

Evidence Compass



Technical Report

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

Rapid Evidence Assessment
September 2018

Disclaimer

The material in this report, including selection of articles, summaries, and interpretations is the responsibility of the Monash Centre for Occupational and Environmental Health, School of Public Health and Preventive Medicine, Monash University, and does not necessarily reflect the views of the Australian Government. The Monash Centre for Occupational and Environmental Health does not endorse any particular approach presented here. Evidence was based on, but not limited to medical scientific literature published since 2000. Readers are advised to consider new evidence arising post publication of this review. It is recommended the reader source not only the papers and reports described here, but other sources of information if they are interested in this area.

© Commonwealth of Australia 2018

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from the Commonwealth. Requests and inquiries concerning reproduction and rights should be addressed to the publications section, Department of Veterans' Affairs or emailed to publications@dva.gov.au.

Please address any comments or queries about this report to

EvidenceCompass@dva.gov.au

Authors

Monash University, School of Public Health and Preventive Medicine

Dr Helen Kelsall, Monash Centre for Occupational and Environmental Health (MonCOEH)

Associate Professor Deborah Glass, MonCOEH

Professor Malcolm Sim, MonCOEH

Mr Loyal Pattuwage, MonCOEH

Professor Brian Priestly, Australian Centre for Human Health Risk Assessment (ACHHRA)

Associate Professor David Newman, Aviation Medicine Unit

Professor Robin Bell, Women's Health Research Program

Andrology Australia, Monash University; Hudson Institute of Medical Research and Monash Medical Centre

Professor Robert McLachlan

Monash University, Department of Obstetrics and Gynaecology and Ritchie Centre, Hudson Institute of Medical Research

Professor Euan Wallace

Other

Professor William Webster

Acknowledgements

This project was funded by the Department of Veterans' Affairs (DVA). We acknowledge the contribution of the steering committee for this project, which comprised senior personnel from DVA and the Defence Work, Health and Safety Branch.

For citation: Kelsall HL, Glass DC, Priestly BG, McLachlan R, Bell RJ, Pattuwage L, Newman DG, Wallace EM, Webster WS, Sim MR. 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.

Table of Contents

Authors.....	3
Acknowledgements	4
List of Abbreviations	6
Executive Summary	7
Introduction	11
Jet fuels	11
Adverse reproductive health outcomes investigated	13
Aims	14
Methods	14
Defining the review questions	15
Search methods for identification of studies	16
Electronic searches	16
Selection of studies.....	18
Evaluation of evidence	20
Results	22
Results of the search	22
Primary studies	24
Reports	29
Discussion.....	30
Conclusion	33
Appendix 1: Population Exposure Comparison Outcome (PECO) Framework	34
Appendix 2: Search strategy	35
Appendix 3: Checklist for considering the quality of descriptive, observational and prevalence studies.....	37
Appendix 4: Evidence profile of included studies	39
Observational Studies.....	39
Reports.....	45
References.....	47

List of Abbreviations

ADF	Australian Defence Force
ATSDR	Agency for Toxic Substances and Disease Registry
AVTUR	Aviation turbine fuel
BMI	Body mass index
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
DSRS	Deseal/Reseal
DVA	Department of Veterans' Affairs
EPA	Environmental Protection Agency
F-111 DSRS	F-111 Deseal/Reseal
FSH	Follicle stimulating hormone
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
MonCOEH	Monash Centre for Occupational and Environmental Health
MeSH	Medical Subject Headings
MATF	Military Aviation Turbine Fuel
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	Personal exposure limits
POF	premature ovarian failure
PECO	Population, Exposure, Comparison group, Outcome framework
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RAAF	Royal Australian Air Force
REA	Rapid Evidence Assessment
SCSA	Sperm chromatin structure assay
SHOAMP	Study of Health Outcomes in Aircraft Maintenance Personnel
TLV	Threshold limit values
TOXLINE	Toxicology Literature Online
TOXNET	Toxicology Data Network
TTP	Time-to-pregnancy
UK	United Kingdom
US	United States of America
USAF	United States Air Force
WHO	World Health Organization

Executive Summary

- Following concerns expressed by some women in the Royal Australian Air Force (RAAF), in 2017 the Department of Veterans' Affairs (DVA) requested Monash Centre for Occupational and Environmental Health (MonCOEH) to conduct a Rapid Evidence Assessment (REA), on associations between occupational exposure to Military Aviation Turbine Fuels (MATFs) (herein referred to as jet fuels) and adverse reproductive health outcomes in women.
- The 2017 MonCOEH report¹ found that there were a limited number of studies that investigated the effects of jet fuel exposure and adverse reproductive health outcomes in women. The available data showed limited evidence of associations between jet fuel exposure and adverse fertility and pregnancy outcomes. The data showed some evidence of effects of jet fuel on hormones relevant to menstrual cycle function that could potentially affect fertility.
- Adverse reproductive health effects in male workers were not investigated in that review.
- The aim for this project was to conduct a literature review of adverse sexual and reproductive health outcomes in men from occupational exposure to jet fuels of the types used in the Australian military. The REA was restricted to evidence from human studies rather than from animal toxicology.
- Specifically, the review aimed to determine whether there are any associations between occupational exposure to military jet fuels and any of the following adverse sexual and reproductive health outcomes in men:
 - 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 and fertility outcomes in female partners), altered reproductive hormones (testosterone, oestradiol, luteinising hormone (LH) and follicle stimulating hormone (FSH))
 - Adverse sexual outcomes: Erectile dysfunction, libidosexual dysfunction, psychosexual dysfunction

- Fuels most relevant to the military to include in the review were:
 - Military jet fuels: JP-4, JP-5, JP-7 JP-8, F 33, F 34
 - Civilian jet fuels: Jet A, Jet A-1, Jet B
- Using a comprehensive strategy, a search was conducted in 10 electronic scientific databases and an online military health journal to identify peer-reviewed studies in humans, published between January 2000 and April 2018 in the English language. This 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 jet fuels 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. The study quality implications were discussed conforming to the REA methodology protocol for the project.
- A total of eight records met the inclusion criteria; five primary studies²⁻⁶ and three reports.⁷⁻⁹ Of the primary studies, two were based on the same Australian retrospective cohort study (Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP))^{2, 4} The remaining three studies were from the USA; one was a prospective cohort study,⁶ one was a cross sectional study,⁵ and one was a case control study.³ Each of the five primary studies reported on different outcomes: male sexual function,² semen profile,⁶ pregnancy outcomes in partners,⁴ reproductive hormone assays,⁵ and incidence of birth defects.³
- The three reports, which were publicly available and included reviews of literature included reviews of literature were a US Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for jet fuels,⁷ a US Institute of Medicine Committee on Gulf War and Health report⁸ and a US National Research Council Subcommittee on Reproductive and Developmental Toxicology report.⁹
- One study reported adverse sexual health effects² (i.e. erectile dysfunction and poor sexual function) in exposed male personnel compared to non-exposed. However, the participants were potentially exposed to a range of solvents in addition to jet fuel.

- The available evidence⁴ reported no evidence of an association between male exposure to jet fuels and miscarriage or stillbirths and difficulties⁴ or difficulties in getting pregnant⁴ for partners of exposed men. There was also no evidence that exposure to jet fuels is associated with changes in semen profile in men or serum levels of testosterone, oestradiol, luteinising hormone, prolactin or cortisol.⁵ Very limited evidence was available suggesting an association between congenital abnormalities of children born to fathers working in the petroleum and gas industry.³
- The range of the available studies was limited and did not enable all the adverse reproductive outcome endpoints identified in the aims to be assessed, including very limited assessment of hypogonadism⁵ and infertility.⁶ No studies were identified that investigated the relationship between jet fuel exposure and the following male reproductive outcomes: primary testicular failure, androgen (testosterone) deficiency, and reduced reproductive success measures of involuntary childlessness, not achieving desired family size, and low fecundity. For reported pregnancies, the SHOAMP asked about difficulties getting pregnant and if reported seeing a specialist but not specifically about increased time-to-pregnancy or use of assisted reproductive technologies.
- This REA summarised the limited literature in relation to adverse reproductive health outcomes in men following occupational exposure to jet fuels. There was limited evidence of adverse sexual health outcomes. A limited number of studies and methodological limitations resulted in a relatively weak body of evidence. More substantial high quality evidence is needed to draw firm conclusions.
- The data limitations included the small number of studies, studies with a small number of participants or cases and limited power to detect statistical significant differences in adverse reproductive outcomes, limitations in exposure assessment or in health outcome assessment such as self-reported exposure and health outcomes, possible recall bias, and co-exposure with other solvent(s) or other chemical(s), which made it difficult to attribute any health effect to fuel exposure.
- Limitations of the REA include the omission of possibly relevant papers that were published prior to 2000 or after April 2018 and of non-English language papers. However, an ATSDR toxicological profile for JP-5, JP-8 and Jet A Fuels published as recently as 2017⁷ did not identify articles not included in this review.
- Although the effects of occupational exposure of male service members to jet fuels used in the Australian military was of prime interest, the search was not restricted to articles on

military populations. This resulted in few additional articles. This could be the result of scarcity of evidence on this topic and/or the restricted search period.

