Evidence Compass

Technical Report

Literature review of effects of fuel and solvent exposure on human female reproductive outcomes

Rapid Evidence Assessment

September 2017

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List of Abbreviations

ADF	Australian Defence Force
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body mass index
BTEXs	Benzene, toluene and xylenes
CARC	Chemical Agent Resistant Coating
CHD	Congenital heart defect
CL/P	Cleft lip/palate
CONCAWE	Conservation of Clean Air and Water in Europe
COT	Committee of Toxicology
CP	Cleft palate
DART	Development and Reproductive Toxicology
DCOH	Defence Centre for Occupational Health
DSRS	Deseal/Reseal
DVA	Department of Veterans' Affairs
E1C	Estrone conjugates
$E_1$3G	Estrone 3-glucuronide
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
EU	European Union
F-111 DSRS	F-111 Deseal/Reseal
FSH	Follicle stimulating hormone
GEs	Glycol ethers
HC	Hydrocarbons
IARC	International Agency for Research on Cancer
ILA	International Labour Organisation
IOM	Institute of Medicine
IPA	Isopropanol
JEM	Job-exposure matrix
JFES	Jet Fuel Exposure Syndrome
JP	Jet Propellant
JP fuels	Jet Propulsion fuels
JP8	Jet propulsion-8 aviation fuel (type of Jet Propulsion Fuel)
LCD	Liquid crystal display
LH	Luteinizing Hormone
MEK	Methyl Ethyl Ketone

MeSH	Medical Subject Headings
MATF	Military Aviation Turbine Fuel
2-MPA	2-methoxypropionic acid
NRC	National Research Council
NTD	Neural tube defects
OFC	Orofacial clefts
PdG	Pregnanediol-3-glucuronide
Pd3G	Pregnanediol 3-glucuronide
PECO	Population Exposure Comparison Outcome framework
PEL	8-hr time weighted average permissible exposure level
PGME	Propylene glycol monomethyl ether; Synonym Methoxypropanol
PICO	Population Intervention Comparison Outcome framework
POF	Premature ovarian failure
Ppb	Parts per billion
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RAAF	Royal Australian Air Force
REA	Rapid Evidence Assessment
R numbers	Risk phrases from EU, e.g. R60 may impair fertility
RVOT	Right ventricular outflow tract
SGA	Small for gestational age
SHOAMP	Study of Health Outcomes in Aircraft Maintenance Personnel
TCE	Trichloroethylene
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
VOCs	Volatile organic compounds
VSD	Ventricular septal defect

Executive Summary

- Concern has been expressed by some women in the Royal Australian Air Force (RAAF) about perceived high rates of early miscarriage, and is due, in part, to two reported cases of early ovarian failure, thought to be as a result of work duties associated with Military Aviation Turbine Fuels (MATFs) and solvents.
- The proposed aim of the Departments of Defence and Veterans' Affairs for this project was to conduct a literature review of adverse reproductive health outcomes on service women from their occupational exposure to MATFs (herein referred to as jet fuels) and solvents used in the Australian military, with a main focus on evidence from human studies.
- More specifically, the review aimed to determine whether there is an association between occupational exposure to jet fuels and an agreed selection of specified solvents of most relevance to the military and the following adverse reproductive health outcomes in women:
    - Adverse fertility and pregnancy outcomes: early foetal loss, still birth, miscarriage, foetal malformations or congenital anomalies, pre-term birth, intra-uterine growth retardation, low birth weight, neonatal death; reduced fertility; not achieving desired family size; and
    - Premature Ovarian Failure (POF) and early onset menopause.
- Jet fuels and specified solvents of most relevance to the military were finalised in consultation with the DVA Research Section and DVA Principal Medical Adviser and the Defence Centre for Occupational Health (DCOH) as:
    - military jet fuels - JP-4, JP-5, JP-7, JP-8, F33, F34 and civilian fuels Jet A, Jet A-1 and Jet B; and
    - solvents - ethyl acetate, ethyl benzene, toluene, xylenes, acetone, isopropanol, methyl ethyl ketone, propylene glycol monomethyl ether (PGME), white spirit and trichloroethylene.
- Scientific literature was searched (1 January 2000 – May 2017) in multiple electronic databases for published papers and high quality occupational health guidelines or reports. Inclusion criteria were: published, peer-reviewed research studies based on but not limited to scientific literature published in the search period, quantitative studies with outcome data that assessed an association between an exposure to jet fuels or the specified solvents and adverse female reproductive health outcomes, based on human female adults of reproductive age (18-55 years of age), in the English language, and guidelines/reports were underpinned by a systematic review of relevant studies, had recommendations or conclusions generated by a group of content or research experts

and included ratings of the strength of the evidence. Key peer review publications that were identified through the search were sourced and reviewed for inclusion/exclusion within the parameters of the review. The search results of records were systematically presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scheme.

