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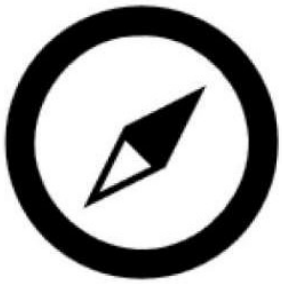

Technical Report

Literature review on the role of epigenetic mechanisms on the association between jet fuel and/or solvent exposure and human male reproductive outcomes

Rapid Evidence Assessment

February 2019

Disclaimer

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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)

Dr Joanne Ryan, Department of Epidemiology and Preventive Medicine, Monash University

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

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List of Abbreviations

DNA	deoxyribonucleic acid
DSRS	Deseal/Reseal
DVA	Department of Veterans' Affairs
F-111 DSRS	F-111 Deseal/Reseal
FSH	Follicle stimulating hormone
IOM	Institute of Medicine
JFES	Jet Fuel Exposure Syndrome
JP	Jet Propellant
JP-8	Jet propulsion Fuel 8 (type of aviation fuel)
LH	Luteinising Hormone
MEK	Methyl ethyl ketone
miRNA	microRNA
MonCOEH	Monash Centre for Occupational and Environmental Health
MATF	Military Aviation Turbine Fuel
PGME	Propylene glycol monomethyl ether
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RAAF	Royal Australian Air Force
REA	Rapid Evidence Assessment
RNA	Ribonucleic acid
TCE	Trichloroethylene
TOXLINE	Toxicology Literature Online
TOXNET	Toxicology Data Network
US	United States of America
USAF	United States Air Force

Executive Summary

- The aim of this Rapid Evidence Assessment (REA) was to conduct a literature review of effects of occupational exposure to jet fuel and/or specified solvents on epigenetic mechanisms that affect human male reproductive outcomes.
- The human male reproductive outcomes included in this review were:
    - 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, low fecundity, use of assisted reproductive technologies, and adverse pregnancy outcomes or reduced fertility in female partners), altered reproductive hormone levels (testosterone, oestradiol, luteinising hormone (LH) and follicle stimulating hormone (FSH))
    - Adverse sexual outcomes: Erectile dysfunction, libidosexual dysfunction, psychosexual dysfunction
- Fuels most relevant to the Australian military included 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
- Solvents most relevant to the Australian military included in this review were:
    - ethyl acetate, ethyl benzene, toluene, xylenes, acetone, isopropanol, methyl ethyl ketone (MEK), propylene glycol monomethyl ether (PGME), white spirit, and trichloroethylene (TCE).
- Using a comprehensive strategy, a search was conducted in nine electronic databases to identify peer-reviewed English language studies in humans, published between January 2000 and 29 November 2018. In addition, the Journal of Military and Veterans' Health was electronically hand searched to identify relevant studies. This strategy 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/or specified solvents which reported sexual

function or sexual or reproductive health outcomes mediated via epigenetic mechanisms were included.

- One report published in the United States of America (US) met the inclusion criteria. The report was a publicly available, government advisory committee report.
- No studies were identified that investigated any association between jet fuel and/or specified solvents exposure and reproductive and sexual outcomes in men, while also measuring epigenetic mechanisms.
- The lack of evidence may be the result of a combination of relative scarcity of epidemiological evidence on jet fuel and/or specified solvent exposure and male reproductive health outcomes, and epigenetics being an emerging field.
- Limitations of the REA include: the omission of possibly relevant papers that were published prior to 2000, although this is unlikely as epigenetics is a relatively new field of research, and the omission of non-English language papers.
- Although the effects of occupational exposure of male service members to jet fuels and/or specified solvents used in the Australian military was of prime interest, the search was not restricted to articles on military servicemen and included other occupational groups with jet fuel and/or specified solvent exposure. The search did not identify articles of relevance in other occupational groups exposed to jet fuels and/or specified solvents.
- This REA has identified that there is a lack of research evidence from human studies on this topic. Epigenetics is an emerging field and epidemiological research studies on associations between jet fuel and/or specified solvents and adverse reproductive health outcomes in men are limited. This is an area that could be considered for future research. Research focused on epigenetic modifications in human germ cells following exposure to jet fuel and/or specified solvents, transmission of epigenetic modifications, and the effect of confounding factors (e.g. stress, diet, smoking or environmental pollution) on those modifications, are current gaps in knowledge and important areas for future research.

Introduction

In the Royal Australian Air Force (RAAF) F-111 Deseal/Reseal (DSRS) programmes between 1975 and 1999 there was exposure to jet-propulsion fuel-8 (JP-8) aviation fuel and several solvents. This was associated with later ill health in DSRS personnel who had potentially been exposed to these solvents. The fourth study of mortality and cancer incidence also showed an estimated increase in overall cancer incidence of 23-30% in men in the DSRS study group compared to both unexposed comparison groups which was statistically signicicant.[1, 2] In addition, poorer mental health outcomes (i.e. risk of depression, anxiety and poorer general mental health)[3] were reported in DSRS personnel compared with unexposed comparison groups. The number of females identified as having participated in the DSRS programmes were small (4%),[3] and therefore these mental health outcomes are largely reflective of those in males. The exposed DSRS men were also found to report increased problems with sexual function and loss of interest in sex compared to men in unexposed comparison groups.[4] These findings of poorer health in DSRS personnel were identified in studies undertaken many years after the DSRS programme exposure.

The Jet Fuel Exposure Syndrome (JFES) *in vitro* study[5] reported on cellular effects, including toxicity, of JP-8 jet fuel and DSRS solvents, and potential molecular processes that may be associated with the longer-term reported adverse health effects of jet fuel exposure. The JFES study found that JP-8 fuel and, to a lesser extent, the DSRS solvents have the capacity to cause cellular toxicity. While the JFES study did not find any evidence of genetic or chromosomal changes, small changes in the expression of regulatory microRNAs, non-coding RNAs that may control activity of other genes or cellular processes, were identified. The interpretation of the function of the microRNAs and possible significance to human health is not known, however this raises the possibility that jet fuels and/or solvents may alter epigenetic patterns and could account for longer term health effects.

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 and early onset menopause. In 2017 and 2018, the Monash Centre for Occupational and Environmental Health (MonCOEH), in the School of Public Health and Preventive Medicine, Monash University conducted rapid evidence assessments (REAs) on the effects of occupational exposure to Military Aviation Turbine Fuels (MATFs), (herein referred to as jet fuels), and a selection of specified solvents of most relevance to the military, on adverse reproductive health outcomes in women[6] and men.[7, 8]

These literature reviews summarised the available evidence on associations between jet fuel and/or specified solvent exposure and adverse reproductive/sexual health in exposed men[7, 8] but also identified the limited available research in the field. No review has yet been undertaken to investigate whether exposure to jet fuel and/or solvents is associated with changes to underlying epigenetic patterns which could help account for an association between jet fuel and/or solvent exposure and reproductive health outcomes in men.