- This REA provides the Department of Veterans' Affairs and Department of Defence with a summary of the available evidence of the effects of jet fuel exposure on human reproductive health in male service members of the military.

Introduction

In 2017, the Monash Centre for Occupational and Environmental Health (MonCOEH), in the School of Public Health and Preventive Medicine, at Monash University conducted a literature review 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.¹

There had been exposure to jet-propulsion-8 (JP-8) aviation fuel and several solvents in the Royal Australian Air Force (RAAF) F-111 Deseal/Reseal (DSRS) program between 1975 and 1999 and this was associated with later ill health including symptoms consistent with solvent or isocyanate exposure in DSRS personnel who had potentially been exposed and a probable estimated increase in cancer of 50% in the DSRS group, which was of borderline statistical significance.¹⁰⁻¹³ The subsequent Jet Fuel Exposure Syndrome (JFES) *in vitro* study investigated the cellular toxicity of JP-8.¹⁴ Following the release of this 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 fertility, adverse pregnancy outcomes, premature ovarian failure (POF) and early onset menopause. The 2017 MonCOEH literature review¹ found that there were a limited number of studies that investigated the effects of jet fuel exposure and adverse reproductive health outcomes in women. The available data showed limited evidence of associations between jet fuel exposure and adverse fertility and pregnancy outcomes. The data showed some evidence of effects of jet fuel on hormones relevant to menstrual cycle function that could potentially affect fertility. The review was funded by the Department of Veterans' Affairs (DVA) and used a Rapid Evidence Assessment (REA) methodology.¹⁵

The current literature review was undertaken to examine adverse reproductive health outcomes in men who had been exposed to jet fuels. A second report will present data on male reproductive health effects and exposure to selected solvents of interest.

Jet fuels

Fuel is a critical component of military capability. A 2002 Auditor General's report identified eight different types of fuel used by the Australian Defence Force (ADF).¹⁶ Of these, four are military specification fuels including aviation turbine fuels.

Jet propellant (JP) fuels are used in military and civilian aircraft. These fuels are refined and distilled from various grades of crude oil. The refining of crude oil is complex with various product streams producing a number of different types of fuels. All the fuels are mixtures of aliphatic, alicyclic and aromatic hydrocarbons and the fractions are blended with additives to ensure the required fuel performance specifications are met.¹⁷

Kerosene-based jet fuels have been used for over 60 years.^{7, 18} JP-8 is a kerosene-based distillate that is currently the fuel of choice in military aircraft and has replaced JP-4, first used by the USAF in 1951, because it has a higher flash point, being composed of longer chain hydrocarbons.⁹ JP-5 is chemically similar to JP-8, and is used in naval aircraft. Jet A and Jet A-1 are the fuels commonly used in commercial civilian jet aircraft. These fuels are nearly identical, but Jet A-1 contains a static dissipater additive and is refined to have a lower maximum freezing point (-47°C) than Jet A (-40°C). The lower freezing point makes Jet A-1 a better choice for international flights. Jet B is a wide cut jet fuel used in colder climates.¹⁹

Currently, the primary military fuel is JP-8 (similar to commercial Jet A-1). Jet fuels may also contain various additives such as antioxidants and additives to prevent icing in the fuel lines. The main grades of jet fuels are summarised in table 1.

Table 1: Main grades of jet fuels²⁰

Jet A-1	Kerosene type fuel used in civil aircraft. Max freezing point -47°C
Jet A	As Jet A-1, but with freezing point of -40°C maximum
Jet B	Wide cut type fuel used in civilian aircraft. In 'wide cut' type fuels the kerosene components are blended with low flashpoint naphthas
JP-4	Wide cut type fuel used in military aircraft
JP-5	High flash point kerosene type fuel used in naval aircraft
JP-8	Kerosene type fuel used in military aircraft

Note: The flash point of a volatile material is the lowest temperature at which vapours of the material will ignite, when given an ignition source.

Occupational exposure to jet fuels can occur during refuelling and defueling operations, cold engine starts and during maintenance activities. Exposure in military personnel may occur through the inhalation (aerosolised or vaporised fuel), dermal and/or oral routes of exposure, although the oral route is unusual.²¹

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.”⁷ 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.²² In women, reproductive toxicants can act on oogenesis, ovulation, hormonal production by granulosa cells and even on the fallopian tube.²³ Male reproductive system toxicants 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.²³ In addition, toxicants may act on the neuroendocrine control at the pituitary or testicular level (e.g. Leydig cells which secrete testosterone in response to pituitary luteinising hormone (LH)) and interfere with epididymal and accessory sex glands (seminal vesicles, prostate, and bulbourethral glands) function (androgen effects).²⁴

The effect of exposure to jet fuels on the reproductive system has been studied in animal models but their effect on the male human reproductive health remains inconclusive.²⁵⁻²⁷

MonCOEH was asked to undertake a literature review to summarise available evidence on occupational exposure to jet fuels and human male adverse sexual and reproductive health outcomes.

Aims

The aim of this project was to conduct a literature review on the effects of occupational exposure of service men to Military Aviation Turbine Fuels (MATFs) (i.e. jet fuels) 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 military jet fuels 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 hormones (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 Rapid Evidence Assessment (REA) methodology as requested by the Departments of Veterans' Affairs and Defence.¹⁵ This was the same methodology as that used for the literature review of jet fuels and solvents and adverse reproductive outcomes in women.¹

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 in 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 pilot 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 some systematic reviews 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).¹⁵ A complete description of the research question based on the PECO framework is given in [Appendix 1](#).

To ensure relevancy of results, key components related to the questions, and specific inclusion and exclusion criteria, were established for the search and for screening studies into 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 for studies to be included in this review. The previous REA in women¹ 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 jet fuels which reported relevant human male adverse reproductive health outcomes.

The exposures of interest were to jet fuels most relevant to military personnel as previously finalised:¹

- Military jet fuels: JP-4, JP-5, JP-7, JP-8, F33, F34
- Civilian fuels: Jet A, Jet A-1 and Jet B

This review focussed on scientific studies that investigated occupational exposures. Studies investigating environmental exposures through residential exposure, for example living close to petrol stations, municipalities close to petrochemical refineries, or environmental air pollution were excluded, as the populations may have had other exposures and/or confounding factors such as socioeconomic status, which could not be evaluated.

The adverse male reproductive outcomes of interest were:

- 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, still birth, 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 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. These included terms relating to jet fuel exposure, such as JP-8, kerosene, jet fuel, MATF, AVTUR; and terms relating to reproductive health such as hypogonadism, semen, libido and fecundity. The final Medline strategy is given in [Appendix 2](#).

The search was limited to English language studies in human subjects published between 1 January 2000 and 13 April 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 is consistent with the REA literature review methodology.¹⁵ Studies published before 2000, identified from full text articles, were also considered for inclusion.

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 April 04 2018
- Embase (Ovid): 1974 to 2018 April 06
- 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 key words "jet fuel" and "aviation fuel". This Australian based journal is dedicated to military and veteran health related research and therefore may have published research findings on this topic.

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 relevant publicly available 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

Papers were directly 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.

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 information was 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)
- How the exposure was assessed
- How the outcomes were assessed
- Findings of the study

Table 2: 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 13 April 2018○ Quantitative studies with outcome data that assessed exposure in men and investigated associations between an exposure to jet fuels 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 relationship between exposure to jet fuels in men and adverse male reproductive health outcomes○ 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 evidence

The REA methodology¹⁵ 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.,²⁸ 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.¹⁵ Two reviewers independently used the tool²⁸ 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 jet fuels. Population variability that might influence this component include age, ethnicity and non-military occupations.