- An assessment was conducted for each of the included observational studies, with regard to quality and risk of bias.
- For jet fuels, a total of 11 records met the inclusion criteria. Of these, four were scientific peer review publications of observational studies, one was an unpublished report of a study, and six were publicly available government agency or independent medical scientific advisory committee reports, toxicological profiles, or risk assessments (guidelines/reports) assessing health outcomes of jet fuels.
- For the specified solvents, a total of 27 records met the inclusion criteria. Of these, 13 were scientific peer review publications of observational studies, two were peer review publications summarising or updating guidelines' findings, and the other 12 were government agency or other independent scientific body reports or risk assessments (guidelines/reports) that had reviewed and synthesised scientific literature and included a peer review process.
- There was a limited number of observational studies identified that investigated the relationship between jet fuels and the specified solvents and each of the adverse reproductive health outcomes in women. The Evidence Profile and Summary of Evidence provide further detail that should be considered in relation to these studies, in particular limitations or strengths in relation to the evidence, but in the interest of summarising some findings of the studies the following is provided.
- One study was identified that investigated the potential effects of low-dose hydrocarbons in fuel (primarily stated as JP-8) on menstrual cycle function relating to conception. This study found that preovulatory luteinising hormone (LH) levels were lower in otherwise healthy reproductive age women who had higher internal doses of aliphatic hydrocarbons (HCs), as measured by exhaled breath levels, suggesting that exposure has the potential to impact fertility. However the study's authors indicated that further research is needed to investigate impact on other LH-dependent physiological functions and fertility. A further study finding was that jet fuel exposure was not statistically significantly associated with dysmenorrhea in fuel handlers. In other studies of the relationship between jet fuel exposure and adverse reproductive health outcomes, reported exposure to petroleum products was not associated with adverse live-birth outcomes of low birth weight, preterm birth, small for gestational age, birth defect, or foetal distress prior to or during delivery, based on self-report; and reported exposure to

aliphatic hydrocarbons was not associated with congenital anomalies of conotruncal heart defects, limb deficiencies or oral cleft defects in the study population.

- The Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP) found no evidence of an increased risk in female Deseal/Reseal personnel or female partners of male Deseal/Reseal personnel of miscarriage or stillbirth, or of reported difficulties getting pregnant or seeing a fertility specialist.
- A limited number of epidemiological studies of the association between jet fuel exposure and adverse reproductive effects in women was acknowledged in the included guidelines/reports in relation to an evidence base.
- Studies that investigated the relationship between specified solvents and adverse reproductive health outcomes were grouped under the broad adverse reproductive health outcomes areas of menstrual disturbances, infertility and adverse birth outcomes.
- Neither total BTEX (benzene, toluene, ethylbenzene, and *m,p,o*-xylenes) nor toluene were significantly associated with any of the hormone levels of menstrual cycle function relating to conception in USAF employees. Exposure to xylene was associated with oligomenorrhea in petrochemical workers in China. Toluene exposure was reportedly associated with abnormal menstrual cycle length in another study of Chinese petrochemical workers.
- In two separate studies based on a French cohort study, 2-MPA, a metabolite of PGME was not associated with a longer time to pregnancy (relating to fertility), but was associated with major malformations and urinary tract malformations.
- Maternal exposure to Stoddard solvent was not associated with any neural tube defect (NTD) or with NTD phenotypes although for the NTD phenotypes the number of cases was small. There were no significant associations between exposure to Stoddard solvent and any orofacial cleft malformations or phenotypes (cleft palate or cleft lip ± cleft palate) or association with small for gestational age. One study reported that Stoddard solvent was not associated with any congenital heart defect (CHD) or categories of CHDs based on one exposure assessment methodology but that exposure was associated with d-transposition of the great arteries, right ventricular outflow tract (RVOT) obstruction defects, and pulmonary valve stenosis based on an alternative exposure assessment methodology.
- Occupational exposure to trichloroethylene was non significantly associated with cleft palate. Toluene and mineral oil exposures were not significantly associated with oral clefts. A prospective cohort study found no association between maternal exposure to xylene or acetone and pregnancy duration or miscarriages.

- The guidelines/reports that were included for the specified solvents varied in availability of epidemiological studies for an evidence base for the relationship between the specified solvents and adverse reproductive effects in women, generally considered as reproductive and developmental effects. The emphasis was on guidelines/reports published since 2000, but none were identified as published during this period for some specified solvents and earlier guidelines/reports were included for completeness.
- No studies were identified that reported the relationship between jet fuels or specified solvents and not achieving desired family size, or that investigated the relationship between jet fuels or specified solvents and POF or early onset menopause.
- Overall limitations of individual studies of the association between jet fuel or specified solvent exposure and adverse female reproductive health outcomes included the small numbers of cases for adverse reproductive health outcomes, limitations in exposure assessment or in health outcome assessment such as in self-reported outcomes, recall bias, and co-exposure with other chemical(s) or solvent(s) or fuel exposures at the workplace which made it difficult to attribute any effect to the specified solvent or jet fuel.
- Limitations of the REA include: the omission of possibly relevant papers that were published prior to or after the defined search period; the omission of non-English language papers; and reference lists of included papers were not fully hand searched to find other relevant studies, as would usually be done in a full systematic review.
- The findings of the individual studies and some of the common limitations of individual studies are summarised, and the evidence presented and evaluated in the report.
- Overall, it was difficult to reach definitive conclusions about an association between exposure to jet fuels or the specified solvents and adverse reproductive health outcomes based on the individual epidemiological studies and/or the body of evidence identified in the REA.
- Whilst the body of literature on fuels and solvents and health effects *per se* is quite extensive, the evidence relating to jet fuels and to specified solvents and any of the adverse reproductive health outcomes under consideration was relatively limited. Furthermore, only three of the epidemiological studies identified had been conducted in female military populations. The individual epidemiological studies relevant to jet fuels and to the specified solvents provided limited evidence of associations with the adverse reproductive health outcomes under consideration. It was difficult to establish more definitive conclusions without a more substantial body of evidence. There were no studies identified that considered POF or early onset menopause, and only one study which investigated the relationship of specified solvents with fertility.

