

Evidence Compass



Technical Report

Literature review of effects of solvent
exposure on human male reproductive
outcomes

Rapid Evidence Assessment

January 2019

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List of Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ADF	Australian Defence Force
ATSDR	Agency for Toxic Substances and Disease Registry
AVTUR	Aviation turbine fuel
BMI	Body mass index
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CONCAWE	Conservation of Clean Air and Water in Europe
COT	Committee of Toxicology
DART	Development and Reproductive Toxicology
DNA	deoxyribonucleic acid
DHEAS	Dehydroepiandrosterone sulphate
DSRS	Deseal/Reseal
DVA	Department of Veterans' Affairs
EPA	Environmental Protection Agency
F-111 DSRS	F-111 Deseal/Reseal
FSH	Follicle stimulating hormone
γ -GT	γ -Glutamyltransferase
IIEF	International Index for Erectile Function
IOM	Institute of Medicine
JFES	Jet Fuel Exposure Syndrome
JP	Jet Propellant
JP fuels	Jet Propulsion fuels
JP8	Jet propulsion-8 aviation fuel (type of Jet Propulsion Fuel)
LH	Luteinizing Hormone
MEK	Methyl ethyl ketone
MD	Mean Difference
MonCOEH	Monash Centre for Occupational and Environmental Health
MeSH	Medical Subject Headings
MATF	Military Aviation Turbine Fuel
2-MPA	2-methoxypropionic acid
NBDPS	National Birth Defects Prevention Study
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
PEL	Permissible exposure limits
PGME	Propylene glycol monomethyl ether
POF	Premature ovarian failure
PECO	Population, Exposure, Comparison group, Outcome framework
PUNP	Periods of unprotected intercourse not leading to pregnancy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRL	Prolactin
RAAF	Royal Australian Air Force
REA	Rapid Evidence Assessment
RNA	Ribonucleic acid
SCSA	Sperm chromatin structure assay
SE	Standard error
SHBG	Sex-hormone binding globulin
SHOAMP	Study of Health Outcomes in Aircraft Maintenance Personnel

TCA	Trichloroacetic acid
TCE	Trichloroethylene
TWA	Time-weighted average
TLV®	Threshold limit values
TOXLINE	Toxicology Literature Online
TOXNET	Toxicology Data Network
TTP	Time-to-pregnancy
TUI	Time of unprotected intercourse
UK	United Kingdom
US	United States of America
USAF	United States Air Force
WHO	World Health Organization

Executive Summary

- The aim of this Rapid Evidence Assessment (REA) was to conduct a literature review of adverse sexual and reproductive health outcomes in men from occupational exposure to specified solvents relevant to the Australian military and any of the following health outcomes:
 - Adverse reproductive outcomes: hypogonadism / primary testicular failure, androgen (testosterone) deficiency, impaired semen quality, reduced reproductive success (infertility, involuntary childlessness, not achieving desired family size, increased time-to-pregnancy (TTP), low fecundity, use of assisted reproductive technologies, and adverse pregnancy outcomes or reduced fertility in female partners), altered reproductive hormone levels (testosterone, oestradiol, luteinising hormone (LH) and follicle stimulating hormone (FSH))
 - Adverse sexual outcomes: Erectile dysfunction, libidosexual dysfunction, psychosexual dysfunction
- Solvents relevant to the military included in this review were:
 - ethyl acetate, ethyl benzene, toluene, xylenes, acetone, isopropanol, methyl ethyl ketone (MEK), propylene glycol monomethyl ether (PGME), white spirit and trichloroethylene (TCE).
- Using a comprehensive strategy, a search was conducted in 10 electronic databases to identify relevant peer-reviewed studies in humans, published between January 2000 and June 2018 in the English language. Additionally, one military and veteran health journal was electronically searched to identify any published studies. This process was supplemented by a website search to identify any publicly available relevant government agency or independent medical scientific advisory committee reports, toxicological profiles, or risk assessment reports (herein referred to as reports).
- The studies were screened against strict inclusion and exclusion criteria. Only studies with male populations exposed to one or more of the specified solvents and which reported sexual function or sexual or reproductive health outcomes were included.
- The studies that were included were assessed for quality and were evaluated for risk of bias, the data source, quantity of evidence and the generalisability of the body of evidence.

- A total of 34 records met the inclusion criteria. Of these, 18 records were publications (from 14 primary observational studies) and 16 records were reports. Three publications¹⁻³ were based on the same population of degreasing workers in Singapore, two were based on the same Australian retrospective cohort study (Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP)),^{4, 5} and another two were based on a group of men monitored for exposure to organic solvents by the Finnish Institute of Occupational Health between 1965–1983.^{6, 7}
- The designs of the 14 studies were: one prospective cohort (one publication⁸), one retrospective cohort (two publications^{4, 5}), one case referent (two publications^{6, 7}) and 11 cross-sectional (13 publications^{1-3, 9-18}) studies.
- Ten publications reported outcomes related to fertilityⁱ and/or fecundityⁱⁱ; six^{2, 8, 9, 13, 15, 18} conducted semen analysis in exposed men, two reported time to pregnancy (TTP),^{11, 14} one investigated fecundity ratios,⁶ and the other⁵ reported number of pregnancies, problems getting pregnant and visiting a specialist regarding fertility issues in partners of exposed men. The exposures varied across these studies and only three publications reported outcomes assessed in relation to a single specified solvent exposure; two reported on TCE^{2, 15} and one on toluene.¹⁴ In all the other publications, exposures to several solvents and associations with reproductive outcomes were reported and the men had been exposed to more than one solvent.
- Of the six publications that investigated semen profile, sperm motility was reported in five^{8, 9, 18, 2, 13} a significant decrease in sperm motility was reported in three^{8, 9, 18} and two^{2, 13} reported no association with sperm motility. Benzene, toluene and xylene were present as co-exposures in all three studies that reported a reduction in sperm motility. The other two publications reported no association of TCE² or PGME (assessed through a urinary metabolite, 2-methoxypropionic acid (2-MPA))^{2, 13} with sperm motility.
- Five publications^{1, 3, 10, 16, 17} from four cross-sectional studies reported endocrine profiles. Four publications^{1, 10, 16, 17} reported serum levels of FSH, LH and testosterone. Toluene was investigated in three publications^{10, 16, 17} and TCE in two.^{1, 3} For TCE, exposure dose was quantified based on the number of years of occupational exposure to TCE. In TCE exposed workers, the studies found that the mean serum FSH, LH, and testosterone levels decreased with the number of years' exposure up to seven years of exposure, FSH levels

ⁱ the ability to deliver a live-born infant.¹⁹

ⁱⁱ biological capacity for conception and may encompass hormonal profiles, gynecological health, sexual function, time to pregnancy (TTP), conception delays, pregnancy loss and (premature) reproductive senescence or menopause.¹⁹

were lower than those with greater than seven years of exposure. The association between exposure to toluene and reproductive hormone outcomes were equivocal; two publications^{10, 17} reported no significant associations with FSH, LH and testosterone levels in the exposed group compared to the comparison group. However, one of these studies¹⁷ reported significantly lower levels of FSH and LH in a subgroup of workers less than 40 years old. The third study¹⁶ reported that exposure to toluene was associated with significantly lower levels of FSH, LH and free testosterone.

- Four studies (four publications) reported pregnancy outcomes in partners of exposed men; three^{7, 11, 12} reported on spontaneous abortion and one on miscarriage.⁵ Three publications^{5, 7, 11} reported co-exposure to a number of solvents, including solvents in general.^{5, 7} None of the publications reported significant associations with pregnancy outcomes in partners of exposed men when the exposed group was compared with the comparison group without subgroup analysis. However, one publication⁷ conducted a subgroup analysis and found a significant increase in risk of spontaneous abortion in the high toluene exposure subgroup and solvents in general.
- Two publications^{7, 11} reported on the incidence of birth defects. One publication¹¹ found a significantly higher risk of congenital defects in the solvent-exposed group based on quantitative model predicted exposure estimates using toluene as a marker, but the numbers were low; based on 37 birth defects (398 pregnancies) in the exposed group and 11 birth defects (302 pregnancies) in the unexposed group. However, it was difficult to establish any clear association between exposure and outcome due to uncertainty in the specific solvent exposures. The other publication⁷ did not find any association between toluene or xylene exposure and birth defects.
- One publication⁴ reported adverse sexual health effects (i.e. erectile dysfunction and poor sexual function) in solvent exposed male Deseal/Reseal (DSRS) personnel compared to non-exposed personnel. However, the participants had been exposed to a wide range of solvents.
- The range of the available studies was limited and did not investigate associations between specified solvents and all the specific adverse reproductive outcome endpoints identified in the aims. As an example, studies investigating not achieving desired family size and use of assisted reproductive technologies were not identified.
- The limitations of individual studies investigating associations between specified solvents and adverse male sexual and reproductive health outcomes included the small number of studies, limitations in exposure assessment or in health outcome assessment such as in

self-reported outcomes, recall bias, and co-exposure with other solvent(s). For instance, some significant adverse effects were associated with exposure to a mixture of chemicals, some of which were not the aim of this REA. Therefore, establishing clear exposure-outcome associations was difficult. The omission of possibly relevant papers that were published prior to 2000 or after June 2018 and the omission of non-English language papers may have been minor limitations, but this was partly addressed by including relevant studies that were found during a reference check of included publications.

- The effects of occupational exposure of male service members to specified solvents used in the Australian military was of prime interest. However, the search was not restricted to articles on military servicemen and the review considered evidence on reproductive and sexual function outcomes in other occupational groups exposed to these solvents.

In summary, in relation to the specified solvents considered, this review found:

- The most commonly assessed exposures were toluene, xylene and TCE; the evidence base for other specified solvents of interest was extremely limited.
- There was some limited evidence that occupational exposure to high concentration of a combination of solvents, including solvents of interest in this review such as TCE and BTEX, may be associated with changes in characteristics of semen.
- There was limited evidence of association with TTP or low fecundity but this did not suggest that specified solvent exposure in men was associated with increased time to pregnancy or reduced fecundity in couples.
- The evidence supporting an association of specified solvent exposure in men with increased risk of spontaneous abortion in their partners is limited and weak.
- The evidence of association of specified solvent exposure with stillbirth or preterm birth was very limited and did not provide evidence that specified solvent exposure in men was associated with increased risk of stillbirth and preterm birth in partners.
- There was limited evidence to suggest that specified solvent exposure to toluene in men is associated with a higher risk of congenital malformations in babies of partners. However, co-exposure to solvents, including solvents that were not in the scope of this REA, may have occurred.
- There is some weak and limited evidence to suggest that high TCE or toluene exposure in men is associated with lower serum levels of FSH, LH and testosterone.

- The strength of available evidence was weak due the limited number of studies and the limitations of study designs. The majority of evidence came from cross-sectional studies and in some studies co-exposure with other solvent(s) or chemical(s) at the workplace made it difficult to ascertain specific exposure-outcome associations. The quality of the studies varied. Overall limitations of individual studies of the association between specified solvent exposure and adverse male reproductive health outcomes included limitations in study design, the small numbers of cases for adverse reproductive health outcomes, limitations in exposure assessment or in health outcome assessment such as in self-reported outcomes, and recall bias. The evidence from recent studies was scarce and many studies were conducted before 2000.
- It is difficult to establish strong conclusions on specific solvents without more high-quality evidence.
- This REA provides the Department of Veterans' Affairs and Department of Defence with a summary of the available evidence of the effects of specified solvent exposure on human reproductive health in male service members of the military.

Introduction

In the Royal Australian Air Force (RAAF) F-111 Deseal/Reseal (DSRS) programs between 1975 and 1999 there had been exposure to jet-propulsion-8 (JP-8) aviation fuel and several solvents. This was associated with later ill health, including symptoms consistent with solvent or isocyanate exposure in DSRS personnel who had potentially been exposed to these solvents. There was also an estimated increase in cancer of 50% in the DSRS group, which was of borderline statistical significance.^{5, 20-22} The subsequent Jet Fuel Exposure Syndrome (JFES) *in vitro* study investigated the cellular toxicity of JP-8.²³ The JFES study found that JP-8 fuel and, to a lesser extent, the DSRS solvents have the capacity to cause cellular toxicity. Small changes in the expression of regulatory microRNAs, non-coding RNAs that may control activity of other genes or cellular processes were identified. However, the interpretation of the function of the microRNAs and possible significance to human health was not known. The JFES study did not find any evidence of genetic or chromosomal changes. Following the release of the JFES report in June 2014, concerns were expressed by some women in the RAAF about adverse reproductive health outcomes and exposure to jet fuel. These concerns included adverse effects on fertility, adverse pregnancy outcomes, premature ovarian failure (POF) and early onset of menopause.

In 2017, the Monash Centre for Occupational and Environmental Health (MonCOEH), in the School of Public Health and Preventive Medicine, Monash University conducted a Rapid Evidence Assessment (REA)²⁴ of the effects of occupational exposure to Military Aviation Turbine Fuels (MATFs), (herein referred to as jet fuels), and a selection of specified solvents of most relevance to the military, on adverse reproductive health outcomes in women, funded by the Department of Veterans' Affairs (DVA).²⁵ A further literature review was undertaken in 2018 to examine adverse reproductive health outcomes in men who had been exposed to jet fuels.²⁶

The current literature review presents the available findings on male reproductive health effects and exposure to selected solvents of most relevance to the military.

Solvents

The term 'solvents' is generic, encompassing broad groups of substances, many of which are organic chemicals, and some of which are commonly used in Australian military settings. Military personnel may use some solvents in regular military tasks such as cleaning, degreasing, vehicle maintenance and repair, paint stripping and thinning oil-based paints. Some Australian personnel have been exposed in more specific settings, such as the RAAF F-111 DSRS. The solvents of interest are listed in the Methods section.

Adverse reproductive health outcomes investigated

Reproductive toxicity has been defined as “the occurrence of adverse effects on the reproductive system that may result from exposure to a chemical.”²⁷ The toxicity may be directed to the reproductive organs and/or the related endocrine system and have adverse effects on sexual behaviour, fertility, pregnancy outcomes, or other functions dependent on these systems.²⁸ Male reproductive system toxins may act at several levels. They can affect spermatogenesis and impair the number, structure, mobility and/or viability of sperm and cause loss of chromatin integrity and DNA damage. Toxicants may act on Sertoli cells (essential for the proliferation and maturation of sperm) and cause impairment of semen quality. In addition, toxins may act on the neuroendocrine control at the pituitary or testicular level (Leydig cells which secrete testosterone in response to pituitary luteinising hormone (LH)) and/or interfere with the functions of the epididymal and accessory sex glands (seminal vesicles, prostate, and bulbourethral glands) (androgen effects).²⁹

MonCOEH was asked to undertake a literature review to summarise the available evidence on occupational exposure to solvents of most relevance to the military and human male adverse sexual and reproductive health outcomes.

Aims

The overall aim of this project was to conduct a literature review on the effects of occupational exposure of service men to any of a number of specified solvents on adverse human male sexual and reproductive health outcomes.

More specifically, the review aimed to determine whether there is an association between occupational exposure in men to any of a number of specified solvents and the following adverse reproductive and sexual health outcomes:

- Hypogonadism / primary testicular failure
- Androgen (testosterone) deficiency
- Impaired semen quality (semen volume, sperm concentration, number, motility, vitality and morphology)
- Reproductive success (infertility, involuntary childlessness, not achieving desired family size, time-to-pregnancy, low fecundity, use of assisted reproductive technologies, and adverse pregnancy and fertility outcomes in female partners)

- Altered reproductive hormone levels (testosterone, oestradiol, luteinising hormone (LH) and follicle stimulating hormone (FSH))
- Adverse sexual outcomes: Erectile dysfunction, libidosexual dysfunction, psychosexual dysfunction.

Methods

This project was conducted using the REA methodology²⁴ as requested by the Departments of Veterans' Affairs and Defence. This was the same methodology as that used for two previous literature reviews: exposure to jet fuel and adverse reproductive outcomes in men²⁶ and jet fuel and specified solvent exposure and reproductive outcomes in women.²⁵

The REA is a research methodology which uses the same methods and principles as a systematic review but makes concessions to the breadth or depth of the process, in order to suit a shorter timeframe. The purpose of an REA is to provide a balanced assessment of higher quality research literature pertaining to a specific issue.

The REA is considered rapid, because the methodology places a number of limitations in the search criteria and on how the evidence is assessed. For example, REAs often limit the selection of studies to a specific and stated time frame (e.g. the past 10 years), to peer-reviewed, published, English language studies (i.e. do not include unpublished studies, difficult-to-obtain material and/or non-English language publications).

While the strength of the evidence is assessed in a rigorous way and according to a protocol, a REA review is not as exhaustive as a traditional systematic review. However, a REA can inform policy and decision makers within a relatively short space of time compared to a traditional systematic review. A REA review may also include relevant grey literature, such as relevant reports and unpublished sources of information obtained from relevant websites, to supplement the evidence identified from published literature, which systematic reviews usually do not.

Defining the review questions

The review was based on the PECO framework in conformity with the REA methodology; population (P), exposure (E), comparison group (C) and outcomes (O). A complete description of the research question based on the PECO framework is given in [Appendix 1](#).

To ensure relevance of results, key components related to the questions and specific inclusion and exclusion criteria, were established for the search and for screening studies for inclusion

in this REA. As part of these operational definitions, adult men who are or who were employed in defence or military related forces were defined as the target population of interest. The previous REAs highlighted the scarcity of evidence on this topic in military personnel. Consequently, we included papers on male non-military personnel in occupational groups exposed to specified solvents which reported relevant adverse reproductive health outcomes.

This review focussed on scientific studies that investigated occupational exposures. Studies investigating environmental exposures experienced from residential exposure or environmental air pollution were excluded, as the populations will have had other exposures and/or confounding factors such as socioeconomic status, which could not be evaluated.

The exposures of interest were solvents. A list of specified solvents (and related terms) most relevant to military personnel (based on common solvents identified in the SHOAMP Study of the F-111 DSRS workers²²) were finalised in consultation with the DVA Research Section and DVA Principal Medical Adviser and the (former) Defence Centre for Occupational Health (DCOH). This solvent list was that used previously for the female reproductive outcome review²⁵ and adopted without modification.

- ethyl acetate, ethyl benzene, toluene, xylenes, acetone, isopropanol, methyl ethyl ketone (MEK), propylene glycol monomethyl ether (PGME), white spirit and trichloroethylene (TCE).

Combinations of solvents such as ethylbenzene, benzene, toluene and xylene (BTEX) were considered for inclusion because it contained three constituents (toluene, ethyl benzene and xylene) that were of interest in this review.

The adverse male reproductive outcomes of interest were used in the jet fuel exposure and male reproductive outcomes review²⁶ and were adopted for this review without modification:

- Hypogonadism / primary testicular failure
- Androgen (or testosterone) deficiency
- Impaired semen quality (semen volume, sperm concentration, number, motility, vitality and morphology)
- Reproductive success: infertility, involuntary childlessness, not achieving desired family size, time-to-pregnancy, low fecundity (fecundity defined as probability of a couple to conceive in a menstrual cycle), use of assisted reproductive technologies, and adverse pregnancy and fertility outcomes (early foetal loss, neonatal death, stillbirth, miscarriage, foetal malformations or congenital

anomalies, pre-term birth, intra-uterine growth retardation or low birth weight, reduced fertility, reduced libido) in unexposed female partners.

- Altered levels of reproductive hormones (testosterone, oestradiol, LH and FSH)
- Adverse sexual outcomes: Erectile dysfunction, reduced libido sexual function, psychosexual dysfunction.

Search methods for identification of studies

Electronic searches

A comprehensive search strategy was developed using relevant Medical Subject Headings (MeSH) and relevant key words to identify published literature. Terms relating to ethyl acetate, ethyl benzene, toluene, xylenes, acetone, isopropanol, MEK, PGME, white spirit and TCE were used. The final Medline strategy is given in [Appendix 2](#).

This search strategy was adapted as necessary to query the following 10 electronic databases.

- Medline (Ovid): Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE ® Daily, Ovid MEDLINE and Versions (R) 1946 to 26 June 2018
- Embase (Ovid): 1974 to 27 June 2018
- Cochrane Central
- Scopus
- CAB Direct
- TOXLINE via TOXNET (Toxicology Literature Online)
- DART via TOXNET (Developmental and Reproductive Toxicology Database)
- SciFinder
- ProQuest Military database
- NIOSHTIC-2 (The National Institute for Occupational Safety and Health)

In addition, the electronic version of the Journal of Military and Veterans' Health was hand searched using each solvent name as key words. This Australasian based journal is dedicated to military and veteran health related research and therefore may have published research findings on this topic.

The search was limited to English language studies in male human subjects published between 1 January 2000 and 27 June 2018. The search was conducted within a defined and limited time frame and it was considered that this period was wide enough to identify relevant studies. The search time period constraint is consistent with the REA literature review methodology.²⁴ However, studies published before 2000, identified from full text articles, were also considered for inclusion if they were relevant.

- The search included a list of pre-determined websites, to identify any relevant unpublished reports from online sources. The following websites were screened to identify any publicly available relevant government agency or independent medical scientific advisory committee reports, toxicological profiles, or risk assessment reports (herein referred to as reports).
 - Agency for Toxic Substance and Disease Registry (ATSDR)
 - US Department of Veterans Affairs
 - Department of Veterans' Affairs Australia
 - US Department of Defense
 - National Defence and the Canadian Armed Forces
 - Veterans' Affairs Canada
 - National Academies of Sciences, Engineering and Medicine (formerly Institute of Medicine)

Selection of studies

Records were imported into the bibliographic software Endnote X8 after the literature search of each database. A screening process was adopted for titles/abstracts and papers eligible for a full text assessment were identified.

Following the removal of duplicates, one reviewer screened all the titles and abstracts against the predetermined inclusion and exclusion criteria in table 2. A second reviewer independently assessed a sample of 10% of the titles and abstracts. The screening decisions were compared and any discrepancies were resolved through consensus and the discussion was used to inform the selection decisions. Full text versions of all studies which satisfied the screening criteria were obtained. Studies were also included for full text assessment where there was uncertainty; for example, if it was not clear from the title and/or

abstract whether the article included data on at least one of the specified solvents and/or its relationship with a male reproductive outcome.

The process was repeated after obtaining full text versions of the selected titles and abstracts. One reviewer assessed all full texts against inclusion and exclusion criteria and a second reviewer independently assessed a sample of 20%.

Data were extracted from the included studies to a standard data extraction table. The following variables were collected:

- First author
- Year of publication
- Country in which the study was conducted
- Study design
- Sampling method
- Information about study population (both exposed and comparison groups)
- How the exposure was assessed
- How the outcomes were assessed
- Findings of the study

Reports identified through the website search were also screened according to the inclusion and exclusion criteria. All the references in the relevant sections of the included reports were screened to identify any relevant peer-reviewed publications and other reports of interest.

Table 1: Inclusion and exclusion criteria

Inclusion
<ul style="list-style-type: none">○ Published, peer-reviewed research studies○ Reports that were underpinned by a systematic review of relevant studies○ Based on, but not limited to, medical scientific literature published since 1 January 2000 to 27 June 2018○ Quantitative studies with outcome data that assessed exposure in men and investigated associations between an exposure to solvents and adverse male reproductive health outcomes including adverse pregnancy outcomes in unexposed-female partners○ Studies based on human male adults (i.e. 18 years of age or older)○ English language○ The reports had recommendations or conclusions generated by a group of content experts or research experts○ Articles published before 2000 and identified from checks of the reference lists of relevant articles or websites
Exclusion
<ul style="list-style-type: none">○ Papers / reports published before 1 January 2000 (unless key papers or reports)○ Qualitative studies○ Non-English language○ Reports that did not consider the association between exposure to specified solvents in men and adverse male reproductive health outcomes○ Studies that determined exposure based only on job category and did not provide information on specific solvents○ Reports not underpinned by a systematic review of literature○ Reports where recommendations or conclusions were not generated by a group of content experts or research experts and/or not containing ratings of the strength of evidence○ Conference presentations and PhD theses/dissertations○ Animal studies○ If full text version was not readily available to the research team and reasonable attempts to retrieve the full text were unsuccessful○ Environmental pollution studies (i.e. air, water)

Evaluation of the evidence

The REA methodology²⁴ recommends assessing the quality of included studies for prevalence questions on four categories:

1. Quality and risk of bias
2. Data source (primary or secondary)
3. Quantity of evidence
4. The generalisability of the body of evidence to the target population

The studies and their quality assessment are described in the Evidence Profile and in the Summary of Evidence of this Technical Report.