Results

Results of the search

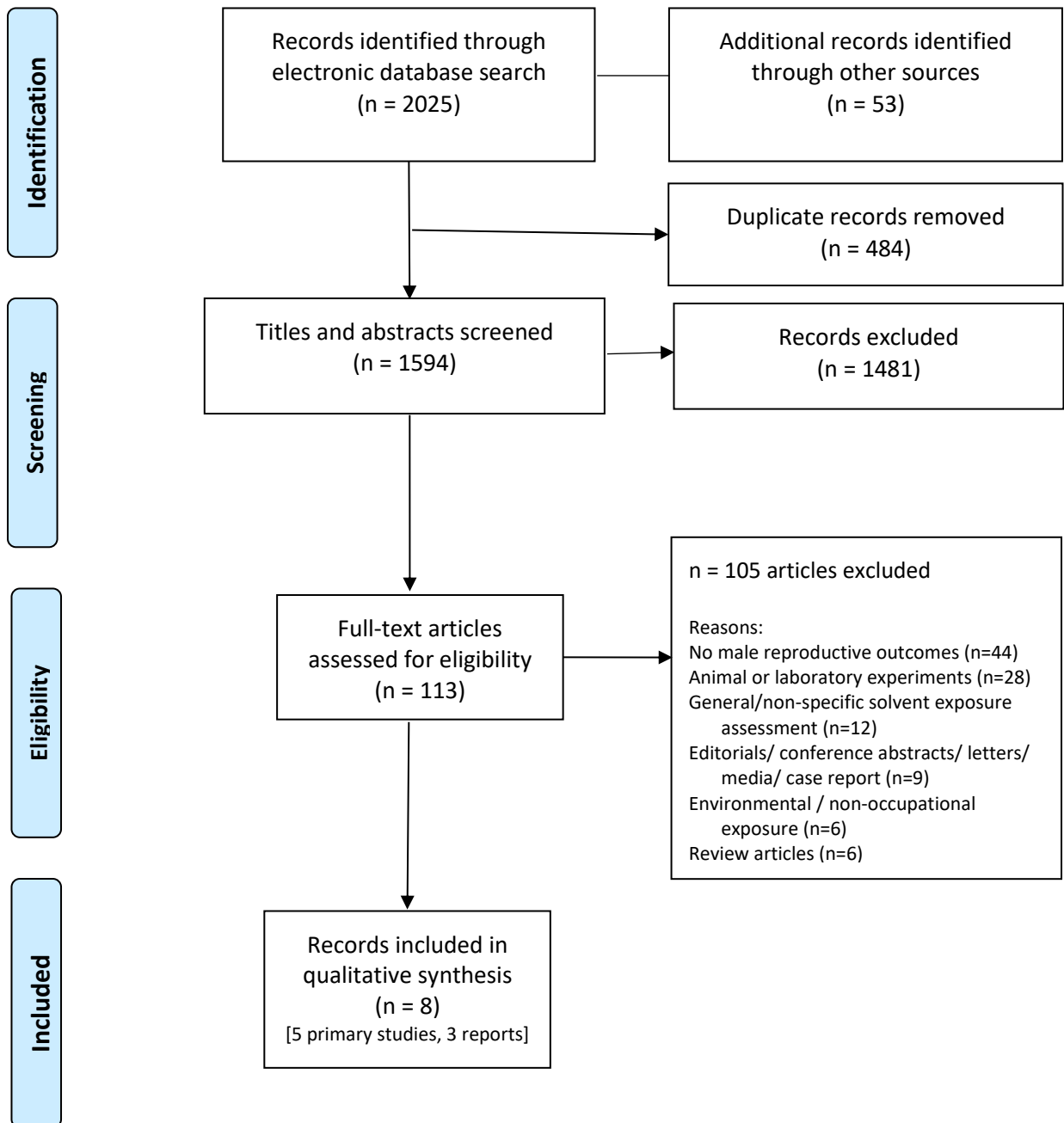
Ten electronic databases and an online military health journal were searched in April 2018 and generated 2025 records. The reference list search of full text papers and the web site search yielded an additional 53 records. Following removal of duplicates, 1594 unique records were exported to “Covidence” (www.covidence.org), Cochrane Collaboration's recommended online tool for review production.²⁹ Following titles and abstract screening in Covidence, 113 full texts were retrieved to be assessed for eligibility, and eight met the inclusion / exclusion criteria and were included. Of these eight records, two originated from the electronic database search,^{2, 5} and the reference list search of full text papers and the website search identified a further six records.^{3, 4, 6-9} Thus, the final papers which were evaluated consisted of five primary observational studies²⁻⁶ and three reports.⁷⁻⁹ The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)³⁰ flowchart for study selection is given in Figure 1.

Two primary studies reported outcomes from a retrospective cohort study; the SHOAMP, in Australia of fuel tank maintenance workers who participated in RAAF F-111 DSRS programs.^{2, 4} One of these studies was published in a peer-reviewed journal and reported outcomes on adverse male sexual function.² The findings on adverse male sexual function and the pregnancy outcomes of female partners of exposed males were presented in the main study report.⁴ In order to avoid duplicating the results, adverse male sexual function outcomes were extracted from the published paper² and only the pregnancy outcomes were extracted from the study report.⁴

The other primary studies were from populations in the United States of America (US),^{3, 5, 6} and included: one prospective cohort study of aircraft maintenance personnel,⁶ one case control study of petroleum and gas industry workers³ and one cross sectional study of fuel tank-entry personnel.⁵

Each of the five primary studies reported on different outcomes: male sexual function,² reproductive hormone assays,⁵ semen characteristics,⁶ pregnancy outcomes in partners⁴ and incidence of birth defects.³

Figure 1: PRISMA flow chart



All five primary studies assessed exposure and reported diverse sexual health or reproductive outcomes. Therefore, the findings of each study is narratively described here with emphasis on the quality and risk of bias, data source and generalisability consistent with the REA methodology.¹⁵ The risk of bias assessment of the primary included studies is based on the modified checklist (see Appendix 3)²⁸ and conforms to REA methodology.¹⁵

The three reports reviewed existing research evidence on the toxicological or epidemiological effects of exposure to fuels or related agents on the male reproductive system.⁷⁻⁹ They did not present new research findings.

Primary studies

The Australian SHOAMP^{2, 4} was a retrospective cohort study of the health of F-111 Deseal/Reseal (DSRS) workers and assessed whether any of the wide range of reported adverse health outcomes were associated with their involvement in the DSRS programs.

Brown *et al*² compared 577 men who participated in the DSRS programme between 1975 and 1999 with two groups:

- (1) 399 subjects who worked in the same base but were not involved in DSRS activities: (“same base-different job”),
- (2) group of aircraft maintenance personnel who did similar maintenance activities but in different aircraft (“different base-similar job”).

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 depressed and anxious compared to the comparison groups. They were more likely to report loss of interest in sex, poor sexual function and poorer erectile function compared to the men in the comparison groups. These outcomes were significantly correlated with the reported incidence of depression and anxiety in the cohorts, but the relationships 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 the DSRS men had on average, a two-fold increase in the odds of reporting sexual dysfunction compared to either comparison groups.² 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)³¹ to assess erectile dysfunction and the Composite International Diagnostic Interview

(CID) 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.³¹ Limitations in the instrument's assessment of nonerectile components of sexual response and the partner relationship were acknowledged. The author's noted that the IIEF should be viewed as an adjunct to rather than a substitute for a detailed sexual history.³¹ The exposed population was compared to comparison groups that also consisted of military personnel, therefore the findings did not compare sexual function in these men with what is expected 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 aircraft maintenance workers who work in different work environments as their exposures may be different from those encountered by the DSRS workers.

The SHOAMP report⁴ reported the pregnancy outcomes and the difficulty in getting pregnant in female DSRS workers and female partners of exposed male personnel who participated in the DSRS activities, whose outcomes were combined in the analysis. The study included 552 females who reported 1327 pregnancies eligible to be included in the analysis. Overall, there were 1072 live births, 235 miscarriages (18.5%) and 20 stillbirths (1.5%). The SHOAMP report found no evidence of an increased risk of miscarriage or stillbirth (20% in exposed compared to 17%, Amberley and 20%, Richmond control groups) in female partners of male DSRS personnel. The questionnaire also included questions on difficulties in getting pregnant and whether they had seen a specialist about fertility problems and 657 women answered these questions. There was no significant difference between reported difficulties in getting pregnant in the exposed group (30%) compared to control groups (21%, Amberley and 27%, Richmond) ($p=0.18$). Of the exposed group, 14% reported seeing a specialist compared to similar proportions in the control groups (11%, Amberley and 18%, Richmond) ($p=0.21$).

The target population was clearly identified in the SHOAMP. Pregnancies reported by female partners of DSRS workers and female DSRS workers were referenced to a posting date and events occurring prior to or after the 1975 to 1999 DSRS period were excluded from the analysis. However, several study limitations were identified. Outcomes were combined for the 767 female partners of male DSRS workers and the 24 female DSRS workers. The responses were self-reported (e.g. outcomes of pregnancies) and were not validated, e.g. through birth defect registries or birth or death certificates. Male participants were instructed to pass the Reproductive Questionnaire in an envelope to their current or past female partner/s, (corresponding to the period worked in the DSRS activities), but there was no guarantee that the men passed the envelope on, or that the female recipient completed and returned it. Therefore, the number of women who were potentially eligible could not be reliably determined,

and information was not available on non-responders. Further analysis was not possible for difficulties in getting pregnant and visits to a specialist for fertility problems as key confounders such as maternal age at the time were not collected.

There were some methodological and sampling limitations. These included uncertain sampling frames, self-identification of 'exposed' DSRS workers (exposure was classified *post hoc*, based on a self-reported questionnaire), eligible female partners of male DSRS workers might not have received the questionnaire, and the denominator for the eligible female partners of DSRS male workers (who were trying to have children) was not provided.⁴ It is also possible that responders were aware of reported concerns and the aims of the study because recruitment advertisements mentioned the reasons for instigating the study, and this may have contributed to participation bias. SHOAMP personnel were likely to have been exposed to several materials including jet fuels, desealants, sealants and a range of solvents. The mix of exposures varied over time with the different DSRS programs and participants were asked about exposures that could have occurred up to 30 years earlier, with further categorisation of exposure by DVA. In view of the above factors, recall bias in respect of exposures could have occurred.