- Although the effects of occupational exposure of service women to jet fuels and specified solvents used in the Australian military was of prime interest, the search was not restricted to articles that assessed occupational exposures in women in military services. This would have considerably limited the number of articles for consideration and occupational exposures to the jet fuels or specified solvents that occurred in other occupational groups were also considered relevant to adverse reproductive health outcomes. However, the generalisability of the findings may be less given the nature of industries and ethnicity of participants. Furthermore, the range of co-exposures of fuels and/or solvents that they may have experienced were likely different from exposures of service women in the Australian military.
- This Rapid Evidence Assessment does however provide the Department of Veterans' Affairs and Department of Defence with a summary of the available evidence for consideration in relation to exposures and preventive measures in relation to the relevant occupational exposures to jet fuels and specified solvents in women in the military.

Introduction

Concern has been expressed by some women in the Royal Australian Air Force (RAAF) about perceived high rates of early miscarriage, and is due, in part, to two reported cases of early ovarian failure, thought to be as a result of work duties associated with Military Aviation Turbine Fuels (MATFs) (herein referred to as jet fuels) and solvents. Concerns were raised in the context of the Jet Fuel Exposure Syndrome (JFES) Study and its release in June 2015. The *in vitro* study found adverse cellular effects from JP8, predominantly from the kerosene component. The JFES Study[1] investigated whether exposure to jet propulsion-8 (JP-8) aviation fuel or the Deseal/Reseal solvents were toxic to cells and that may explain health effects in former RAAF F-111 Deseal/Reseal workers that were reported in the earlier Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP).[2] The JFES Study is of limited usefulness in relation to objectives of the current study as it primarily reported on effects of jet fuel and solvents on cells *in vitro* and the SHOAMP Study focused on male personnel.

A systematic review of the relationship between military service and sexual and reproductive health outcomes conducted by Lawrence-Wood et al[3] on published literature between 2000 to 2015 reported limited information in relation to occupational exposures and the reproductive health effects of occupational exposures. Solvents and jet fuel as exposures were not specific topics of the 2016 review.

Jet fuels

Fuel is a critical component of military capability.[4] A 2002 Auditor General report identified eight different types of fuel used by the Australian Defence Force (ADF). Of these, four are military specification fuels, including aviation turbine fuels.[4]

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.

JP-4 was the first official hydrocarbon based jet fuel used by the US Airforce in 1951.[5] JP-4 was a wide cut fuel, taken from the distillation phase to include both the naphtha and kerosene fractions.

Kerosene-based jet fuels have been used for over 60 years.[6] JP-8 is a kerosene based distillate that is currently the fuel of choice in military aircraft and has replaced JP-4 because it has a higher flash point, being composed of longer chain hydrocarbons.[7] JP-5 (high flash point kerosene) is chemically similar to JP-8 which is used in naval aircraft and contains blends of kerosene hydrocarbons. JP-7 fuel is made by refining kerosene and blending these kerosene distillates. JP-7 has a higher flash point and was used in advanced supersonic aircraft.[8] Jet A and Jet A-1 are the type of fuels used in commercial civilian aircraft. These fuels are nearly identical; however the most important difference between them is that Jet A-1 is refined to have a lower maximum freezing point (-47°C) than Jet A (-40°C) and Jet A-1 normally contains a static dissipater additive. 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.[9]

Currently, the primary military fuel is JP-8 (similar to commercial Jet A-1), and this fuel has replaced JP-4. The composition of JP-8 and JP-5 is that of kerosene, the middle distillate. JP-8 and JP-5 have similar chemical and physical characteristics. The fuels JP-5 and JP-8 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.

Occupational exposure to jet fuels can occur during refuelling and defueling operations, cold engine starts and during mechanical 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.[7]

Table 1: Main grades of jet fuels[10]

Jet A-1	Kerosene type fuel used in civil aircraft. Max freezing point -47^{o}C
Jet A	As Jet A-1, but with freezing point of -40^{o}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.

Solvents

The term ‘solvents’ is generic, encompassing many broad groups of organic substances, 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 personnel have been exposed in more specific settings such as the RAAF F-111 Deseal/Reseal programs (DSRS).

Reproductive toxicity definition

Reproductive toxicity has been defined as “the occurrence of adverse effects on the reproductive system that may result from exposure to a chemical.”[6] 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.[6] In women, reproductive toxicities can be evidenced by abnormalities in menstrual cycles, altered fecundity i.e. fertility (e.g. defined as reproductive potential and measured time to pregnancy), or adverse pregnancy outcomes (e.g. spontaneous abortions, stillbirth, congenital malformations or low birth weight).[6]

Toxicity to the foetus can also result in developmental or teratogenic defects such as prenatal and postnatal death, structural abnormalities e.g. heart defects, altered growth, e.g. low birth weight, or functional deficiencies, e.g. mental retardation.

In addition, gene mutations, exposure to harmful physical (e.g. radiation) or chemical agents (occupational, therapeutic or environmental agents including smoking, alcohol and other drugs, and pharmaceutical agents), infections, and maternal metabolic imbalances are known aetiological factors in reproductive toxicities.[11-13]

Aim

The proposed aim of the Departments of Defence and Veterans’ Affairs for this project was to conduct a literature review of adverse reproductive health outcomes on service women from their occupational exposure to MATFs and solvents used in the Australian military, with a main focus on evidence from human studies.