1. Quality and risk of bias:

This reflects how well the studies are conducted and was assessed using a modified version of a tool developed by Giannakopoulos et al.³⁰ which is provided in [Appendix 3](#). A 'gold standard' quality of evidence includes random sampling methodology (to ensure that the sample is representative of the population), clear definitions of the target population and health outcome of interest, measurement reliability such as the use of standardised instruments or validated tools, information on non-responders, and consideration of additional information, such as the use of appropriate statistical analytical methods.²⁴ Two reviewers independently used the tool³⁰ to assess the quality of included primary studies and any discrepancies were resolved through consensus.

2. Data source:

The REA protocol also assesses bias in terms of the data source, i.e. whether the data collected in each study were primary (e.g. clinical interview, questionnaires) or secondary (e.g. medical chart review or other routine health data source).

Primary data sources are collected with purposeful intention by researchers to measure a particular outcome(s) of interest; the researcher can control relevant variables to increase the likelihood of assessing the true prevalence rate. In comparison, secondary data sources are collected at a time point after the diagnosis was made, where at the time of diagnosis, neither the patient nor the clinician were aware that the diagnosis would be used for research purposes. Therefore, by nature, secondary data sources are opportunistic, and this may increase or decrease risk of bias depending on the outcome(s) of interest.

3. Quantity of evidence:

The REA protocol takes into account the number of studies included as the evidence base for each category. In prevalence studies, the quantity assessment also takes into account the number of participants included in the studies.

4. Generalisability:

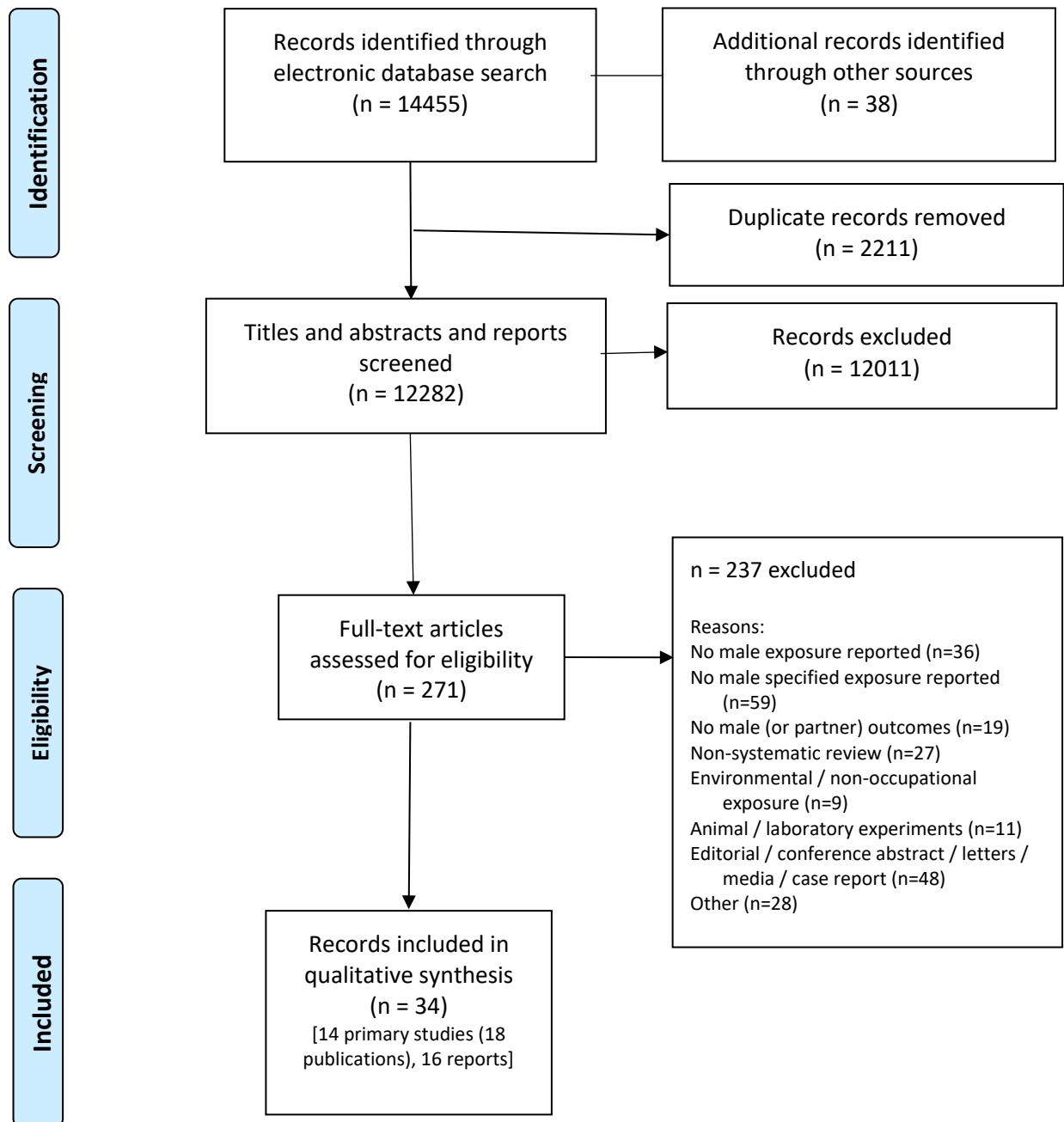
This covers how well the participants and settings of the included studies can be generalised to the target population. These factors could include significant documented exposures to substances not present in solvents. Population variability that might influence this component include age, ethnicity and non-military occupations.

Results

Results of the search

Ten electronic databases and an online military and veteran health journal were searched in June 2018 and this generated 14,455 records. The reference list search of full text papers and the web site search yielded an additional 38 records. Following removal of duplicates, 12,282 unique records were exported to “Covidence” (www.covidence.org), Cochrane Collaboration's recommended online tool for review production.³¹ Following titles and abstract screening in Covidence, 273 full texts were retrieved to be assessed for eligibility, and 34 met the inclusion / exclusion criteria and were included. Of these 34 records, five originated from the electronic database search.^{8, 9, 11, 13, 18} The reference list search of full text papers and the pre-determined website search identified a further 29 records.^{1-7, 10, 12, 14-17, 32-47} Finally, records of 18 publications¹⁻¹⁸ from 14 studies and 16 reports³²⁻⁴⁷ were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)⁴⁸ flowchart for study selection is given in Figure 1.

Figure 1: PRISMA flow chart⁴⁸



Characteristics of primary studies

The following summarises the characteristics of primary studies, exposures reported and associations with adverse male reproductive health outcomes, and the occupational groupings of workers. The primary studies grouped by main adverse male reproductive health outcome reported and the evaluation of the evidence is then presented in more detail.

The designs of the included 14 studies (18 publications) were; 11 cross-sectional (13 publications),^{1-3, 9-18} one retrospective cohort (two publications),^{4, 5} one case-referent (two publications)^{6, 7} and one prospective cohort (one publication).⁸

Three publications reported outcomes from the same study population of factory workers in Singapore who used TCE for degreasing.¹⁻³ The wives of workers who were monitored after exposure to organic solvents by the Finnish Institute of Occupational Health, were the focus in one study and two publications.^{6, 7} Two publications reported outcomes from a retrospective cohort study in Australia; the SHOAMP, of fuel tank maintenance workers who participated in the DSRS programmes.^{4, 5} The findings on adverse male sexual function and the pregnancy outcomes of female partners of exposed men were presented in the main study report, a publicly available online document.⁵ Adverse outcomes for male sexual function in this report were published in a peer-reviewed journal.⁴ In order to avoid duplicating the results, adverse male sexual function outcomes were extracted from the journal publication⁴ and pregnancy outcomes were extracted from the study report⁵ and presented in this review.

The exposed workers were printers in publications that specifically reported toluene exposure^{10, 14, 16, 17} and degreasers in publications that specifically reported TCE exposure.^{1-3, 15} Aircraft maintenance personnel were investigated in three studies (three publications^{4, 5, 8}), rubber factory workers⁹ in one publication, municipality workers¹³ in one publication and shoemaking or spray painting or paint manufacturing workers¹⁸ in another publication. One publication investigated painters¹¹ exposed to various solvents and two publications were based on workers who were exposed to organic solvents and were monitored by Finnish Institute of Occupational Health.^{6, 7}

Three publications each were based on populations in Singapore¹⁻³ and Finland.^{6, 7, 12} Two publications each were identified for populations in Australia,^{4, 5} Sweden^{16, 17} and Germany.^{10, 14} One publication was identified for populations in Denmark,¹⁵ Netherlands,¹¹ China,¹⁸ France,¹³ USA⁸ and Mexico.⁹

The most commonly reported solvent was toluene, reported in nine studies (11 publications^{4-10, 14, 16-18}) followed by xylene in five studies (7 publications^{4-9, 18}) and TCE in four studies (7 publications^{1-3, 6, 7, 12, 15}).

Findings for Toluene

Even though toluene exposure was reported in 11 publications, it was the sole reported exposure in only four publications.^{10, 14, 16, 17} Printers were the exposed group in these four studies. The largest study (n=768 printers and helpers) reported no significant effects on serum FSH, LH and testosterone compared to non-printers.¹⁰ The participants had high exposure to toluene (the median air concentration was 91 mg/m³ and median blood concentration of 39 µg/litre blood). The comparison group (non-printers) were from the same industry but at lower exposure and lower median blood concentration of toluene (14 µg/litre blood). The second largest study¹⁴ consisting of 150 male printers did not find any association between various concentrations of exposure (high, medium and low) and fecundity in their partners. The third,¹⁷ with 47 exposed printers, reported significant reduction in FSH and LH levels in a subgroup of workers less than 40 years old, but not when the exposed workers were compared with the unexposed group. The blood concentration of toluene in workers varied from 0.05-8.0 µmol/l. The fourth study¹⁶ of 20 printers without signs of solvent induced toxic encephalopathy, reported a significant decline in serum FSH, LH and testosterone levels in the exposed workers (median blood concentration of 1.7 µmol/l (range 1-6.6)) compared with the unexposed group.

In two other publications,^{6, 7} toluene specific exposure outcomes were reported along with associations with several other solvents. There is limited evidence on toluene specific exposure and spontaneous abortion in the partners of exposed men and came from a case-referent study (one publication).⁷ A significantly increased risk of spontaneous abortion was found in the partners of men with high/frequent exposure but not in partners of men with intermediate or low/rare exposure to toluene. High/frequent compared with those unexposed to toluene was associated with decreased fecundability among primigravida but not among couples with at least one previous pregnancy.⁶ The exposure was quantified predominantly based on the frequency of solvent usage and biological data in a limited number where available and not on air concentrations.

In all the other five publications,^{5, 6, 9, 18, 10} toluene was reported as an exposure, but no toluene-specific exposure outcome associations were reported. Instead, the outcomes were reported for collective solvent exposure that also included toluene. Exposure in DSRS program studied in the SHOAMP included a range of approximately 60 hazardous substances, including several organic solvents.^{5, 6} The exposures investigated in De Celis et al. (2000)⁹ were ethylbenzene,

benzene, toluene and xylene. Collective exposure to benzene, toluene and xylene was reported in Xiao et al. (2001).¹⁸ The exposures studied in workers in Lemasters et al. (1999)⁸ were 1,1,1-trichloroethane (TCA), toluene, MEK, xylene, and methylene chloride.

Findings for TCE

TCE was the sole exposure reported in two studies (four publications^{1-3, 15}) and one of several solvent exposures reported in two other studies (three publications^{6, 7, 12}). One publication reported that high exposure (urinary TCA ≥ 25 mg/g creatinine) was associated with significantly lower sperm density compared with the low exposure group, but both groups were still above the WHO reference range, and there were no significant differences in other semen parameters.² The other three publications did not report an association of TCE with increased risk of spontaneous abortion^{7, 12} or indications of low fecundity⁶ in partners of exposed men.

Findings for other solvents

No studies that investigated xylene exposure exclusively were identified (five studies, seven publications^{4-9, 18}). None of the studies that investigated other specified solvents, i.e. MEK, acetone, ethyl acetate, ethyl benzene, isopropanol or PGME reported solvent-specific outcomes, but reported outcomes for combined solvent exposure that also included exposure to the specified solvent.

The workers in the two Australian studies were exposed to a large number of agents (e.g. fuels, desealants, metal surface protectors, primers, resins) including solvents (MEK, isopropanol, ethyl acetate, naphtha, xylene, and others).²² Information on corresponding outcomes for specific exposures were not reported.

One Finnish study (two publications^{6, 7}) included workers who were monitored biologically by the Finnish Institute of Occupational Health for exposure to six commonly used solvents (TCE, tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, and toluene). The other Finnish study¹² reported exposure to several solvents including benzene, methylene chloride and TCE.

The exposure was five ethylene glycol derivatives and one propylene glycol ether derivative, i.e. PGME with biological monitoring of a metabolite 2-methoxypropionic acid (2-MPA, a metabolite of the minor β isomer of PGME) in Multigner et al. (2007).¹³

Primary studies

All primary studies assessed exposure and reported a range of adverse sexual health or reproductive outcomes and therefore the finding of each study is narratively described under four main outcome categories, with emphasis on the quality and risk of bias, data source and generalisability consistent with the REA methodology.²⁴ The risk of bias assessment of the primary included studies is based on the modified checklist ([Appendix 3](#)) and conforms to REA methodology.²⁴

Male sexual function

One study⁴ was identified that reported male sexual functioning outcomes following exposure to solvents. The SHOAMP^{22, 49} was a retrospective cohort study of the health of F-111 Deseal/Reseal (DSRS) workers and assessed whether any of the reported adverse sexual health outcomes (i.e. erectile dysfunction, self-reported loss of interest in sex and self-reported problems with sexual functioning) were associated with their involvement in the DSRS programs. The DSRS activities involved using a range of approximately 60 hazardous substances, including several organic solvents.

Brown et al.⁴ compared 577 men who participated in the DSRS programme between 1975 and 1999 with two groups:

- (1) non-technical personnel who worked at the same base but were not involved in DSRS activities: (“same base-different job”) (n=399)
- (2) aircraft maintenance personnel who did similar maintenance activities but in different aircraft (“different base-similar job”) (n=503).

The three groups were statistically similar in rank, posting (location of work duties assigned to an individual) and age. The exposed (DSRS) group was more likely to be depressed and anxious compared to the comparison groups. They were also more likely to report loss of interest in sex, poorer sexual function and poorer erectile function compared to the comparison groups. These sexual function outcomes were significantly correlated with the reported incidence of depression and anxiety in the cohorts, but the association persisted after adjustment for these and other potentially confounding variables of age, posting, rank, civilian exposure to organic solvents, lead, smoking and body mass index. The authors concluded that DSRS male workers had on average, a two-fold increase in the odds of reporting sexual dysfunction compared to either comparison group. The two comparison groups reported similar outcomes for loss of interest in sex, problems with sexual function and erectile dysfunction.

The study employed validated instruments such as the International Index for Erectile Function (IIEF)⁵⁰ to assess erectile dysfunction and the Composite International Diagnostic Interview (CIDI) to assess anxiety and depression in clinical assessments. The IIEF was designed to be self-administered in research or clinical settings as a broad measure of sexual function across five domains.⁵⁰ Limitations in the instrument's assessment of non-erectile components of sexual response and the partner relationship were acknowledged, and the authors noted that the IIEF should be viewed as an adjunct to, rather than a substitute for, a detailed sexual history.⁵⁰ The exposed population was compared to military personnel comparison groups, the investigators did not compare sexual function in these men with that for unexposed men in the general population. The study findings may only be applicable to the population who took part in the DSRS activities in the RAAF; and caution should be exercised in generalising to other aircraft maintenance workers, as their exposures are different from those encountered by the DSRS workers and they were the baseline or comparison group in the SHOAMP study.

Endocrine profile

Five cross-sectional studies reported on endocrine profile.^{1, 3, 10, 16, 17} Four studies reported serum levels of FSH, LH and testosterone^{1, 10, 16, 17} and three reported sex-hormone binding globulin (SHBG) levels.^{1, 3, 16} The exposure was toluene in three studies^{10, 16, 17} and TCE in two studies.^{1, 3} Two studies did not include a comparison group and investigated the same population of degreasing workers who were exposed to TCE, basing the analysis on the years of exposure. The other three studies^{10, 16, 17} reported outcomes in printing workers exposed to toluene compared to workers who were unexposed (or minimally exposed) to organic solvents. Chia et al (1997)¹ found that the mean serum levels of FSH, LH, testosterone and SHBG in TCE exposed workers declined with increased years of exposure until 5-7 years of exposure, and then LH, testosterone and SHBG levels remained stable. However, mean FSH levels were also lower in the 7 or more years exposure group and significantly lower when compared with levels in those exposed for fewer than 3 years. The association between exposure to toluene and reproductive hormone outcomes were equivocal; two publications^{10, 17} reported no significant difference in levels of FSH, LH and testosterone in the exposed group compared with the non-exposed referent group. However, one of these studies¹⁷ reported significantly lower levels of FSH and LH in a subgroup of workers less than 40 years old. The other study¹⁶ reported significantly lower levels of FSH, LH and free testosterone in the exposed group.

Chia et al. (1997)¹ in a cross-sectional study, investigated the serum hormonal profile of testosterone, FSH, LH, and SHBG levels of degreasing workers exposed to TCE. No comparison group was used, and the adjusted means by years of exposure to TCE were compared. Mean FSH, LH and testosterone levels declined with increasing number of years

of exposure, after adjusting for age, testicular size and smoking history, until 5-7 years of exposure. The mean levels of FSH were lower in those with seven or more years of exposure compared with levels in those exposed for fewer than 3 years, while levels of LH, SHBG and testosterone stabilised at that point.

Goh et al. (1998)³ in a cross-sectional study, investigated the effects of duration of TCE exposure on serum testosterone and SHBG (and serum levels of insulin and some adrenal steroid hormones and urine analysed for trichloroacetic acids (TCAs)) on the same study population.¹ Mean serum levels of testosterone and SHBG declined with increasing duration of years of exposure, with significantly lower serum levels of SHBG in the 4-6 year and more than 6 year exposure groups compared with fewer than 2 year exposure group and confirmed the results by Chia et al. (1997).¹ TCE was not associated with significant changes to adrenal steroid hormone levels.³

These two papers^{1, 3} were based on the same male study population of degreasing workers in an electronics factory. Relevant information regarding age and employment were provided. The sample was selected from volunteers who consented to participate in a free medical examination conducted by a doctor. Personal exposure during an 8-hour working period was monitored, and individual urinary TCA levels, a metabolite of TCE, was collected from a subsample of workers across the factory. Years of exposure (duration of service in the facility) was used as a metric to assess association with the endocrine profile of workers^{1, 3} (whereas exposure based on urinary TCA was used to assess the association with semen characteristics²). Standard laboratory tests and techniques were used for hormonal assays and monitoring. Information on past medical history and occupational exposures were collected using a questionnaire during the medical interview and clinical examination. No information was available for participants who did not volunteer for the medical check-up. Very limited conclusions can be derived from these studies due to non-inclusion of a comparison group. Exposure to TCE was observed to be below the TLV. The then threshold limit value (TLV) of 50 ppm for TCE was high compared to current ACGIH TLVs[®] for TCE, which has been 10 ppm⁵¹ since 2006.

Gericke et al. (2001)¹⁰ in a cross-sectional study compared male workers employed in 12 rotogravure printing factories (printers and helpers) who were exposed to toluene, with non-printers who worked in the same companies. Previously, it was estimated that printers and their helpers were at greater risk of toluene exposure than non-printers.⁵² Workers were randomly selected by an industrial professional body, then asked to participate. If they elected not to participate, then the next randomly selected person was asked. Exclusion criteria included interchanging of jobs with different types of exposures. Blood samples were

assessed for levels of serum FSH, LH and testosterone and compared to reference values. There was no significant difference in the number of workers with values outside reference ranges for serum FSH, LH and testosterone between printers and non-printers. The authors concluded that there was no evidence that long term occupational exposure to toluene in the study of workers in the rotogravure printing industry was associated with alteration in the levels of male sex hormones.

The target population in Gericke et al. (2001)¹⁰ was workers who participated in a previous study conducted between 1993 and 1995.⁵² The exposure had been measured for several jobs and the association between toluene exposure and job had been previously established.⁵² The male printers and helpers had been previously reported to have a mean blood toluene concentration of 373.4 µg/l compared to printing form preparers (mean 135.2 µg/l), printed material processors (mean 85.8 µg/l) and workers in other areas (mean 78.1 µg/l)⁵² indicating that printers and the helpers were the most highly toluene-exposed workers in the study. The comparison was therefore between printers and helpers versus non-printers in the same industry who had experienced some low toluene exposure. The exposure was measured in ambient workplace air using personal monitors. Blood toluene levels were measured from samples collected before and after work shifts. Participants were randomly selected and asked to participate and there was no information on workers who did not want to volunteer or who dropped out.

Svensson et al.¹⁷ (1992b) in a cross-sectional study compared male printers exposed to toluene with unexposed referents from the metal industry. Average exposure to toluene was calculated based on blood and workplace air measurements. The number of years in employment was used to calculate the cumulative exposure index in combination with blood and air toluene concentrations. The outcomes of interest were levels of blood FSH, LH, prolactin (PRL) and testosterone. There was no statistically significant difference in serum LH between exposed workers and referents. However, when stratified by age, workers less than 40 years age in the exposed group had significantly lower median blood LH levels ($p < 0.01$) compared to the referent group. . A similar pattern was observed in FSH levels; no significant difference was identified between the groups as a whole, but significantly lower ($p < 0.05$) FSH levels were seen in the exposed men less than 40 years age. However, no association was found for PRL or for testosterone levels and toluene exposure analysed with or without age stratification.

The target population was rotogravure printers. The method of selection of the study population was not clear. Breathing zone samples on workers were taken and area sample and spot samples covering various operational areas were obtained to assess the workplace

air concentrations of toluene. Pre and post shift venous blood was obtained from workers to assess blood toluene levels. The exposure and outcomes were measured using standard laboratory methods. No information was provided on non-responders. The analysis was adjusted for age.

Svensson et al.¹⁶ (1992a) compared hormone levels among 20 toluene-exposed rotogravure printers without signs of solvent-induced toxic encephalopathy to those in a reference population who were not exposed. A cumulative exposure index was calculated for each subject as the sum of exposure levels x exposure time (years) during employment. The outcomes of interest were serum levels of LH, FSH, PRL, SHBG and free testosterone. Serum levels of FSH, LH and free testosterone were significantly lower in the exposed group compared to the referent group. Serum levels of PRL and SHBG were not significantly different.

The method of sample selection was not clear nor was the appropriateness of the screening tool⁵³ to assess solvent induced chronic toxic encephalopathy, although the source was cited. Toluene was measured in blood, air and subcutaneous fat and historical exposure was determined through interviews. Blood and workplace air toluene concentrations were measured using standard methods. There was no information on non-responders reported. The study population was small. Svensson et al. (1992a,b)^{16, 17} concluded that the observed hormone level differences were likely to be a result of the exposure to toluene, and considered that the findings indicated an effect of toluene exposure on the hypothalamic-pituitary axis, with a secondary decrease in testosterone secretion.

Pregnancy outcomes in partners

Four studies (four publications^{5, 7, 11, 12}) reported pregnancy outcomes in partners of solvent-exposed men; three on spontaneous abortion^{7, 11, 12} and one on miscarriage.⁵ Three studies reported exposure to several solvents, but only some of the solvents were relevant to this review.^{5, 7, 12} One study compared solvent exposed painters with non-exposed carpenters,¹¹ while the exposure was assessed using a previously published model of toluene based on a similar occupational group in the same country. None of the studies reported significantly higher risk of spontaneous abortion in partners of exposed men when compared to unexposed men without subgroup analysis. However, one study reported a significant increase in risk of spontaneous abortion in the high/frequent exposure subgroup (i.e. daily exposure or biological measurements above reference values for the general population) only.⁷ Two studies reported birth defect outcomes.^{7, 11} One study found a significantly increased risk of congenital defects in the organic solvent-exposed group compared with unexposed group based on quantitative model predicted exposure estimates using toluene as a marker.¹¹ The other study⁷ did not find

any association of toluene or xylene exposure with birth defects. It is difficult to establish a clear association of exposure with outcome in these studies due to co-exposure of the men to other solvents.