A case control study in the US National Birth Defects Prevention Study (NBDPS)³ compared the paternal occupation of babies with non-syndromic isolated and multiple defects (study group) with those of babies with no major defects (control group). The data were obtained from hospital records of birth certificates. Analysis included data of 71 fathers who worked in the gas and petroleum industry (study group) (0.7% of the study population) and 20 fathers (0.5%) in the control group. The study found paternal occupation in the gas and petroleum industry was associated with a statistically significant increased risk of birth defects (atrial septal defects (n=11), limb deficiency (n=2), colonic atresia/stenosis (n=1)), and glaucoma/anterior chamber defects (n=1), compared to the referent group who did not work in this industry.

This study included a clearly defined target population (cases with birth defects), and used clinical registry data to identify the study group. The control group were live born infants with no major birth defects, randomly selected from hospital records or birth certificates.³² The gas and petroleum industry consists of a variety of activities and exposures; drilling, hydraulic fracturing, extraction, processing, transportation and disposal.³³ The exposure classification was broad and at industry level (e.g. all workers in the gas and petroleum industry were categorised into one exposure group) and no information was available on occupational sub groups within these broad groups. The analyses were adjusted for potential confounding factors, such as use of supplementary folic acid, prenatal vitamins, maternal smoking and

alcohol use. The database contained a large dataset (9998 cases), and the study considered the relationship between 63 paternal occupations and birth defects, but the proportion of fathers who worked in the gas and petroleum industry was less than one per cent (n=71). The number of cases of birth defects was small, and so the confidence intervals around the odds ratios were wide in these analyses. It is difficult to generalise the study findings to men exposed to jet fuels due to likely differences in types and extent of exposure.

A cross sectional study⁵ assessed reproductive hormonal levels among 153 United States Air Force (USAF) male fuel tank-entry workers with at least nine months of persistent exposure to jet fuels (i.e. one-hour entry, twice a week, validated against records). The control group was USAF personnel who were not regularly exposed to jet fuels. The number of participants who completed a questionnaire was not reported for exposed and the control groups. The concentrations of FSH, LH, prolactin, cortisol, oestradiol, inhibin B, total and free testosterone in morning venous blood were measured and reported in 134 male participants. Statistical analysis included linear models to assess the effect of exposure and months on the job, controlling for age, smoking and alcohol use. The study reported that there was a possibility that male personnel who were exposed longer (i.e. more months on the job to fuels in the high exposure group, but not in the low or moderate exposure groups) may have significantly higher FSH serum levels and inhibin B levels. The FSH secretion is regulated by the levels of circulating testosterone and inhibin (both produced in the testes) through negative feedback.³⁴ Therefore, elevated testosterone and inhibin levels downregulate FSH secretion. Adverse effects on spermatogenesis therefore could result in low inhibin levels and high FSH levels. It was not clear why both FSH and inhibin levels were high in this study. The authors suggested two possible mechanisms; exposure to fuel stimulating FSH secretion (thus leading to elevated inhibin B levels) or desensitisation of the feedback mechanism. Semen analysis was not conducted and therefore it is not known how these changes affected spermatogenesis. The study did not identify any statistically significant effect from fuel exposure or months-on-the-job on serum levels of testosterone, oestradiol, LH, prolactin or cortisol.

The target population in this study was clearly defined, but it is not clear how the sample was derived and it may have been a convenience sample. A self-reported questionnaire was used to gather information on job, exposure, medical and demographic information. The exposure to jet fuel was measured using a surrogate measure of “months on the job”, although standard laboratory methods for assessing the outcomes (hormonal assays) were used. Information was not reported on basic characteristics including age, months on the job, body mass index, smoking status, alcohol consumption of the exposed and non-exposed groups. Although the study stated adjusting for confounding factors including these, limited information on statistical analysis was reported. Even though the exposed study group of male tank-entry personnel

with exposure to jet fuel would appear relevant to the study population of interest in this review, caution is required in interpreting the study findings due to the limited information available.

A prospective cohort study⁶ investigated semen characteristics of civilian or active duty 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 workers, flight line workers, sheet metal workers and paint shop workers) and who were potentially exposed to different levels of jet fuel or other chemicals. An additional eight people who performed clerical activities served as an unexposed comparison group (in whom mean age was similar (26.0 vs 24.1 years) but fewer were Caucasian (38% vs 80%) compared to the jet fuel worker 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 (i.e. sperm concentration, percent motile, sperm morphology, sperm morphometrics and sperm chromatin structure assay (SCSA)) 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 SCSA) for the unexposed group (values not reported) and the combined exposed group (consisted of all four exposed groups) generally remained within the WHO reference ranges³⁵ throughout the 30 weeks. However, the percentages of motile sperm were lower than the reference range³⁵ in both combined exposed group and the control group during the study period. The percentage of motile sperm depends on time postejaculation and sample analysis, and the average time elapsed during transport (samples were produced at home) was 52.4 (SD 21.4) minutes (which was slightly greater than 45 minutes transport time stated in the paper's methods) over all three sampling periods and was similar in the exposed and unexposed groups.

The study⁶ concluded that jet fuel exposure to concentrations well below American Conference of Government Industrial Hygienists (ACGIH) recommended threshold limit values (TLV) and those mandated by the Occupational Safety and Health Administration (OSHA) as personal exposure limits (PEL)⁶ did not have an apparent effect on semen quality in aircraft maintenance personnel.

This study included a well-defined study group, although the sampling strategy was not reported. The participants were volunteers and they were divided into groups based on the type of work they performed and which were also used as surrogate indicators for jet fuel and solvent exposure. The exposure was assessed using industrial hygiene techniques based on the type of job activity and probability of exposure (unexposed performed office filing, typing

and clerical and assumed to have no to minimal exposure). The semen profiles were assessed using standard laboratory methods. Participants and non-participants were similar in age, race and religion, but the participants were more likely to have attended college (52% versus 20%). The analyses were adjusted for age, race, smoking, alcohol consumption, having a sexually transmitted disease, hot baths and the season the sample was collected. The exposures for jet fuels as naphtha , total solvents (i.e. methyl ethyl ketone, methylene chloride, xylenes, toluene, and 1,1,1- trichloroethane) and benzene were measured in air and breath. Levels, except some measurements of benzene, were well below the ACGIH recommended TLV⁶ indicating that the findings are likely to be relevant to work environments with similar 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. The number of participants was small (n=58) and the low statistical power could have masked a possible effect.

Reports

The reports' findings were not able to be rated for the quality of evidence in the same manner as peer review publications. The findings are reported in the Evidence Profile for this review and summarised below. The findings of these reports are likely to have been based on *in vitro* and animal studies as well as human studies.

The Agency for Toxic Substances and Disease Registry (ATSDR) evaluates the effect on public health of hazardous substances. ATSDR toxicological profiles characterise the toxicological and adverse health effects on a given hazardous substance. Each profile is a comprehensive and extensive evaluation, summary and interpretation of available toxicological and epidemiological information on the substance. The profiles are peer-reviewed.

Two ATSDR profiles that reported on reproductive health and jet fuels were identified; a recent report published in 2017 on kerosene based fuels⁷ (JP-5, JP-8 and Jet-A) and an earlier report published in 1995 on JP-4 and JP-7.³⁶ Adverse reproductive effects and developmental effects were reported from various routes of exposure (i.e. inhalation, oral or dermal).

The 1995 profile did not identify any studies that reported reproductive effects or developmental effects in humans after exposure to JP-4 and JP-7.³⁶ The 2017 profile also

reported that no data were identified on toxicity following inhalation, oral or dermal exposure to JP-5, JP-8, or Jet A fuels on the male human reproductive system or effects on development.⁷

The Institute of Medicine (IOM) produced a report to assist the US Veterans Affairs and Congress to evaluate the scientific literature regarding exposures that might have occurred in the 1990-1991 Gulf War.⁸ The IOM appointed a committee with knowledge of the available toxicological and epidemiological data on fuels. The report included a chapter that examined the reproductive and developmental outcomes of exposure to fuels and combustion products. The reproductive and developmental outcomes of interest included infertility, preterm birth and low birth rate, birth defects and childhood cancers. The report identified only one human study⁶ on the association between exposure to jet fuels and semen characteristics, which our search had also identified and is discussed above.

The National Research Council (NRC), the operating agency of the National Academy of Sciences and the National Academy of Engineering, provides services to the US government, the public and scientific communities. It assigned the Committee on Toxicology (COT) to review the available toxicological, epidemiologic, and other relevant data, including potential reproductive and developmental toxicity, on JP-8 and formed the Subcommittee on Jet-Propulsion Fuel 8 to prepare the report.⁹ The evaluation provided a summary of the risk posed by the substance, and background information on the chemical and its toxicological parameters. The report included male and female reproductive toxicity data and was independently reviewed by a range of technical experts. The report identified only one human study that reported on exposure to jet fuels or solvents and the effect on semen characteristics,⁶ which our search had identified and is described above.