More specifically, the review aimed to determine whether there is an association between occupational exposure to MATFs and an agreed selection of specified solvents of most relevance to the military and the following adverse reproductive health outcomes in women:

- adverse fertility and pregnancy outcomes:
    - early foetal loss,
    - still birth,
    - miscarriage,
    - foetal malformations or congenital anomalies,
    - pre-term birth,
    - intra-uterine growth retardation,
    - low birth weight,
    - neonatal death,
    - reduced fertility,
    - not achieving desired family size.
- Premature Ovarian Failure (POF) and early onset menopause.

Method

To enable response in a reasonable timeframe to concerns of ill health from fuel and solvent exposure that were raised soon after the release of the JFES Study in June 2015, it was considered important that any significant effects were quickly elucidated. As requested by the Departments of Defence and Veterans' Affairs, this project utilised a rapid evidence assessment (REA) methodology.[14] 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 about a specific issue.

To make a REA rapid, 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. not including 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 systematic review. An advantage, however, is that an REA can inform policy and decision makers within a relatively short space of time compared to a systematic review and may also include relevant grey literature, such as relevant reports and unpublished sources of information obtained from relevant websites, which systematic reviews do not.

Defining the review questions

The components of these questions were defined in terms of the PECO framework (population (P), exposure (E), comparison group (C), and outcomes (O)) (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 into this REA. As part of these operational definitions, the population of interest was defined as adult females of reproductive age who are or who have been employed in defence or military related forces.

The exposures of interest were to MATFs (herein referred to as jet fuels) and solvents. A proposed list of jet fuels and specified solvents (and related terms) most relevant to military personnel (based initially on fuels used in the military and on common solvents identified in the SHOAMP Study of the F-111 DSRS workers[2]) were finalised in consultation with the DVA Research Section and DVA Principal Medical Adviser and the Defence Centre for Occupational Health (DCOH) as:

- military jet fuels - JP-4, JP-5, JP-7, JP-8, F33, F34 and civilian fuels Jet A, Jet A-1 and Jet B; and
- solvents - ethyl acetate, ethyl benzene, toluene, xylenes, acetone, isopropanol, methyl ethyl ketone, propylene glycol monomethyl ether (PGMA), white spirit and trichloroethylene.

The review focussed on scientific studies which investigated occupational exposures. To maintain relevance, studies investigating environmental exposures through residential exposure, for example living close to petrol stations, municipalities close to petrochemical refineries, or environmental air pollution were not included, as the populations may have had other exposures and/or confounding factors such as socioeconomic status.

Female military personnel employed or previously employed in defence or military related forces were defined as the target population for studies to be included in this review. However, papers that were identified and which were based on human studies conducted in female occupational groups exposed to the jet fuels or solvents of interest, other than military personnel, and which reported agreed human female adverse reproductive health outcomes were also included.

Search Strategy

Scientific literature was searched (1 January 2000 – May 2017) in multiple electronic databases. The search needed to be conducted within a defined and limited time frame and

it was considered a time frame back to 2000 would be wide enough to identify studies in relation to exposures of relevance for the target population.

This time period established a scope for the search consistent with practice in conducting a literature review protocol and the REA protocol. Where key earlier studies were identified through the search, they were also included.

To identify the relevant literature for the REA, a search strategy was developed using relevant Medical Subject Headings (MeSH) for each database and additional keywords. The search strategies were filtered by date, English language and human studies.

Systematic bibliographic searches were performed to identify articles or guidelines/reports from the following databases: Ovid MEDLINE, Medline In Process, EPub ahead of print, PubMed, EMBASE, Cochrane library, Scopus, Web of Science, Development and Reproductive Toxicology (DART) and TOXLINE databases from the TOXNET databases of the U.S. National Library of Medicine, Expanded Academic ASAP, CAB Direct (includes Global Health database), ProQuest Environmental Science Collection (including Military and Public Health databases), REACH, New Zealand Libraries Catalogue (which contains New Zealand Defence Force references), and the Journal of Military and Veterans' Health. An example of the search strategy using the Medline database is in Appendix 2.

In addition, a search of the grey literature on Australian, United States (US), United Kingdom (UK) and Canadian Departments of Veterans' Affairs and Defence, The National Academy of Sciences, Engineering and Medicine Health and Medicine Division (formerly referred to as the US Institute of Medicine), and Australian Commonwealth Government websites was undertaken to identify relevant guidelines or reports based on the inclusion and exclusion criteria. Guidelines or reports included publicly available reports of studies, independent medical scientific advisory committee reports, toxicological profiles, or risk assessments assessing health outcomes of jet fuels or specified solvents.

Search Terms

A comprehensive list of terms was developed to be inclusive of adverse reproductive outcomes, jet fuels, solvents, and military personnel. Terms were identified by extraction from other systematic reviews,[3, 15-17] by exploding (expanding) Medical Subject Headings (MeSH) terms and with assistance from the librarian at the Ian Potter Library, Alfred Hospital.

The list of free text and MeSH terms corresponding to the review's PECO (Population, Exposure, Comparison, Outcome) question were developed. The proposed concepts were:

A: Military Personnel (Population)

B1: Military Aviation Turbine Fuels (MATFs) (Exposure 1)

B2: Defined relevant solvents (Exposure 2)

C: Human female adverse reproductive health outcomes (Outcome)

The Comparison Group (C in PECO) in relation to the review's question was identified within each study where applicable.

The terms included in searching the Title/s, Abstract/s, MeSH terms, keyword lists and in searching the websites are listed below:

A: Military Personnel Terms

Military personnel, veterans, United States Department of Veterans Affairs, military medicine, naval medicine, occupational health, veterans' health, defence, servicewomen.