D'Este et al. (2004)⁵ reported the pregnancy outcomes in female DSRS workers and female partners of exposed male personnel who participated in the DSRS program. Combined outcomes for exposed women (n=24) and the partners of exposed men (n=767) were presented in the analysis. Only pregnancies reported between 1975 and 1999 were included, limiting the outcomes to the period that DSRS activities were conducted. D'Este et al. (2004)⁵ found no evidence of an increased risk of miscarriage or stillbirth in the exposed group compared to the unexposed group for all exposed or for Programs 1 or 2 and there was no dose response effect.

The target population was workers who had participated in the DSRS programmes as stated in the SHOAMP report.⁵ However, some methodological and sampling limitations were identified. These included; uncertain sampling frames, self-identification of 'exposed' DSRS workers (exposure was classified *post hoc*, based on a self-reported questionnaire) and possible non-inclusion of eligible female partners of male DSRS workers if they did not receive the survey questionnaire (male workers were asked to pass on the survey to the woman who was their partner during DSRS activities – response rate 48%). The recruitment was conducted through advertisements and the participants were aware of the reasons for the government instigating the study, so there is likely participation bias. SHOAMP personnel were likely to have been exposed to several materials including jet fuels, desealants, sealants and a range of solvents. The combination of exposed female DSRS workers (n=24) with partners of exposed male DSRS workers in the analysis was likely to have combined females with different levels of exposure in analysis of pregnancy outcomes. The mix of exposures varied over time with the different DSRS programmes and participants were asked about exposures that could have occurred up to 30 years earlier. In view of the above factors, recall bias in respect of exposures could have occurred.

A cross-sectional study by Hooiveld et al. (2006)¹¹ compared a random sample of male commercial painters with carpenters and assessed the risk of spontaneous abortion in the wives and of birth defects in the offspring. Even though the exposure was determined purely on the job description (i.e. painters), the exposure was quantified based on a model developed previously in a similar population.⁵⁴ In this model, toluene was selected as a marker for solvent exposure as measured hydrocarbon exposures (i.e. toluene, xylene, ethyl-benzene, n-decane, and n-hexane) were reported as strongly correlated.⁵⁴ The painters were potentially exposed to paints, thinners, or cleaning agents.

There was no significantly increased risk of prolonged time to pregnancy (TTP), low fecundity, spontaneous abortion or preterm birth among the wives of painters compared to carpenters. However, the risk of reported birth defects (which were categorised as structural congenital malformations (e.g. cardiovascular, gastrointestinal, and oro-facial cleft malformations) and functional developmental disorders) in the offspring of painters was significantly higher compared to unexposed carpenters. This was mainly due to a higher risk of congenital malformations (n=37 birth defects, 398 pregnancies in exposed group; 11 birth defects, 302 pregnancies in unexposed group. OR 6.2; 95% CI 1.4-27.9 after adjusting for potential confounders). Congenital malformations reported by painters were: cardiovascular (n=4), gastrointestinal (n=2), central nervous system, eye, urogenital malformations, orofacial clefts, Down's syndrome (all n=1), and other syndromes (n=3). The authors concluded that painters with potentially high occupational exposure to organic solvents in the pre-conceptional period showed an increased risk of congenital malformations in offspring compared to carpenters with no or negligible exposure.

In this study, job category was used as a surrogate for quantitative solvent exposure assessment supported by evidence from a previous study⁵⁴ in commercial painters in the same geographical region. However, this matrix included several toxic solvents, such as n-hexane, that are not considered as a specified solvent in this current review. Exposed painters were categorised, using tertiles of the estimated exposures in order to determine dose-response associations. However, this approach may not necessarily account for individual variations in exposure as painting jobs and methods differ (e.g. using solvent-based or water-based paints, working indoors or outdoors). A random sample from a trade membership register was used to select the participants and the information was collected through a self-reported mailed questionnaire. No biologic tests or clinical examinations were conducted to assess exposure. The response rate was slightly lower for the exposed group (41% vs 46%). Limited information was available for workers who actively refused to participate by returning the questionnaire such as the reason for non-participation, and they were found to be slightly older and similarly likely (98%) to be employed compared with participants. Information on non-responders was not available. There also could have been recall bias in assessing TTP. This study was informative about the population in that geographical area, but it is difficult to generalise the study findings due to uncertainty of solvents the workers were exposed to.

Lindbohm et al. (1991)¹² conducted a registry based analysis of spontaneous abortion in the wives of male workers who may have been exposed to mutagenic agents. Information about women with clinically recognised spontaneous abortion was retrieved from hospital records and a nationwide hospital discharge registry. This information was matched with the husbands' job category reported in census data. An industrial hygienist used the job category

to likely identify chemical exposures in that industry. The list of agents in the classification included 25 exposures that were suspected mutagens, based mainly on data from the International Agency for Research on Cancer.¹² A number of potential exposures were determined including TCE. However, paternal exposure to TCE was not associated with an increased rate of spontaneous abortion in the wives of male workers.

This study used registry data and hospital records data to assess outcomes and this is likely to have increased its accuracy over self-reported data. Misclassification of outcomes (recording spontaneous abortion as induced abortion and vice versa) was likely to be small as abortion in the country of the study was not illegal, spontaneous abortion was medically diagnosed, and data were obtained from hospital records,. Exposure was determined based on job categories reported in the census and may not have been specific enough to accurately assess exposure. Therefore, misclassification of exposure status may be an important and likely source of bias in this study. If non-differential misclassification of exposure occurred it would likely bias the result toward the null. The generalisability of this study is limited because of uncertainty in exposure assessment.

Taskinen et al. (1989)⁷ used a case referent design to evaluate the risk of spontaneous abortion and congenital malformations in offspring in the wives of men exposed to a variety of solvents. The source of the study population was a cohort of male workers monitored for organic solvent exposure by the Finnish Institute of Occupational Health during 1965-1983. The wives of solvent exposed men who had a spontaneous abortion or an offspring with a congenital malformation were selected as cases and matched for age at conception with women who did not have a spontaneous abortion or offspring with congenital malformations (referents). Cases were defined as wives of solvent exposed men who had a registered spontaneous abortion or baby with a congenital malformation and matched for age at conception with women who did not have a spontaneous abortion or offspring with congenital malformations during the study period (1973-1983) (referents). Exposure assessment in the cohort study had included urine and blood measurements of solvent metabolites on some male workers. Occupational exposure related to the study pregnancy was assessed through a mailed questionnaire that included questions on employment, occupation, and workplace during the year of conception, and participants were asked to describe their work tasks and whether they had handled any of the monitored solvents or other solvents, e.g. white spirit, petroleum benzene, thinner, acetone. The exposure was quantified into three categories (i.e. high/frequent, intermediate and low/rare) based on paternal occupation, job description, reported solvent or other chemical usage, and biological monitoring data where available. The study found that paternal exposure to toluene was associated with increased risk of spontaneous abortion in the high/frequent exposure group but not in the lower exposure

subgroups, adjusting for potential confounding factors, and that paternal exposure to xylene or TCE was not associated with risk of spontaneous abortion.

The exposure assessment was mainly based on job description collected in a postal self-reported questionnaire from the men, so the study was prone to information bias which is a common limitation of case-referent studies. The information on pregnancy outcomes was obtained from registries and confirmation was requested from the female participant in the questionnaire, limiting potential response bias. The response rate was 74.7% but no information on non-responders was reported. The study investigated several solvent exposures (e.g. styrene, TCE, xylene, tetrachloroethylene, toluene and 1,1,1 trichloroethane), and some are not relevant to this review. Therefore the results should be generalised with caution.

Fertility / fecundity

Fertility and fecundity both refer to the natural capability to produce offspring. In a research context, fertility refers to the ability to deliver a live-born infant, and fecundity to the biological capacity for conception and this may encompass hormonal profiles, gynaecological health, sexual function, TTP, conception delays, pregnancy loss and (premature) reproductive senescence or menopause.¹⁹ Ten publications reported outcomes related to fertility and/or fecundity; six conducted semen analysis in exposed men,^{2, 8, 9, 13, 15, 18} two reported fecundity ratios,^{6, 14} one investigated TTP¹¹ and the other⁵ reported number of pregnancies, difficulty in getting pregnant and visits to a specialist regarding fertility issues in partners of exposed men. The exposures varied across studies, and only three studies reported outcomes specific to a single solvent exposure; two related to TCE^{2, 15} and one to toluene.¹⁴ In the other studies, several solvent exposures were reported including combinations of some solvents relevant to this review and other solvents not included in this review (e.g. styrene, tetrachloroethylene or 1,1,1-trichloroethane).

The most commonly reported semen parameters were sperm motility, count, volume, morphology and density. Motility was reported in five publications; three reported a significant decrease^{8, 9, 18} and the other two^{2, 13} reported no association. Benzene, toluene and xylene exposures were reported in all three studies that reported reduction in sperm motility.^{8, 9, 18} The exposures reported in men in two other studies that reported no association with motility were TCE³⁶ or 2-MPA.^{2, 13} Sperm count was an outcome in four studies; one reported a significant reduction in the exposed,⁹ while the others reported no association.^{8, 13, 18} The three studies that reported semen volume and density did not identify any associations.^{2, 13, 18} The exposures of interest in participants were to either TCE² or 2-MPA¹³ in two studies and to benzene, toluene and xylene in the other.¹⁸ The percentage of normal sperm was reported in three

studies, and two reported no association^{8, 13} while the third reported an association of TCE exposure with a reduction in percentage of normal sperm compared to laboratory reference values.²

Chia et al. (1996)² investigated a male population of workers who used TCE for degreasing in an electronics factory. The workers were offered a free medical examination. Only the workers who had no prior history associated with risk of infertility (e.g. diabetes mellitus, long term medication use, testicular injury or urinary tract infections) were selected to participate in the study. Urine was assessed for TCA as an indicator of TCE exposure. The comparison was with WHO reference values and then between the high and low exposure groups based on urinary TCA. Additionally, 8-hour personal air samples of 12 workers were obtained. Workers with urinary TCA of ≥ 25 mg/g creatinine were considered "high exposure" while workers with TCA of < 25 mg/g creatinine were considered "low exposure". Blood and semen samples were obtained for analysis.

The workers were generally exposed below the then TLV⁵⁵ of 50 ppm for TCE. However this value has been changed to 10ppm since 2006. All the sperm parameters were within the WHO reference ranges⁵⁶ when all participants were analysed together. The high exposure group had significantly lower sperm density compared to the low exposure group, but both groups were still above the WHO reference range.² The authors concluded that occupational exposure to TCE at an air concentration of less than 29.6 ppm and mean urine TCA concentration of less than 22.4 mg/g creatinine is unlikely to affect sperm volume, density and motility.

This study used volunteer male degreasing workers in an electronics factory during a free medical examination. Relevant information regarding age and employment was provided. Standard laboratory tests and techniques were used for hormonal assays. Information on past medical history and occupational exposures were collected using a questionnaire during medical interview and clinical examination. No information was available for participants who did not volunteer for the medical check-up, including response rate. Limited description of the analyses used was provided including the possible confounding factors that different analyses may have been adjusted for. A further limitation of the study was that it did not include a non-exposed comparison group.

A cross-sectional study by De Celis et al. (2000)⁹ compared workers in the production area of a rubber factory who were exposed to a mixture of hydrocarbons (i.e. ethylbenzene, benzene, toluene and xylene (BTEX)) to non-exposed administrative staff in the same company. Environmental air monitoring was used to determine concentration of these chemicals. Semen characteristics of each participant were analysed from three semen samples collected weekly.

Blood and urine were not assessed for the presence of the solvents or their metabolites. The study found significant differences in abnormalities in semen viscosity, percentage of aggregated sperm, liquefaction, sperm count, motility, and percentage of abnormal spermatozoa detected in exposed compared with unexposed workers. There were no significant differences in the volume of semen and the mean percentage of live sperm between the groups. No association was found between smoking or alcohol intake and alteration in the semen profile. The study authors concluded that exposure to the above mixture of hydrocarbons could damage the spermatogenic process, however it was not possible on the basis of the study to assess the overall status of their fertility.

The target population was defined but the method of selecting the sample of workers was not described, and a comparison of participants and non-responders was not reported. Environmental exposure measurements were determined by continuous monitoring of factory areas during the work day. The exposure and the semen were analysed to established criteria^{56, 57} but the presence of solvents in blood or their metabolites in urine were not measured. The information on the medical and reproductive history were collected by a questionnaire. Adjustment for possible confounding factors in the analysis was not reported.

Lemasters et al. (1999)⁸ investigated semen characteristics of civilian or active duty United States Air Force (USAF) personnel who were involved in aircraft maintenance work. During the study period the USAF was using JP-4 fuel, a fuel type with a high content of benzene. Following the study conclusion, JP-4 was replaced by JP-8, with a lower benzene content. The study enrolled 50 men who worked on different tasks (jet fuel, flight line, sheet metal and paint shop workers) and who were potentially exposed to different levels of jet fuel or other chemicals (i.e. 1,1,1-trichloroethane, toluene, MEK, xylene, and methylene chloride). An additional eight people who performed clerical activities served as an unexposed comparison group. Industrial hygiene sampling and expired breath sampling were conducted to identify exposure to various chemical agents, including naphthas, at 15 and 30 weeks. Semen analysis was performed at the start, 15 and 30 weeks of the study.

The mean values for sperm concentration, sperm morphology, sperm morphometry and percentage of DNA denatured cells (measured through sperm chromatin structure assay (SCSA)) for the unexposed group and the combined exposed group (all four exposed groups combined) remained within the WHO reference ranges throughout the 30 weeks. The percentage of motile sperm was lower than the reference values⁵⁸ in the combined exposed group and compared with the unexposed group during the study period. The percentage of motile sperm depends on time post-ejaculation and sample analysis. The average transport time (samples were produced at home) was 52.4 (SD 21.4) minutes (which was slightly longer

than 45 minutes target transport time stated in the paper's methods) over all three sampling periods and was similar in the exposed and unexposed groups. Some changes were observed when jobs were analysed by exposure groups; the paint shop group had a significant proportional (percent) decline in sperm motility of 19.5% at 30 weeks compared with baseline. However, a limitation was the small number of overall (n=50) exposed workers and in the subgroups, e.g. n=8 paint shop workers and n=8 unexposed workers in the comparison group.

This study included a defined study group, although the sampling strategy was not reported. Participants and non-participants were similar in age, race and religion, but the participants were more likely to have attended college (52% versus 20%). Semen profiles were assessed using standard laboratory methods. The participants were volunteers and they were divided into groups based on the type of work they performed. These subgroups were used as surrogate indicators for jet fuel and solvent exposure based on the type of job activity and probability of exposure (unexposed performed office filing, typing and clerical and were assumed to have none to minimal exposure). The exposure to jet fuels, total solvents (i.e. MEK, methylene chloride, xylenes, toluene, and 1,1,1- trichloroethane) and benzene was measured using industrial hygiene air samples and in breath measurements.

Industrial hygiene measurements for each solvent was conducted, but not reported. Nearly all of the exposed participants had values less than 10ppm for specific solvent exposure in industrial hygiene measurements. The ACGIH recommended TLVs at the time of the study were; MEK 200ppm, methylene chloride 50ppm, xylene 100ppm, toluene 50ppm (currently 20ppm), 1,1,1- trichloroethane 350ppm. A 'total solvent' value was derived by summing the concentrations of the above solvents because the workers were likely to be exposed to more than one solvent. The mean industrial hygiene level for total solvents was 1.6 (SD 6.9) ppm for the all exposed workers. These low exposures, that were well below the then ACGIH recommended TLV⁸ suggest that the findings are likely to be relevant to work environments with similar low exposure levels. However, the internal dose exposure, assessed using exhaled breath, was measured only once and may not accurately reflect the absorbed dose if exposure varies over time. Dermal exposure may also be important to consider. Therefore a number of assessments over time would be needed to fully characterise the internal dose.

Multigner et al. (2007)¹³ compared permanent workers employed in the Paris municipality who were exposed to glycol-ether containing products to workers who were not exposed during the previous 10 years. Two urine samples, one month apart were collected at the end of two working weeks to assess metabolites of PGME (2-MPA) and five ethylene glycol ether derivatives. Exposure was quantified using a continuous exposure index based on the category of products used, frequency and duration of use, and the mean percentage of glycol

ethers present in that category. Blood was collected for reproductive hormone assessment and semen characteristics were recorded. Urinary 2-MPA levels were not associated with semen characteristics or with serum levels of testosterone, FSH, LH and inhibin-B.

The study consisted of a clearly defined population and the volunteer participants were selected after information sessions. A physical examination was undertaken by an andrologist, unaware of the participant's exposure status, to assess any external abnormalities relevant to fertility based on WHO criteria.⁵⁹ The exposure assessment relevant to use of products likely to contain PGME or glycol ethers was determined by interview questionnaire and limited to the last 10 years as recall for longer periods became poor. Some participants reported non occupational exposure. It was considered that the effect of any exposure misclassification on estimates would tend towards the null. Urine samples were collected and analysed for metabolites, and semen samples were analysed according to standard WHO criteria.⁶⁰ Although associations were reported for 2-MPA and semen quality, the participants were also potentially exposed to glycol ethers.

A cross-sectional study by Plenge-Böning & Karmaus (1999)¹⁴ compared toluene exposed workers in the printing industry with unexposed workers and assessed fecundity using a fecundity ratio estimated from time of unprotected intercourse (TUI) that was determined from TTP and periods of unprotected intercourse not leading to pregnancy (PUNP). Participants were allocated to exposure categories based on the work history; high, medium, low and unexposed. No biological samples were collected. Information on periods of unprotected intercourse, pregnancy outcomes, chronic metabolic diseases, pelvic inflammatory disease or reproductive surgery, lifestyle factors and working history were collected through an interview questionnaire. After adjustment for age and smoking of the partner, there was no association found between exposure of men to toluene and the duration of TUIs (and Fecundity Ratio) including when exposure subgroups were considered. The authors concluded that male workers who had been exposed to different concentrations of toluene did not show a reduction in fecundity with their partners.

This study¹⁴ had recruited a representative cross-section of 300 male workers selected by stratified random sampling according to the proportion of employees in individual companies. A modified version of the European Study on Infertility and Subfecundity questionnaire⁶¹ was used. Quantification of exposure was based on job description and not on measurements of actual exposure (i.e. air or biological samples). Recall bias cannot be ruled out due to retrospective data collection (i.e. the time elapsed between interviews and the periods of unprotected intercourse was not clear). The female partners of exposed male workers were not interviewed and information on TTP and PUNP were collected from male workers.

Rasmussen et al. (1988)¹⁵ investigated sperm count and morphology and the presence of two fluorescent bodies in Y chromosomes in spermatozoa, that may suggest Y chromosomal non-disjunction during spermiogenesis, in metal degreasing workers exposed to high TCE levels. Only those who were degreasing with TCE for ≥ 20 hours per week were included and were compared with 14 non-exposed physicians working at a university institution. The study found no significant association between TCE exposure and sperm count and morphology and no significant increase in fluorescent bodies in mature spermatozoa in the exposed group. The authors concluded that no effect on male germ cells (the cells that give rise to sperm) was demonstrated.

The sample included all identifiable metal degreaser workers who consented to participate from a well-defined geographical area. Of those identified, 99 (85%) participated in a clinical examination programme and 15 met inclusion criteria (degreasing with TCE for ≥ 20 hours per week). Exposure was assessed through an occupational medical interview and not by biological assessment. Twelve workers provided semen samples for analysis using WHO methods.⁶² No analysis results were reported after adjusting for possible confounding factors, but the study stated in the text that no association was found in bivariate analysis after adjusting for x-ray examination, febrilia (not defined but may mean fever or fever of unknown origin), viral disease during the prior three months and alcohol consumption. The reference material for this genotoxic study was acknowledged as not ideal (consisting of a concurrently sampled population study and parents of offspring with stable chromosome alterations) and for which no data on confounding factors was available to the researchers. Due to the small sample size and above limitations, this study provides only very weak evidence, which should be interpreted with caution.

Sallmén et al. (1998)⁶ investigated fecundability in the wives of male workers exposed to organic solvents including TCE, tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, toluene, aromatic, aliphatic and halogenated hydrocarbons. Three exposure levels were used, based on frequency of use of these chemicals and low and intermediate exposure groups were grouped together in the outcome analysis. The study found no significant association between paternal exposure to TCE, toluene or xylene and fecundity, irrespective of exposure level after adjusting for possible confounding factors. An association between high/frequent exposure to organic solvents and lower fecundity in primigravida was observed, but not among couples with at least one previous pregnancy. The authors concluded further studies with careful design are warranted, that the findings from the study provided very limited support for paternal organic solvents exposure being associated with lower fecundity.

The exposure was assessed using information from a previous study⁷ that investigated incidence of spontaneous abortion in the wives of solvent exposed men, and which is included in this REA. New information for the current study⁶ was collected through a questionnaire. However, in 31% of included men, exposure was assessed only through the questionnaire because biological measurements were not available and this could have introduced information bias in that group. Several individual exposures were assessed in association with outcomes and co-exposures may have occurred in the association between a specified solvent and outcome. Possible sources of bias were discussed by the authors. The study may have been susceptible to response bias because participation of the wives of unexposed men (response rate 69/86 = 80%) was greater compared to the wives of exposed men (247/352 = 70%). Recall bias is a concern because data on TTP were collected eight to 18 years after the pregnancies. The direction of potential response and recall bias could not be assessed.

A cross-sectional study by Xiao et al. (2001)¹⁸ compared workers who were exposed to high airborne concentrations of benzene, toluene and xylene in shoemaking, spray painting or paint manufacturing industries to non-exposed managers matched for age, occupation and physical activity. Blood and semen samples were collected from workers who consented and were analysed to identify the presence and concentrations of benzene, toluene and xylene. Mean concentrations of airborne benzene, toluene and xylene in work environments and presence or absence of these chemicals in blood and semen were reported. The outcomes investigated were sperm and semen characteristics including acrosin activity (acrosin is a protease that plays an important role in the fertilisation process),⁶³ lactate dehydrogenase C4 (LDH-C4) the isozyme of LDH produced by germ cells (the cells that give rise to spermatocytes), seminal fructose which provides energy for the action of sperm, and γ -Glutamyltransferase (γ -GT) the activity of which reflects function of the prostate gland. Benzene or xylene was present in the semen of nearly half of the exposed group and toluene was detected in 25% of the exposed group. However, it was not clear whether any of the workers had multiple chemicals in their blood or semen. There was no significant difference in mean values of volume of semen, pH value, liquefaction time, vitality, sperm density, total sperm count and semen fructose between exposed and unexposed groups. However, sperm activity, acrosin activity, γ -GT and LDH-C4 were significantly lower in the exposed group. The authors concluded that the findings suggested that this solvent mixture could affect the quality of semen and sperm by influencing the function of the testicle and/or the accessory sex glands.

The extent of the target population was not very clear. The workers were selected from several industries and could have been exposed to one or more of the solvents of interest (or other solvents used in the industry) and this was not clearly stated in the study. No information was available on the sampling method. The semen and blood analyses were conducted based on

standard methods and subjects were interviewed about their occupational, past medical and reproductive histories. The unexposed group consisted of managers and they did not differ significantly on demographic, tobacco and alcohol use characteristics. Sample size was small (n=56 exposed and n=40 controls) and only data from 43% and 66% of exposed participants were available for semen and blood analysis respectively. Information on non-responders was not available. No information was reported on whether statistical adjustment for confounding factors was made in analyses. Some correlations between semen characteristics and variables such as working duration, drinking volume, and benzene, xylene or toluene levels in blood were reported but not all, so it was not possible to assess whether others were analysed or not. Limitations of this study included small sample size, lack of information on specific solvent exposure and the possible presence of other confounding factors, such as exposure to other solvents not investigated in this study.

A cross-sectional study by Hooiveld et al. (2006)¹¹ compared reported TTP in a random sample of male commercial painters with that of carpenters. This study was described in detail earlier under pregnancy outcomes. The study found that there was no increased risk of prolonged TTP in partners of painters compared to carpenters. Exposure was determined purely on the job description (i.e. painters), with job category used as a surrogate for quantitative solvent exposure assessment based on a model developed previously in a similar population.⁵⁴ No biologic tests or clinical examinations were performed to ascertain exposure.

The SHOAMP reported by D'Este et al. (2004)⁵ investigated pregnancy outcomes during the period of the DSRS program and for a pregnancy whether or not they had visited a specialist for any fertility problems. This study has been described in detail under pregnancy outcomes. There was no significant difference between reported problems in getting pregnant in the exposed group (n=72, 30%) compared to the unexposed control groups (n=34, 21%, Amberley and n=69, 27%, Richmond) (p=0.18). Of the exposed group, 14% (n=35) reported seeing a specialist compared to similar proportions in the control groups (n=18, 11%, Amberley and n=45, 18%, Richmond) (p=0.21). Further analysis was not possible in relation to problems getting pregnant and visits to a specialist for fertility problems, as key confounders such as maternal age at the time were not collected.