Discussion

The aim of this literature review was to identify research evidence on human male adverse reproductive health outcomes from their occupational exposure to MATFs (jet fuels) used by the Australian military. Although the main aim of the project was to investigate associations between jet fuels and reproductive health in servicemen, the review widened the focus by including human studies conducted in male occupational groups other than military personnel exposed to jet fuels.

This literature review identified a very limited number of primary studies (n=5) that investigated sexual or reproductive outcomes following male occupational exposure to jet fuels. This review

identified some evidence to suggest that exposure to jet fuels may affect reported sexual functioning in exposed men, although this was limited. The available evidence suggests exposure to jet fuels in men did not significantly affect ability to conceive or pregnancy outcomes in female partners and low levels of exposure to jet fuels in men did not significantly affect semen characteristics. The evidence for these findings was based on two retrospective cohort studies^{2, 4} and one prospective cohort study,⁶ but there were limitations in study design and/or methodology. The findings of a cross sectional study suggested that exposure to jet fuels could be associated with alterations in some reproductive hormone levels in men (i.e. FSH) but limited information was reported and the health implications are unclear.⁵ One case-control study reported an association between paternal occupation in the gas and petroleum industry three months preceding and after the expected date of conception³ and an increase in birth defects (i.e. atrial septal defects, limb deficiency, colonic atresia/stenosis and glaucoma/anterior chamber defects). However the number of cases of birth defects was small. Also, the exposure classification was based on industry group and generalisability of the findings to the military may be limited.

One limitation encountered in these studies is the difficulty in clearly attributing the relationship with the outcomes to exposure to jet fuels. Co-exposure to solvents and other chemicals may also have occurred, and these may be associated with adverse reproductive outcomes. In the case control study, solvent-exposed occupations were significantly associated with birth defects including neural tube defects, eye defects, oral clefts, gastrointestinal defects, limb deficiencies and heart defects.³ However, the gas and petroleum industry occupation was not categorised as one of the occupations potentially exposed to solvents.

There is evidence linking exposure to occupational environmental factors such as organic solvents with erectile ill health.³⁷ Some known reproductive system toxicants such as organic solvents, ethylene glycol esters and aromatic hydrocarbons^{38, 39} were considered relevant to the DSRS programme.² Recall bias could have affected the reported outcomes because the SHOAMP was conducted 2000-2002 but the DSRS activities took place between 1977 and 1999.⁴⁰ Further, there were a number of exposures experienced during DSRS, and the reported adverse health outcomes can only be associated with the DSRS programme as a whole and not specifically with jet fuels. A prospective cohort did not identify any statistically significant association between exposure to jet fuels and human semen quality.⁶ In this study, the study groups were exposed to concentrations of jet fuel and solvents that were well below the permissible industry exposure limits (ACGIH recommended TLVs and those mandated by the OSHA).⁶

There was a scarcity of studies that reported congenital birth defects in babies born to partners of men exposed to aviation fuel. A small case-control study³ did not focus on exposure to jet fuels but reported birth defect outcomes for male gas and petroleum industry workers. There is limited information on how jet fuel exposure affects the human male reproductive hormone profile and the only study that investigated that outcome reported limited details.⁵ It included fuel tank-entry workers but limitations included a one-off blood sample hormonal assay, lack of exposure measurements and limited reporting of methodology, which made further inference difficult.

This literature review utilised a REA methodology and included a search of 10 electronic databases which covered medical, science, toxicological and military literature and one military health journal through its website. Numerous government, military and other research organisational websites were also searched to identify unpublished relevant reports. One of the strengths of this REA is the comprehensive coverage of resources in order to identify publications published in or after 2000.

The search was conducted to identify articles published in English, in or after 2000 consistent with the REA study protocol. Therefore, studies published prior to 2000 were not generally included. However, an ATSDR toxicological profile for JP-5, JP-8 and Jet A fuels published as recently as 2017⁷ did not include relevant citations of articles not identified in this current literature review.

A list of jet fuels most relevant to military personnel (based initially on fuels used in the military and identified in the SHOAMP¹²) was agreed previously.¹ Our search was not limited to military use and covered similar fuels used by civilian aircraft. Four primary studies were conducted in military settings^{2, 4-6} and two were from Australia,^{2, 4} which increased the relevance to the population of interest in this review, although SHOAMP investigated a process and exposure not now in use.

Overall, there was limited evidence on the relationship between occupational exposure to jet fuel and adverse reproductive health outcomes in men. There is some limited and weak evidence to suggest that exposure to jet fuel is associated with reported sexual health problems in men but no evidence was identified to suggest that exposure is associated with adverse reproductive health outcomes in men. Existing evidence, even though weak, suggests that jet fuel exposure does not adversely affect pregnancy outcomes of partners of exposed men. The evidence included studies with methodological shortcomings and each study reported different distinct reproductive outcomes. It was difficult to evaluate the findings without a more substantial body of evidence. Some studies were more than 17 years old and the exposures may be less relevant now. For instance, USAF changed its fuel type from JP-

4 which has high content of benzene, which is known to compromise sperm integrity,⁴¹ to JP-8 which has a lower benzene content.⁶ The DSRS process resulted in a number of exposures of which jet fuel was only one. Therefore, implications of occupational exposure to jet fuels in men should be considered in the light of the study findings and their limitations.

Conclusion

This REA summarised the limited literature in relation to adverse reproductive health outcomes in men following occupational exposure to jet fuels. There was very limited evidence of adverse sexual health outcomes. A paucity of studies and methodological limitations resulted in a relatively weak body of evidence. More substantial high quality evidence is needed to draw firm conclusions.

Appendix 1: Population Exposure Comparison Outcome (PECO) Framework

Question:	
In males who are or who have been employed in defence or military related forces, or in occupational groups exposed to jet fuels, is exposure associated with an increased risk of adverse reproductive health outcomes compared with males employed or previously employed in defence or military related forces or in occupational groups who have not been exposed or compared to adult males in the general population?	
Population (P)	Males Employed or previously employed in aviation industry (i.e. occupationally exposed)
Exposure (C)	Jet fuel or MATFs (JP-4, JP-5, JP-7 JP-8, Jet A, Jet A-1, Jet B, F34 and F44)*
Comparison (C)	Not exposed to MATFs
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 males) ○ 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
* a list of jet fuels most relevant to Australian military personnel was developed previously and are consistent in this report . ¹	

MATFs: Military Aviation Turbine Fuels

Appendix 2: Search strategy

The Medline search strategy is included below.

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

1. ((Aviation or jet* or aircraft*) and fuel*).mp.
2. matf*.mp.
3. exp Kerosene/
4. Keros#ne.mp.
5. Kerosene*.mp.
6. exp Petroleum/
7. exp Fuel Oils/
8. petroleum distillate*.mp.
9. Petroleum Naphtha.mp.
10. "Aviation Keros#ne".mp.
11. AVTUR.mp.
12. "Fuel System Icing Inhibitor".mp.
13. ("JP4" or "JP-4" or "Nato F-40" or "MIL-DTL-5624").mp.
14. (JP5 or JP-5).mp.
15. (JP7 or JP-7 or "MIL-DTL-38219").mp.
16. (JP8 or JP-8 or "JP-8+100" or "MIL-DFL-83133").mp.
17. ("Civilian Jet A" or "Jet A").mp.
18. ("Civilian Jet A-1" or "Jet A-1").mp.
19. "Jet B".mp.
20. ("F33" or "F-33" or "F 33").mp
21. ("F34" or "F-34" or "F 34").mp.
22. ("F44" or "F-44" or "F 44").mp.
23. Or/1-22
24. exp Hypogonadism/et [Etiology]
25. Hypogonadism.mp.
26. exp Testosterone/bl, df, se
27. Testosterone.mp
28. exp ANDROGENS/bl, df, se
29. Androgen*.mp.
30. (hypoandrogenism or hypo-androgenism or "hypo androgenism").mp.
31. exp ANDROPAUSE/
32. "testicular failure".mp.
33. (Male adj2 sex hormone*).mp.
34. ((Male or men*) adj5 (oestradiol or estradiol or luteini#ing hormone or "LH" or follicle stimulating hormone or FSH)).mp.
35. Or/24-34
36. exp SEMEN/
37. semen.mp.
38. exp SPERMATOZOA/
39. sperm*.mp.
40. or/36-39
41. exp libido/
42. SEXUAL DYSFUNCTIONS, PSYCHOLOGICAL/ or SEXUAL DYSFUNCTION, PHYSIOLOGICAL/
43. (Dysfunction adj2 (sexual or libidosexual or libido-sexual or psychosexual or psycho-sexual)).mp.
44. Or/41-43
45. exp Male/ or (male or males or men).tw.
46. 44 and 45
47. exp infertility, male/
48. exp erectile dysfunction/
49. erectile d#sfunction.mp.
50. exp penile erection/
51. exp Premature Ejaculation/