Therefore, the current literature review was undertaken to identify any evidence on the role of epigenetic mechanisms on the association between jet fuel and/or solvent exposure and human male reproductive outcomes.

Epigenetics

Epigenetics describes molecular modifications which occur 'above' the level of the deoxyribonucleic acid (DNA) sequence in a gene; they do not alter the genetic code but can influence the activity of the DNA, including the extent to which a gene encoded by the DNA is expressed.[9] They are highly dynamic during development and play an essential role in normal cell development and enable tissue differentiation. Epigenetic modifications are influenced by underlying genetics, but are also sensitive to environmental stimuli and can result in long-term changes in gene activity. Epigenetics thus enables adaptation and response to the external environment and epigenetic patterns can in turn influence individual traits, behaviours and risk for disease.

It is now well established that environmental factors such as smoking,[10] stress/trauma[11] and pollution,[12] have an effect on epigenetic patterns. Epigenetics mechanisms have been clearly implicated in cancer, and are widely accepted as playing an important role in the programming of disease risk. There is thus increasing speculation that underlying epigenetic mechanisms play a role in linking a range of adverse exposures to later health outcomes. Emerging research, largely from animal studies, also indicates that epigenetics could be transmitted from parent to offspring, providing a plausible mechanisms for the intergenerational transmission of risk.[11]

The main epigenetic modifications/mechanisms include DNA methylation, histone modifications and small, non-coding ribonucleic acids (RNAs).[13]

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.[14] 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.[15]

Kerosene-based jet fuels have been used for over 60 years.[16, 17] 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.[18] 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 fuels[20]

Jet A-1	Kerosene type fuel used in civil aircraft. Max freezing point -47ºC
Jet A	As Jet A-1, but with freezing point of -40ºC 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]

Solvents

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

They were finalised in consultation with the DVA Research Section and DVA Principal Medical Adviser and the (former) Defence Centre for Occupational Health.

Adverse male reproductive outcomes

Reproductive toxicity has been defined as "the occurrence of adverse effects on the reproductive system that may result from exposure to a chemical."[22] 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.[23] Male reproductive system toxins may act at several levels. The adverse male reproductive outcomes of interest in this literature review are listed in the Methods.

Aim

The aim of this project was to conduct a literature review on the role of epigenetic mechanisms on the association between jet fuel and/or solvent exposure and human male reproductive outcomes.

Method

This project was conducted using the rapid evidence assessment (REA) methodology[24] as requested by the Departments of Veterans' Affairs and Defence. This was the same methodology that was used for the previous literature reviews: the effects of exposure to jet fuel and specified solvents on human male reproductive outcomes[7, 8] and effects of exposure to jet fuel and specified solvents on human female reproductive outcomes.[6]

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 a 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) and limit selection of studies 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. The REAs may also include relevant grey literature, such as relevant reports and unpublished sources of information obtained from relevant websites, to supplement the evidence identified from published literature, which systematic reviews usually do not.

Defining the review question

The review was based on the PECO framework in conformity with the REA methodology; population (P), exposure (E), comparison group (C) and outcomes (O).[24] A complete description of the research question based on the PECO framework is given in Appendix 1.

To ensure relevance of results, key components related to the questions and specific inclusion and exclusion criteria, were established for the search and for screening studies for inclusion 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 REAs highlighted the scarcity of evidence on this topic in military personnel. Thus, we included papers on male non-military personnel in occupational groups exposed to jet fuels and/or specified solvents which reported relevant adverse reproductive health outcomes, and considered more broadly any epigenetic effect of jet fuel and/or specified solvent exposure that could affect sexual or reproductive health in men.

The exposures of interest were jet fuel and specified solvents (based on common solvents identified in the Study of Health Outcomes in Aircraft Maintenance Personnel of the F-111 DSRS workers[25]) (and related terms) most relevant to military personnel, and were finalised in consultation with the DVA Research Section and the DVA Principal Medical Adviser and the (former) Defence Centre for Occupational Health. These jet fuel and solvent lists were those used previously for the male[7, 8] and female reproductive outcome reviews[6] and adopted without modification.

The exposures of interest to jet fuels most relevant to military personnel as previously finalised were:[6]

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

This specified solvents list was that used previously for the male[7, 8] and female reproductive outcome reviews:[6]

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

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

The adverse male reproductive outcomes of interest were used in the male reproductive outcomes and jet fuel and specified solvents exposure reviews[7] and were adopted for this review without modification:

- 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 (early foetal loss, neonatal death, stillbirth, miscarriage, foetal malformations or congenital anomalies, pre-term birth, intra-uterine growth retardation or low birth weight, reduced fertility, reduced libido) in unexposed female partners.
- Altered levels of reproductive hormones (testosterone, oestradiol, luteinising hormone (LH) and follicle stimulating hormone (FSH))
- Adverse sexual outcomes: Erectile dysfunction, reduced libido sexual function, psychosexual dysfunction.

The epigenetic modifications/mechanisms included were:

- DNA methylation, histone modifications, small, non-coding RNAs, microRNA, hydroxymethylation, and acetylation.[13]

Search methods for identification of studies

Electronic searches

A comprehensive search strategy was developed using relevant Medical Subject Headings and relevant key words to identify published literature. Terms relating to jet fuel and to specified solvent exposure, see Methods, were used to identify jet fuel and specified solvent related records. The two searches were combined with the Boolean operator "OR" to identify any records related to jet fuel and/or specified solvent exposure. A search strategy for epigenetics that encompassed concepts such as epigenomics, histone modifications, non-coding RNAs, CpG Islands and epigenetics were combined with Boolean operator "AND" to the jet fuel and solvent search strategies to form the final search. The search was conducted to 29 November 2018 and was limited to English language human studies published in or after January 2000. The final Medline search strategy is given in appendix 2 and was adapted as necessary to query the nine electronic databases given below. As a review on this topic had not been conducted previously, but previous reviews had identified a limited number of studies of the association of exposure to jet fuel and specified solvents and adverse male reproductive outcomes, the search was not restricted to outcomes of interest. Therefore, any record that stated jet fuel and/or specified solvent exposure and epigenetics were retrieved and the titles and abstracts were assessed for inclusion.

The following nine electronic databases were searched:

- Medline (Ovid): Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE ® Daily, Ovid MEDLINE and Versions (R) 1946 to 29 November 2018
- Embase (Ovid): 1974 to 29 November 2018
- Cochrane Central
- Scopus
- TOXLINE via TOXNET (Toxicology Literature Online)
- DART via TOXNET (Developmental and Reproductive Toxicology Database)
- SciFinder

- ProQuest Military database
- NIOSHTIC-2 (The National Institute for Occupational Safety and Health)

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

The search was limited to English language studies in men published between January 2000 and 29 November 2018. The search was conducted within a defined and limited time frame and it was considered that this period was wide enough to identify relevant studies. The search time period constraint is consistent with the REA literature review methodology.[24] However, studies published before 2000, identified from full text articles, were also considered for inclusion if they were relevant.