B1: Military Aviation Turbine Fuels Terms

((Aviation or jet/s or aircraft/s) and fuel/s), MATF/s, kerosene, petroleum, fuel oils, petroleum distillate/s, JP4, Petroleum Naphtha, JP5, aviation kerosene, JP7, JP8, Jet A, Jet A-1, Jet B, AVTUR, AVCAT, Fuel F34, Fuel F44.

B2: Defined relevant solvents

Ethyl acetate, ethyl benzene, toluene, methyl benzene, xylene, acetone, 2-propanol, isopropanol, methyl ethyl ketone, propylene glycol monomethyl ether, white spirit (naphtha, Stoddard Solvent (a volatile organic compound and petroleum mixture that is similar to white spirits), mineral spirits), trichloroethylene.

C: Human female adverse reproductive health outcomes

Reproductive medicine, reproductive health, reproduction, reproduct, fertility, infertility, subfertility, fecundity, reproductive techniques, pregnancy, pregnancy complications, infant mortality, foetal mortality, foetal, fetal, foetus, fetus, infant/s, perinatal, prenatal, stillbirth, miscarriage, abortion/s, pregnancy, congenital hereditary and neonatal diseases and abnormalities, congenital, premature birth, infant low birth weight, growth disorders, foetal development, foetal weight, birth weight, growth retardation, libido, time to pregnancy, conception, menstruation disturbances, family size, primary ovarian insufficiency, ovarian failure, menopause, premature menopause.

The proposed search strategy of (A) AND (B1 or B2) AND (C), was initially trialled on Medline and Embase. Following an initial search of these two databases, the search terms for military personnel (A) were not included, as relevant articles were not identified and it was appropriate to identify and consider relevant studies in non-military settings using the agreed search terms (e.g. the petroleum industry). The modified search strategy was adjusted to (B1 or B2) and (C) and was used for searching the remaining databases. The main defined jet

fuels and solvents and adverse reproductive health outcomes were used as key words to search the grey literature websites.

Paper Selection

Studies were evaluated according to the following inclusion and exclusion criteria. For published papers and high quality occupational health guidelines or reports (for example Occupational Health and Safety (OHS) guidelines or Occupational Exposure Guidelines or Reports) the following inclusion/ exclusion criteria were applied:

Included
1. Published, peer-reviewed research studies 2. The assessments of the guidelines or reports were underpinned by a systematic review of relevant studies 3. Based on, but not limited to, medical scientific literature published since 1 January 2000 to 10 May 2017 and recorded in relevant databases 4. Quantitative studies with outcome data that assessed exposure or an association between an exposure to MATFs (jet fuels) or solvents and adverse female reproductive health outcomes 5. Studies based on human female adults of reproductive age (i.e. 18-55 years of age). 6. English language 7. The guidelines or reports had recommendations or conclusions generated by a group of content experts or research experts 8. The guidelines or reports included ratings of the strength of the evidence
Excluded
1. Papers where a full-text version is not readily available 2. Conference presentations and PhD theses/dissertations 3. Papers/ guidelines or reports published before 1 January 2000 (unless key papers were identified through search that were published prior to 2000) 4. Qualitative studies. 5. Studies based on human female adults > 55 years of age) 6. Non-English language papers 7. Guidelines or reports where a full-text version was not readily available to the research team 8. Guidelines or reports that did not consider the relationship between exposure to the selected solvents or MATFs (jet fuels) and adverse female reproductive health outcomes 9. Guidelines or reports not underpinned by a systematic review of relevant studies 10. Guidelines or reports where recommendations or conclusions were not generated by a group of content experts or research experts. 11. Guidelines or reports with no ratings of the strength of the evidence

Information management

Papers were directly imported into the bibliographic tool Endnote X8 after the literature search of each database. A screening process was adopted for titles/abstracts and the eligibility of papers identified.

Screening step 1: Screening titles and abstracts:

Following the removal of duplicates, titles and abstracts were screened to identify those for full-text review using the specified inclusion and exclusion criteria, and those in which inclusion could not be definitively determined. A sample of approximately 10% of titles and abstracts titles was extracted and screened by one reviewer and independently by a second reviewer. The screening decisions were compared and discussed in respect of the specified inclusion and exclusion criteria, or those in which inclusion could not be definitively determined, in order to establish consensus and inform the screening process. Any discrepancies were resolved through discussion. Full text versions of all studies which satisfied the screening criteria or studies in which inclusion could not be definitively determined were obtained.

Screening step 2: Full paper:

The reviewer read the full text version of the paper (or guidelines/reports), and decided whether the paper (or guidelines/report), should be included or excluded, based on the predefined criteria. To ensure relevance of results to the fuel and solvent exposures of interest in this review, the reviewer identified the relevant fuel or solvent as a predominant exposure or at least identified fuel or solvent exposure specific associations with adverse reproductive health outcomes in women. The study may in addition have presented a more general effect measure of association with fuel or solvent exposure. The second reviewer randomly selected 20% of the papers and also screened them. The screening decisions were compared and discussed in respect of the specified inclusion and exclusion criteria, or those in which inclusion could not be definitively determined, in order to establish consensus and inform the screening process. Any discrepancies were resolved through discussion. The summary results of the inclusion/exclusion of these papers are in Appendix 4.

Data extraction:

Following the application of the inclusion and exclusion criteria to this subset, information about the study and participant characteristics (authors and year of publication, study design, country in which the study was conducted, study population and sampling methodology, study group and comparison group (where applicable), primary outcome measures and their

definitions, exposure assessment methods, age and gender of participants), results and main findings were extracted into tables in the Evidence Profile (Appendix 3).