52. Impotence.mp.
53. ((Achiev* or maintain* or sustain*) adj erection).mp.
54. Or/46-53
55. (fertility or infertility).mp.
56. exp Male/ or (male or males or men).tw.
57. 55 and 56
58. exp fertility/
59. exp Reproduction/
60. exp reproductive health/
61. exp Reproductive medicine/
62. exp Time-to-Pregnancy/
63. exp Reproductive Techniques, Assisted/
64. fecund*.mp.
65. involuntary childlessness.mp.
66. family size.mp.
67. (time-to-pregnancy or "time to pregnancy").mp.
68. ("IVF" or "In Vitro Fertilization" or "In-Vitro-Fertilization").mp.
69. "Assisted reproductive technolog* ".mp.
70. (Conception or conceiv*).mp.
71. (fertility or infertility).mp.
72. Or/57-71
73. exp Pregnancy Outcome/
74. exp Pregnancy Complications/
75. exp Abortion, Spontaneous/
76. exp Infant mortality/
77. exp Fetal mortality/
78. exp Premature birth/
79. exp Infant/
80. exp Fetal Death/
81. exp Fetal weight/
82. exp Birth weight/
83. exp Infant, Low Birth Weight/
84. exp Fetal growth retardation/
85. (Stillbirth* or still-birth or miscarriage* or abortion).mp.
86. (growth retardation or IUGR or "low birth weight").mp.
87. (((prem* or pre-term or "pre term") adj birth) or deliver* or labo?r).mp.
88. ((foetal or fetal or foetus or fetus or infant* or perinatal* or "peri natal" or peri-natal or neonatal or neonatal) adj2 (loss or mortality or death)).mp.
89. (aborted adj (foetus or fetus)).mp.
90. Or/73-89
91. exp "congenital, hereditary, and neonatal diseases and abnormalities" / or exp congenital abnormalities/
92. exp Infant, Newborn, Diseases/
93. exp fetal development/
94. ("foetal malformation*" or "fetal malformation*").mp.
95. ((Congenital adj anomalies) or anomaly or malformations*).mp.
96. Or/91-95
97. 35 or 40 or 54 or 72 or 90 or 96
98. 23 and 97
99. exp animals/ not humans.sh.
- 100.98 not 99
- 101.Limit 100 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)²⁸

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):⁴²

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):⁴²

- 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

Authors & Year Country	Study design	Study pop ⁿ and sampling methodology	Study Group (N)	Comparison Group (N)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Brown et al. (2009) ² Australia	Retrospective cohort Postal questionnaire and clinical assessments	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: 15 item self-reported questionnaire - International Index of Erectile Function (IIEF)³¹ 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.⁴³</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) 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>							

Authors & Year Country	Study design	Study pop ⁿ and sampling methodology	Study Group (N)	Comparison Group (N)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
<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>							
D'Este et al. 2004 ⁴ Australia	Retrospective cohort Self-reported Female Reproductive Questionnaire administered in the Study of Health Outcomes in Aircraft Maintenance personnel (SHOAMP)	Female F-111 DSRS workers and female partners of male study participants who reported pregnancies during five posting periods over 1975-1999. Female DSRS workers (n=24) and female partners of male DSRS workers (n=767)	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: • 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. still birth 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: 16-46 y Female
<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: Program 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>							

Authors & Year Country	Study design	Study pop ⁿ and sampling methodology	Study Group (N)	Comparison Group (N)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
<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. 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 association with group for all exposed (p=0.54), Program 1 (p=0.50) or Program 2 (p=0.34) in multiple regression (Amberley vs exposed OR=1.13, CL 0.75-1.72, Richmond vs exposed OR=0.92, CL 0.65-1.3)</p> <p>For Program 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)</p> <p>For Program 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> <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> <p>Conclusions: There was no evidence of an association in female DSRS personnel or female partners of male DSRS personnel and miscarriage or stillbirth, or in reported difficulties getting pregnant or seeing a fertility specialist.</p>							
Desrosiers et al. 2012 ³ USA	Case control study	National Birth Defects Prevention Study (NBDPS) eligible live births with 60 major birth defect categories and controls randomly selected from hospital records or birth certificates without major defects. 1997 to 2005 Study popn: 1492 cases, 5771 controls*	Fathers of 9998 cases N=71* fathers of cases who worked in gas and petroleum industry	Fathers of 4066 controls N=20* fathers of babies without major defects who worked in gas and petroleum industry	Babies with non-syndromic isolated and multiple birth defects reported in the NBDPS database Defect categories were considered to be associated with an occupation if 95% credible interval (CI) around the odds ratio (OR) for occupation-defect combinations with any exposed cases excluded the null, or if OR was ≥ 2.0 or ≤ 0.5 for either isolated defects or for all cases combined.	Paternal occupation histories reported by mothers in telephone interview re fathers' jobs 3 months preceding expended date of conception through the first month of pregnancy. <i>A priori</i> set of maternal confounding factors incl. residence at delivery, age, race/ethnicity, education, use of supplemental folic acid or prenatal vitamins, smoking and alcohol use.	No information on fathers across occupational groups incl. gas and petroleum workers were available
<p>* only outcomes related to gas and petroleum workers are reported here</p> <p>Findings:</p>							

Authors & Year Country	Study design	Study pop ⁿ and sampling methodology	Study Group (N)	Comparison Group (N)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
<p>71 (0.7%) fathers worked in the gas and petroleum industry in the study group and 20 (0.5%) in control group. There were 11 cases of atrial septal defects in the study group (OR 1.6; 95% CI 1.0-2.4), 2 cases of limb deficiency (OR 2.6; 95% CI 1.1-6.5), 1 case of colonic atresia/stenosis (OR 2.8; 95% CI 0.9-9.1) and 1 case of glaucoma/anterior chamber defects (OR 2.0; 95% CI 0.8-5.1).</p> <p>The authors concluded that paternal petroleum and gas worker occupation was associated with increased prevalence of birth defects in offspring.</p> <p>Several occupations were also associated with an increased prevalence of 3 or more birth defect categories, including: mathematical, physical and computer scientists; artists; photographers and photo processors; food service workers; landscapers and groundskeepers; hairdressers and cosmetologists; office and administrative support workers; sawmill workers; petroleum and gas workers; chemical workers; printers; material moving equipment operators; and motor vehicle operators, compared with manager/administrators and sales workers groups combined (primary referent group).</p>							
Kesner et al. 2001 ⁵ USA	Cross-sectional study (situated in a larger risk assessment) Questionnaire and venous blood samples	Personnel from United States Air Force (USAF) bases Sampling method not reported	Male tank-entry personnel with ≥9 months of persistent exposure to jet fuel, (i.e., one hour entry, twice a week) N=134	N=not reported USAF from 3 bases who did not routinely work with or have significant exposure to fuels or solvents	Venous blood analysed for endocrine concentrations: • Follicle stimulating hormone (FSH) • Luteinising hormone (LH) • Prolactin • Cortisol • Oestradiol • Inhibin-B • Total and free testosterone	A self-reported questionnaire including job, months on the job, exposure, medical and demographic information. Correlation coefficients derived for each of the 8 hormonal endpoints against variables. Linear models assessed effect of months on the job and exposure and their interaction, controlling for confounders.	Males. Age not reported
<p>Findings:</p> <p>Study group characteristics were not reported.</p> <p>For FSH, the main effect of exposure was significant ($p = 0.03$), though none of the adjusted means were significantly different from each other. The slope for the high exposure group tended to greater than zero ($B=0.015$, $p=0.055$) FSH level was also directly related to age ($b = 0.10$, $p = 0.005$).</p> <p>The main effect of exposure was significantly related to inhibin B levels ($p<0.035$) Adjusted serum levels of the high exposure group were significantly greater than for the low exposure group.</p> <p>The association between months on the job and total testosterone was significant ($r=0.263$; $p=0.002$) Months on the job was inversely correlated with testosterone level but this association disappeared when adjusted against age in the multivariate analysis.</p> <p>The authors concluded that FSH levels may be higher in personnel who have worked longer in jobs with higher naphthalene exposure and that the results also suggest that men with higher naphthalene exposure have elevated inhibin B levels. The authors suggested this finding could be consistent with an exposure effect stimulating FSH secretion leading to elevated inhibin B levels, and/or a relative desensitisation of the feedback setting.</p>							
LeMasters et al. 1999 ⁶	Prospective cohort (repeated measure design)	Volunteer civilian or active-duty military personnel at one USAF base who	Jet fuel workers (N=15) Flight line workers (N=23)	Not exposed (N=8)	Sperm production, structure and function: • Sperm concentration (million per ml)	Questionnaires: included medical and occupational history, lifestyle characteristics	Males ≤51 years