The search included a list of pre-determined websites, to identify any relevant unpublished reports from online sources. The following websites were screened to identify any publicly available relevant government agency or independent medical scientific advisory committee reports, toxicological profiles, or risk assessment reports (herein referred to as reports).

- Agency for Toxic Substance and Disease Registry (ATSDR)
- US Department of Veterans Affairs
- Department of Veterans' Affairs Australia
- Department of Defence Australia
- US Department of Defence
- National Defence and the Canadian Armed Forces
- Veterans' Affairs Canada
- National Academies of Sciences, Engineering and Medicine (formerly Institute of Medicine)

Additionally, Professor Frank Bowling, the principal investigator of the JFES report, was contacted for advice regarding existing human studies.

Selection of studies

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

Following the removal of duplicates, one reviewer screened all the titles and abstracts against the predetermined inclusion and exclusion criteria in table 4. A second reviewer independently assessed a sample of 10% of the titles and abstracts. The screening decisions were compared and any discrepancies were resolved through consensus and the discussion was used to inform the selection decisions. Full text versions of all studies which satisfied the screening criteria were obtained. Studies were also included for full text assessment where there was uncertainty; for example, if it was not clear from the title and/or abstract whether the article included data on exposure to jet fuel or at least one of the specified solvents and epigenetic mechanisms.

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%.

Reports identified through the website search were also screened according to the inclusion and exclusion criteria. Data were extracted from the included reports to a standard data extraction table. The following variables were collected:

- Institute / organisation that published the report
- Year of publication
- Country of the publishing institute / organisation
- Publication title and scope
- Exposure and routes of exposure
- Reproductive health outcomes reported
- Relevant references identified
- Main findings of the report

The REA methodology[24] recommends assessing the quality of included primary 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 quality of included studies are expected to be assessed using a modified version of a tool developed by Giannakopoulos et al. which is provided in Appendix 3. However, these criteria are not applicable to reports.

Table 4: Inclusion and exclusion criteria

Inclusion
○ 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 29 November 2018 ○ Quantitative studies with outcome data that assessed epigenetic mechanisms in humans in relation to jet fuel and/or relevant specified solvent exposure and 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 ○ Relevant articles published before 01 January 2000 and identified from checks of the reference lists of relevant articles or websites
Exclusion
○ Papers / reports published before 01 January 2000 (unless key papers or reports) ○ Studies of genetic (rather than epigenetic) mutations ○ Studies that described epigenetic changes following jet fuel and/or specified solvent exposure but no reproductive effects due to these changes ○ Studies that described epigenetic changes and reproductive outcomes in men, but no associated jet fuel and/or specified solvent exposure ○ Qualitative studies ○ Non-English language ○ Reports that did not consider epigenetic mechanisms in humans in relation to jet fuel and/or specified solvent exposure in men and adverse male reproductive health outcomes ○ Reports not underpinned by a systematic review of literature

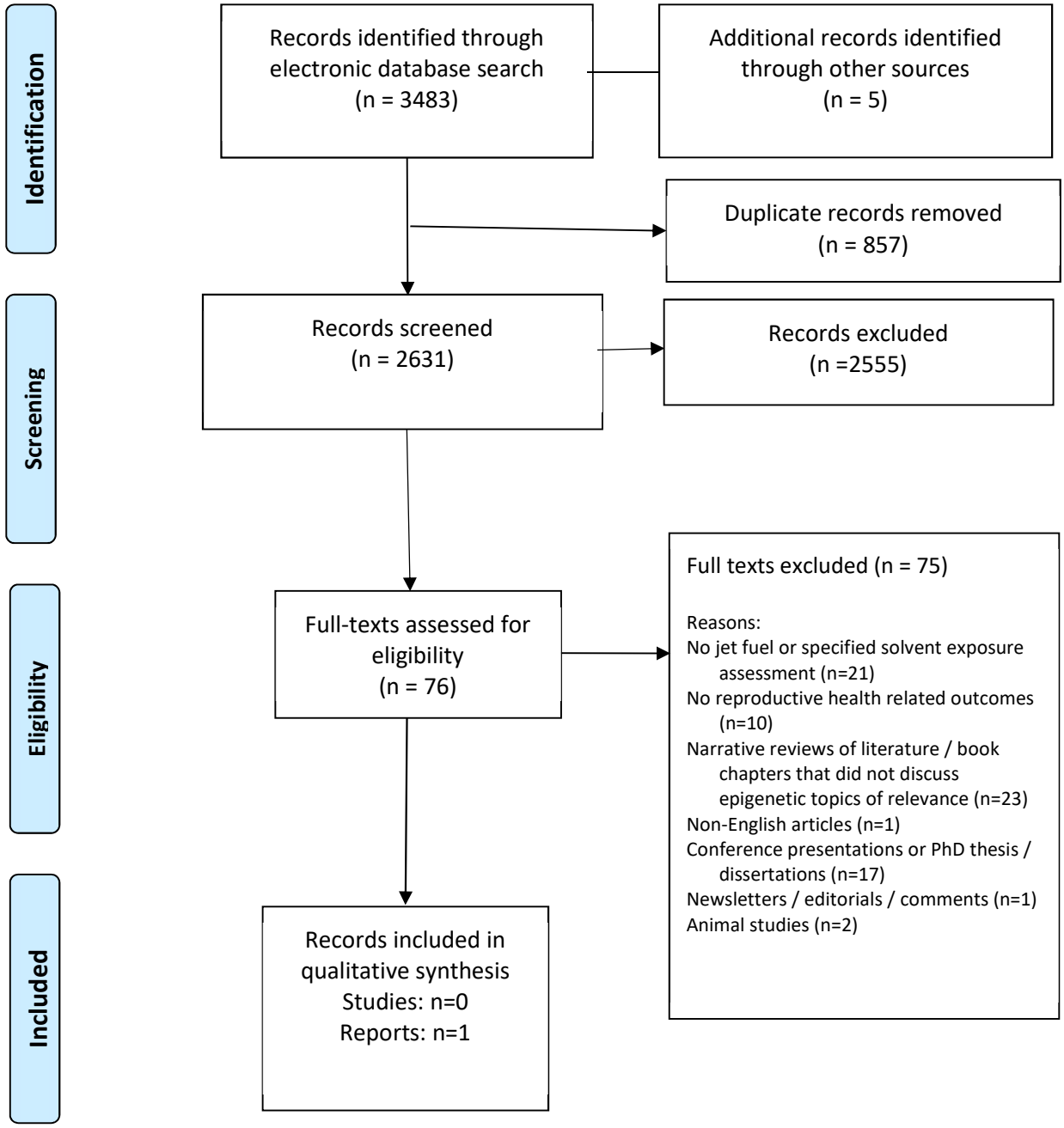
- Reports where recommendations or conclusions were not generated by a group of content experts or research experts and/or not containing ratings of the strength of evidence
- Conference presentations and PhD theses/dissertations
- Animal studies
- If full text version was not readily available to the research team and reasonable attempts to retrieve the full text were unsuccessful
- Environmental pollution studies (i.e. air, water)

Results

Results of the search

Nine electronic databases and an online military and veteran health journal were searched in November 2018 and this generated 3483 records. The reference list search of full text papers and the web site search yielded an additional five records.