Reports

A total of 16 reports were identified from the pre-determined website search. The findings are reported in the Evidence Profile. Only findings of reproductive outcomes related to occupational solvent exposure in men were extracted (if reported) as the conclusions of these reports were likely to have been based on *in vitro* and animal studies as well as human studies. Some of the studies cited in the reports investigated the effect of unspecified solvents (e.g. reproductive health effects have been investigated in relation to organic solvent exposure in general). This REA is confined to the list of specified solvents itemised under the Methods section, therefore reports only on unspecified solvents were outside the scope of the REA and uninformative about the solvents of interest. Each of the relevant reports is described below with a summary of any conclusions in relation to male reproductive effects and exposure to solvents of relevance to this REA. More details can be found in [Appendix 4](#).

An Agency for Toxic Substances and Disease Registry (ASTDR) toxicological profile characterises the toxicological and adverse health effect findings by extensively reviewing the key peer reviewed published literature of substances. Eight records^{32, 35-38, 45-47} of ATSDR profiles (herein referred to as Reports) and two records of addendums^{33, 34} were identified. Addendums were updates to the profiles from scientific data collated from published journal articles since the release of the original profile. However, neither addenda^{33, 34} provided new evidence on reproductive health outcomes but are cited here for completeness.

The National Research Council (NRC), the operating agency of the National Academy of Sciences and the National Academy of Engineering, provides independent guidance on scientific issues to support an objective and scientifically balanced health risk assessment to the US government, the public and scientific communities. Two reviews^{43, 44} (herein referred to as Reports) produced by the Committee on Human Health Risks of the NRC were identified.

The Health Council of the Netherlands, is an independent scientific advisory body and advises the Dutch government and Parliament on the current level of knowledge with respect to public health issues. Three reports³⁹⁻⁴¹ prepared by the Committee for Compounds Toxic to Reproduction by the Health Council of the Netherlands were identified.

Of the above reports, four reports^{35, 41, 43, 47} included a review of TCE. The Health Council of the Netherlands (2003) report⁴¹ identified five publications^{1-3, 7, 15} on three studies. These five publications are included in the current REA review. The report concluded that the results of the human studies on the potential effects of occupational exposure to TCE on fertility did not show significant effects or the results of the studies were inconsistent and difficult to interpret. Therefore, the committee decided not to classify trichloroethylene with respect to effects on

fertility because of a lack of appropriate data. Both the US Environmental Protection Agency (2011)³⁵ and the ATSDR (2014)⁴⁷ produced reports that included eight publications on TCE exposure in men and reproductive outcomes. Five publications were included in this REA^{1-3, 6, 15} while the other three were excluded because they reported unspecified solvent exposure⁶⁴ or were not key papers e.g. were published prior to 2000 that had not been consistently cited in other research and were outside the scope of the current REA review.^{65, 66} The NRC report (2007)⁴³ identified seven publications, and five^{1-3, 7, 15} are included in this REA. The other two were excluded from this REA because they were published prior to 2000 and were outside the scope of the current REA review.^{64, 65} The NRC report recommended more research to better understand the effects of TCE on sperm and consequences for reproduction.

Three reports^{40, 44, 46} included a review of toluene. The Health Council of the Netherlands (2000)⁴⁰ identified five publications^{7, 8, 14, 16, 17} that investigated occupational exposure in men and reproductive health effects. The ATSDR report (2017)⁴⁶ identified six publications^{7, 10, 12, 14, 16, 17} and the NRC report (2014)⁴⁴ identified three publications^{10, 16} including one experimental study.⁶⁷ All except the experimental study are included in this REA. All three reports acknowledged the scarcity of evidence and concluded that the available evidence did not provide convincing evidence for any association between occupational toluene exposure in men and any adverse reproductive health outcomes.

Xylene was investigated in two reports.^{36, 39} The Health Council of the Netherlands (2000)³⁹ identified three relevant publications⁷⁻⁹ and concluded that occupational exposure to a mixture of organic solvents including xylene has been shown to be associated with an increased risk of spontaneous abortion among the wives of exposed men and with abnormal sperm. The ATSDR report (2007)³⁶ identified one publication⁷ and concluded that definitive conclusions could not be drawn, due to the small number of subjects and concurrent exposure to other solvents. All three publications in the reports are included in this REA.

One ATSDR report on Stoddard Solvent (1995)³⁸ identified two publications^{68, 69} on inhalation exposure and reproductive hormones⁶⁸ or semen characteristics.⁶⁹ One publication reported a significant reduction in serum FSH levels after the commencement of exposure compared to pre-exposure levels. The other publication reported no change in sperm count, motility or morphology after three months of exposure. These two studies were published before 2000 and were not included in this REA.

The Institute of Medicine (IOM) (2003) reported on exposures to insecticides and solvents.⁴² Fourteen publications that investigated occupational exposure of men to organic solvents were identified: eight reported on semen characteristics,^{1, 3, 8, 15, 16, 70-72} three on infertility,^{6, 14, 73} two on spontaneous abortion^{7, 12} and one study on congenital malformations.⁷⁴ Five^{1, 3, 8, 15, 16} of

the eight publications that reported on sperm characteristics were identified and discussed in this REA. The exposure was determined based on job categories in one publication⁷² and two publications reported unspecified solvent exposure^{70, 71} and therefore did not meet inclusion criteria for this REA. The report observed that even though a number of studies had examined the potential effects of occupational exposure to solvents on semen characteristics, few studies had investigated persistent effects after cessation of exposure and concluded that there is insufficient evidence to determine whether an association exists following exposure to specific solvents or solvent mixtures and infertility after cessation of exposure. Two of the three publications identified in the IOM report on infertility are included in this REA,^{6, 14} and the third⁷³ was excluded because of unspecified solvent exposure. These two publications did not find any association between fertility and male solvent exposure.

Both publications identified in the IOM report relating to risk of spontaneous abortion were included in this REA.^{7, 12} The report concluded that there is inadequate or insufficient evidence to determine whether an association exists between paternal preconception exposure to specific organic solvents under review or solvent mixtures and spontaneous abortion or other adverse pregnancy outcomes. The IOM report identified one study on congenital malformations that was not included in this REA because of the unspecified solvent exposure.⁷⁴

In conclusion, the coverage of this REA is comprehensive. We did not identify any key relevant publications by scrutinising the reports that met inclusion criteria and were missing from this review.

Discussion

The aim of this literature review was to identify research evidence on adverse reproductive health outcomes in human males from occupational exposure to specified solvents of most relevance to use in the Australian military. Non-military male occupational groups who were exposed to the specified solvents were included because of the scarcity of research in military populations, evident from previous reviews.^{25, 26}

This REA identified 14 primary observational studies (18 publications) that reported adverse male reproductive health outcomes including those relevant to reproductive success of low fertility/fecundity, time-to-pregnancy, and adverse pregnancy outcomes in female partners; altered reproductive hormone levels; and adverse sexual functioning outcomes. The most evidence was identified for fertility and/or fecundity outcomes (10 studies, 10 publications^{2, 5, 6, 8, 9, 11, 13-15, 18}) and the least evidence was identified for male sexual functioning (one study, one publication⁴). There was some evidence identified for reproductive hormone levels (three studies, five publications^{1, 3, 10, 16, 17}) and pregnancy outcomes (four studies, four publications^{5, 7, 11, 12}). The evidence base for each of these outcomes is discussed below.

Summary of evidence base for male reproductive outcomes of interest

Fertility / fecundity

The evidence presented in this REA suggests that the spermatogenic process and semen characteristics may be affected when exposed to high concentration of a mixture of solvents, but there was some inconsistency in findings between studies. Sometimes these mixtures may have contained solvents that are suspected reproductive toxicants, but were not relevant to this REA, such as benzene.⁷⁵ Therefore, it is difficult to ascertain specific exposure-outcome associations for the solvents of relevance to this REA.

The limited number of studies that reported exposure to a specified solvent e.g. TCE did not identify any significant adverse male reproductive effects.^{2, 6} One of these studies,² reported reduced sperm density in the high TCE exposure group, but the comparison was within the exposed group and still within WHO reference range, and the study did not include an unexposed comparison group. Reduced sperm motility was associated with relatively high solvent exposure, based on modelled toluene exposure, in subgroup analysis but not overall analysis.² No significant association was found between paternal exposure to specified exposures of TCE, toluene or xylene and fecundity, irrespective of exposure level, however an association between high/frequent exposure to organic solvents and decreased fecundity in primigravida was observed, but not among couples with at least one previous pregnancy.⁶

The authors concluded further studies with careful design are warranted. In another study, exposure to a mixture of hydrocarbons, i.e. BTEX was associated with some abnormalities in sperm parameters but not with other parameters.⁹ A cross-sectional study¹⁸ found that workers who were exposed to high airborne concentrations of benzene, toluene and xylene had no significant difference in mean values of several parameters of sperm and semen (mean volume of semen, pH, liquefaction time, sperm density and total sperm count) but other parameters such as sperm activity, acrosin activity, γ -GT and LDH-C4 were significantly lower in the exposed group compared with the unexposed group. In another study, there was no significant association found between TCE exposure and sperm count and morphology and no effect on male germ cells (the cells that give rise to sperm) was concluded.¹⁵ Urinary 2-MPA levels were not associated with abnormal semen characteristics.¹³

Very limited evidence was available on TTP and fecundity. A cross-sectional study found that there was no increased risk of prolonged TTP in partners of painters compared to carpenters,¹¹ where exposure to toluene was quantified based on a model developed previously in a similar population, and toluene was not associated with TTP and low fecundity in another study.¹⁴ The SHOAMP⁵ found there was no significant difference in reported problems getting pregnant or in seeing a specialist for fertility problems in the DSRS exposed group compared to the unexposed comparison groups

Endocrine profile

The adverse reproductive health outcome of altered reproductive hormone levels is considered here. The evidence presented in this REA suggests that only high TCE exposure may be associated with lower levels of serum FSH, LH, testosterone and SHBG but was not associated with differences in adrenal steroid hormone levels.³ However, the evidence was weak and came from a study in which duration of exposure was the basis of analysis in exposed workers and which did not include an unexposed comparison group.^{1,3} The association of exposure to toluene with reproductive hormone outcome levels was equivocal. Two of the three included publications reported no significant association of toluene exposure with FSH, LH and testosterone levels compared to the comparison group,^{10, 17} but significantly lower levels in serum FSH, LH and testosterone were observed in toluene exposed workers less than 40 years old.¹⁷ It is possible that younger workers may have been more heavily or more intensely exposed to toluene than the older workers, but the explanation was not conclusive. The third publication¹⁶ reported significantly lower levels of FSH, LH and free testosterone in the exposed group but the number of exposed workers was small in this study (n=20).

Pregnancy outcomes in partners

The evidence identified in this REA on specified male solvent exposure and pregnancy outcome is limited (four publications from four studies). The findings of these studies suggest that toluene, TCE or xylene exposure was not associated with spontaneous abortion in the partners of exposed men^{5, 11, 12} except for an association in men who were high/frequently exposed to toluene but not in lower exposure subgroups of toluene.⁷ It was not clear whether this increased risk of spontaneous abortion was due to take-home exposure or to another biological effect. There was very limited evidence available on reported miscarriage, stillbirth or preterm birth, but studies did not indicate an association of DSRS solvent exposures with reported miscarriage or stillbirths⁵ or toluene exposure was associated with preterm birth.¹¹ There is limited evidence to suggest that the offspring of painters have a higher risk of having congenital malformations, based on a modelled exposure with toluene selected as a marker for solvent exposure,¹¹ but the painters were potentially exposed to several organic solvents that may include several toxic solvents that are outside the scope of this review.

Male sexual function

The evidence base is very limited and came from a retrospective cohort study conducted in Australia from participants in the DSRS programme who used a large number of chemical agents. The study found that men exposed to solvents in the DSRS group were more likely to report sexual dysfunction (i.e. erectile dysfunction, loss of interest in sex and self-reported sexual functioning) compared to men in the unexposed comparison groups. It was difficult to attribute these adverse effects to a single specified solvent of relevance to this REA, as the participants were potentially exposed to a number of chemical agents including some which are no longer used by the military.

Summary of evidence base for male reproductive outcomes by specified solvents

Toluene

Toluene was the most studied solvent either as the sole exposure or in combination with other solvents. To understand the toluene associated reproductive effects, the findings of studies that reported toluene as the sole exposure are likely to be the most useful.^{10, 14, 16, 17} All the toluene-only exposure studies were conducted in the printing industry. The largest two studies^{10, 14} with high specified toluene exposure did not suggest that toluene significantly affects sex hormone levels¹⁰ or fecundity¹⁴ in men. The median air exposure was 91 mg/m³ (the current ACGIH TLV[®] for toluene is 20 ppm⁵¹ (approx. 75 mg/m³)) and median blood

concentration was 39 µg/litre blood (the current ACGIH BEI[®] for toluene in blood is 0.02 mg/l⁵¹ (approx. 20.0 µg/l)) in the exposed workers which indicated high exposure in one publication,¹⁰ and in the second, the exposure assessment was measured based on tasks.¹⁴ Evidence to the contrary came from two smaller studies (n=20¹⁶ and n=47¹⁷ exposed), which reported significantly lower blood levels of FSH, LH and free testosterone in the exposed group¹⁶ and significant differences in serum sex hormones limited to exposed workers less than 40 years age.¹⁷ The association between exposure to toluene and reproductive hormone levels was equivocal. Two of these studies were published in the early 1990s and two in the early 2000s. Exposures and practices may have changed over that period and to the present day. Methods of measuring steroid hormone levels have also improved during this time.

The evidence on toluene-specific exposure and spontaneous abortion in partners of exposed men is limited and came from a subgroup analysis of 48 persons from a case referent study that reported exposure to several solvents including TCE, styrene, xylene, tetrachloroethylene, and 1,1,1 trichloroethane.⁷ Significantly increased risk of spontaneous abortion was found in wives of men in the high/frequent exposure group and not in wives of men low or intermediate exposure groups. The exposure was quantified based on the frequency of solvent usage and on limited biological information where available. Based on this limited evidence, it is difficult to determine whether the partners of exposed men have an elevated risk of spontaneous abortion.

Several publications reported reproductive health effects when toluene exposure occurred with other solvent exposure. Adverse associations with semen parameters were found in workers who were exposed to toluene, xylene, benzene and ethylbenzene.⁹ Significantly lower levels of sperm vitality and activity were found when toluene exposure coincided with benzene and xylene.¹⁸ Environmental air concentrations or blood solvent levels suggested high exposure in the workers of above studies. However, the effects were unclear when occupational exposure was low and well below the TLV[®] (50 ppm for toluene).⁸ Sperm motility was low in the exposed and unexposed workers, otherwise semen parameters remained within the reference ranges in the exposed workers.⁸ Toluene was one solvent amongst many solvents used in the DSRS programme. An association with adverse sexual function was reported in DSRS exposed men⁴ but no significantly increased risk of spontaneous abortion⁵ in the partners was identified. It is difficult to determine a specific association between toluene exposure and adverse reproductive health outcomes when co-exposure to several other solvents occurred. There was no increased risk of prolonged TTP, low fecundity, spontaneous abortion or preterm births in partners of painters compared to carpenters, utilising a model in which toluene was selected as a marker for solvent exposure.¹¹ Birth defects (comprising congenital malformations functional development disorders) in offspring of painters were

significantly higher compared to unexposed carpenters, mainly due to a higher risk of congenital malformations.¹¹ Paternal exposure to toluene was not associated with risk of congenital malformations.⁷

Xylene

Xylene featured in five studies (seven publications^{4-9, 18}) and co-exposure was reported except in two.^{6, 7} These two studies did not find any significant association with low fecundity⁶ or with spontaneous abortion in partners of exposed men.⁷ There was some evidence to suggest that co-exposure of benzene and toluene together with xylene may be associated with adverse sperm parameters, at least at high exposure.^{9, 18} However, it is difficult to attribute this association solely to xylene due to the co-exposure to other solvents. Paternal exposure to xylene was not associated with risk of congenital malformations.⁷

Trichloroethylene

Four studies (seven publications^{1-3, 6, 7, 12, 15}) investigated TCE exposure and adverse reproductive outcomes in men. To understand the associations between TCE and adverse reproductive health outcomes, the findings of studies that reported TCE as the sole exposure are likely to be the most useful. However, only in two studies (four publications^{1-3, 15}), was TCE the sole reported exposure. One publication found that exposure to TCE was not associated with adverse changes in semen parameters except workers exposed to high concentrations (characterised by urinary TCA of ≥ 25 mg/g creatinine) had lower sperm density.² Other semen parameters were not different. It was not clear whether this finding alone was associated with adverse fertility outcomes. Another cross-sectional study that reported TCE as the sole exposure found the mean levels of FSH, LH, SHBG and testosterone reduced by years of exposure up to seven years. However, the strength of evidence was also limited by absence of an unexposed comparison group.^{1, 3} The available limited evidence of TCE exposed workers¹⁵ on the presence of two fluorescent bodies did not indicate a genotoxic association.

The other three publications did not report an increased risk of spontaneous abortion^{7, 12} or of low fecundity⁶ in partners of exposed men. Therefore, current evidence on exposure to TCE and reproductive outcomes in men are limited and available evidence do not support an association with adverse male reproductive health.

Propylene glycol monomethyl ether

The evidence on association of PGME with semen characteristics is very limited and came from a cross-sectional study¹³ that investigated the association between 2-MPA, a urinary

metabolite of PGME, and characteristics of semen. The study did not identify any association between urinary 2-MPA and semen characteristics or serum levels of reproductive hormones.

Other solvents

Evidence was very limited on association of exposure to isopropanol, ethyl benzene, methyl ethyl ketone and acetone in men and association with adverse reproductive outcomes. Available evidence is based on the two publications from the SHOAMP²² based on the DSRS programme. Many chemicals were used in the DSRS programme and ascertainment of exposure to a specific solvent and quantification was not possible. The SHOAMP was conducted some years after the actual exposure occurred and the existing records on participants and exposure were incomplete. Therefore, to determine the exposure-effect associations relationship for the specified solvents of interest would be based on limited and unreliable evidence and was not attempted.

Strengths and limitations

The majority of the included studies were cross-sectional in design and compared an exposed group with an unexposed or minimally exposed group. Some of the studies were based on existing registry or database data and, additional information (if needed) were collected through self-reported questionnaires. In some studies of weaker study design, the target population was identified but the use of a sampling frame was not described and information on response rate and or non-responders may not have been available or reported. Some studies¹⁻³ did not include a comparison group. There were fewer studies conducted or published post 2000 (7 of 18 publications, see Evidence Profile) with the most recent identified as published nine years ago in 2009. Earlier studies and exposures may reflect different working conditions to that experienced currently. Also, methods of measuring steroid hormone levels have improved during this time.

Toluene was the most commonly reported solvent followed by xylene and TCE. However, co-exposures may also have occurred, and this makes it difficult to attribute an outcome to a specified solvent of relevance to this REA. During the review process, the studies in which the exposure was based only on the job categories⁷⁰ without providing evidence of solvents that a specific job category was exposed to, as well as studies that reported exposure to unspecified solvents⁷⁶⁻⁷⁹ were excluded.

The search strategies from two previous reviews; solvent terms from the 2017 report²⁵ and male outcomes terms from the 2018 report²⁶ were combined to finalise the search strategy used for this REA. This literature review searched 10 electronic databases which covered medical, science, toxicological and military literature. One military health journal was hand

searched through its website. Numerous government, military and other research organisational websites were also searched to identify relevant unpublished reports. One of the strengths of this REA is the comprehensive coverage of resources to identify papers published in or after 2000. Therefore, studies published prior to 2000 may not have been included. However, the reference lists of included publications were searched to identify potentially relevant studies published before 2000, and this process together with predetermined website search identified a further 29^{1-7, 10, 12, 14-17, 32-47} records in addition to five^{8, 9, 11, 13, 18} records identified from the electronic database search, that were included in this REA. The reference lists of included reports were also screened to identify any relevant publications. Therefore, we consider it very likely that all the key peer-reviewed publications are covered irrespective of the date of publication. However, only English articles were included, therefore potentially relevant non-English articles were not included. From the 12,282 titles and abstracts initially identified through the search, it was not always readily identifiable whether the publication was eligible for inclusion, in particular whether exposure to one or more of the specified solvents of interest was reported and, if so, whether a reproductive health outcome in men or pregnancy outcome in their partners was reported. In the process, 271 full text versions of articles were obtained for review for eligibility, and 237 were excluded.

Another strength of the REA is the inclusion of reports from reputed medical, scientific and government institutions that provide information to government authorities. This provides an opportunity to compare the included studies in this REA with the studies included in the reports. This strategy is valuable to identify any important article published before 2000, due to limitations on search period, consistent with the REA methodology. This REA did not exclude any relevant article, even published before 2000, which was confirmed through the cross-check with the included studies in the reports.

Implications

This REA has identified peer reviewed, published studies and high quality report evidence available in relation to the effects of specified solvent exposure and adverse reproductive outcomes in men. The Summary of Evidence and Evidence Profile highlight where associations between occupational exposure to solvents and adverse reproductive outcomes have been reported and the strengths or limitations in relation to these outcomes. The number of studies identified for associations with male fertility / fecundity, levels of reproductive hormones, sexual function, and pregnancy outcomes in the partners of exposed men was limited. Very limited epidemiological evidence was available for the research question for men in military settings. The implications for occupational exposures for men in the military needs to be considered in the light of the findings of studies and the limitations of the evidence.

Conclusion

This REA identified peer reviewed studies of the effects of occupational exposure of specified solvents in men and adverse effects on reproductive health outcomes. The search was comprehensive and 34 records including relevant studies prior to 2000 have been considered in the REA. The existing body of literature for those specified solvents and male reproductive outcomes was limited and establishing specific solvent-outcome association was also complicated by co-exposures of solvents within the scope of this review, as well as solvents that are beyond its scope.

In summary, in relation to the specified solvents considered, this review found:

- The most commonly assessed exposures were toluene, xylene and TCE; the evidence base for other specified solvents of interest was extremely limited.
- There was some limited evidence that occupational exposure to high concentration of a combination of solvents, including solvents of interest in this review such as TCE and BTEX, may be associated with adverse changes in the characteristics of semen.
- There was limited evidence of association with TTP or low fecundity and this did not suggest that specified solvent exposure in men was associated with increased time to pregnancy or reduced fecundity in couples.
- The evidence supporting an association of specified solvent exposure in men with increased risk of spontaneous abortion in their partners is limited and weak.
- The evidence of association of specified solvent exposure with stillbirth or preterm birth was very limited and did not provide evidence that specified solvent exposure in men was associated with increased risk
- There was very limited and conflicting evidence to suggest that specified solvent exposure to toluene in men is associated with higher risk of congenital malformations in babies of partners, and in relevant studies co-exposure of solvents including solvents that were not in the scope of this REA may have occurred.
- There is some weak and limited evidence to suggest that high TCE or toluene exposure in men is associated with reduced serum levels of FSH, LH and testosterone.
- The strength of available evidence was weak because there is a limited number of studies and weak study designs. The majority of evidence came from cross-sectional

studies and, in some studies, co-exposure of specified solvents with other solvent(s) or chemical(s) at the workplace made it difficult to ascertain specific exposure-outcome associations. The quality of the studies varied. Overall, limitations of individual studies of the association between specified solvent exposure and adverse male reproductive health outcomes included limitations in study design, the small numbers of cases for adverse reproductive health outcomes, limitations in exposure assessment or in health outcome assessment such as in self-reported outcomes, and recall bias. The evidence from recent studies was scarce and many studies were conducted before 2000.

- It is difficult to establish strong conclusions on specific solvents without more high-quality evidence.