Authors & Year Country	Study design	Study pop ⁿ and sampling methodology	Study Group (N)	Comparison Group (N)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Questionnaires administered face to face; exposure assessment and semen analysis	performed aircraft maintenance duties (N=58)	Sheet metal workers (N=6) Paint shop workers (N=6)		<ul style="list-style-type: none"> Percent motile sperm Percent normal morphology Morphometry: <ul style="list-style-type: none"> Length (µm) Width (µm) Width to length ratio Standard chromatic 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 	Standard personal industrial hygiene (IH) sampling and expired breath samples according to National Institute for Occupational Safety and Health (NIOSH) guidelines to measure following 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) Comparison: 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>Findings:</p> <p>Exposure: The exposure assessment revealed that all the workers had low exposures for solvents (mean of <6 ppm, which was <10% of the Occupational Safety and Health Administration [OSHA] standard for all chemicals except benzene). For all exposed subjects, mean breath level of jet fuels measured as naphtha was 19.1 ppb (OSHA permissible exposure limit was 100 ppm).</p> <p>Reproductive assays:</p> <p>Sperm concentration (million/ml): The flight line group demonstrated 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). Jet fuel group demonstrated 9.7% and 9.0% increase at the same time points, and 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. The mean sperm concentration was 66.4 (±32.6) at baseline, 72.4 (±46.9) at 15 weeks and 73.8 (±47.7) at 30 weeks of exposure for the combined exposed groups (n=50). The reference values* were ≥20 (±60).</p> <p>Mean sperm concentration (million/ml): was 66.4 (± 32.6) at baseline, 72.4 (± 46.9) at 15 weeks and 73.8 (± 47.7) at 30 weeks of exposure for the combined exposed group (n=50). Mean reference vale* was ≥20 (±60).</p>							

Authors & Year Country	Study design	Study pop ⁿ and sampling methodology	Study Group (N)	Comparison Group (N)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
<p>Sperm length (μm): Sperm length demonstrated a significant 2.1% ($p=0.02$) and 2.9% ($p=0.02$) decline at 15 and 30 weeks in the sheet metal group, but a significant ($p \leq 0.01$) 2.5% decline at 15 weeks and non-significant 1.1% decrease at 30 weeks also was found in the unexposed group. Paint shop workers reported 1.2% decrease at 15 weeks and no change at 30 weeks. Jet fuel group demonstrated 1.5% and 0.8% increase at 15 and 30 weeks respectively. The flight line group demonstrated a decrease of 0.3% and 1.6% at 15 and 30 weeks respectively.</p> <p>Mean sperm length (μm): was 4.26 (± 0.28) at baseline, 4.25 (± 0.27) at 15 weeks and 4.21 (± 0.25) at 30 weeks of exposure for the combined exposed group ($n=50$). Mean reference value* was 4.5 (± 63).</p> <p>Sperm width to length ratio: This ratio significantly declined in the unexposed (3.1%, $p=0.05$) and the paint shop (3.4%, $p=0.02$) 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% as well as the jet fuel group (1.1% and 0.1%). Flight line group reported a decrease of 0.4% and 1.2% for the same time points.</p> <p>Mean sperm width/length ratio was 0.67 (± 0.05) at baseline, 0.67 (± 0.04) at 15 weeks and 0.67 (± 0.04) at 30 weeks of exposure for the combined exposed group ($n=50$). Mean reference value* was 0.6 (± 63).</p> <p>Percentage motility of sperm: Both unexposed group (15.9% and 8.1%) and flight line group (2.9% and 7.2%) reported an increase, but statistically non-significant, at 15 and 30 weeks respectively. For the same time points, sheet metal group (4.6% and 3.2%) and jet fuel group (2.1% and 6.2%) reported a decline. Paint shop group reported 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 reported a proportional decline of 3.5% to 43.7% between baseline and 30 weeks.</p> <p>The mean percent (%) motile sperm was 44.5 ($12 \pm$) at baseline, 43.7 (± 14.9) at 15 weeks and 42 (± 12.3) at 30 weeks of exposure for the combined exposed group ($n=50$). The reference values* were ≥ 50 (60).</p> <p>Percent normal morphology: The mean percent normal morphology was 18.4% (± 6.6) at baseline, 17.8% (± 8.6) at 15 weeks and 18.1% (± 9.1) at 30 weeks of exposure for the combined exposed group ($n=50$). The mean reference value* was $\geq 14\%$ (± 60).</p> <p>Sperm directional movement: as measured by linearity (VSL/VCL) was significantly depressed at 30 weeks in the sheet metal (8.8%, $p=0.03$) and the jet fuels (7.7%, $p=0.02$) groups. The unexposed group also reported a decline (5.1% and 3.9%) for the same time points.</p> <p>The mean percent DNA denatured cells was 18.3% (± 11.9) at baseline, 19.0% (± 11.4) at 15 weeks and 17.1% (± 9.3) at 30 weeks of exposure for the combined exposed group ($n=50$). The reference value* was 16.8% (± 7.2).</p> <p>The authors reported that the findings indicated that for most sperm measures the mean values remained in normal range during the 30 weeks of exposure. When jobs were analysed by exposure groups some adverse changes were observed. The paint shop group had a significant decline in sperm motility at 30 weeks. Internal dose measures did not show a significant association with spermatogenic changes. Exposure to jet fuels did not indicate any obvious effect on semen quality. However, the authors cautioned about the low statistical power when interpreting results and suggested further research to determine whether there could be effects from exposure to solvents (i.e. in paint shop group).</p> <p>*Reference values for WHO are consensus numbers. OSHA Permissible Exposure Limit (PEL) and ACGIH recommended Threshold Limit Value (TLV) for individual solvents, benzene, and jet fuel as naphthas are listed and identical unless reported otherwise. 1,1,1 trichloroethene=350 ppm; MEK=200 ppm; toluene 200 ppm PEL and 50 ppm TLV; methylene chloride=500 ppm PEL and 50 ppm TLV; benzene=1.0 ppm PEL and 0.5 ppm TLV; jet fuel as naphtha is 100 ppm PEL and unavailable for TLV.</p>							

Reports

Authors & Year	Country	Title and scope	Exposure (s) route	Reproductive and Developmental Effects	References
Agency for Toxic Substances and Disease Registry (ATSDR) (2017) ⁷	USA	Toxicological profile for JP-5, JP-8 and Jet A Fuels.		Health Effects: A few epidemiological and human dosimetry studies have examined the effects of exposure to JP-8 on human health. These studies examined occupationally exposed subjects and provided some evidence suggesting that long-term exposure to JP-8 may be associated with adverse neurological effects. There were no epidemiological studies on adverse reproductive outcomes.	
		The profile was prepared in accordance with guidelines developed by ATSDR and the US Environmental Protection Agency (US EPA).	Inhalation	No studies were located regarding developmental effects in humans after inhalation exposure to JP-5, JP-8, or Jet A fuels.	
		An ASTDR toxicological profile succinctly characterises the toxicological and adverse health effects information for the toxic substances of the profile. The peer-review profile identifies and reviews the key literature of a substance's 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.	Oral	No studies were located regarding reproductive effects or developmental effects in humans after oral exposure to JP-5, JP-8, or Jet A fuels.	
		The health effects section and human studies findings were considered in relation to this Evidence Profile	Dermal	No studies were located regarding human reproductive, developmental or endocrine effects after dermal exposure to JP-5, JP-8, or Jet A fuels.	
Findings: The profile reported that there were limited data on the toxicity of JP-5, JP-8, or Jet A fuels in humans; the available studies had evaluated neurologic, reproductive, genotoxic, or carcinogenic end points following inhalation exposure. No studies were identified on the effect of jet fuel exposure on reproductive health in men.					
Institute of Medicine (IOM) (2005) ⁸	USA	Gulf War and Health: Volume 3. Fuels, combustion products and propellants. The IOM appointed the Committee on Gulf War and Health, Literature Review of Selected	Any	Reproductive and developmental outcomes of interest included infertility, preterm birth and low-birth rate, birth defects and childhood cancers. The committee found one study on exposure to jet fuels and semen characteristics.	LeMasters 1999 ⁶ [reported above]

Authors & Year	Country	Title and scope	Exposure (s) route	Reproductive and Developmental Effects	References
		Environmental Particulates, Pollutants and Synthetic Chemical Compounds 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 during the Gulf War.		No studies of infertility in women and exposure to fuels met the committee's inclusion criteria. No studies were reported for spontaneous abortion in veterans or that included occupational exposures.	
<p>Findings: The committee concluded that overall it was difficult to reach conclusions on the epidemiological studies of adverse reproductive outcomes and exposure to fuels due to limitations of the small number of studies on each health outcome, possibility of recall bias and lack of specificity of exposure to agents of concern. The committee concluded that, from its assessment of the epidemiological literature, that there was inadequate/insufficient evidence to determine whether an association exists between exposure to fuels and adverse reproductive or developmental outcomes, including infertility, spontaneous abortion and several childhood cancers.</p>					
National Research Council (NRC) (2003) ⁹	USA	Evaluating chemical and other agent exposures for reproductive and developmental toxicity. The NRC assigned this project to the Committee on Toxicology (COT), which assembled the Subcommittee on Reproductive and Developmental Toxicology to prepare this report/assessment.	Inhalation and Dermal	One human study was identified that reported on exposure to jet fuels or solvents and effects on semen characteristics.	LeMasters 1999 ⁶ [reported above]
<p>Findings: One human study was identified that reported on possible reproductive toxicity following exposure to jet fuels or chemicals.</p>					