Figure 1: PRISMA flow chart[26]



Following removal of duplicates, titles and abstracts of 2631 unique records were screened and 76 full texts were retrieved to be assessed for eligibility. Only one of the full texts met inclusion criteria and was included.[27] This was a report recently published by the National Academies of Science on generational health effects of serving in the Gulf War (appendix 4).

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[26] flowchart for study selection is given in Figure 1.

A hierarchy of reasons for exclusion for the full texts was developed and is presented in table 5.

Table 5: Hierarchy of reasons for exclusion of full texts

Category	Reason for exclusion	Number of excluded studies (%)
1	No jet fuel or specified solvent exposure assessment	21 (28)
2	No reproductive health related outcomes	10 (13)
3	Narrative reviews of literature / book chapters that did not discuss epigenetic topics of relevance	23 (31)
4	Non-English articles	1 (1)
5	Conference presentations or PhD thesis / dissertations	17 (23)
6	Newsletters / editorials / comments	1 (1)
7	Animal studies	2 (3)

The highest proportion of excluded studies were narrative reviews/book chapters (31%) followed by studies that did not include jet fuel and/or specified solvents as the exposure (28%). A high proportion of conference abstracts (23%) and studies that did not report on reproductive health or pregnancy related outcomes following exposure in men were also identified and excluded. Two animal studies (3%), one non-English article (1%) and one newsletter (1%) were also excluded.

A small number of studies which had compared epigenetic patterns (predominantly of microRNA (miRNA)) between individuals exposed to solvents and a control group of unexposed individuals were identified.[5, 28-34] However, none of these studies attempted to link these findings with reproductive-related outcomes, nor measured outcomes in offspring. Furthermore, all these studies measured epigenetic modifications in peripheral blood samples rather than, for example, in sperm which could have direct relevance to male reproductive health. Thus none of these studies met our inclusion criteria and were excluded.

In discussion with Professor Frank Bowling, he informed us that he was unaware of any relevant human study published to 2014.

The list of full texts assessed and reasons for exclusion based on the aforementioned hierarchy is presented in appendix 5.

Characteristics of the included study

One relevant report[27] was identified from the pre-determined website search. The objectives stated in this report were:

1. evaluating the scientific and medical literature on reproductive and developmental effects and health outcomes associated with Gulf War and Post-9/11 exposures

2. determining those research areas requiring further scientific study on potential health effects in the descendants of veterans of any era.

This report examined any epidemiological evidence on effects of exposure to pesticides, combustion products including fuel and various solvents on reproductive outcomes. Additionally, it examined whether there was evidence suggestive of any transgenerational / epigenetic effects following exposure to the above. Only transgenerational / epigenetic-related findings of reproductive outcomes following jet fuel and/or specified solvent exposure in men were extracted (where reported) as the conclusions of this report were based on *in vitro* and animal studies as well as human studies.

The report did not identify any epigenetic / transgenerational research evidence in men suggesting that exposure to TCE, xylenes, or PGME could affect reproductive health in men or pregnancy outcomes in partners. This report also recognised a paucity of studies relevant to reproductive effects specific to veterans' exposures during deployment.[27]

Discussion

The aim of this literature review was to identify research evidence on the role of epigenetic mechanisms on the association between jet fuel and/or solvent exposure of most relevance to the Australian military and human male reproductive outcomes.

Non-military male occupational groups who were exposed to jet fuel and/or specified solvents and/or were included in the criteria because of the scarcity of research in military populations,

evident from previous reviews[6, 7] conducted by the MonCOEH. However, after a comprehensive search this REA identified only one report which was published recently in 2018. This 2018 report[27] had also conducted a literature search and review and did not identify any relevant human studies, which was consistent with our literature search outcome. (Appendix 4).

The lack of evidence on this topic is consistent with previous research in this field. The limited number of epidemiological studies on jet fuel and/or solvent exposure and human reproductive health outcomes was highlighted in the previous REAs.[6, 7] Epigenetics is still a relatively new field, particularly in the context of the effects of environmental exposures on health outcomes in humans, with potential mediation via epigenetic mechanisms. To date, most research has focused on commonly studied exposures such as tobacco[10] and psychological stress.[35] The majority of human studies also measure epigenetic patterns in blood or other peripheral tissue (e.g. saliva/buccal cells), with research on sperm epigenetic patterns largely limited to animal studies to date.[36, 37] In addition, transgenerational epigenetic inheritance is an emerging field of research, with as yet, very few human studies across all subject areas.[37, 38]

The report[27] included in this review identified knowledge gaps particularly in relation to deployment specific exposures and reproductive or developmental effects and genetic or epigenetic effects. These knowledge gaps include effects of these exposures on adverse reproductive effects in veterans and development in offspring, including data on dose-response relationships, windows of susceptibility, duration and co-exposures. In relation to genetic or epigenetic alternations induced by environmental exposures identified knowledge gaps included effects that occur in parental germ cells, what happens when exposure ceases, and if and how life course events compound epigenetic modifications. Research on the transmission, persistence, gene/environment interactions and modifiers such as stress and diet, of epigenetic and genetic effects were identified as needed to understand the impact of deployment exposures on veterans and their descendants.[27]

Strength and limitations

The search terms for solvents and jet fuels were obtained from two previous REAs.[6, 7] The epigenetics search strategy was developed by an author on this review (JR) who is an expert in epigenetics. We screened all records of studies that reported jet fuel and the specified solvents in association with epigenetic modifications; such as DNA methylation, histone modifications or miRNA changes and no limitations were placed initially on the outcomes to maximise the yield. This literature review searched nine electronic databases which covered medical, science, toxicological and military literature. One military health journal was hand

searched through its website. Numerous governmental, military and other research organisational websites were also searched to identify relevant reports.

One of the strengths of this REA is the extensive coverage of resources to identify papers published in or after 2000. However, due to this strategy, studies published prior to 2000 could have been missed. Therefore, the reference lists of excluded narrative reviews were searched to identify potentially relevant studies published before or after 2000. Only English articles were included, therefore potentially relevant non-English articles were missed. Nevertheless, a very recently published report[27] did not identify any relevant human evidence that was missed in this REA and which therefore supported our approach.