Evaluation of the evidence

A quality assessment for prevalence or incidence type questions was carried out. This process, based on the REA protocol for identifying rates of disorders (such as a prevalence or incidence rate), i.e. Evaluation of the evidence for prevalence questions,[3] encompasses four components:

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

Quality and risk of bias reflects how well the studies have been conducted.[14] Quality and risk of bias reflect scientific benchmarks for prevalence studies and criteria are set out by Giannakopoulos et al.[18] A 'gold standard' quality of evidence includes random sampling methodology (for representativeness), 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.[14]

Data source: The REA protocol also assesses bias in terms of the data source, whether the data collected in each study were primary (e.g. clinical interview, questionaries) or secondary (e.g. medical chart review).

Primary data sources are collected with purposeful intention by researchers to measure a particular outcome 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, which may increase or decrease risk of bias depending on the outcome of interest.

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 study.

Generalisability: This covers how well the participants and settings of the included studies can be generalised to the target population. Population variability that might influence this component include gender, age, ethnicity and non-military.

An assessment was conducted for each of the included studies, with regard to quality and risk of bias criteria utilising the checklist "Checklist for considering the Quality of Descriptive, Observational Prevalence Studies" as modified from Giannakopoulos, Rammelsberg, Eberhard, Schmitter (2012)[18] provided in the REA protocol (refer Appendix 4). Two members of the research team assessed each study according to this checklist.

Ranking the evidence: The evidence was not ranked because the REA protocol requires summary comments, rather than evidence ranking. The latter is more appropriate in intervention studies.

Results

The results and Summary of Evidence for jet fuels and solvents are presented in separate sections. For jet fuels and solvents the search results are systematically presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scheme.[19] Summary data and relevant results from the articles and guidelines or reports are presented in the Evidence Profile in Appendix 3 and a summary of the evidence is presented below.

Summary of the Evidence

Jet fuels

Figure 1 shows that the search yielded 9,528 records with 40 records identified through additional sources, with 6,107 records remaining after removal of duplicates. After title/abstract review, 64 full-text records were identified for further review. Information on papers or guidelines/reports which had a full screen is presented in Appendix 4.

From all the sources searched, a total of 11 records met the inclusion criteria and were included in the final report of articles. Of these, four were scientific peer review publications of observational studies,[20-23] one was an unpublished report of a study[2] (included with the observational studies), and six were publicly available government agency or independent

medical scientific advisory committee reports, toxicological profiles, or risk assessments (guidelines/reports) assessing health outcomes of jet fuels[6-8, 10, 24, 25] that had reviewed and synthesised literature and included a peer review process. Three studies (four papers) were conducted in US populations[20-23] and one in an Australian population.[2]

Observational studies' papers

A study investigated the potential effects of low-dose hydrocarbons (HC) in fuel (primarily stated as JP-8) and solvent exposure on menstrual cycle function relating to conception.[20] The cross-sectional study found that internal dose of compounds in fuel was associated with reduced luteinising hormone (LH) levels prior to ovulation in women of reproductive age but this was not associated with progesterone levels (a marker of luteal function). Nonetheless, if hydrocarbon exposures chronically alter LH levels, the study authors considered that it was feasible that these effects may impact the LH-dependent process and reproduction. The statement in relation to impact was not qualified further with any estimates of risk. The aliphatic and aromatic HCs measured were also considered likely to be markers of exposure to other compounds in fuels and solvents, including additives and combustion by-products. Confirmation of these findings were recognised as necessary to determine if fuels and solvent exposure may impact other LH dependent functions and to examine effects on conception.

This cross-sectional study[20] was conducted in a defined target population of female US Air Force employees with the age range of 18-42 years of age. While the sample was invited from across 10 United States Air Force (USAF) bases, the representativeness of the sample was not clear as the total number screened for eligibility was not reported, nor was a method of probability sampling used. Of the eligible 335 participants, only 170 participants provided data, 100 provided complete diary data and urine samples and 63 provided breath samples. The study utilised a primary data source and objective analysis of hormone levels based on those predictive of conception and used breath samples for exposure assessment. The breath analyses were used to group the women into high and low aliphatic exposure groups. In terms of the LH changes, there was a difference in mid-cycle LH levels observed between the high and low exposure groups, with lower LH levels seen in the high exposure group. The authors report that the magnitude of the difference seen in LH levels between the high and low exposure groups was consistent with what has been reported in other studies which have studied LH levels in ovulatory and anovulatory cycles. Although the evidence is indirect, the investigators state in their discussion that the evidence suggests that exposure has the potential to impact fertility. Limitations included that there were small numbers in the analysis

of low (n=11) and high (n=11) aliphatic exposure groups based women. In terms of the relationship between self-reported exposures and objective measures of exposure, reported hours of exposure were consistent with job categories but were similar for women with high and low levels of aliphatic and BTEX HCs in exhaled breath and some possible explanations were considered. Whilst no specific information was reported on non-responders or non-participants, comment was made about the likelihood that over-representation of women with concerns about their reproductive health could have resulted in bias due to self-selection and non-response; however this was thought to be limited as similar proportions of exposed and non-exposed women reported pre-existing reproductive symptoms. The study was conducted in a USAF base population and in this respect has generalisability to the RAAF population of interest.

An earlier paper[23] that referred to this wider study investigating hormonal effects of exposure to jet fuel in women (though it did not reference it) reported a non-statistically significant increase in dysmenorrhea in fuel handlers, although the authors cautioned that it could not be certain if this finding related to exposure or other work related factors such as physical activity. The study[23] overall has been described above, the menstrual outcome variables and report of fuel handling were based on self-report, drawn from replies to standardised questions in an unvalidated questionnaire.

