].

Subsequently, the effects of other pesticides were studied, some of which were found to damage reproduction, although not as spectacularly as DBCP. Some studies have focused on men with known exposure levels. Ethylene dibromide (EDB) is a component of some pesticides. Men using EDB in a papaya plantation had decreased sperm count, and fewer motile and morphologically normal sperm cells [99]. In addition, reduced fertility was observed among workers in one plant manufacturing EDB but could not be confirmed in others [100]. Vinclozolin possesses anti-androgenic properties and a study has reported increased follicle-stimulating hormone level among exposed workers [101]. Carbaryl is a widely used insecticide but human studies among exposed workers have shown inconsistent results [102,103]. Chlordenecon is an insecticide with oestrogenic activity. Chronically exposed workers have been found to have decreased sperm motility [104–107] but no effect on fertility was observed [104,105].

In a case–control setting comparing men from Missouri and Minnesota with poor and good semen quality, the following agents were elevated in cases: herbicides alachlor and atrazine, insecticide diazinon (2-isopropoxy-4-methyl-pyrimidinol) [108]. A Dutch study among fruit growers and their wives reported a longer TTP during the spraying season [109]. This stimulated semen quality and TTP studies among Danish occupationally exposed male farmers and greenhouse workers. Among greenhouse workers, sperm density and motility declined with increasing duration of work in the greenhouses. In addition, the highly exposed workers (measured by transfer from leaves to hand) had a marked reduction in sperm density and motility [110,111]. The men were followed up, and sperm concentration was reduced by 28% post-spraying compared to pre-spraying. Also, their sperm morphology was affected.

Two cross-sectional studies among members of the organic farmers associations and members of an organic group showed that they had a median sperm density that was almost double compared to other occupational groups [112,113]. These findings are difficult to interpret because these men may be selected and have a different
lifestyle from other occupationally exposed men. Therefore, the more correct control group is conventional farmers and a Danish study between these two groups was undertaken. No difference in semen quality and fecundity among these groups was observed. In addition, no significant effect of spraying was observed [33,114–116].

Many pesticides, such as DDT and chlordane, are persistent in the environment and/or bioaccumulate in the food chain. As many possess endocrine-disrupting abilities, their adverse effects on human reproduction may have far-reaching consequences. Most are no longer used in the developed world but some are still widely used in less developed countries (for malaria control), often without proper safety precautions.

A few recent studies indicate that persistent organochlorine pollutants including polychlorinated biphenyls interfere with sperm motility and sperm DNA integrity at exposure levels that are encountered in populations with high body burdens related to marine diet and environmental contamination [117,118].

Psychological exposures

Occupational stress and burn-out have been related to male infertility and reduced semen quality [119,120]. Case–control studies have shown higher stress levels among infertile men than among fertile controls [121–123]. The direction of causality is uncertain, because infertile men may be more distressed or especially vulnerable to the stress, and therefore the importance of stress exposure on semen quality needs to be studied in longitudinal studies where stress levels are reported before the couples learn about their reproductive capability. After the Kobe earthquake, a decrease in sperm motility was noticed among 27 patients [124] but it is difficult to interpret whether normal men would be affected. Giblin et al. [125] assessed semen quality among 28 healthy volunteers who also reported their perceived level of stress and social support. Stress was negatively correlated with the proportion of normal sperm. A study among 164 men found no association between work stress or life events and semen quality [126]. Reduced motility was found among 12 men who had experienced a recent death of a family member. A Danish study among 430 first semen planners found no effect of daily perceived stress (measured with the Job Content Questionnaire developed by Karasek) and semen quality [127,128].

The effect of psychological stress on semen quality and male reproductive health is currently not determined.

Conclusion and recommendation for future studies

Several occupational and environmental exposures and toxins have known or suspected deleterious actions to male reproductive function. For some specific agents, such as heat, ionizing radiation, inorganic lead, DBCP, EDB, some ethylene glycol ethers, carbon disulfide and welding operations, the evidence is strongly supported in well-designed epidemiological studies. For other agents, the association is only suspected or suggested and needs further evaluation before conclusions can be drawn. Little is known of the importance of occupational exposures in causing infertility in Western societies at large, but a higher level of attention towards environmental risk factors in infertility settings might unravel clinical cases that are seldom identified today. It is also important to bear in mind that many workers in the non-Western world still are exposed to substances that are banned in the Western world, sometimes in high concentrations.

We therefore suggest that future studies should have sufficient power and homogeneous case groups with an appropriate unexposed control group. Exposure assessment should be made as accurate as possible, preferably confirmed by environmental and/or biological monitoring and targeted to specific exposures. In addition, endpoints should be multiple because toxins act at different sites of the reproductive system. We suggest using TTP as an outcome instead of infertility rates.

Conflicts of interest

None declared.

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