When screening titles and abstracts, it was not always apparent whether any association between jet fuel and/or specified solvents and reproductive health outcomes was reported. To address this and to ensure relevant articles were not missed, any title and abstract that indicated jet fuel and/or solvents and an epigenetic-related term was obtained in full text and assessed.

Another strength of the REA is the inclusion of reports from relevant government agency or independent or independent medical, scientific and government institutions that provide information to government authorities. Eight such websites were searched to identify relevant reports.

This REA did not identify any studies on the role of epigenetic mechanisms on the association between jet fuel and/or solvent exposures and human male reproductive outcomes. Epigenetics is an emerging field and epidemiological research studies on associations between jet fuel and/or specified solvents and adverse reproductive health outcomes in men are limited. Therefore, research focused on epigenetic modifications in human germ cells following exposure to jet fuel and/or specified solvents, transmission of epigenetic modifications, and the effect of confounding factors (e.g. stress, diet, smoking or environmental pollution) on those modifications, are current gaps in knowledge and important areas for future research.

Appendix 1: Population Exposure Comparison Outcome (PECO) Framework

Question: **In men who are or who have been employed in defence or military related forces, or in occupational groups exposed to jet fuels and/or specified solvents, is exposure associated with epigenetic changes that may affect reproductive health outcomes in men, compared to non-exposed personnel?**	
Population (P)	Males Employed or previously employed in in defence or military related forces (i.e. occupationally exposed)
Exposure (C)	Jet fuel: Military (JP-4, JP-5, JP-7, JP-8, F33, F34) or civilian (Jet A, Jet A-1 and Jet B) Specified solvents: ethyl acetate, ethyl benzene, toluene, xylene, acetone, isopropanol, methyl ethyl ketone, propylene glycol monomethyl ether, white spirit and trichloroethylene
Comparison (C)	Not exposed to jet fuel and/or specified solvents mentioned above

Outcomes (O)	• Adverse male reproductive outcomes
	  ○ Hypogonadism / primary testicular failure
	  ○ Androgen (testosterone) deficiency
	  ○ Impaired semen quality (volume, concentration, number, motility, vitality and morphology)
	  ○ Reduced reproductive success (infertility, involuntary childlessness, not achieving desired family size, increased time-to-pregnancy, low fecundity (fecundity defined as the probability of a couple to conceive in a menstrual cycle), increased use of assisted reproductive technologies, adverse pregnancy and fertility outcomes in female partners (i.e. early foetal loss, neonatal death, stillbirth, miscarriage, foetal malformations or congenital anomalies, pre-term birth, intra-uterine growth retardation or low birth weight, reduced fertility, reduced libido in female partners of exposed men)
	  ○ Altered reproductive hormones (testosterone, oestradiol, luteinising hormone and follicle stimulating hormone)
	• Adverse male sexual outcomes
	  ○ Erectile dysfunction
	  ○ Libidosexual dysfunction
	  ○ Psychosexual dysfunction

Appendix 2: Search strategy

The Medline search strategy is included below.

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

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

30 exp Fuel Oils/

31 petroleum distillate*.mp.

32 Petroleum Naphtha.mp.

33 "Aviation Keros#ne".mp.

34 AVTUR.mp.

35 "Fuel System Icing Inhibitor".mp.

36 ("JP4" or "JP-4" or "Nato F-40" or "MIL-DTL-5624").mp.

37 (JP5 or JP-5).mp.

38 (JP7 or JP-7 or "MIL-DTL-38219").mp.

39 (JP8 or JP-8 or "JP-8+100" or "MIL-DFL-83133").mp.

40 ("Civilian Jet A" or "Jet A").mp.

41 ("Civilian Jet A-1" or "Jet A-1").mp.

42 "Jet B".mp.

43 ("F33" or "F-33" or "F 33").mp

44 ("F34" or "F-34" or "F 34").mp.

45 ("F44" or "F-44" or "F 44").mp.

46 Or/24-45

47 *EPIGENOMICS/

48 *DNA Methylation/

49 *S-Adenosylmethionine/

50 *CpG Islands/

51 ((histone* or chromatin* or dna or rna or long interspersed) adj3 (acetylat* or demethylat* or methylat* or phosphorylat* or ubiquitinat* or modif* or hydroxy?methylat* or hydroxy methylat*)).ab,ti,kf.

52 ("s adenosylmethionine" or cpg or epigenetic* or epigenomic*).ab,ti,kf.

53 (non coding RNA* or non?coding RNA* or ncRNA or lncRNA or microRNA or miRNA or circular RNA or circRNA or small interfering RNA or siRNA or piwi interacting RNA or piRNA).ab,ti,kf.

54 OR/47-53

55 23 OR 46

56 54 AND 55

57 exp animals/ not humans.sh.

58 56 NOT 57

59 limit 58 to yr="2000 -Current"

60 limit 59 to English language

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

Modified from Giannakopolous, Rammelsberg, Eberhard, Schmitter (2012)[39]

Completed		
Yes	**No**	
		1. Target Population
		• Target population clearly defined, including: age, sex, employment, ethnicity, religion **AND** • relevant data from health questionnaire of sampled persons, *if appropriate*
		• Target population not clearly defined : limited data available on: age, sex, employment, ethnicity, religion **AND** • relevant data from health questionnaire of sampled persons, *if appropriate*
		• Target population poorly defined: little or no information on age, sex, employment, ethnicity, religion **OR** • little or no information from relevant data from health questionnaire of sampled persons, *if appropriate*
		2.Sampling method (Representativeness)
		• Sophisticated probability sampling used** (e.g. stratified sampling; cluster sampling; multistage sampling; multiphase sampling)
		• Simple probability sampling used:* (e.g. simple random sampling)
		• No probability sampling used
		3. Measurement (Reliability)
		• Standardised data-collection methods (e.g. validated clinical interview or diagnostic instrument/criteria) **OR** • reliable survey instruments (e.g. validated self-report measure / validated screening instrument)
		• Non-standardized data collection **OR** • Non-validated interview or non-validated self-report measure
		4. Information about non-responders

Completed		
Yes	**No**	
		• Analysis of differences conducted on non-responders
		• No analysis of differences information provided on non-responders **OR** • 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):[40]
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):[40]

- 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

Reports (n=1)

Authors & Year	Country	Title and scope	Exposure(s)	Epigenetic / transgenerational effects on Male Reproductive Health, Pregnancy in Partners or Foetal Development	References
Institute of Medicine (IOM) of the National Academies (2018)[27]	USA	Gulf War and Health: Volume 11: Generational Health Effects of Serving in the Gulf War The IOM appointed the Committee on Gulf War and Health to determine the extent to which available scientific data permits meaningful conclusion in relation agents, hazards, medicines, vaccines or illnesses. The IOM assisted the US Veterans Affairs and Congress in evaluating the scientific literature regarding exposures to the Gulf War. This volume addresses two major tasks: 1. evaluating the scientific and medical literature on reproductive and developmental effects and health outcomes associated with Gulf War and Post-9/11 exposures 2. determining those research areas requiring further scientific study on potential health effects in the descendants of veterans of any era	Jet fuels (JP-8), kerosene, gasoline, diesel	No human studies were identified	
			Toluene	No human studies were identified	
			Xylenes	No information was reported	
			Trichloroethylene	No human studies were identified	
			Ethylene and glycol ethers	No information was reported	

Findings: Note: findings and committee conclusions in relation to fuels and specified solvents and male reproductive health outcomes are reported below.