A case control study[21] investigated the association between occupational exposures and five adverse live-birth outcomes of low birth weight, preterm birth, small for gestational age, birth defect, or foetal distress prior to or during delivery, based on self-report. The study found no evidence of association of these adverse live-birth outcomes and the reported exposure to petroleum products or solvents in this group of US Navy military female personnel. The target population was clearly defined, including all active duty females identified from hospital records who had made an obstetric visit to any of three selected Navy hospitals over the study period. However, only about one-third of women were eventually included in the analysis due to absence of contact details, non response, and the definition of cases and controls.

Non-responders included a greater proportion of women with foetal deaths, and this resulted in a decision to only include women with live births (n=1032) and 109 civilian women as controls. Effects causing miscarriage or foetal death would therefore not be detected. The sample size for analysis of birth defects was relatively small (n=33). The birth defects were reported by mothers and categorised as any birth defect, and the study would have had limited power to detect increases in individual malformations which is of greater relevance in

the relation to any association with specific exposures. Data on outcomes and on exposures (occurring two years prior) were derived from questionnaires completed by mothers, a primary source, but was not reported to be based on use of a standardised but unvalidated survey instrument.[21] In a case control study design with self-reported exposure data there is a strong possibility of recall bias by cases. The study was conducted in a US Navy military female population and in this respect has generalisability to our study population of interest.

Another case control study[22] investigated the association of selected congenital anomalies and maternal occupational exposures to chemicals. The study examined data from a large Californian population-based case control study. Overall in this study, although potential associations were observed, between maternal exposure to aliphatic hydrocarbons and congenital anomalies, these were not statistically significant. The number of cases was noted to be small. Most results suggested that maternal occupational exposures to a variety of chemicals did not contribute substantially to the risk of conotruncal heart defects, limb deficiencies or oral cleft defects in the population. The target population was clearly identified with probability sampling in controls only.

Participation rate was greater than 80% for mothers of cases and 76% for controls, although an assessment of the difference between responders and non-responders was not reported. The data were from a primary source, the mothers of cases and controls, and an industrial hygienist undertook a telephone interview of occupational work history and subsequent categorisation of likelihood of exposure to chemical groups based on an assessment of occupational tasks. A clinical geneticist validated case eligibility from hospital records. The case control design of the study allowed the possibility of recall and reporting bias, particularly because participants were being asked nearly four years after the birth about peri-conceptual exposures to chemicals. The study reviewed exposure to hydrocarbons in the occupational setting, not in a specifically military personnel group.

The Australian Department of Veterans' Affairs SHOAMP report[2] investigated various health outcomes of which sexual function and reproductive health was a part. The retrospective cohort study of the health of F-111 Deseal/Reseal (DSRS) aimed to assess whether adverse health outcomes reported by the DSRS personnel were associated with their involvement in the DSRS programs.

The SHOAMP study found no evidence of an increased risk in female DSRS personnel or female partners of male DSRS personnel of miscarriage or stillbirth, or of reported difficulties getting pregnant or seeing a fertility specialist. The study only included women who had a

pregnancy in the reported period. Whilst the target population was clearly identified, some methodology and sampling limitations included no probability sampling of the control group, self-identification of 'exposed' DSRS workers in response to advertisements or recruitment processes that identified possible health risks (and were sent a questionnaire directly), female partners of male DSRS workers may or may not have been forwarded a questionnaire, and a denominator for the recruitment of female partners of DSRS male workers was not evident. A reproductive questionnaire was administered but this was not reported to be a validated measure. Recall of exposures could relate to a period up to 30 years prior. SHOAMP personnel may have been exposed to a number of materials including jet fuels, desealants, sealants and specified solvents, and exposures varied over time. Some *post hoc* reclassification of exposure to individuals occurred on the basis of response to the questionnaire.

No information was available on non-responders or refusers. Data on a small number of female DSRS personnel (n=24) and a majority of female partners (n=767) of male DSRS personnel who completed the reproductive questionnaire were available for analysis. The broader focus of the SHOAMP Study was on the larger group of male DSRS.

Guidelines or Reports

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

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 had assigned the Committee on Toxicology (COT) to review reproductive and developmental toxicity of chemicals. Committees and subcommittees of scientific professionals have evaluated JP-8.[7, 25]

In the included NRC report,[7] the NRC was required to evaluate chemicals and physical agents for their potential to cause reproductive and developmental toxicity. The evaluation provided a summary of the risk posed by the substance, and background information on the chemical and its toxicological parameters. The US Navy had concerns about the health effects in its personnel; including reproductive and developmental effects and requested NRC evaluate JP-8 fuel. The report[7] aimed to evaluate male and female reproductive toxicity data. The report was independently reviewed by technical experts with diverse perspectives.

Following an evaluation of the toxicity of JP-8 under normal conditions, they concluded (2001) that there were no human studies available to assess female reproductive or developmental toxicity caused by exposure to JP-8 or any other kerosene based fuel.[7]

Another report was a toxicological assessment of JP-8.[25] In 1996, the US Navy's 8-hr time weighted average permissible exposure level (PEL) for JP-4, JP-5 and JP-8 was 350 mg/m^3 which was considered to be adequate to protect the health of Navy personnel occupationally exposed to vapours from those fuels, based on available data at the time. However, it recommended that the PEL for the three jet-fuel vapours be considered interim until completion of further research. The US Air Force requested the NRC to conduct another assessment of all available toxicological, epidemiological and other relevant data for JP-8.