Appendix 1: Population Exposure Comparison Outcome (PECO) Framework

Question:	
In men who are or who have been employed in defence or military related forces, or in occupational groups exposed to specified solvents, is exposure associated with an increased risk of adverse reproductive health outcomes compared with men employed or previously employed in defence or military related forces or in occupational groups who have not been exposed or compared to adult men in the general population?	
Population (P)	Men Employed or previously employed in aviation industry (i.e. occupationally exposed)
Exposure (C)	Specified solvents: ethyl acetate, ethyl benzene, toluene, xylene, acetone, isopropanol, methyl ethyl ketone, propylene glycol monomethyl ether, white spirit and trichloroethylene
Comparison (C)	Not exposed to specified solvents above
Outcomes (O)	<ul style="list-style-type: none"> • Adverse male reproductive outcomes <ul style="list-style-type: none"> ○ Hypogonadism / primary testicular failure ○ Androgen (testosterone) deficiency ○ Impaired semen quality (volume, concentration, number, motility, vitality and morphology) ○ Reduced reproductive success (infertility, involuntary childlessness, not achieving desired family size, increased time-to-pregnancy, low fecundity (fecundity defined as the probability of a couple to conceive in a menstrual cycle), increased use of assisted reproductive technologies, adverse pregnancy and fertility outcomes in female partners (i.e. early foetal loss, neonatal death, stillbirth, miscarriage, foetal malformations or congenital anomalies, pre-term birth, intra-uterine growth retardation or low birth weight, reduced fertility, reduced libido in female partners of exposed men) ○ Altered reproductive hormones (testosterone, oestradiol, luteinising hormone and follicle stimulating hormone) • Adverse male sexual outcomes <ul style="list-style-type: none"> ○ Erectile dysfunction ○ Libidosexual dysfunction ○ Psychosexual dysfunction

Appendix 2: Search strategy

The Medline search strategy is included below.

[The Medline filter was adapted accordingly to search other databases]

- 1 ethyl acetate.mp.
- 2 ethyl benzene.mp.
- 3 2-propanol.mp. or exp 2-Propanol/
- 4 isopropanol.mp.
- 5 IPA.mp.
- 6 acetone.mp. or exp ACETONE/
- 7 dimethyl ketone.mp.
- 8 exp BUTANONES/
- 9 Ethyl methyl ketone.mp.
- 10 BUTANONES.mp.
- 11 "MEK".mp.
- 12 propylene glycol monomethyl ether.mp.
- 13 exp TOLUENE/ or toluene.mp.
- 14 Methylbenzene.mp.
- 15 Toluol.mp.
- 16 xylene.mp. or exp Xylenes/
- 17 dimethylbenzene.mp.
- 18 methyl toluene.mp.
- 19 white spirit.mp.
- 20 Stoddard Solvent.mp.
- 21 mineral spirit*.mp.
- 22 Trichloroethylene.mp. or exp TRICHLOROETHYLENE/
- 23 BTEX.mp. AND solvents/to [Toxicity]
- 24 or/1-23
- 25 exp Hypogonadism/
- 26 Hypogonadism.mp.
- 27 exp Testosterone/
- 28 Testosterone.mp
- 29 exp ANDROGENS/

- 30 Androgen*.mp.
- 31 Androgen.mp. or exp ANDROGENS/
- 32 (hypoandrogenism or hypo-androgenism or "hypo androgenism").mp.
- 33 exp ANDROPAUSE/
- 34 "testicular failure".mp.
- 35 (Male adj2 sex hormone*).mp.
- 36 ((Male or men*) adj5 (oestradiol or estradiol or luteinizing hormone or "LH" or follicle stimulating hormone or FSH)).mp.
- 37 exp semen/
- 38 semen.mp.
- 39 exp SPERMATOZOA/
- 40 sperm*.mp.
- 41 exp libido/
- 42 (SEXUAL DYSFUNCTIONS, PSYCHOLOGICAL/ or SEXUAL DYSFUNCTION, PHYSIOLOGICAL/ or (Dysfunction adj2 (sexual or libidosexual or libido-sexual or psychosexual or psycho-sexual)).mp.) and (men or male or males).mp.
- 43 exp infertility, male/
- 44 exp erectile dysfunction/
- 45 erectile d#sfunction.mp.
- 46 exp penile erection/
- 47 exp Premature Ejaculation/
- 48 Impotence.mp.
- 49 ((Achiev* or maintain* or sustain*) adj erection).mp.
- 50 ((fertility or infertility) and (male or males or men)).mp.
- 51 exp fertility/
- 52 exp Reproduction/
- 53 exp reproductive health/
- 54 exp Reproductive medicine/
- 55 exp Time-to-Pregnancy/ or (time-to-pregnancy or "time to pregnancy").mp.
- 56 exp Reproductive Techniques, Assisted/
- 57 fecund*.mp.
- 58 involuntary childlessness.mp.
- 59 family size.mp.
- 60 ("IVF" or "In Vitro Fertilization" or "In-Vitro-Fertilization").mp.
- 61 "Assisted reproductive technolog*".mp.
- 62 (Conception or conceiv*).mp.

- 63 (fertility or infertility).mp.
- 64 exp Pregnancy Outcome/
- 65 exp Pregnancy Complications/ or (complication* adj2 pregnancy).mp.
- 66 exp Abortion, Spontaneous/ or spontaneous abortion.mp.
- 67 exp Infant mortality/
- 68 exp Fetal mortality/
- 69 exp Premature birth/
- 70 exp Fetal Death/ or ((death adj2 fetus) or foetus or foetal or fetal).mp.
- 71 exp Fetal weight/ or ((weight adj2 fetus) or foetus or foetal or fetal).mp.
- 72 exp Birth weight/ or (weight adj2 birth).mp.
- 73 exp Infant, Low Birth Weight/
- 74 exp Fetal growth retardation/
- 75 (Stillbirth* or still-birth or miscarriage* or abortion).mp.
- 76 (growth retardation or IUGR or "low birth weight").mp.
- 77 (((prem* or pre-term or "pre term") adj birth) or deliver* or labo?r).mp.
- 78 ((foetal or fetal or foetus or fetus or infant* or perinatal* or "peri natal" or peri-natal or neonatal or neo-natal) adj2 (loss or mortality or death)).mp.
- 79 (aborted adj (foetus or fetus)).mp.
- 80 exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp congenital abnormalities/
- 81 exp Infant, Newborn, Diseases/
- 82 exp fetal development/
- 83 ("foetal malformation*" or "fetal malformation*").mp.
- 84 ((Congenital adj anomalies) or anomaly or malformations*).mp.
- 85 or/25-84
- 86 24 and 85
- 87 exp animals/ not humans.sh.
- 88 86 not 87
- 89 limit 88 to (english language and yr="2000 -Current")

Appendix 3: Checklist for considering the quality of descriptive, observational and prevalence studies

Modified from Giannakopoulos, Rammelsberg, Eberhard, Schmitter (2012)³⁰

Completed		
Yes	No	
		1. Target Population
		<ul style="list-style-type: none"> Target population clearly defined, including: age, sex, employment, ethnicity, religion <p>AND</p> <ul style="list-style-type: none"> relevant data from health questionnaire of sampled persons, <i>if appropriate</i>
		<ul style="list-style-type: none"> Target population not clearly defined : limited data available on: age, sex, employment, ethnicity, religion <p>AND</p> <ul style="list-style-type: none"> relevant data from health questionnaire of sampled persons, <i>if appropriate</i>
		<ul style="list-style-type: none"> Target population poorly defined: little or no information on age, sex, employment, ethnicity, religion <p>OR</p> <ul style="list-style-type: none"> little or no information from relevant data from health questionnaire of sampled persons, <i>if appropriate</i>
		2.Sampling method (Representativeness)
		<ul style="list-style-type: none"> Sophisticated probability sampling used** (e.g. stratified sampling; cluster sampling; multistage sampling; multiphase sampling)
		<ul style="list-style-type: none"> Simple probability sampling used:* (e.g. simple random sampling)
		<ul style="list-style-type: none"> No probability sampling used
		3. Measurement (Reliability)
		<ul style="list-style-type: none"> Standardised data-collection methods (e.g. validated clinical interview or diagnostic instrument/criteria) <p>OR</p> <ul style="list-style-type: none"> reliable survey instruments (e.g. validated self-report measure / validated screening instrument)
		<ul style="list-style-type: none"> Non-standardized data collection <p>OR</p> <ul style="list-style-type: none"> Non-validated interview or non-validated self-report measure
		4. Information about non-responders

Completed		
Yes	No	
		<ul style="list-style-type: none"> • Analysis of differences conducted on non-responders
		<ul style="list-style-type: none"> • No analysis of differences information provided on non-responders <p>OR</p> <ul style="list-style-type: none"> • Only proportion (e.g. %) of non-respondents supplied without any other information
		5. Additional information
		Information that may affect the overall rating (e.g. were special features accounted for? Were there satisfactory/appropriate statistical analyses, confidence intervals, etc.?)

*Simple sampling methods (from Boyle, 1998):⁸⁰

Predetermined number of units (individuals, families, households) selected from the sampling frame so each unit has an equal chance of being chosen

**Complex sampling methods (from Boyle, 1998):⁸⁰

- Stratified Sampling: a population is divided into relatively homogeneous subgroups (strata) and samples selected independently and with known probability from each strata;
- Cluster Sampling: population divided into affiliated units or clusters e.g. neighbourhoods or households and a sample of clusters selected with known probability;
- Multistage Sampling: samples are selected with known probability in hierarchical order e.g. a sample of neighbourhoods, then sample of households, then sample of individuals;
- Multiphase Sampling: sampled individuals are screened and subsets selected with known probability for more intensive assessment.

Appendix 4: Evidence profile of included studies

In the following tables, odds ratios (OR) or effect estimates presented are the adjusted OR or adjusted effect estimates.

Observational studies

Male sexual function (n=1)

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Brown 2009 ⁴	Retrospective cohort Postal questionnaire and clinical assessments	Australia	Personnel who participated in any F-111 DSRS activities between 1975-1999 N=1479 (males only) Eligible participants identified through maintenance logs, squadron photos, newspaper ads, websites and snowballing techniques	Exposed group at Amberley N=577	Technical personnel posted at RAAF base Richmond (NSW) (n=503)* Other personnel (non-technical) posted at Amberley base (n=399)*	<ul style="list-style-type: none"> Erectile function: self-reported questionnaire - International Index of Erectile Function (IIEF)⁵⁰ General sexual functioning (two questions on loss of interest in sex and problems with sexual functioning) Prevalence and severity of anxiety and depression (Composite International Diagnostic Interview (CIDI)), a fully structured interview 	<p>“Exposure Questionnaire”, a mailed postal questionnaire, in which respondents indicated the programme(s) they had been involved in, duties, and the length of time.</p> <p>Assessment of possible confounding factors including BMI, blood pressure, medical conditions, psychological health, alcohol use, civilian use of chemicals.</p>	All males Mean age 44 to 45 years
<p>* comparison groups were obtained using stratified random sampling from the computerised Air Force Personnel Executive Management System, with stratification by gender, 5-year age group, posting1 category, and rank category. In analysis, the IIEF scale was dichotomised, with a cut-off score of 25 or less out of 30 providing an indication of clinically significant erectile dysfunction.⁸¹</p> <p>Findings: No differences between the three groups with respect to the matching variables of rank, posting and age. Exposed at Amberley: mean 44 (±9.3) years BMI mean 28 (±4.1); Richmond mean 45 (±7.9) years, BMI mean 29 (±4.1); Non-technical at Amberley 44 (±7.8) years, BMI mean 30 (±4.9).</p>								

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
<p>Those in the exposed group were more likely to be depressed (n=66; 12%), compared to Amberley (n=24; 6.3%) or Richmond (n=26; 5.2%) groups (p=0.0002). Those in the exposed group were more likely to be anxious (n=106; 19%), compared to Amberley (n=49; 13%) or Richmond (n=36; 7.3%) groups (p=0.001).</p> <p>Greater proportion of exposed group reported loss of interest in sex (n=234; 38%) compared to Amberley (n=105; 22%) (OR 1.91; 95% CI 1.37-2.67) and Richmond (n=126; 22%) (OR 1.72; 95% CI 1.26-2.33) groups.</p> <p>Greater proportion of exposed group reported problems with sexual function (n=197; 32%) compared to Amberley (n=93; 19%) (OR 1.91; 95% CI 1.34-2.75) or Richmond (n=91; 16%) groups (OR 2.33; 95% CI 1.64-3.29).</p> <p>Greater proportion of exposed group reported erectile dysfunction (n=169, 33%) compared to Amberley (n=91; 21%) (OR 1.71; 95% CI 1.24-2.36) or Richmond (n=104; 20%) (OR 1.87; 95% CI 1.39-2.52) groups.</p> <p>The findings indicated a significant association between exposure group and reported sexual function outcomes, after adjustment for other potentially confounding factors including depression and anxiety. Sensitivity analyses excluding participants who indicated no sexual partner or activity for the month did not influence the outcome.</p> <p>The study did not find a linear association between dose (duration of exposure) and loss of interest in sex (p=0.06) or loss of sexual function (p=0.2) between groups; no-dose-response relationship was evident.</p> <p>The authors concluded that there was an average two-fold increase in the odds of sexual dysfunction including erectile dysfunction in the DSRS exposed group compared to “different base, similar job” cohort (Richmond) and “same base-different job” cohort (Amberley).</p>								

Endocrine profile (n=5)

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Chia 1997 ¹	Cross-sectional Information collected through a medical examination & an interview questionnaire	Singapore	Male workers in an electronics factory who used trichloroethylene (TCE) as a degreaser N=450	Workers who volunteered for a free medical check and agreed for blood to be taken for hormonal assessment n=85	No comparison group	Hormonal assays of testosterone, Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH), dehydroepiandrosterone sulphate (DHEAS) and Sex-Hormone Binding Globulin (SHBG) were assessed via a single morning venous blood sample Covariates: Age, smoking history, and size of testes	Air: Measured using organic vapour monitors in 12 workers Urine: Spot sample analysed for trichloroacetic acid (a metabolite of TCE)	All male Age mean (SD) 27.8 (3.0) years Range 22-39 years
<p>Note: The analysis is based on years of exposure.</p> <p>Findings:</p>								

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
<p>Workers were generally exposed to below the threshold limit value (TLV) of 50 ppm in the air for toluene. However, the current ACGIH TLVs[®] for TCE is 10 ppm.⁵¹</p> <p>Mean hormonal levels of serum FSH, testosterone, LH and SHBG showed a decrease by years of exposure until 5-7 years of exposure and mean serum testosterone, LH and SHBG were at similar levels at ≥7 years. Mean FSH was lower at ≥7 years and significantly lower when compared with levels <3years (p<0.05).</p> <p>FSH: <3 years: 2.6, 3-5 years: 1.69, 5-7 years: 1.66, ≥7 years: 1.51 (IU/l)</p> <p>Testosterone: <3 years: 5.27, 3-5 years: 5.14, 5-7 years: 4.40, ≥7 years: 4.75 (ng/ml)</p> <p>LH: <3 years: 5.03, 3-5 years: 5.0, 5-7 years: 4.62, ≥7 years: 4.95 (IU/l)</p> <p>SHBG: <3 years: 33.00, 3-5 years: 28.90, 5-7 years: 23.20, ≥7 years:24.30 (nmol/ml)</p> <p>Authors considered that the findings indicated that reductions in FSH and testosterone in men exposed to TCE could be due to disruption of peripheral endocrine function via TCE induced reduction in liver production of SHBG, but that the longer terms implications of such findings remain ill-defined.</p>								
Gericke 2001 ¹⁰	Cross-sectional Data from a multi-centre controlled field trial conducted between 1993-1995 in 12 participating factories ⁵²	Germany	N=1077 (recruited) Current rotogravure printing workers who volunteered to participate and randomly selected by an industry association	n=768 (analysed) Male printers or helpers exposed to toluene	Non-printers n=309 External reference group from paper industry (n=109)	Serum FSH, LH and testosterone Covariates: age	Air: Ambient air at the work area through personal monitors ⁵² Blood: Before and after work-shift ⁵²	All males Not reported
<p>Note: Only male reproductive system-related outcomes are reported here. Median (range) exposure for toluene: [mg toluene / m³ air] Printers and helpers: 91 (1.6 – 800), Non-printers 17 (0.3-200); [µg toluene/litre blood] Printers and helpers 39 (1.7 – 911), Non-printers 14 (0.7 – 876). (10 mg toluene/m³=2.7 ppm)</p> <p>Findings:</p> <p>The study found no significant effect on serum FSH, LH, or serum testosterone when printers and helpers were evaluated against non-printers. Of exposed printers and helpers, 9% had FSH levels outside reference ranges (i.e. increased or decreased) compared to 10% non-printers (p=0.42). For LH, 8% of printers and 8% of non-printers were outside reference range (p=0.47) as well as 9% of printers and helpers compared to 13% of non-printers (p=0.07) for testosterone.</p> <p>The authors concluded that no clear-cut alteration in levels of male sex hormones was found in workers with long terms occupational exposure to toluene.</p>								
Goh 1998 ³	Cross-sectional Information collected through a medical	Singapore	Male workers in an electronics factory who used trichloroethylen	Workers who volunteered for a free medical check-up and agreed for blood to be	No comparison group	Serum testosterone and sex hormone binding globulin (SHBG) were measured in a single morning venous blood sample Covariates:	Air: Measured using organic vapour monitors in 12 workers Urine:	All males Mean age (SD) 27.8 (3.0) years

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	examination & an interview questionnaire		e (TCE) as a degreaser N=450	taken for hormonal assessment n=85		Age, smoking, size of testis	Spot samples analysed for trichloroacetic acid	
<p>Note: The analysis is based on years of exposure</p> <p>Findings: A reduction in mean (SE) testosterone levels (ng/ml) was observed with years of exposure (<2 yrs: 5.71 (0.6), 2-4 yrs: 5.69 (0.6), 4-6 yrs: 5.28 (0.4) and ≥6 yrs: 4.60 (0.3). Mean (SE) SHBG levels (nmol/l) decreased with years of exposure (<2 yrs: 37.8 (3.8), 2-4 yrs: 33.0 (3.9), 4-6 yrs: 27.4 (2.4) and ≥6 yrs: 24.8.60 (1.8)), and mean levels in 4-6 year and ≥6 years of exposure groups were significantly less than the group with <2years of exposure</p>								
Svensson 1992a ¹⁶ (Title: Hormone status...)	Cross-sectional	Sweden	Toluene-exposed rotogravure printers, without signs of solvent-induced toxic encephalopathy N=20	Exposed n=20	Referents: male industrial workers from a margarine factory and a gelatin-extracting company, without exposure to organic solvents n=44	Serum levels of LH, FSH, prolactin (PRL), sex hormone binding globulin (SHBG), total and free testosterone (t-Test & f-Test) from two blood samples taken within 60 minutes interval at mid-day, mid-week, while in supine condition	Air: Personal sampling, drawn from the subject's respiratory zone at work was used to calculate daily time-weighted average (TWA) Blood: Two midday blood samples within 1hour interval to assess blood toluene, in the middle of a working week Adipose tissue: Biopsies of subcutaneous fat	All males Exposed mean age 48.2 (range 30-63) years Referents mean age 39.0 (range 23-63) years
<p>Note: Participants were assessed for signs of toxic encephalopathy by a screening questionnaire by Hogstedt et al.⁵³</p> <p>Findings: Median weekly TWA air level of toluene for the printers was 36 ppm (range 8-111 ppm). The exposed workers had a blood toluene of 1.7 µmol/l (median, range 1-6.6 µmol/l). Only six of the 21 referents who had their toluene analysed had concentrations above the detection limit with 0.1 µmol/l as the highest value. Median (range) of serum FSH, LH and f-Test were significantly lower in the exposed group compared to the referent group: FSH 3.2 (1.8-7.2) vs. 4.9 (1.8-17.3) IU/l (p=0.008); LH 6.1 (3.8-9.4) vs. 7.2 (4.9-14.4) IU/l (p=0.02) and f-Test 76.8 (48.6-107.2 vs. 86.8 (21.5-141.5) pmol/l (p=0.05) respectively. However, median serum PRL, SHBG and total t-Test were not significantly different: PRL 2.8 (1.3-6.2) vs. 3.4 (1.4-9.2) µg/l, SHBG 1.5 (0.9-3.7) vs. 1.6 (0.6-3.0) mg/ml and t-Test 5.8 (2.7-8.2) ng/ml vs. 6.6 (0.6-3.0) ng/ml, respectively. In eight printers, levels of FSH and LH increased during a 4 week vacation and levels of thyroid hormones decreased during the same period. The study concluded that the observed hormone level changes are likely to have been due to exposure to toluene, and that the results indicated a slight, reversible effect of toluene that could have been on the cortical level or on hypothalamic-pituitary axis.</p>								

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Svensson 1992b ¹⁷ (Title: Neuroendocrine effects...)	Cross-sectional Clinical examination, information from medical records and personal interviews	Sweden	Rotogravure printers from two companies N=47	Printers exposed to toluene n=47	Unexposed referents from metal industry or hospital workshops n=46	Plasma concentrations of Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH), prolactin (PRL) and total testosterone (Test) were measured in a midweek venous blood sample Outcomes were categorised as: influence of present exposure and influence of cumulative exposure Covariates: age	Current exposure to toluene: Air: Personal sampling (workers wearing motor-powered syringes) and spot and area sampling Blood: Via pre and post shift venous blood	All males Exposed: Mean (range) 44.4 (23-62) years Referent group: Mean (range) 43.5 (20-61) years
<p>Note: The normal reference ranges for FSH, LH, PRL, and Test were considered as 0.3-2.7 µg/l, 0.3-1.4 µg/l, 2-12 µg/l, and 6-30 nmol/l respectively. Swedish threshold limit value (TLV) for toluene is 80 ppm at the time of the sampling.</p> <p>Findings:</p> <p>Toluene concentrations in blood ranged from 0.05-0.83 µmo/l pre-shift to 0.09-8.0 µmo/l post shift.</p> <p>There was no statistically significant difference in serum LH, FSH, PRL and total Test between total exposed workers compared with referents (0.9 vs. 1.0 µg/ml, 0.9 vs. 1.1 µg/ml, 3.0 vs 3.2 µg/ml and 15.8 vs. 16.0 nmol/l respectively). However, when stratified for age, significantly lower median serum hormone concentration levels of LH (0.8 vs. 1.1 µg/ml, p<0.01) and FSH (0.4 vs. 1.0 µg/ml, p<0.05) were observed in workers <40 years (n=14) in the exposed group compared to the referent group.</p> <p>For subjects exposed to toluene (six classes of average exposure concentrations <5 to >45ppm), increasing toluene exposure concentrations were significantly associated with decreasing concentrations of plasma LH (tau= -0.21, p=0.02) and testosterone (tau = -0.25, p = 0.02). No effects were seen with cumulative exposure.</p> <p>The study showed effects of toluene exposure on some hormone concentrations, although no statistically significant differences were found in any hormone concentrations between the total exposed compared with referent group. The authors concluded the study could indicate an effect of low toluene exposure on the hypothalamic pituitary axis, with a secondary decrease in testosterone secretion.</p>								

Pregnancy outcomes in partners (n=4)

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
D'Este 2004 ⁵	Retrospective cohort Self-reported Female	Australia	Female DSRS workers (n=24) and female partners of male DSRS	Exposed (n=206 reported 484 pregnancies in exposure	Technical personnel posted at RAAF base Richmond	Reproductive health outcomes referenced to a posting date: <ul style="list-style-type: none"> Pregnancy outcomes during the F-111 DSRS period 	Exposure was difficult to define. Advisors and key decision makers defined exposure at the program level.*	Age: 16-46 y Female (of male study)