Fuels

The committee found some evidence to suggest that epigenetic effects were associated with exposure to JP-8 in rats[41] and epigenetic and transgenerational effects are possible in animals.[37] The committee concluded that there is inadequate/insufficient evidence to determine whether an association exists between exposure to fuels and reproductive or developmental effects in humans.

Toluene

The committee concluded that there is inadequate/insufficient evidence to determine whether an association exists between exposure to toluene and reproductive effects in men, or with adverse pregnancy outcomes. The committee found that there are no data on the role of toluene exposure in the transgenerational transmission of adverse health effects or in epigenetic effects in humans or animals.

Xylene

The committee concluded that there is inadequate/insufficient evidence to determine whether an association exists between exposure to xylenes and reproductive effects in men, or with adverse pregnancy outcomes. However, no comments were provided in relation to epigenetic mechanisms in humans.

Authors & Year	Country	Title and scope	Exposure(s)	Epigenetic / transgenerational effects on Male Reproductive Health, Pregnancy in Partners or Foetal Development	References
TCE The committee concluded that there is limited/suggestive evidence of an association between trichloroethylene and reproductive effects in men, or adverse pregnancy outcomes. However, no comments were provided in relation to epigenetic mechanisms in humans. Glycol ethers The committee concluded that there is limited/suggestive evidence of an association between exposure to glycols and glycol ethers and reproductive effects in men. The committee concluded that there is inadequate/insufficient evidence to determine whether an association exists between exposure to glycols and glycol ethers and adverse pregnancy outcomes. However, no comments were provided in relation to epigenetic mechanisms in humans.					

Appendix 5: List of excluded studies

Based on the hierarchy reported in table 5.

No jet fuel and/or specified solvents were reported as exposure (n=21)

#	Citation
1	Alavian-Ghavanini A, Risen RS, Tang M, Ruegg J, Alavian-Ghavanini A, Ruegg J, et al. Prenatal Bisphenol A Exposure is Linked to Epigenetic Changes in Glutamate Receptor Subunit Gene Grin2b in Female Rats and Humans. Sci Rep. 2018;8(1):11315.
2	Albert O, Jegou B. A critical assessment of the endocrine susceptibility of the human testis to phthalates from fetal life to adulthood. Hum Reprod Update. 2014;20(2):231-49.
3	Alegria-Torres JA, Barretta F, Batres-Esquivel LE, Carrizales-Yanez L, Perez-Maldonado IN, Baccarelli A, et al. Epigenetic markers of exposure to polycyclic aromatic hydrocarbons in Mexican brickmakers: A pilot study. Chemosphere. 2013;91(4):475-80.
4	Alfano R, Nawrot TS, Plusquin M, Herceg Z, Ghantous A, Nawrot TS, et al. The Impact of Air Pollution on Our Epigenome: How Far Is the Evidence? (A Systematic Review). Curr Environ Health Rep. 2018;5(4):544-78.
5	Carré J, Gatimel N, Moreau J, Parinaud J, Léandri R. Does air pollution play a role in infertility?: A systematic review. Environ Health. 2017;16(1):82.
6	Devoz PP, Gomes WR, Ladeira De Araujo M, Ribeiro DL, Pedron T, Greggi Antunes LM, et al. Lead (Pb) exposure induces disturbances in epigenetic status in workers exposed to this metal. J Toxicol Environ Health, Part A. 2017;80(19-21):1098-105.
7	Duale N, Gutzkow KB, Hofer T, Lindeman B, editors. Impact of environmental pollutants on placentation2016: CRC Press.
8	Fenga C, Gangemi S, Costa C. Benzene exposure is associated with epigenetic changes (Review). Mol Med Rep. 2016;13(4):3401-5.
9	Godderis L, De RK, Tabish AM, Poels K, Maertens N, De RK, et al. Epigenetic changes in lymphocytes of solvent-exposed individuals. Epigenomics. 2012;4(3):269-77.
10	Godderis L, Maertens N, de Gelder V, De Lamper A, De Ruyck K, Vernimmen M, et al. Genetic susceptibility in solvent induced neurobehavioral effects. Neurotox Res. 2010;17(3):268-78.
11	Hammoud SS, Nix DA, Hammoud AO, Gibson M, Cairns BR, Carrell DT. Genome-wide analysis identifies changes in histone retention and epigenetic modifications at developmental and imprinted gene loci in the sperm of infertile men. Hum Reprod. 2011;26(9):2558-69.
12	Hou L, Zhang X, Wang D, Baccarelli A. Environmental chemical exposures and human epigenetics. Int J Epidemiol. 2012;41(1):79-105.
13	Kile ML, Fang S, Baccarelli AA, Tarantini L, Cavallari J, Christiani DC. A panel study of occupational exposure to fine particulate matter and changes in DNA methylation over a single workday and years worked in boilermaker welders. Environ Health. 2013;12:47.
14	Li J, Zhang X, He Z, Sun Q, Qin F, Huang Z, et al. MGMT hypomethylation is associated with DNA damage in workers exposed to low-dose benzene. Biomarkers. 2017;22(5):470-5.
15	Li J, Zhu X, Yu K, Jiang H, Zhang Y, Liu X, et al. Exposure to Polycyclic Aromatic Hydrocarbons and Accelerated DNA Methylation Aging. Environ Health Perspect. 2018;126(6):067005.
16	Lifeng T, Shoulin W, Junmin J, Xuezhao S, Yannan L, Qianli W, et al. Effects of fenvalerate exposure on semen quality among occupational workers. Contraception. 2006;73(1):92-6.
17	Palma-Gudiel H, Cirera F, Crispi F, Eixarch E, Fananas L. The impact of prenatal insults on the human placental epigenome: A systematic review. Neurotoxicol Teratol. 2018;66:80-93.
18	Ruan HB, Crawford PA. Ketone bodies as epigenetic modifiers. Curr Opin Clin Nutr Metab Care. 2018;21(4):260-6.
19	Walker VR, Boyles AL, Pelch KE, Holmgren SD, Shapiro AJ, Blystone CR, et al. Human and animal evidence of potential transgenerational inheritance of health effects: An evidence map and state-of-the-science evaluation. Environ Int. 2018;115:48-69.
20	Yamashita S, Kishino T, Takahashi T, Shimazu T, Charvat H, Kakugawa Y, et al. Genetic and epigenetic alterations in normal tissues have differential impacts on cancer risk among tissues. Proc Natl Acad Sci

	U S A. 2018;115(6):1328-33.
21	Zhang L, McHale CM, Rothman N, Li G, Ji Z, Vermeulen R, et al. Systems biology of human benzene exposure. Chem-Biol Interact. 2010;184(1-2):86-93.