References

1. 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 [\[https://www.dva.gov.au/sites/default/files/Question_14_Fuel_and_Solvent_Exposure_Technical_Report_Sept_2017.pdf\]](https://www.dva.gov.au/sites/default/files/Question_14_Fuel_and_Solvent_Exposure_Technical_Report_Sept_2017.pdf), Accessed (22/04/2018)
2. 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.
3. Desrosiers TA, Herring AH, Shapira SK, Hooiveld M, Luben TJ, Herdt-Losavio ML, et al. Paternal occupation and birth defects: findings from the National Birth Defects Prevention Study. *Occup Environ Med.* 2012;69(8):534-42.
4. 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 [\[https://web.archive.org/web/20080309023912/http://www.defence.gov.au/health/research/shoamp/i-SHOAMP.htm\]](https://web.archive.org/web/20080309023912/http://www.defence.gov.au/health/research/shoamp/i-SHOAMP.htm), Accessed (22/04/2018)
5. Kesner JS, Lemasters GK, Knecht EA, Krieg EF, Jr., Reutman SR. The effects of JP8 jet fuel on serum endocrine concentrations in men: risk assessment of acute exposure to jet fuel. In: Kendall RK, Smith E, editors. JP8: final risk assessment Kendall RK, Smith E, eds Brooks City-Base, TX: Air Force Institute for Operational Health. Air Force Institute for Operational, Health Risk Analysis Directorate, Texas. 2001. p. 91-6.
6. 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.
7. Agency for Toxic Substances and Disease Registry (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 [\[https://www.atsdr.cdc.gov/toxprofiles/tp121.pdf\]](https://www.atsdr.cdc.gov/toxprofiles/tp121.pdf), Accessed (22/04/2018)
8. Institute of Medicine (IOM). Gulf War and Health: Volume 3: Fuels, Combustion Products, and Propellants. Washington, DC: The National Academies Press; 2005. 516 p.
9. National Research Council (NRC). Toxicologic Assessment of Jet-Propulsion Fuel 8. Washington, DC: The National Academies Press; 2003. 229 p.
10. 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.

11. Australian Institute of Health and Welfare. 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: AIHW. 2016.
12. 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 [\[http://www.defence.gov.au/Health/SHC/docs/Study_of_Health_Outcomes_Aircraft_Maintenance_Personnel.pdf\]](http://www.defence.gov.au/Health/SHC/docs/Study_of_Health_Outcomes_Aircraft_Maintenance_Personnel.pdf), Accessed (18/09/2018)
13. D'Este C, Attia JR, Brown AM, Gibson R, Gibberd R, Tavener M, et al. Cancer incidence and mortality in aircraft maintenance workers. *Am J Ind Med.* 2008;51(1):16-23.
14. 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 [\[http://www.defence.gov.au/FOI/Docs/Disclosures/123_1415_Report.pdf\]](http://www.defence.gov.au/FOI/Docs/Disclosures/123_1415_Report.pdf), Accessed (22/04/2018)
15. 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 [\[https://www.dva.gov.au/sites/default/files/files/A%20Developers%20Guide%20to%20Undertaking%20REAs%20-%20June%202016.pdf\]](https://www.dva.gov.au/sites/default/files/files/A%20Developers%20Guide%20to%20Undertaking%20REAs%20-%20June%202016.pdf), Accessed (22/04/2018)
16. The Auditor General. Australian Defence Force Fuel Management, Department of Defence. Australian National Audit Office; 2002. Contract No.: Audit Report No. 44 2001-02. Available at [\[https://www.anao.gov.au/sites/g/files/net616/f/anao_report_2001-2002_44.pdf\]](https://www.anao.gov.au/sites/g/files/net616/f/anao_report_2001-2002_44.pdf), Accessed (22/04/2018)
17. International Agency for Research on Cancer (IARC). Occupational Exposures in Petroleum Refining: Crude Oil and Major Petroleum Fuels. World Health Organization, editor: International Agency for Research on Cancer - World Health Organization; 1989.
18. Mattie DR, Sterner TR. Past, present and emerging toxicity issues for jet fuel. *Toxicology and applied pharmacology.* 2011;254(2):127-32.
19. Chevron Corporation. Aviation Fuels Technical Review. Chevron Global Aviation, Chevron Products Company; 2006. Available at [\[https://skybrary.aero/bookshelf/books/2478.pdf\]](https://skybrary.aero/bookshelf/books/2478.pdf), Accessed (11/06/2018)
20. van de Sandt P, Carter M, Money C, Pizzella G, van Rijn R, Viinanen R, et al. Human exposure information for EU substance risk assessment of kerosine. Brussels: Report no

- 6/07. European Oil Company Organisation for Environment, Health and Safety (CONCAWE) Brussels; 2007. Available at [https://www.concawe.eu/wp-content/uploads/2017/01/rpt_07-6-2007-01315-01-e-2.pdf], Accessed (22/04/2018)
21. National Research Council (NRC). Subcommittee on Reproductive Developmental and Toxicology. Evaluating chemical and other agent exposures for reproductive and developmental toxicity: Washington, D.C. : National Academy Press; 2001.
22. 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)
23. Mattison DR, Plowchalk DR, Meadows MJ, Al-Juburi AZ, Gandy J, Malek A. Reproductive toxicity: male and female reproductive systems as targets for chemical injury. *Medical Clinics of North America*. 1990;74(2):391-411.
24. Bonde JP. Workplace exposures and reproductive health. 10th ed. ed. Baxter P, Cockcroft A, Durrington P, Harrington J, editors: London: CRC Press; 2010.
25. National Research Council (NRC). In: Subcommittee on Jet-Propulsion Fuel 8, editor. Toxicologic Assessment of Jet-Propulsion Fuel 8. Washington (DC)2003.
26. Briggs GB, Price WA, Still KR, Malcolm WJ. JP-8 jet fuel toxicity study in rats: potential effects on the regulation of male reproductive toxicity. *Teratology*. 2001;63(6):280.
27. Harris DT, Sakiestewa D, He X, Titone D, Witten M. Effects of in utero JP-8 jet fuel exposure on the immune systems of pregnant and newborn mice. *Toxicol Ind Health*. 2007;23(9):545-52.
28. 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.
29. University of Tasmania. Systematic Reviews for Health: Systematic Review Tools. 2018. Available at [<https://utas.libguides.com/SystematicReviews/Tools>], Accessed (13/06/2018)
30. Swartz MK. The PRISMA statement: a guideline for systematic reviews and meta-analyses. *J Pediatr Health Care*. 2011;25(1):1-2.
31. 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.

32. Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al. The National Birth Defects Prevention Study. *Public Health Rep.* 2001;116 Suppl 1:32-40.
33. Balise VD, Meng CX, Cornelius-Green JN, Kassotis CD, Kennedy R, Nagel SC. Systematic review of the association between oil and natural gas extraction processes and human reproduction. *Fertility and sterility.* 2016;106(4):795-819.
34. Burger HG. Evidence for a negative feedback role of inhibin in follicle stimulating hormone regulation in women. *Hum Reprod.* 1993;8 Suppl 2:129-32.
35. 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.
36. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for jet fuels JP-4 and JP-7. Atlanta, Georgia: U.S. Department of Health and Human Services, Public Health Service Agency for Toxic Substances and Disease Registry; 1995. Available at [<https://www.atsdr.cdc.gov/toxprofiles/tp76.pdf>], Accessed (11/06/2018)
37. Burnett AL. Environmental erectile dysfunction: can the environment really be hazardous to your erectile health? *J Androl.* 2008;29(3):229-36.
38. Kumar S. Occupational exposure associated with reproductive dysfunction. *J Occup Health.* 2004;46(1):1-19.
39. Tas S, Lauwerys R, Lison D. Occupational hazards for the male reproductive system. *Crit Rev Toxicol.* 1996;26(3):261-307.
40. Parliament of Australia. Sealing a just outcome : Report from the inquiry into RAAF F-111 Deseal/Reseal workers and their families. Forshaw M, editor. Canberra, A.C.T.: Canberra, A.C.T. : Joint Standing Committee on Foreign Affairs, Defence and Trade; 2009.
41. Katukam V, Kulakarni M, Syed R, Alharbi K, Naik J. Effect of benzene exposure on fertility of male workers employed in bulk drug industries. *Genet Test Mol Biomarkers.* 2012;16(6):592-7.
42. Boyle MH. Guidelines for evaluating prevalence studies. *Evidence Based Mental Health.* 1998;1:37-9.
43. 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.