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Reproductive Questionnaire administered in the Study of Health Outcomes in Aircraft Maintenance personnel (SHOAMP)		workers (n=767) who reported pregnancies during five posting periods over 1975-1999	period of interest)	(NSW) (n=203 reported 492 pregnancies in exposure period). Non-technical posted at Amberley base (n=143 reported 351 pregnancies in exposure period)	<ul style="list-style-type: none"> For any pregnancies recorded, asked if there were reported difficulties getting pregnant and if reported seeing a specialist Analysed female DSRS workers and female partners combined as: Pregnancy result- live birth vs other incl. stillbirth or miscarriage	Exposure sub grouped for analysis by DSRS Program as: Program 1 1977-1982 Program 2 1991-1993	participants)
<p>*SHOAMP had 4 programs: Program 1 (1977-1982), Wing program (1985-1992), Program 2 (1990-1993) and Spray seal (1996-1999)</p> <p>Subgroups: as there was overlap between the 4 programs, the 2 subgroups for exposure were: Programme 1 and 2 as they had the greatest number of participants. Spray seal had very few participants.</p> <p>DVA assigned 3 exposure categories: Category 1- directly involved in F-111 DSRS or had exposure to DSRS chemicals, Category 2- worked in close proximity to F-111 DSRS activities and Category 3- had been at the RAAF Base Amberley during the exposure period of interest. Final exposure classification: Exposed group and not exposed. Three categories for duration of exposure (dose): Mild (up to 9 months), Moderate (10-29 months) and prolonged (30 months or more).</p> <p>Findings:</p> <p>N=552 total females included in analysis who reported pregnancies within exposure period of interest. N=1327 reported pregnancies eligible to be used in the analyses.</p> <p>For pregnancies overall there were 1072 live births (80%), 20 stillbirths (1.5%) and 235 miscarriages (18%). Unadjusted proportions with stillbirths or miscarriages were similar for Amberley (17% of births), Richmond (20%) and exposed group (20%).</p> <p>There was no evidence of an association in female DSRS personnel or female partners of male DSRS personnel and miscarriage or stillbirth.</p>								
Hooiveld 2006 ¹¹	Cross-sectional Self-administered mailed questionnaire focused on most recent pregnancy. Two reminders at 2 & 4 weeks for non-responders	Netherlands	A random sample of male painters and carpenters born between 1950 and 1975, in the membership register of the Trade Union for Construction	Male painters who ever fathered a pregnancy and were exposed to solvents at 3 months before pregnancy n=398	Carpenters with nil or negligible exposure to solvents n=302	Information collected through the self-administered questionnaire: <ul style="list-style-type: none"> Preterm delivery (delivery <37 weeks of gestation) Low birth weight (<2.5kg) Birth defects in offspring Spontaneous abortion (a pregnancy that ended <20 weeks of gestation) Time to pregnancy (TTP) (cut off point 12 months) 	Exposure was assessed based on responses to questionnaire; job title at 3 months before pregnancy were combined with self-reported exposure to paints, thinners or cleaning agents. For quantitative exposure assessment the model described by Burstyn and Kromhout. ⁵⁴ was used as developed in a similar population in the Netherlands. Toluene was selected as a marker for solvent exposure, since	Not reported

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
			Workers in 2001 N=700			Covariates: year of pregnancy, maternal age at conception, paternal smoking and alcohol use before pregnancy, maternal smoking, alcohol use, chemical occupational exposure, physical occupational exposure, medication use during pregnancy	measured hydrocarbon exposures appeared strongly correlated ¹¹	
<p>Findings: There was no increased risk of prolonged TTP, low fecundity, spontaneous abortion (OR 1.1; 95% CI 0.4-2.7) or preterm births (OR 1.2; 95% CI 0.7-2.2) in partners of painters compared to carpenters. Birth defects in offspring of painters were significantly higher compared to unexposed carpenters (OR 2.4; 95% CI 1.2-4.9), mainly due to a higher risk of congenital malformations (OR 6.2; 95% CI 1.4-27.9). Malformations reported by painters were: cardiovascular (n=4), gastrointestinal (n=2), central nervous system (n=1), eye (n=1), urogenital malformations (n=1), oro-facial clefts (n=3), Down's syndrome (n=1), and other syndromes (n=3). Non-exposed workers reported 1 urogenital defect and 1 hip dysplasia</p>								
Taskinen 1989 ⁷ [See Sallmén et al. 1998 ⁶ for follow-up]	Case referent Mailed questionnaire Information on occupational exposures related to the study pregnancy was collected from men and, lifestyle factors and medical issues from the wives using a mailed questionnaire	Finland	Male workers who were monitored for organic solvent exposure* by the Finnish Institute of Occupational Health during 1965-1983 and in their first marriage during 1985 and with wives 18-40 years at first trimester n=371	Cases: Wives who had a spontaneous abortion or a congenitally malformed child n=120	Referents: Women who did not have a registered spontaneous abortion or a registered malformed child between 1973-1983 matched for age at conception (within 30 m) n=251	Pregnancies were identified from hospital discharge registers Spontaneous abortion were obtained from hospital polyclinics Congenital malformations were obtained from the Finnish Register of Congenital Malformations Covariates: paternal exposure to dusts, maternal exposure to organic solvents, heavy lifting, and previous spontaneous abortion	Exposure to various solvents were determined and quantified based on the responses to the questionnaire and biological monitoring data (blood and urine concentrations of some parameters) available at Finnish Institute of Occupational Health Quantification of exposure: High/frequent: daily exposure or biological measurements above reference values Intermediate: usage 1-4 days a week and biological measurements indicated intermediate/low exposure Low/rare: solvent handling occurred more rarely	Age not reported
<p>*trichloroethylene (TCE), tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, and toluene Note: Only outcomes related specifically to paternal exposure to toluene, xylene, acetone and/TCE are reported here.</p> <p>Findings:</p>								

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
<p>Spontaneous abortion:</p> <p>Toluene: Risk of spontaneous abortion was significantly increased in the wives of high/frequent exposure group (OR 2.3; 95% CI 1.1-4.7, p<0.05) but not in low/rare (OR 0.9; 95% CI 0.4-2.2) or intermediate (OR 0.7; 95% CI 0.3-1.7) exposure groups.</p> <p>Xylene: risk of spontaneous abortion was not increased in the wives of low/rare, intermediate or high exposed workers (OR 1.2; 95% CI 0.4-3.3, OR 1.7; 95% CI 0.7-4.2, OR 1.6; 95% CI 0.8-3.2 respectively).</p> <p>Paternal exposure to TCE and to acetone were not associated with spontaneous abortion (OR 1.0; 95% CI 0.6-2.0, OR 1.0; 95% CI 0.6-1.7 respectively) when not controlled for confounders. Adjusted values were not reported.</p> <p>Congenital malformations:</p> <p>The results available for congenital malformation were limited. In multivariate analysis when hip luxation was excluded, paternal exposure to toluene (OR 1.5; 95% CI 0.4-5.4) and xylene (OR 1.6, 95% CI 0.4-5.7) was not associated with risk of congenital malformations when adjusted for paternal dust exposure and maternal febrile diseases in the first trimester of pregnancy.</p>								
Lindbohm 1991 ¹²	Nationwide Hospital Discharge Register and hospital records (1973-1982) data on spontaneous abortion linked with census data (1975 & 1980)	Finland	All pregnancies with a diagnosis of spontaneous abortion (ICD-8 codes 643 and 645), induced abortion (ICD-8 codes 640-642) and birth (ICD-8 codes 650-662) between 1973 and 1982 N=99186	Incidence of spontaneous abortion from medically recognised pregnancies of the wives of men exposed to mutagenic agents n=959 (n=11570, all pregnancies)	Incidence of spontaneous abortion of medically recognised pregnancies of the wives of men not exposed to mutagenic agents n=7772 (n=87616, all pregnancies)	Data on spontaneous abortion between 1973 and 1982 were collected from nationwide hospital register and hospital clinics	Census data was used to identify the job category in husbands. Occupational exposure was determined by assessing job categories against Institute of Occupational Health measurements and Finnish register of Employees Occupationally Exposed to Carcinogens Three levels of exposures were determined: moderate/high, potential/low and no exposure	Not reported
<p>Note: Only results for trichloroethylene (TCE) (low and moderate or high exposure) are reported here.</p> <p>Findings:</p> <p>TCE was not associated with spontaneous abortion in the wives of exposed workers; 5 spontaneous abortions were reported in 66 pregnancies (OR 0.9; 95% CI 0.3-2.1, adj for age).</p>								

Fertility / fecundity (n=10)

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Chia	Cross-sectional	Singapore	Male workers in an	Workers who volunteered for	No comparison	Semen was analysed for volume, sperm density,	Air:	All male

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
1996 ²	Information collected through a medical examination and an interview questionnaire		electronics factory who used trichloroethylene (TCE) as a degreaser N=450	a free medical check-up and agreed to have their semen analysed n=85	group. Results compared to WHO criteria	percent motile sperm, percent normal sperm morphology-measured in a morning semen sample after 3 days of sexual abstinence Covariate: marital status	Measured using organic vapour monitors in 12 workers Urine: Spot samples analysed for trichloroacetic acid (TCA)	Age Mean (SD) 27.8 (3.0) years
<p>Findings: The workers were generally exposed to below the threshold limit value (TLV) of 50 ppm in the air for TCE. The current ACGIH TLVs[®] for TCE is 10 ppm.⁵¹ For all workers, mean semen volume, sperm density and mean sperm motility were within WHO reference ranges, except for mean percent normal sperm morphology which was below the WHO reference value. Mean (SD) [WHO reference values]: Volume: 2.6 (1.2) ml [≥2], sperm density: 59.8 (2.7) million/ml [≥20.0], sperm motility: 50.8 (14.0) % [≥50], normal morphology: 25 (9.4) % [≥30]. Comparison between high exposure (urinary TCA ≥25 mg/g creatinine) and low exposure (urinary TCA <25 mg/g creatinine): There was no statistically significant difference between high and low exposure groups in volume, sperm motility and normal morphology. However mean sperm density was significantly lower in the high exposure group compared to the low exposure group (mean (SD) 56.9 (3.0) vs. 63.6 (2.2), p=0.0442), although both groups were above the WHO standard normal sperms density of 20million/ml of ejaculate.</p>								
De Celis 2000 ⁹	Cross-sectional Medical history (including reproductive history) & physical examination	Mexico	Workers employed in a rubber factory in Mexico City N=90	Workers from the production area exposed to a mixture of hydrocarbons for ≥2 years n=48	Workers from the administrative office not exposed to this mixture of hydrocarbons n=42	Semen was analysed for liquefaction, volume, pH, viscosity, sperm agglutination, nonspecific aggregation, sperm count, % spermatozoa with motility of grades 1–3 and immotile sperm, and concentration of white blood cells from three weekly semen samples obtained following sexual abstinence for 3 days	Air: Continuous monitoring of environmental concentrations by passive organic vapour monitor during a workday	Exposed Mean (SD) age 32 (5) years Unexposed 31.5 (5) years All males
<p>Findings: Workers were exposed to the following hydrocarbon concentrations: ethylbenzene; 220.7–234 mg/m³ (50–53 ppm), benzene; 31.9–47.8 mg/m³ (10–15 ppm), toluene: 189.7–212.5 mg/m³ (50–56 ppm), and xylene, 47–56.4 mg/m³ (10–12 ppm). The current ACGIH TLVs[®] are: ethylbenzene 20 ppm, benzene 0.5 ppm, toluene 20 ppm, xylene 100 ppm.⁵¹ The proportion of subjects with ejaculates with normal characteristics was greater in the unexposed compared with exposed group (76% vs 17%). The exposed group had significantly increased abnormal semen viscosity (OR 4.00, 95% CI 1.53-10.58; p<.001), liquefaction (OR 3.99, 95% CI 1.45-11.44; p<.002), sperm aggregation (p<0.001), sperm count (OR 14.13, 95% CI 3.60-78.72; p<.001) and mean motile sperm (p<0.001). Asthenozoospermia (reduced sperm motility) and abnormal spermatozoa were more common in the exposed workers compared to the unexposed workers (OR 9.67, 95% CI 3.11-32.91; p<.001 and OR 27.82, no CI provided, p<.001 respectively).</p>								

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
No differences were found in the volume of semen and mean percentage of live spermatozoa between exposed and unexposed workers. The authors concluded that exposure to the hydrocarbons possibly results in damage to the spermatogenic process.								
D'Este 2004 ⁵	Retrospective cohort Self-reported Female Reproductive Questionnaire administered in the Study of Health Outcomes in Aircraft Maintenance personnel (SHOAMP)	Australia	Female DSRS workers (n=24) and female partners of male DSRS workers (n=767) who reported pregnancies during five posting periods over 1975-1999	Exposed (n=206) reported 484 pregnancies in exposure period of interest)	Technical personnel posted at RAAF base Richmond (NSW) (n=203) reported 492 pregnancies in exposure period). Non-technical posted at Amberley base (n=143) reported 351 pregnancies in exposure period)	Reproductive health outcomes referenced to a posting date: <ul style="list-style-type: none"> Pregnancy outcomes during the F-111 DSRS period For any pregnancies recorded, asked if there were reported difficulties getting pregnant and if reported seeing a specialist Analysed female DSRS workers and female partners combined as: Pregnancy result- live birth vs other incl. stillbirth or miscarriage	Exposure was difficult to define. Advisors and key decision makers defined exposure at the program level.* Exposure sub grouped for analysis by DSRS Program as: Program 1 1977-1982 Program 2 1991-1993	Age range: 16-46 y (Wives of male study participants)
<p>*SHOAMP had 4 programs: Program 1 (1977-1982), Wing program (1985-1992), Program 2 (1990-1993) and Spray seal (1996-1999)</p> <p>Findings:</p> <p>N=552 total females included in analysis who reported pregnancies within exposure period of interest. N=1327 reported pregnancies eligible to be used in the analyses.</p> <p>There was no association between all exposed (in all programmes) and unexposed (p=0.54) in number of pregnancies (Amberley vs exposed OR=1.13, CL 0.75-1.72, Richmond vs exposed OR=0.92, CL 0.65-1.3). Similar results were observed when analysis was performed based on the programme (see below).</p> <ul style="list-style-type: none"> Programme 1 (Amberley vs exposed OR=1.24, confidence limit (CL) 0.79-1.96, Richmond vs exposed OR=1.01, CL 0.68-1.51) (p=0.5) Programme 2 (Amberley vs exposed OR=0.87, CL 0.5-1.51, Richmond vs exposed OR=0.71, CL 0.43-1.17) (p=0.34) <p>There was no dose response relationship for mild, moderate or prolonged exposure (p=0.99).</p> <p>Formal analysis for pregnancy outcomes regarding difficulties getting pregnant and visits to a specialist for fertility problems was not possible as key confounders such as maternal age were not collected. Of women who reported a pregnancy, the proportions of comparison and exposed groups who reported difficulties getting pregnant (p=0.18) and seeing a specialist (p=0.21) were not significantly different.</p>								
Hooveld 2006 ¹¹	Cross-sectional Self-administered mailed	The Netherlands	A random sample of male painters and carpenters born between 1950 and	Male painters who ever fathered a pregnancy and exposed to solvents at 3	Carpenters with nil or negligible exposure to solvents	Following information was collected through the self-administered questionnaire: <ul style="list-style-type: none"> Preterm delivery (delivery <37 weeks of gestation) 	Exposure was assessed based on responses to questionnaire; job titles at 3 months before pregnancy were combined with self-reported exposure to paints, thinners or cleaning agents and compared to	Not reported

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	questionnaire focused on most recent pregnancy. Two reminders at 2 & 4 weeks for non-responders		1975, in the membership register of the Trade Union for Construction Workers in 2001 N=700	months before pregnancy n=398	n=302	<ul style="list-style-type: none"> Low birth weight (<2.5kg) Birth defects in offspring Spontaneous abortion (a pregnancy that ended <20 weeks of gestation) Time to pregnancy (TTP) (cut off point 12 months) Covariates: year of pregnancy, maternal age at conception, paternal smoking and alcohol use before pregnancy, maternal smoking, alcohol use, chemical occupational exposure, physical occupational exposure, and medication use during pregnancy	the model described by Burstyn and Kromhout. ⁵⁴ in a similar population in the Netherlands	
Findings:								
There was no increased risk of prolonged TTP in partners of painters compared to carpenters (OR 1.1; 95% CI 0.7-1.9).								
Lemasters 1999 ⁸	Prospective cohort (repeated measure design) Questionnaires administered face to face; exposure assessment and semen analysis	USA	Volunteer civilian or active-duty military personnel at one USAF base who performed aircraft maintenance duties (N=58)	Jet fuel workers (n=15) Flight line workers (n=23) Sheet metal works (n=6) Paint shop workers (n=6)	Not exposed n=6	Sperm production, structure and function: <ul style="list-style-type: none"> Sperm concentration (million per ml) Percent motile sperm Percent normal morphology Morphometry: <ul style="list-style-type: none"> Length (µm) Width (µm) Width to length ratio Sperm chromatin structure assay (SCSA) <ul style="list-style-type: none"> % cells DNA denatured Time points of outcome assessment: <ul style="list-style-type: none"> Baseline, at 15 weeks, at 30 weeks 	Questionnaires: included medical and occupational history, lifestyle characteristics Standard personal industrial hygiene (IH) sampling and expired breath samples according to National Institute for Occupational Safety and Health (NIOSH) guidelines to measure exposures: <ol style="list-style-type: none"> Jet fuel (primarily JP-4) as naphtha Total solvents [methyl ethyl ketone (MEK), methylene chloride, xylenes, toluene, and 1,1,1-trichloroethane (TCA)] Benzene 	Mean age, years (SD) Jet fuel workers: 24.1 (7.2) Flight line: 24.8 (8.3) Sheet metal: 34.5 (3.6) Paint shop: 31.7 (13.0)

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
						Covariates: age, race, smoking, alcohol consumption, presence of sexually transmitted diseases, hot baths and season the sample was taken		Comparis on group: 26.0 (6.0)
<ul style="list-style-type: none"> • Jet fuel workers: mainly exposed to jet fuel (JP-4) and purging fluid; duties consisted of fuel delivery, fuelling/defueling aircraft, repairing fuel systems of F-16 aircraft • Flight line workers: exposed to jet fuel and exhaust, solvents, and occasionally paint • Sheet metal workers: performed assembly and maintenance activities, were exposed mainly to solvents, adhesives, and sealants, some purging fluid and jet fuel • Paint shop workers: exposed to mainly solvents and paints <p>Only outcomes related to flight line workers, sheet metal workers and paint shop workers are reported here because they were most likely to be exposed to solvents</p> <p>Findings:</p> <p>Exposure: Most men were exposed to more than one solvent that was consistently low, therefore a “total solvent” value was derived by summing the concentrations of the analytes MEK, methylene chloride, xylenes, toluene and TCA for the two exposure cycles. The exposure assessment identified that all the workers had low exposures to solvents (mean <6 ppm, which was <10% of the Occupational Safety and Health Administration [OSHA] standard for all chemicals except benzene).</p> <p>Reproductive assays:</p> <p>Mean (SD) values for all exposed workers at baseline, 15 weeks, and 30 weeks of exposure respectively compared to [WHO reference values]:</p> <ul style="list-style-type: none"> ○ Sperm concentration (million per ml): 66.4 (32.6), 72.4 (46.9), and 73.8 (47.7) [≥ 20 (60)] ○ Percent motile sperm (%): 44.5 (12.0), 43.7 (14.9), and 42.0 (12.3) [≥ 50 (60)] ○ Percent normal morphology (%): 18.4 (6.6), 17.8 (8.6), and 18.1 (9.1) [≥ 14 (60)] <p>For most sperm measures, mean values remained in the normal range throughout the 30 weeks of exposure.</p> <p>Analysis by job groups:</p> <p>Sperm concentration (million/ml): Flight line group had a significant increase of 34.0% ($p=0.01$) at 15 weeks and 32.9% ($p=0.02$) at 30 weeks. Paint shop group demonstrated a statistically non-significant increase of 33.4% (15 weeks) and 43.8% (30 weeks). Unexposed group also demonstrated an increase (1.4% and 23.7%) for the same time points. Only sheet metal group demonstrated a decrease (18.3% and 19.5%) at weeks 15 and 30 respectively.</p> <p>Sperm length (μm): Sheet metal group had a significant 2.1% ($p=0.02$) and 2.9% ($p=0.02$) decline at 15 and 30 weeks, but unexposed group also had a significant 2.5% ($p\leq 0.01$) decline at 15 weeks and non-significant 1.1% decrease at 30 weeks. Paint shop workers had a 1.2% decrease at 15 weeks and no change at 30 weeks. The flight line group had a decrease of 0.3% and 1.6% at 15 and 30 weeks respectively.</p> <p>Sperm width to length ratio: This ratio declined significantly in the paint shop (3.4%, $p=0.02$) and unexposed (3.1%, $p=0.05$) groups at 30 weeks. The unexposed group also reported a non-significant decrease at 15 weeks (1.5%) but the paint shop group reported an increase of 1.0% at the same time point. Sheet metal group reported an increase of 0.6% and 2.0%. Flight line group reported a decrease of 0.4% and 1.2% for the same time points.</p> <p>Percentage motility of sperm: Both flight line group (2.9% and 7.2%) and unexposed (15.9% and 8.1%) groups had a statistically non-significant increase at 15 and 30 weeks respectively. For the same time points, sheet metal group (4.6% and 3.2%) had a decline. Paint shop group had a decline of 6.4% at 15 weeks and a significant 19.5% decline ($p=0.04$) at 30 weeks. Five out of six painters had a proportional decline of 3.5% to 43.7% between baseline and 30 weeks.</p>								

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
The authors concluded that when jobs were analysed by exposure subgroups, some adverse changes were observed: men involved in aircraft painting operations, with relatively high exposure to solvents, had a significant decline in sperm motility at 30 weeks. Internal dose measurements were not associated with spermatogenic changes.								
Multigner 2007 ¹³	Cross-sectional Medical interviews to assess medical, surgical, urogenital and reproductive history through a standardised questionnaire and clinical examination	France	Men employed in a permanent position at the Paris Municipality during the period 2000–2001 and aged 20–55 years and volunteered to participate N=98	Workers exposed to ethylene and/or propylene glycol ethers (who declared using a glycol-ether containing product in last 10 years) n=48	Workers not exposed to chemicals between years 1990-2000 n=50	Semen characteristics: volume (ml), sperm density (million/ml), total sperm count (millions) motile sperm (%), sperm morphology (%) were assessed in samples collected after 3-5 days of sexual abstinence 2-3 months after exposure measurement Morning blood samples: assessed for FSH (IU/l), LH (IU/l) and Inhibin B (pg/ml) concentrations collected 2-3 months after exposure measurement Covariates: age, body mass index, alcohol and tobacco consumption, history of genital infections and season of sperm analysis	Exposure to glycol ethers and other agents with reproductive toxicity during last 10 years was assessed by direct interview on professional and/or domestic use Urine: Two urine samples, one month apart collected at the end of two working weeks assessed for metabolites of one propylene glycol ether derivative (2-methoxypropionic acid [2-MPA, derived from the minor β isomer of propylene glycol methyl ether or PGME]) and five ethylene glycol derivatives.	All males Exposed age mean (SD) 41.6 (8.7) years Non-exposed 40.3 (8.1) years
Note: only outcomes of associations with 2-MPA are reported below Findings: Urinary 2-MPA was not significant correlated with seminal volume, sperm density, sperm count, two measures of motile sperm, and morphology (Standardised coefficients of linear regression R (95% CI): 0.05 (-0.15 to 0.025), 0.03 (-0.18 to 0.23), 0.06 (-0.14 to 0.26), -0.03 (-0.23 to 0.18), 0.01 (-0.19 to 0.21) and -0.03 (-0.24 to 0.18 respectively). Urinary 2-MPA was not significant correlated with serum testosterone, FSH, LH and inhibin-B. (Standardised coefficients of linear regression R (95% CI): -0.21 ((-0.40 to 0.01), -0.12 (-0.31 to 0.08), -0.01 (-0.21 to 0.20) and 0.07 (-0.13 to 0.27) respectively).								
Plenge-Bönig 1999 ¹⁴	Cross-sectional Face-to-face interviews by trained interviewers using a modified	Germany	Male workers in printing industry exposed to toluene were selected by stratified	Time to pregnancy (TTP) n=162 Periods of unprotected	Unexposed comparison group (based on exposure assessment	Fecundability ratio (FR) [based on time to pregnancy (TTP) or periods of unprotected intercourse not leading to pregnancy (PUNP) by survival analysis with proportional hazards model	Exposure was assessed and quantified based on the work history: High: ink controllers or operators Medium: galvanisers, Low: book stackers and binders. No exposure (referent)	57% of men were >40 years