No reproductive health-related outcomes (n=10)

#	Citation
1	An YR, Kim SJ, Yu SY, Yoon HJ, Song MK, Ryu JC, et al. Identification of genetic/epigenetic biomarkers for supporting decision of VOCs exposure. Bioch J. 2013;7(1):1-5.
2	Bowling FG. Report on the Molecular Investigations into the Jet Fuel and solvent exposure in the DeSeal/ReSeal programme conducted at the Mater Research Institute (UQ), Brisbane. 2014. Available at [http://www.defence.gov.au/FOI/Docs/Disclosures/123_1415_Report.pdf], Accessed (22/04/2018)
3	Caldwell J, Lunn R, Ruder A. Trichloroethylene (TCE). Identification of research needs to resolve the carcinogenicity of high-priority IARC Carcinogens. 2010;42:120- 35.
4	Cui Y, Choudhury SR, Irudayaraj J. Epigenetic toxicity of trichloroethylene: A single-molecule perspective. Toxicology Research. 2016;5(2):641-50.
5	Elias Z, Daniere MC, Marande AM, Point O, Terzetti F, Schneider O. Genotoxic and/or Epigenetic Effects of Some Glycol Ethers: Results of Different Short-Term Tests. Occupational Hygiene. 1996;79(2):1-6.
6	Jiménez-Garza O, Baccarelli AA, Byun HM, Márquez-Gamiño S, Barrón-Vivanco BS, Albores A. CYP2E1 epigenetic regulation in chronic, low-level toluene exposure: Relationship with oxidative stress and smoking habit. Toxicol Appl Pharmacol. 2015;286(3):207-15.
7	Kim GW, Hong JY, Yu SY, Ahn JJ, Kim Y, Son SW, et al. Integrative analyses of differential gene expression and DNA methylation of ethylbenzene-exposed workers. Bioch J. 2015;9(3):259-67.
8	Kim SY, Hong JY, Yu SY, Kim GW, Ahn JJ, Kim Y, et al. Identification of potential biomarkers for xylene exposure by microarray analyses of gene expression and methylation. Molecular and Cellular Toxicology. 2016;12(1):15-20.
9	Sha Y, Zhou W, Yang Z, Zhu X, Xiang Y, Li T, et al. Changes in poly(ADP-ribosyl)ation patterns in workers exposed to BTX. PLoS One. 2014;9(9):e106146.
10	Song MK, Ryu JC. Blood miRNAs as sensitive and specific biological indicators of environmental and occupational exposure to volatile organic compound (VOC). Int J Hyg Environ Health. 2015;218(7):590-602.

Narratives reviews of literature / book chapters (n=23)

#	Citation
1	Allen Merritt T, Gadzinowski J, Mazela J, Adamczak AM. Epigenetic influences in the development of bronchopulmonary dysplasia. Archives of Perinatal Medicine. 2011;17(1):17-22.
2	Amdani SN, Yeste M, Jones C, Coward K. Phospholipase C zeta (PLCζ) and male infertility: Clinical update and topical developments. Adv Biol Regul. 2016;61:58-67.
3	Carrell DT, De Jonge C, Lamb DJ. The genetics of male infertility: a field of study whose time is now. Arch Androl. 2006;52(4):269-74.
4	Cui X, Jing X, Wu X, Yan M, Li Q, Shen Y, et al. DNA methylation in spermatogenesis and male infertility (Review). Exp Ther Med. 2016;12(4):1973-9.
5	Dietert RR. Chapter 18: Transgenerational epigenetics of endocrine-disrupting chemicals. Trygve Tollefsbol, editor: Elsevier Inc.; 2014. 239-54 p.
6	Dolinoy DC. Epigenetic gene regulation: early environmental exposures. Pharmacogenomics. 2007;8(1):5-10.
7	Dolinoy DC, Anderson OS, Rozek LS, editors. Epigenetic manifestation of environmental exposures. Nutrition in Epigenetics; 2011: Wiley-Blackwell.
8	Estill MS, Krawetz SA, Krawetz SA. The Epigenetic Consequences of Paternal Exposure to Environmental Contaminants and Reproductive Toxicants. Curr Environ Health Rep. 2016;3(3):202-13.
9	Grace KS, Sinclair KD. Assisted reproductive technology, epigenetics, and long-term health: a developmental time bomb still ticking. Semin Reprod Med. 2009;27(5):409-16.

10	Guerrero-Bosagna C, Skinner MK. Environmental Epigenetics and Effects on Male Fertility. Adv Exp Med Biol. 2013;791(Genetic Damage in Human Spermatozoa):67-81.
11	Guerrero-Bosagna CM, Skinner MK. Epigenetic transgenerational effects of endocrine disruptors on male reproduction. Semin Reprod Med. 2009;27(5):403-8.
12	Hong JY, Yu SY, Ahn JJ, Kim SY, Kim GW, Kim Y, et al. Environmental risk assessment of toxicity exposure: High-throughput expression profiling. Bioch J. 2016;10(1):74-80.
13	Issa J-P. Epigenetic variation and human disease. J Nutr. 2002;132(8S):2388S-92S.
14	Rothstein MA, Harrell HL, Marchant GE. Transgenerational epigenetics and environmental justice. Environ Epigenet. 2017;3(3):1-12.
15	Rusyn I, Chiu WA, Lash LH, Kromhout H, Hansen J, Guyton KZ. Trichloroethylene: Mechanistic, epidemiologic and other supporting evidence of carcinogenic hazard. Pharmacol Ther. 2014;141(1):55-68.
16	Salemi R, Marconi A, Di Salvatore V, Franco S, Rapisarda V, Libra M. Epigenetic alterations and occupational exposure to benzene, fibers, and heavy metals associated with tumor development (review). Mol Med Rep. 2017;15(5):3366-71.
17	Schagdarsurengin U, Steger K. Epigenetics in male reproduction: effect of paternal diet on sperm quality and offspring health. Nat Rev Urol. 2016;13(10):584-95.
18	Sifakis S, Androutsopoulos VP, Tsatsakis AM, Spandidos DA. Human exposure to endocrine disrupting chemicals: effects on the male and female reproductive systems. Environ Toxicol Pharmacol. 2017;51:56-70.
19	Silberman DM, Acosta GB, Zorrilla Zubilete MA. Long-term effects of early life stress exposure: Role of epigenetic mechanisms. Pharmacol Res. 2016;109:64-73.
20	Skakkebaek NE, Rajpert-De Meyts E, Louis GMB, Toppari J, Andersson A-M, Eisenberg ML, et al. Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. Physiol Rev. 2016;96(1):55-97.
21	Song C, Kanthasamy A, Kanthasamy A. Cell Signaling Mechanisms in Developmental Neurotoxicity. Reproductive and Developmental Toxicology: Elsevier Inc.; 2011. p. 835-45.
22	Stuppia L, Franzago M, Ballerini P, Gatta V, Antonucci I. Epigenetics and male reproduction: the consequences of paternal lifestyle on fertility, embryo development, and children lifetime health. Clin Epigenet. 2015;7:120/1-/15.
23	Wyrobek AJ. Methods and concepts in detecting abnormal reproductive outcomes of paternal origin. Reprod Toxicol. 1993;7 Suppl 1:3-16.

Non-English articles (n=1)

#	Citation
1	Ge S, Li W, Wang Y, Zhang L, Zhang Y. Necessity to evaluate epigenetic quality of the sperm for assisted reproductive technology. Shengming De Huaxue. 2011;31(1):157-61.

Conference presentations / Dissertations (n=17)

#	Citation
1	Ahn JJ, An YR, Kim SJ, Hong JY, Ryu JC, Hwang SY. Studies on the effect of toluene on microRNA and DNA methylation alteration. Toxicology and Environmental Health Sciences. 2012;1):S69.
2	An YR, Kim SJ, Ahn JJ, Hong JY, Ryu JC, Hwang SY. Identification of epigenetic biomarkers in the xylene exposed human blood. Toxicology and Environmental Health Sciences. 2012;1):S70.
3	Godderis LG, Tabish AT, Poels KP, Viaene MV, Hoet PH. Solvent-induced DNA methylation changes: A translational study. Occupational and Environmental Medicine Conference: 23rd Conference on Epidemiology in Occupational Health, EPICOH. 2013;70(SUPPL. 1).
4	Hong JY, Ahn JJ, An YR, Kim SJ, Ryu JC, Hwang SY. Investigation of epigenetic biomarker for diagnosis of exposure to ethylbenzene. Toxicology and Environmental Health Sciences. 2012;1):S70.
5	Lim JH, Cho Y, Kim W, Han SO, Ryu JC. Gene expression profiles of exosomal and cellular miRNA from human promyelocytic leukemia cells (HL- 60) exposed to xylene. Toxicology and Environmental Health Sciences. 2016;8 (4):S43.

6	Lim JH, Song MK, Cho Y, Jeong SC, Kim W, Han SO, et al. Gene expression profiles of exosomal miRNA from human promyelocytic leukemia cells (HL-60) exposed to VOCs. Toxicology and Environmental Health Sciences. 2015;7 (4):S49.
7	Rathore K, Wang HCR. Green tea catechin suppression of carcinogenesis and cell proliferation induced by environmental carcinogens 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and benzo[a]pyrene. Cancer Research Conference: 102nd Annual Meeting of the American Association for Cancer Research, AACR. 2011;71(8 SUPPL. 1).
8	Saito M, Kumamoto K, Horikawa I, Robles AI, Furusato B, Okamura S, et al. ING2, a p53- and chromatin-interacting protein, is essential to mammalian spermatogenesis: Implications in male infertility in humans. Cancer Research Conference: 101st Annual Meeting of the American Association for Cancer Research, AACR. 2010;70(8 SUPPL. 1).
9	Seo S, Seo DY, Lee D, Park SR, Song MK, Ryu JC, et al. Exposure to xylene induces ERK1/2 activation and IL-2 activation in occupationally exposed workers. Toxicology and Environmental Health Sciences. 2015;7 (4):S75.
10	Shiao YH. Genetic signature for human risk assessment: Lessons from trichloroethylene. Environ Mol Mutagen. 2009;50(1):68-77.
11	Song MK, Choi HS, Ryu JC. Circulating miRNAs as sensitive and specific biological indicators of environmental and occupational exposure to volatile organic compound (VOC). Toxicology and Environmental Health Sciences Conference: 6th International Conference on Environmental Health Science. 2013;5(Supplement).
12	Song MK, Ryu JC. The Usefulness of microRNAome in Biological Responses and Toxic Mechanism To Environmental Toxicants. Toxicology and Environmental Health Sciences Conference: 6th International Conference on Environmental Health Science. 2013;5(Supplement).
13	Song MK, Ryu JC. The identification of blood miRNA biomarkers of VOC exposure. Toxicology and Environmental Health Sciences. 2015;7 (4):S45.
14	Song MK, Ryu JC. A microRNA signature of volatile organic compounds (VOCs). Toxicol Lett. 2015;1):S61.
15	Song MK, Ryu JC. A miRNA signature of VOCs. Toxicology and Environmental Health Sciences. 2015;7 (4):S44.
16	Song MK, Song M, Choi HS, Ryu JC. Whole blood-derived mirnas, surrogate markers in workers exposed to volatile organic compounds (VOCS). Toxicology and Environmental Health Sciences. 2012;1):S47.
17	Zhang J, Zhang L, Vermeulen R, Hu W, Bassig BA, Wong JY, et al. Occupational exposure to trichloroethylene and DNA methylation: A cross-sectional study. Cancer Research Conference. 2018;78(13 Supplement 1):5313-.

Newsletters / Editorials / Comments (n=1)

#	Citation
1	Ivanov ID, Mensi C, rheim J, Ewers LM, Perkins J, Niven K, et al. The Global Occupational Health Network (GOHNET) Newsletter no. 25. The Global Occupational Health Network. 2015(25):1-20.

Animal Studies (n=2)

#	Citation
1	Gilbert KM, Blossom SJ, Erickson SW, Reisfeld B, Zurlinden TJ, Broadfoot B, et al. Chronic exposure to water pollutant trichloroethylene increased epigenetic drift in CD4+ T cells. Epigenomics. 2016;8(5):633-49.
2	Tracey R, Manikkam M, Guerrero-Bosagna C, Skinner MK. Hydrocarbons (jet fuel JP-8) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. Reprod Toxicol. 2013;36:104-16.

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1. Australian Institute of Health and Welfare (AIHW). Fourth study of mortality and cancer incidence in aircraft maintenance personnel: a continuing study of F-111 Deseal/Reseal personnel 2016. Cancer series no. 99. Cat. no. CAN 98. . Canberra, Australia: Australian Institute of Health and Welfare 2016. Available at [https://www.aihw.gov.au/getmedia/6241bbae-0a7d-400f-b7ec-7ce791d2bf77/20110.pdf.aspx?inline=true], Accessed (14/11/2018)

2. 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.

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