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	version of European study on infertility and subfecundity questionnaire ⁶¹		random sampling N=300	intercourse not leading to pregnancy (PUNP) n=7	in previous years	Covariates: age at time of starting unprotected intercourse, smoking, parity, ethnicity, pelvic inflammatory diseases, planning of the pregnancy and frequency of intercourse		
<p>Note: only data related to partners of male workers are reported here. The two periods, TTP or PUNP, are called time of unprotected intercourse (TUI), independent of their outcome.</p> <p>Findings:</p> <p>There was no association between exposure of men to toluene and duration of TUIs, after adjustment for age and smoking of the partner (FR 1.05; 95% CI 0.93-1.19, p=0.43). Use of the four exposure categories did not affect the result (no exposure reference group n=65 periods; low exposure: n=27 periods (FR 0.78; 95% CI 0.47-1.29), medium exposure: n=17 periods (FR 0.81; 95% CI 0.45-1.46), high exposure: n=60 periods (FR 1.11; 95% CI 0.75-1.62)</p>								
Rasmussen 1988 ¹⁵	Cross-sectional Data collected through occupational medical interview	Denmark	All known working metal degreasers in a well-defined geographical area exposed to high doses of trichloroethylene (TCE) N=99	Workers degreasing for >20h per week and who delivered a semen sample n=12	Non-exposed physicians working at university institutions n=14	Semen characteristics: sperm count (million/ml), sperm morphology, the presence of two fluorescent bodies (YFF%) in spermatozoa (which may indicate the presence of non-disjunction of the Y chromosome during spermiogenesis) Covariates: Evidence for X-ray examination, febrilia (not defined but may mean fever or fever of unknown origin), viral disease during the last three months prior to sampling, and alcohol consumption	Not reported (may have been based on the information collected at occupational medical interview)	All males Age mean (range) Exposed 35.5 (20-62) years Unexposed 36.3 (29-42) years
<p>Findings:</p> <p>Note: Briefly, spermatogonia are immature germ cells that undergo a process of mitotic division, differentiation and meiotic divisions and development into mature sperm</p> <p>There were no significant differences in sperm count and morphology in semen of exposed and unexposed groups.</p> <p>The YFF% was increased in the exposed group but this was not statistically significant (mean 1.7; 95 CI 1.4-2.0 vs. 1.4; 95% CI 1.1-1.7, p>0.10).</p> <p>The authors concluded that no effect on male germ cells was demonstrated.</p>								
Sallmén 1998 ⁶	Cross-sectional	Finland	Men monitored for exposure to organic	Wives with a clinically recognised	Wives of workers who were not-	Fecundability density ratio (FDR)	Paternal work history, detailed work tasks, and details of handling the monitored or other solvents during	Wives of males

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
[Extension of Taskinen et al. 1989] ⁷	A mailed questionnaire to collect information on fertility. New data was collected including on medical and surgical history, treatment for infertility, and menstrual history and cycle.		solvents* by the Finnish Institute of Occupational Health between 1965–1983 N=282	pregnancy of workers who were exposed to solvents n=221	exposed and had given birth without having a spontaneous abortion or a malformed child n=61	Covariates: short menstrual cycle, long or irregular menstrual cycle, older age at menarche, frequency of intercourse, maternal age, maternal exposure to organic solvents, and a variable controlling for missing information	the calendar year in which his wife's pregnancy started had been collected previously ⁷ Three exposure levels were determined: <ul style="list-style-type: none"> high/frequent (the worker handled solvents daily or biological measurements indicated clear occupational exposure) intermediate (the solvent was used 1-4 days a week, and level of exposure was low), low/rare (solvent handling occurred more rarely). 	18-21 years: 7.4% 21-31 years: 75.5% 31-35 years: 11.7% 36-40 years: 5.0%
<p>Note: *trichloroethylene (TCE), tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, and toluene</p> <p>Findings: Paternal exposure to TCE, toluene or xylene were not associated with a significant effect on fecundity when compared to unexposed fathers:</p> <ul style="list-style-type: none"> o TCE: FDR (95% CI) low 0.99 (95% CI 0.63-1.56) and intermediate/high 1.03 (95% CI 0.60-1.76) o toluene: FDR (95% CI) low/intermediate 0.76 (95% CI 0.52-1.09) and high 0.93 (95% CI 0.62-1.40) o xylene: FDR (95% CI) low/intermediate 0.75 (95% CI 0.52-1.09) and high 0.91 (95% CI 0.61-1.36) <p>High/frequent and low/intermediate exposure to organic solvents were related to decreased fecundability among primagravidas (FDR 0.36; 95% CI 0.19-0.66, and (non significantly) FDR 0.53; 95% CI 0.27-1.04 respectively) but not among couples with at least one previous pregnancy.</p>								
Xiao 2001 ¹⁸	Cross-sectional 1994-1996) Information collected via interviews	China	Married workers with ≥1 year working history at shoemaking, spray painting, or paint manufacturing exposed to high airborne levels of benzene, toluene and xylene N=56	Workers who volunteered to donate blood and semen samples n=24	Non-exposed managers matched for age, occupation and physical activity n=37	Semen characteristics including liquefaction time, pH, sperm concentration, total sperm count, percentage vitality, sperm activity, acrosin activity, seminal fructose and γ-Glutamyltransferase (γ-GT) activity were measured in semen samples collected after 48 hours of sexual abstinence Covariates: Not reported	Blood: Analysed for benzene, toluene, and xylene	Exposed Age mean (SD) 33.18 (6.88) years Unexposed 31.78 (6.36) years All males

Authors and Year	Study design	Country	Study pop ⁿ and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Findings:								
Mean concentrations of airborne benzene, toluene, xylene in workplaces were 103.34 (0~7070.3), 42.73 (0~435.8), 8.21 (0~133.1) mg/m ³ respectively (method of measurement not reported). The current ACGIH TLVs [®] are: benzene 0.5 ppm, toluene 20 ppm, xylene 100 ppm. ⁵¹								
Exposed and non-exposed groups were similar for age (years), work standing (years), duration of marriage (years), duration of smoking (years), smoking quantity (pieces per day), duration of drinking (years) and drinking volume (ml/d).								
In exposed group, benzene, toluene and xylene was present in 13, 11 and 11 out of 24 worker's blood respectively. Semen samples were provided by 17 exposed workers and benzene, toluene and xylene was present in 12, 6 and 10 worker's semen respectively. These solvents were not detected in blood and semen in the control group.								
There was no significant difference between mean volume of semen, pH value, liquefaction time, sperm density and total sperm count in exposed and unexposed groups.								
In exposed group the following parameters were reduced: sperm activity (grade) (mean (SD)): 2.52 (0.96) vs. 3.17 (0.75), p<0.01; acrosin activity (mean (SD)): 18.02 (7.24) vs. 30.74 (10.05) U/L, p<0.001. γ -GT activity 1714.43 (873.88) vs 2418.97 (411.92) U/L, p<0.05. LDH-C4 (%) 13.48 (3.64) vs 19.14 (2.10), p<0.001.								
There were negative correlations between sperm vitality, sperm activity, acrosin activity or LDH-C4 relative activity and working duration.								
The authors concluded that the results suggested that the mixture of these solvents could affect the quality of semen and sperm by influencing the function of the testicle and / or the function of the accessory gonad.								

Reports

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Toluene					
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2000) ⁴⁰	The Netherlands	Toluene – Evaluation of the effects on reproduction, recommendation for classification. The peer-reviewed report for toluene was prepared for the Ministry of Social Affairs and Employment, the Netherlands, providing with the advice regarding classifying potentially toxic effects of occupational exposures to toluene.	Toluene	Five publications that investigated occupational exposure of men to toluene (or mixture of organic solvents including toluene) and reproductive health effects were identified. <ul style="list-style-type: none"> One study found spontaneous abortion was slightly, not statistically significantly, higher among the wives of men occupationally exposed to toluene (crude OR 1.5; CI 0.9-2.5). However, high or frequent exposure to toluene was associated with spontaneous abortion OR 2.3; CI 1.1-4.7). Another study found median serum concentration of FSH, LG and free testosterone were lower in the toluene exposed group. 	Taskinen et al. 1989 ⁷ Svensson et al. 1992 ¹⁶

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				<ul style="list-style-type: none"> ○ In another study, increasing concentrations of toluene were significantly associated with decreasing concentrations of LH and testosterone. ○ In a prospective study in which workers were exposed to a number of solvents, mean values of most sperm measures of the exposed group remained within the normal range throughout the 30 weeks exposure period even though some variations in subgroup analysis were observed. ○ Another study reported exposure of male workers did not result in an effect on fecundity (fecundity ratio 1.05; 95% CI 0.93-1.19). 	<p>Svensson et al. 1992¹⁷</p> <p>Lemasters et al. 1999⁸</p> <p>Plenge-Bönig and Karmaus 1999¹⁴</p>
<p>Findings: The committee concluded that it is not clear if the observed effects were due to toluene exposure alone or to other compounds in the working place and concluded that therefore, available data are not sufficient to assess its effects on human fertility and draw any conclusion for toluene.</p>					
Agency for Toxic Substances and Disease Registry (ATSDR) (2017) ⁴⁶	USA	<p>Draft Toxicological Profile for Toluene</p> <p>The profile was prepared in accordance with guidelines developed by ATSDR and the US Environmental Protection Agency (EPA) and in support of Department of Defense needs.</p> <p>The health effects section and human studies findings were considered in relation to this Evidence Profile.</p>	Toluene	<p>Six publications that investigated occupational exposure of men to toluene (or mixture of organic solvents including toluene) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> ○ The incidence of spontaneous abortion exceeded population norms among the wives of small groups of 28–48 male workers exposed to toluene; however, exposure levels were not reported in these studies and only a small number of cases were included. ○ In another study, fecundity was decreased in female workers, but not in male workers. ○ No statistically significant changes were observed in serum FSH, LH, or testosterone levels in male rotogravure workers compared with unexposed referents ○ Significantly decreased serum levels of LH, FSH, and testosterone were found in male toluene-exposed rotogravure printers, compared with unexposed referents. ○ Increasing workplace air concentrations were not significantly ($p>0.05$) associated with plasma concentrations of LH, FSH, testosterone, or prolactin, after adjustments for age, in a study of male toluene-exposed printers 	<p>Lindbohm et al. 1992⁷⁷</p> <p>Taskinen et al. 1989⁷</p> <p>Plenge-Bönig and Karmaus 1999¹⁴</p> <p>Gericke et al. 2001¹⁰</p> <p>Svensson et al. 1992¹⁶</p> <p>Svensson et al. 1992¹⁷</p>
<p>Findings: Current data do not provide convincing evidence that acute or repeated inhalation exposure to toluene in males may cause reproductive effects.</p>					
National Research Council (NRC) 2014 ⁴⁴	USA	Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 17	Toluene	Three publications that investigated exposure of men to toluene and developmental and reproductive health effects were identified.	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		Committee on Acute Exposure Guideline Levels; Committee on Toxicology; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Research Council		<ul style="list-style-type: none"> ○ An experimental study that reported subtle changes in LH and FSH in men following controlled exposure to 3-h, 50 ppm via a mouthpiece. No effect on blood testosterone was found. ○ Another study found no effect of chronic toluene exposure on FSH, LH, or testosterone of 1,077 male subjects compared with a referent group. ○ Some indications of lower concentrations of LH, FSH and testosterone were identified in another study. 	<p>Luderer et al. 1999⁶⁷</p> <p>Gericke et al. 2001¹⁰</p> <p>Svensson et al. 1992¹⁶</p>
<p>Findings: Data regarding human developmental and reproductive toxicity are restricted to chronic exposures and include only continuous occupational or abuse situations. These studies provide little quantitative information regarding dose response.</p>					
<p>Trichloroethylene</p>					
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2003) ⁴¹	The Netherlands	<p>Trichloroethylene – Evaluation of the effects on reproduction, recommendation for classification.</p> <p>The peer-reviewed report for Trichloroethylene was prepared for the Ministry of Social Affairs and Employment, the Netherlands, to provide advice regarding classifying potentially toxic effects of occupational exposures to toluene.</p>	Trichloroethylene	<p>Three publications that investigated occupational exposure of men to trichloroethylene (or mixture of organic solvents including trichloroethylene) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> ○ One study reported no difference between exposed and non-exposed groups in terms of sperm count or morphology, but in the exposed group a slightly higher (statistically insignificant) prevalence of mature spermatozoa containing two fluorescent Y bodies was observed (may be indicative of Y-chromosomal nondisjunction). ○ Another study that investigated exposure to styrene, xylene, toluene, tetrachloroethylene, trichloroethylene and 1,1,1-trichloroethane reported no association between paternal occupational exposures to trichloroethylene and the incidence of spontaneous abortion (crude OR 1.0; 95% CI 0.6-2.0). ○ Another study that included no non-exposed control group compared results with WHO criteria. There were no differences in volume, motility and morphology among the high-exposure (urine trichloroacetic acid concentration > 25 mg/g creatinine) and low-exposure (urine trichloroacetic acid concentration < 25 mg/g creatinine) groups. ○ In the same group of workers serum concentrations of several hormones were measured. Except for a positive correlation between urine levels of trichloroacetic acid and insulin levels there were no consistent relationships 	<p>Rasmussen et al. 1988¹⁵</p> <p>Taskinen et al. 1989⁷</p> <p>Chia et al. 1996²</p> <p>Chia et al. 1997¹ Goh et al. 1998³</p>

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				between the urine concentration of trichloroacetic acid and serum levels of hormones.	
<p>Findings: The report did not identify studies relevant to paternal occupational exposure and developmental toxicity. The human studies on the potential effects of occupational exposure to trichloroethylene on fertility did not show significant effects or the results of the studies were inconsistent and difficult to interpret. Therefore committee decided not to classify trichloroethylene with respect to effects on fertility because of lack of appropriate data.</p>					
Agency for Toxic Substances and Disease Registry (ATSDR) (2014) ⁴⁷ and US Environmental Protection Agency (EPA) 2011 ³⁵	USA	<p>Draft Toxicological Profile for Trichloroethylene</p> <p>An ASTDR toxicological profile succinctly characterises the toxicological and adverse health effects information for the toxic substances of the profile. The profile identifies and reviews the key literature (that has been peer reviewed) of substances' toxicological properties and the pertinent literature is presented but described in less detail than key studies. The focus of the profiles is on health and toxicological information.</p> <p>The health effects section and human studies findings were considered in relation to this Evidence Profile.</p> <p>The US EPA Toxicological Review is intended to provide scientific support and rationale for the hazard and dose-response assessment in Information on the Integrated Risk Information System (IRIS) pertaining to chronic exposure to trichloroethylene.</p>	Trichloroethylene (TCE)	<p>Eight publications that investigated occupational exposure of men to TCE (or mixture of organic solvents including trichloroethylene) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> ○ Men working in dry cleaning or metal degreasing reported 30% decreased potency ○ Male workers in a money printing shop reported decreased libido (33%), compared to 3 men in the control group (10%) ○ TCE exposed metal degreasers reported non-significant increase in percentage of two YFF in spermatozoa, but no effect on sperm count or morphology ○ Another study on Chinese descent working in an electronics factory reported decreased normal sperm morphology and hyperzoospermia ○ Another study on the same population reported increased DHEAS and decreased FSH, SHBG and testosterone levels; dose-response observed ○ Another study on the same population reported decreased serum levels of testosterone and SHBG were significantly correlated with years of exposure to TCE; increased insulin levels for exposure <2 years ○ A study on men occupationally exposed to solvents, no effect on fecundability (as measured by time to pregnancy) was reported. ○ In another study on male mechanics, infertility could not be assessed for association with TCE as the controls were five men also in treatment for infertility 	<p>Bardodej and Vyskocil 1956⁶⁵ El Ghawabi et al. 1973⁶⁶</p> <p>Rasmussen et al. 1988¹⁵</p> <p>Chia et al. 1996²</p> <p>Chia et al. 1997¹</p> <p>Goh et al. 1998³</p> <p>Sallmen et al. 1998⁶</p> <p>Forkert et al. 2003⁶⁴</p>
<p>Note: The two reports are presented together above as both reports included the same primary epidemiological studies.</p> <p>Findings: The reports did not offer conclusions based only on the above studies. The ATSDR report summarised the effects of TCE exposure in men and reproductive behaviour, sperm quality and fertility and did not offer conclusions specific to exposure of TCE in men. However, it stated that toxicity of TCE to the male reproductive system is demonstrated in animals. The EPA reported that observed adverse reproductive health effects of TCE exposure in men were altered sperm morphology, hyperzoospermia, altered endocrine function, decreased sexual drive and function, and altered fertility.</p>					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
National Research Council (NRC) 2007 ⁴³	USA	Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues by Committee on Human Health Risks of Trichloroethylene; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies of the NRC	Trichloroethylene (TCE)	<p>Eight publications that investigated occupational exposure of men to TCE (or mixture of organic solvents including TCE) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> One study reported decreased libido in male workers exposed to TCE but no control group was present. In another study, sperm counts and morphology as well as Y chromosomal nondisjunction during spermatogenesis did not differ between male factory workers exposed to TCE at least 20 hours/week and physician controls In another study, there were no differences between groups for any of the sperm parameters including volume, motility, and morphology; the values for both groups were within the standards of the World Health Organization (WHO) except density. Further analysis of the same group revealed that the age of workers and years of exposure to TCE were significantly negatively correlated with testosterone concentrations. When the men were stratified by years of exposure, FSH was significantly reduced only in men exposed >7 years. LH and testosterone were statistically equivalent for all durations. The third study on the same population found that Sex-hormone-binding globulin was significantly reduced for 4-6 years and for >6 years of TCE exposure. One study examined eight mechanics with clinical infertility who had occupational exposure to TCE for at least 2 years. Seminal fluid from all eight subjects contained TCE, chloral, and trichloroethanol, whereas dichloroacetic acid and trichloroacetic acid were present in only two and one sample, respectively. Neither TCE nor its metabolites was detected in the five control male seminal fluid samples. Spontaneous abortion was associated with increased paternal exposure to solvents (adjusted OR 2.3; 95% CI 1.1, 5.0). 	<p>Bardodej and Vyskocil 1956⁶⁵ Rasmussen et al. 1988¹⁵</p> <p>Chia et al. 1996²</p> <p>Chia et al. 1997¹</p> <p>Goa et al. 1998³</p> <p>Forkert et al. 2003⁶⁴</p> <p>Taskinen et al. 1989⁷</p>
The committee recommended that more research is needed to better understand the effects of TCE on sperm and possible consequences for reproduction. The committee also added mechanistic studies are needed to determine what metabolites are responsible for the effects.					
Xylene					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2000) ³⁹	The Netherlands	Xylene – Evaluation of the effects on reproduction, recommendation for classification. The peer-reviewed report for Xylene was prepared for the Ministry of Social Affairs and Employment, the Netherlands, to provide advice on classifying potentially toxic effects of occupational exposures to xylene.	Xylene	Three publications that investigated occupational exposure of men to xylene (or mixture of organic solvents including xylene) and reproductive health effects were identified. <ul style="list-style-type: none"> One study reported that the incidence of spontaneous abortion among the wives of men frequently exposed to xylene or exposed to high concentrations of xylene was slightly, but not statistically significantly, increased (adjusted OR 1.6; 95% CI 0.8-3.2). This study also found that there was no significant association between paternal exposure to xylene and the incidence of congenital malformations (OR 1.6; 95% CI 0.4-5.7). In a prospective study, in which workers were exposed to a number of solvents mean values of most sperm measures of the exposed group remained within the normal range throughout the 30 week exposure period even though some variations in subgroup analysis were observed. In another study in which the workers were exposed to number of solvents including xylene (ethylbenzene, benzene and toluene), the incidence of abnormal characteristics found in the semen of exposed men was higher than in the semen of unexposed workers, including alterations in viscosity, liquefaction capacity, sperm count, sperm motility and the proportion of sperm with normal morphology. 	Taskinen et al. 1989 ⁷ Lemasters et al. 1999 ⁸ De Celis et al. 2000 ⁹
<p>Findings: In the studies of Taskinen et al.,⁷ no effects of exposure to xylene (no other exposures) on abortion and fecundity were observed. In the studies of Lemasters et al.⁸ and of De Celis et al.⁹ only the effects of exposure to a mixture of solvents on sperm parameters were studied.</p> <p>The committee concluded that occupational exposure to mixtures of organic solvents, including xylenes, has been shown to increase the incidence of spontaneous abortion among the wives of exposed men and to increase the incidence of abnormal characteristics of sperm of exposed men.</p>					
Agency for Toxic Substances and Disease Registry (ATSDR) (2007) ³⁶	USA	Toxicological Profile for Xylene An ASTDR toxicological profile characterises the toxicological and adverse health effects information for the toxic substances of the profile. The profile identifies and reviews the key literature (that has been peer reviewed) of substances' toxicological properties and the pertinent literature	Xylene	One publication that investigated occupational exposure of men to xylene (or mixture of organic solvents including xylene) and reproductive health effects were identified. <ul style="list-style-type: none"> No human data were available regarding endocrine effects following inhalation exposure to mixed xylene or xylene isomers. No studies were located regarding reproductive effects in humans following oral exposure to mixed xylene or individual isomers. 	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		is presented but described in less detail than key studies. The focus of the profiles is on health and toxicological information. The health effects section and human studies findings were considered in relation to this Evidence Profile.		<ul style="list-style-type: none"> No studies were located regarding reproductive effects in humans or animals after dermal exposure to mixed xylene or xylene isomers. However, one study suggested that paternal exposure to xylenes in the workplace may increase the likelihood of abortion; however, this study was limited by the size of the sample population. 	Taskinen et al. 1989 ⁷
<p>Findings: Available studies of developmental or reproductive toxicity from occupational exposure to xylene are not definitive because of the small number of subjects and/or concurrent exposure to other chemicals.</p>					
Ethylbenzene					
Agency for Toxic Substances and Disease Registry (ATSDR) (2010) ⁴⁵	USA	Toxicological Profile for Ethylbenzene	Ethylbenzene	<p>No publication that investigated occupational exposure of men to ethylbenzene (or mixture of organic solvents including ethylbenzene) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> No studies were located regarding reproductive effects in humans following inhalation exposure to ethyl-benzene. No studies were located regarding developmental effects in humans following inhalation exposure to ethylbenzene. No studies were located regarding reproductive effects in humans following oral exposure to ethylbenzene. No studies were located regarding developmental effects in humans or animals following oral exposure to ethylbenzene. No studies were located regarding the reproductive health or developmental effects in humans after dermal exposure to ethylbenzene. 	
<p>Findings: No human studies that investigated occupational exposure of ethylbenzene in men and reproductive health outcomes were identified.</p>					
Stoddard Solvent					
Agency for Toxic Substances and Disease Registry (ATSDR) (1995) ³⁸	USA	Toxicological profile for Stoddard Solvent	Stoddard Solvent	<p>Two publications that investigated exposure of men to Stoddard Solvent and reproductive hormones were identified.</p> <ul style="list-style-type: none"> Seven men who were exposed for 6 hours/day for 5 days to 616 mg/m³ of vaporized white spirits had a decrease (p<0.05) in serum FSH levels at 24 and 96 hours after the initiation of exposure as compared to pre-exposure levels. In another study, 11 men in a printing factory were occupationally exposed to a wide variety of solvents, 	Pedersen and Cohr 1984 ⁶⁸

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				including 294 mg/m ³ of white spirits for 1-17 years. Sperm counts, motility, and morphology were monitored for 2 months, and all values were normal.	Tuohimaa and Wichmann 1981 ⁶⁹
Findings: No human studies for oral or dermal exposure of Stoddard Solvent in men and reproductive health outcomes or developmental abnormalities were identified.					
Multiple solvents					
Institute of Medicine (IOM) of the National Academies (2003) ⁴²	USA	<p>Gulf War and Health: Vol 2 Insecticides and solvents</p> <p>The IOM appointed the Committee on Gulf War and Health to determine the extent to which available scientific data permits meaningful conclusion in relation agents, hazards, medicines, vaccines or illnesses. The IOM assisted the US Veterans Affairs and Congress in evaluating the scientific literature regarding exposures to the Gulf War.</p> <p>The focus of this volume was on long term adverse health outcomes of exposures during Gulf War, and included review of the literature in relation to reproductive and developmental effects of exposure to solvents and mixture of solvents were considered.</p>	Multiple solvents	<p>Eight publications that investigated occupational exposure of men to organic solvents and semen and semen characteristics were identified.</p> <ul style="list-style-type: none"> ○ One study reported that exposure to solvents, defined by work area and personal measurements, was not associated with any decline below normal limits in the measures of semen quality as defined by WHO reference values. There were conflicting results from subgroup analysis based on the job description, and the results were mostly within reference ranges, the study concluded that these conflicting results are even less suggestive of an association between exposure to solvents and semen characteristics. ○ In a case-control study that investigated male painters and their partners for infertility consultation, Changes in semen parameters were not found to be associated with exposure to organic solvents as a general category when evaluated in the total population (OR 0.98; 95% CI 0.60–1.59) or in men with primary infertility (OR 1.15; 95% CI 0.66–1.99).* ○ Reported on two studies in Canada: One study reported increased risk of low active sperm count with high exposure to solvents (OR 3.83; 95% CI 1.37–10.65) and moderate exposure (OR 2.07; 95% CI 1.24–3.44). Another study reported a strong association only in the men with high exposure to solvents (OR 2.90; 95% CI 1.01–8.34).* ○ Another study found associations between solvent exposure and several measures of abnormal semen characteristics (based on WHO guidelines).* ○ A study on metal workers exposed to trichloroethylene found no association between exposure and semen characteristics ○ Two studies found that exposure to toluene was associated with lower blood concentrations of FSH, LH, 	<p>Lemasters et al. 1999⁸</p> <p>Tielemans et al. 1999⁷²</p> <p>Cherry et al. 2001⁷⁰</p> <p>Oliva et al. 2001⁸</p> <p>Rasmussen et al. 1988¹⁵</p> <p>Svensson et al. 1992^{16, 17}</p>

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				<p>prolactin, and testosterone in young male rotogravure printers when compared with factory workers.</p> <ul style="list-style-type: none"> ○ Studies of exposure to trichloroethylene among 85 male workers found moderate decreases in FSH and testosterone with increasing duration of exposure <p>Three publications that investigated occupational exposure of men to organic solvents and infertility were identified.</p> <ul style="list-style-type: none"> ○ One study did not find an effect on TTP in the men who were exposed to toluene on fecundity (FR 1.05; 95% CI 0.93–1.19) and there was no relation to exposure category (none, low, medium, or high). ○ Another study did not find any association between solvent exposure and TTP; an adjusted fecundability measure (fecundability density ratio [FDR]) of 0.80 (95% CI 0.57–1.11) for high or frequent paternal exposure and a similar result for low or intermediate exposure (FDR = 0.74, 95% CI 0.51–1.06). ○ A study of solvent-exposed male workers also found an elevation in the risk of conception delay of more than 6 months (OR 1.69; 95% CI 0.62–4.62).* <p>Two publications that investigated occupational exposure of men to organic solvents and spontaneous abortion were identified.</p> <ul style="list-style-type: none"> ○ One study reported Increased risk associated with exposure to solvents used in petroleum refineries (OR 2.2; 95% CI 1.3–3.8) and solvents used in the manufacture of rubber products (OR 1.9; 95% CI = 1.2–2.8).* ○ Another reported increases in risk in association with high or frequent paternal exposure to toluene (OR 2.3; 95% CI 1.1–4.7), high or frequent use of organic solvents (OR 2.6; 95% CI 1.2–5.9), and high or frequent use of miscellaneous organic solvents (OR 2.1; 95% CI 1.1–3.9). <p>One publication that investigated occupational exposure of men to solvents and congenital malformations were identified.</p> <ul style="list-style-type: none"> ○ One study did not find an increased risk associated with paternal exposure to solvents at any level (OR 0.7; 95% CI 0.4–1.1), low solvent exposure (OR 0.6), or moderate to high solvent exposure (OR 0.9).* 	<p>Chia et al. 1997¹ Goa et al. 1998³</p> <p>Plenge-Bonig and Karmaus 1999¹⁴</p> <p>Sallmén et al. 1998⁶</p> <p>Figa-Talamanca et al. 2000⁷³</p> <p>Lindbohm et al., 1991¹²</p> <p>Taskinen et al., 1989⁷</p> <p>Blatter et al. 1997⁷⁴</p>
<p>Note: *Analysis for general solvent exposure Findings:</p>					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
<p>The committee concluded that there is inadequate/insufficient evidence to determine whether an association exists between exposure to specific organic solvents under review or solvent mixtures and male or female infertility after cessation of exposure.</p> <p>Studies of TTP and other measures of infertility have found inconsistent associations with exposure to solvents regarding paternal exposures.</p> <p>Only a few studies have examined the potential for an association between preconception exposure to solvents among males and spontaneous abortion, and their results have been inconsistent.</p> <p>Few studies of solvent exposure and congenital malformations focused on preconception exposure of either mothers or fathers.</p>					
Methyl ethyl ketone					
Agency for Toxic Substances and Disease Registry (ATSDR) (1992) ³² Addendum 2010 ³³	USA	Toxicological Profile for 2-Butanone The purpose of the addendum is to provide a non-peer reviewed supplement of the scientific data published in the open peer-reviewed literature since the release of the profile in 1992.	Methyl Ethyl ketone		
<p>Findings: No publications that investigated occupational exposure of men to 2-Butanone and reproductive or developmental effects following inhalation, oral or dermal exposure were identified.</p>					
Acetone					
Agency for Toxic Substances and Disease Registry (ATSDR) (1994) ³⁷ Addendum 2011 ³⁴	USA	Toxicological profile for Acetone The purpose of the addendum is to provide a non-peer reviewed supplement of the scientific data published in the open peer-reviewed literature since the release of the profile in 1994.	Acetone		
<p>Findings: No publications that investigated occupational exposure of men to acetone and reproductive or developmental effects following inhalation, oral or dermal exposure were identified.</p>					

References

1. Chia SE, Goh VH, Ong CN. Endocrine profiles of male workers with exposure to trichloroethylene. *Am J Ind Med.* 1997;32(3):217-22.
2. Chia SE, Ong CN, Tsakok MF, Ho A. Semen parameters in workers exposed to trichloroethylene. *Reprod Toxicol.* 1996;10(4):295-9.
3. Goh VH, Chia SE, Ong CN. Effects of chronic exposure to low doses of trichloroethylene on steroid hormone and insulin levels in normal men. *Environ Health Perspect.* 1998;106(1):41-4.
4. Brown A, Gibson R, Tavener M, Guest M, D'Este C, Byles J, et al. Sexual function in F-111 maintenance workers: the study of health outcomes in aircraft maintenance personnel. *J Sex Med.* 2009;6(6):1569-78.
5. D'Este C, Attia J, Brown A, Byles J, Schofield PW, Gibberd R, et al. Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP). Phase III Report on the General Health and Medical Study. Department of Veterans' Affairs 2004. Available at [<https://web.archive.org/web/20080309023912/http://www.defence.gov.au/health/research/shoamp/i-SHOAMP.htm>], Accessed (22/04/2018)
6. Sallmen M, Lindbohm ML, Anttila A, Kyyronen P, Taskinen H, Nykyri E, et al. Time to pregnancy among the wives of men exposed to organic solvents. *Occup Environ Med.* 1998;55(1):24-30.
7. Taskinen H, Anttila A, Lindbohm ML, Sallmen M, Hemminki K. Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand J Work Environ Health.* 1989;15(5):345-52.
8. Lemasters GK, Olsen DM, Yiin JH, Lockey JE, Shukla R, Selevan SG, et al. Male reproductive effects of solvent and fuel exposure during aircraft maintenance. *Reprod Toxicol.* 1999;13(3):155-66.
9. De Celis R, Feria-Velasco A, Gonzalez-Unzaga M, Torres-Calleja J, Pedron-Nuevo N. Semen quality of workers occupationally exposed to hydrocarbons. *Fertil Steril.* 2000;73(2):221-8.
10. Gericke C, Hanke B, Beckmann G, Balthes MM, Kuhl KP, Neubert D. Multicenter field trial on possible health effects of toluene. III. Evaluation of effects after long-term exposure. *Toxicology.* 2001;168(2):185-209.
11. Hooiveld M, Haveman W, Roskes K, Bretveld R, Burstyn I, Roeleveld N. Adverse reproductive outcomes among male painters with occupational exposure to organic solvents. *Occup Environ Med.* 2006;63(8):538-44.

12. Lindbohm ML, Hemminki K, Bonhomme MG, Anttila A, Rantala K, Heikkila P, et al. Effects of paternal occupational exposure on spontaneous abortions. *Am J Public Health*. 1991;81(8):1029-33.
13. Multigner L, Ben BE, Arnaud I, Haguenoer JM, Jouannet P, Auger J, et al. Glycol ethers and semen quality: a cross-sectional study among male workers in the Paris Municipality. *Occup Environ Med*. 2007;64(7):467-73.
14. Plenge-Bonig A, Karmaus W. Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. *Occup Environ Med*. 1999;56(7):443-8.
15. Rasmussen K, Sabroe S, Wohlert M, Ingerslev HJ, Kappel B, Nielsen J. A genotoxic study of metal workers exposed to trichloroethylene. Sperm parameters and chromosome aberrations in lymphocytes. *Int Arch Occup Environ Health*. 1988;60(6):419-23.
16. Svensson BG, Nise G, Erfurth EM, Nilsson A, Skerfving S. Hormone status in occupational toluene exposure. *Am J Ind Med*. 1992;22(1):99-107.
17. Svensson BG, Nise G, Erfurth EM, Olsson H. Neuroendocrine effects in printing workers exposed to toluene. *Br J Ind Med*. 1992;49(6):402-8.
18. Xiao G, Pan C, Cai Y, Lin H, Fu Z. Effect of benzene, toluene, xylene on the semen quality and the function of accessory gonad of exposed workers. *Ind Health*. 2001;39(2):206-10.
19. Buck Louis GM, Lynch CD, Cooney MA. Environmental influences on female fecundity and fertility. *Semin Reprod Med*. 2006;24(3):147-55.
20. Attia JR, D'Este C, Schofield PW, Brown AM, Gibson R, Tavener M, et al. Mental health in F-111 maintenance workers: the study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP) general health and medical study. *J Occup Environ Med*. 2006;48(7):682-91.
21. Australian Institute of Health and Welfare (AIHW). Fourth study of mortality and cancer incidence in aircraft maintenance personnel: a continuing study of F-111 Deseal/Reseal personnel 2016. Cancer series no. 99. Cat. no. CAN 98. . Canberra, Australia: Australian Institute of Health and Welfare 2016. Available at [<https://www.aihw.gov.au/getmedia/6241bbae-0a7d-400f-b7ec-7ce791d2bf77/20110.pdf.aspx?inline=true>], Accessed (14/11/2018)
22. Whitworth J, Moore M, Roder D, Glass D, S. H. Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP). Phase 1, Literature Review, Final Report. 2003 Available at [http://www.defence.gov.au/Health/SHC/docs/Study_of_Health_Outcomes_Aircraft_Maintenance_Personnel.pdf], Accessed (18/09/2018)

23. Bowling FG. Report on the Molecular Investigations into the Jet Fuel and solvent exposure in the DeSeal/ReSeal programme conducted at the Mater Research Institute (UQ), Brisbane. 2014. Available at [http://www.defence.gov.au/FOI/Docs/Disclosures/123_1415_Report.pdf], Accessed (22/04/2018)
24. Varker T, Forbes D, Dell L, Weston A, Merlin T, Hodson S, et al. A Developer's Guide to Undertaking Rapid Evidence Assessments (REAs), Version 2.0. Guide prepared for the Department of Veterans Affairs. Australian Centre for Posttraumatic Mental Health; 2014. Available at [<https://www.dva.gov.au/sites/default/files/files/A%20Developers%20Guide%20to%20Undertaking%20REAs%20-%20June%202016.pdf>], Accessed (22/04/2018)
25. Kelsall HL, Glass DG, Priestly BG, Bell RJ, Newman DG, Wallace EM, et al. Literature review of effects of fuel and solvent exposure on human female reproductive outcomes. Report prepared for the Department of Veterans' Affairs. Monash University; 2017. Available at [https://www.dva.gov.au/sites/default/files/Question_14_Fuel_and_Solvent_Exposure_Technical_Report_Sept_2017.pdf], Accessed (22/04/2018)
26. Kelsall HL, Glass DC, Priestly BG, McLachlan R, Bell RJ, Pattuwage L, et al. Literature review of effects of fuel exposure on human male reproductive outcomes. A Rapid Evidence Assessment. . Report prepared for the Department of Veterans' Affairs. Monash University; 2018. [*Submitted for publication*]
27. ATSDR. Toxicological profile for JP-5, JP-8, and jet A fuels. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry (ATSDR) and U.S. Department of Health and Human Services; 2017. Available at [<https://www.atsdr.cdc.gov/toxprofiles/tp121.pdf>], Accessed (22/04/2018)
28. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for lead. US Department of health and human services. Atlanta, Georgia: U.S. Department of Health and Human Services, Public Health Service Agency for Toxic Substances and Disease Registry; 2007. Available at [<https://www.atsdr.cdc.gov/toxprofiles/tp13.pdf>], Accessed (21/09/2018)
29. Bonde JP. Workplace exposures and reproductive health. 10th ed. ed. Baxter P, Cockcroft A, Durrington P, Harrington J, editors: London: CRC Press; 2010.
30. Giannakopoulos NN, Rammelsberg P, Eberhard L, Schmitter M. A new instrument for assessing the quality of studies on prevalence. Clin Oral Investig. 2012;16(3):781-8.
31. University of Tasmania. Systematic Reviews for Health: Systematic Review Tools 2018 [Available from: <https://utas.libguides.com/SystematicReviews/Tools>].

32. ATSDR. Toxicological Profile for 2-Butanone. Atlanta, Georgia: Agency for Toxic Substances and Disease Registry, U.S. Public Health Service; 1992. Available at [<https://www.atsdr.cdc.gov/ToxProfiles/tp29.pdf>], Accessed (03/10/2018)
33. ATSDR. Addendum to the Toxicological Profile for 2-Butanone. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Division of Toxicology and Environmental Medicine; 2010. Available at [https://www.atsdr.cdc.gov/toxprofiles/2-butanone_addendum.pdf], Accessed (03/10/2018)
34. ATSDR. Addendum to the Toxicological Profile for Acetone. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Division of Toxicology and Environmental Medicine; 2011. Available at [https://www.atsdr.cdc.gov/toxprofiles/acetone_addendum.pdf], Accessed (03/10/2018)
35. Bale A, Barone S, Brown R, Caldwell JC, Chen C, Chiu WA, et al. Toxicological review of trichloroethylene. Washington, DC: US Environmental Protection Agency; 2011. Report No.: EPA/635/R-09/011F. Available at [https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf], Accessed (03/10/2018)
36. Fay M, Risher JF, Wilson JD, Fransen M, L. I. Toxicological Profile for Xylene. Atlanta, Georgia: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR); 2007. Available at [<https://www.atsdr.cdc.gov/ToxProfiles/tp71.pdf>], Accessed (03/10/2018)
37. Hansen H, Wilbur SB. Toxicological Profile for Acetone. Atlanta, Georgia: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR); 1994. Available at [<https://www.atsdr.cdc.gov/ToxProfiles/tp21.pdf>], Accessed (03/10/2018)
38. Harris O, Bittner PM. Toxicological Profile for Stoddard Solvent. Atlanta, Georgia: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR); 1995. Available at [<https://www.atsdr.cdc.gov/ToxProfiles/tp79.pdf>], Accessed (03/10/2018)
39. Health Council of the Netherlands. Committee for Compounds toxic to reproduction. Xylene; Evaluation of the effects on reproduction, recommendation for classification. The Hague; 2000. Report No.: 2000/10OSH. ISBN: 90-5549-405-4. Available at [<https://www.gezondheidsraad.nl/documenten/adviezen/2001/12/20/xyleen-evaluation-of-the-effects-on-reproduction-recommendation-for-classification>], Accessed (03/10/2018)
40. Health Council of the Netherlands. Committee for Compounds toxic to reproduction. Toluene; Evaluation of the effects on reproduction, recommendation for classification. The Hague; 2000. Report No.: 2000/09OSH. ISBN: 90-5549-406-2. Available at [<https://www.gezondheidsraad.nl/documenten/adviezen/2001/12/20/tolueen-evaluation-of-the-effects-on-reproduction-recommendation-for-classification>], Accessed (03/10/2018)

41. Health Council of the Netherlands. Committee for Compounds toxic to reproduction. Trichloroethylene. evaluation of the effects on reproduction, recommendation for classification. The Hague: Health Council of the Netherlands; publication no. 2003/09OSH. ISBN: 90-5549-509-3; 2003. Available at [<https://www.gezondheidsraad.nl/documenten/adviezen/2003/12/22/trichloroethylene>], Accessed (3/10/2018)
42. IOM. Gulf War and Health: Volume 2: Insecticides and Solvents. Washington, DC: Institute of Medicine, The National Academies Press; 2003. 616 p.
43. NRC. Assessing the human health risks of trichloroethylene: Key scientific issues. Committee on Human Health Risks of Trichloroethylene Board on Environmental Studies and Toxicology Division on Earth and Life Studies. Washington, D.C. : National Research Council, National Academies Press 2007. 378 p.
44. NRC. Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 17. The National Academic Press, Washington D.C.: Committee on Acute Exposure Guideline Levels; Committee on Toxicology; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Research Council (NRC); 2014. Report No.: ISBN 978-0-309-38733-0. Available at [<https://www.nap.edu/catalog/18796/acute-exposure-guideline-levels-for-selected-airborne-chemicals-volume-17>], Accessed (04/10/2018)
45. Taylor J, Abadin H, Hicks H, Tarrago O, Cronin D, Klotzbach JM, et al. Toxicological Profile for Ethylbenzene. Atlanta, Georgia: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR); 2010. Available at [<https://www.atsdr.cdc.gov/ToxProfiles/tp110.pdf>], Accessed (03/10/2018)
46. Taylor J, Fay M, Williams R, Wilbur S, McClure P, Zaccaria K, et al. Toxicological Profile for Toluene. Atlanta, Georgia: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR); 2017. Available at [<https://www.atsdr.cdc.gov/ToxProfiles/tp56.pdf>], Accessed (03/10/2018)
47. Todd GD, Ruiz P, Mumtaz M, Taylor JB, Wohlers DW, Diamond GL, et al. Draft Toxicological Profile for Trichloroethylene. Atlanta, Georgia: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR); 2014. Available at [<https://www.atsdr.cdc.gov/ToxProfiles/tp19.pdf>], Accessed (03/10/2018)
48. Swartz MK. The PRISMA statement: a guideline for systematic reviews and meta-analyses. *J Pediatr Health Care*. 2011;25(1):1-2.
49. Guest M, Boggess M, Attia J, D'Este C, Brown A, Gibson R, et al. Hearing impairment in F-111 maintenance workers: the study of health outcomes in aircraft maintenance personnel (SHOAMP) general health and medical study. *Am J Ind Med*. 2010;53(11):1159-69.
50. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49(6):822-30.

51. ACGIH. 2018 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices (ACGIH) ACoGIH, editor. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, Signature Publications; 2018.
52. Neubert D, Bochert G, Gericke C, Hanke B, Beckmann G, Toluene Field Study G. Multicenter field trial on possible health effects of toluene. I. Toluene body burdens in workers of the rotogravure industry. *Toxicology*. 2001;168(2):139-57.
53. Hogstedt C, Hane M, Axelson O. Diagnostic and Health Care Aspects of Workers Exposed to Solvents. Zenz C., editor: Year Book Medical Publishers, Inc., Chicago; 1980. 249-58 p.
54. Burstyn I, Kromhout H. Trends in inhalation exposure to hydrocarbons among commercial painters in The Netherlands. *Scand J Work Environ Health*. 2002;28(6):429-38.
55. American Conference of Governmental Industrial Hygienists (ACGIH). Threshold limit values and biological exposure indices for 1994-1995. 3rd ed. [Cited in: Chia SE, Ong CN, Tsakok MF, Ho A. Semen parameters in workers exposed to trichloroethylene. *Reprod Toxicol*. 1996;10(4):295-9.]. American Conference of Governmental Industrial Hygienists, Cincinnati; 1995.
56. World Health Organization (WHO). Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 3rd ed: Published on behalf of the World Health Organization by Cambridge University Press, New York; 1993.
57. National Institute for Occupational Safety and Health (NIOSH). Manual of analytical methods. 3rd ed. [Cited In: De Celis R, Feria-Velasco A, Gonzalez-Unzaga M, Torres-Calleja J, Pedron-Nuevo N. Semen quality of workers occupationally exposed to hydrocarbons. *Fertil Steril*. 2000;73(2):221-8.]. Second supplement. DHEW (NIOSH) Publication No. 78-210. Cincinnati (OH): National Institute for Occupational Safety and Health; 1987.
58. World Health Organization (WHO). Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 3rd ed. [Cited in: Lemasters GK, Olsen DM, Yiin JH, Lockey JE, Shukla R, Selevan SG, et al. Male reproductive effects of solvent and fuel exposure during aircraft maintenance. *Reprod Toxicol*. 1999;13(3):155-66.]. World Health Organization, Cambridge University Press, New York. (92-13650 CIP). 1992.
59. Rowe PJ, Frank H, Comhaire TB, Hargreave HJM. WHO manual for the standardized investigation and diagnosis of the infertile couple. [Cited In: Multigner L, Ben BE, Arnaud I, Haguenoer JM, Jouannet P, Auger J, et al. Glycol ethers and semen quality: a cross-sectional study among male workers in the Paris Municipality. *Occup Environ Med*. 2007;64(7):467-73.]. 1993.
60. World Health Organization (WHO). Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 4th ed: Published on behalf of the World Health Organization by Cambridge University Press, New York; 1999.

61. Karmaus W, Juul S. Infertility and subfecundity in population-based samples from Denmark, Germany, Italy, Poland and Spain. *Eur J Public Health*. 1999;9(3):229-35.
62. World Health Organization (WHO). Laboratory manual for the examination of human semen and semen-cervical mucus interaction. [Cited In: *Rasmussen K SS, Wohler M, Ingerslev HJ, Kappel B, Nielsen J. A genotoxic study of metal workers exposed to trichloroethylene. Sperm parameters and chromosome aberrations in lymphocytes. Int Arch Occup Environ Health*. 1988;60(6):419-23.], editor: Press concern, Singapore, pp 1-43; 1980.
63. Reichart M, Lederman H, Har-Even D, Kedem P, Bartoov B. Human sperm acrosin activity with relation to semen parameters and acrosomal ultrastructure. *Andrologia*. 1993;25(2):59-66.
64. Forkert PG, Lash L, Tardif R, Tanphaichitr N, Vandevort C, Moussa M. Identification of trichloroethylene and its metabolites in human seminal fluid of workers exposed to trichloroethylene. *Drug Metab Dispos*. 2003;31(3):306-11.
65. Bardodej Z, Vyskocil J. The problem of trichloroethylene in occupational medicine; trichloroethylene metabolism and its effect on the nervous system evaluated as a means of hygienic control. *AMA Arch Ind Health*. 1956;13(6):581-92.
66. El Ghawabi SM, Mansoor MB, El Gamel MS, El Saharti AA, El Enany FF. Chronic trichloroethylene exposure. *J Egypt Med Assoc*. 1973;56(11-12):715-24.
67. Luderer U, Morgan MS, Brodtkin CA, Kalman DA, Faustman EM. Reproductive endocrine effects of acute exposure to toluene in men and women. *Occup Environ Med*. 1999;56(10):657-66.
68. Pedersen LM, Cohr KH. Biochemical pattern in experimental exposure of humans to white spirit. II. The effects of repetitive exposures. *Acta Pharmacol Toxicol (Copenh)*. 1984;55(4):325-30.
69. Tuohimaa P, Wichmann L. Sperm production of men working under heavy-metal or organic-solvent exposure. In: Hemminki K, Sorsa M, Vainio H, editors. *Occupational hazards and reproduction*. Washington, DC: Hemisphere Publishing Corp.; 1981. p. 73-9.
70. Cherry N, Labreche F, Collins J, Tulandi T. Occupational exposure to solvents and male infertility. *Occup Environ Med*. 2001;58(10):635-40.
71. Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. *Hum Reprod*. 2001;16(8):1768-76.
72. Tielemans E, Burdorf A, te Velde ER, Weber RF, van Kooij RJ, Veulemans H, et al. Occupationally related exposures and reduced semen quality: a case-control study. *Fertil Steril*. 1999;71(4):690-6.

73. Figa-Talamanca I, Petrelli G, Tropeano R, Papa G, Boccia G. Fertility of male workers of the Italian mint. *Reprod Toxicol*. 2000;14(4):325-30.
74. Blatter BM, Hermens R, Bakker M, Roeleveld N, Verbeek AL, Zielhuis GA. Paternal occupational exposure around conception and spina bifida in offspring. *Am J Ind Med*. 1997;32(3):283-91.
75. Mandani P, Desai K, Highland H. Cytotoxic effects of benzene metabolites on human sperm function: an in vitro study. *ISRN Toxicol*. 2013;2013:397524.
76. Jensen TK, Bonde JP, Joffe M. The influence of occupational exposure on male reproductive function. *Occup Med (Lond)*. 2006;56(8):544-53.
77. Lindbohm L, Taskinen H, Kyyronen P, Sallmen M, Anttila A, Hemminki K. Effects of parental occupational exposure to solvents and lead on spontaneous abortion. *Scand J Work Environ Health*. 1992;18(Suppl 2):37-9.
78. Logman JF, de Vries LE, Hemels ME, Khattak S, Einarson TR. Paternal organic solvent exposure and adverse pregnancy outcomes: a meta-analysis. *Am J Ind Med*. 2005;47(1):37-44.
79. Snijder CA, te Velde E, Roeleveld N, Burdorf A. Occupational exposure to chemical substances and time to pregnancy: a systematic review. *Hum Reprod Update*. 2012;18(3):284-300.
80. Boyle MH. Guidelines for evaluating prevalence studies. *Evid Based Ment Health*. 1998;1(2):37-9.
81. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology*. 1999;54(2):346-51.