The NRC conducted an independent review of the interim PEL for JP-8. The subcommittee reviewed evidence of adverse health effects of JP-8 and likely exposures to JP-8 from vapours and/or aerosols. The health effects data on JP-8 and related kerosene based fuels (JP-5) were reviewed for a number of endpoints, including reproductive and developmental toxicity.[25]

Exposure scenarios used US military personnel and ambient air monitoring at US Air Force operational aircraft maintenance sites. The section on reproductive toxicity concluded that there were no adequate studies conducted to assess the toxicity potential of inhaled JP-8 for reproductive toxicity and developmental toxicity. As the data were scarce and the military personnel were occupationally exposed to JP-8, the subcommittee recommended that experimental animal studies be conducted to determine reproductive and developmental toxicity potential of JP-8.[25]

The Agency for Toxic Substances and Disease Registry (ATSDR), evaluates the effect on public health of hazardous substances. The ATSDR toxicological profile succinctly characterises the toxicological and adverse health effects. 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.

The ATSDR has two toxicological profiles on jet fuels that reviewed adverse health effects, human exposure and quantification of risk for JP-4 and JP-7 in 1995[8] and for the kerosene based fuels JP-5, JP-8 and Jet A in 2017.[6] Adverse reproductive effects and developmental effects were assessed by various routes of exposure (i.e. inhalation, oral or dermal exposure).

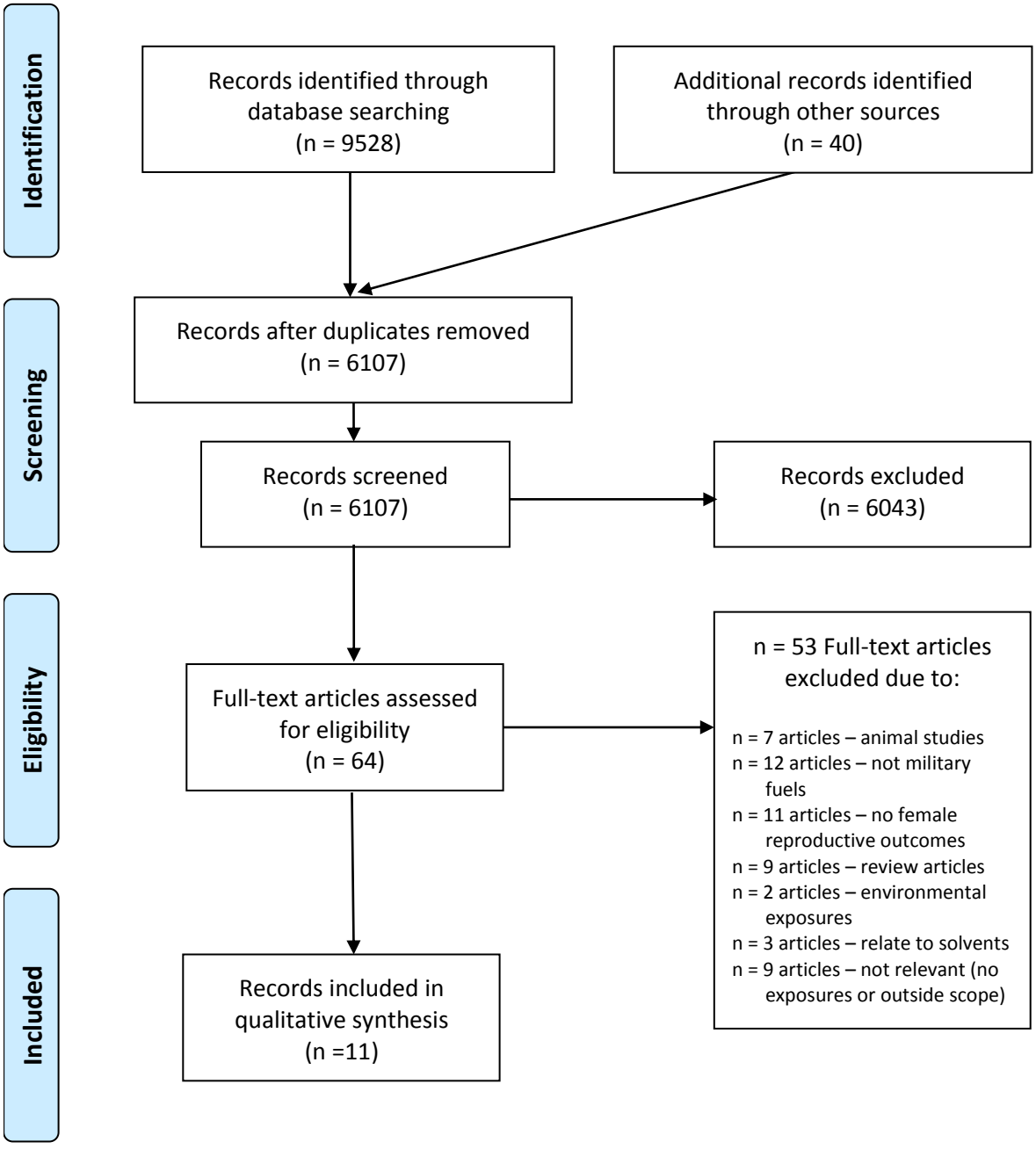
The JP-4 and JP-7 profile located no studies reporting reproductive effects or developmental effects in humans after exposure to JP-4 and JP-7. The JP-5, JP-8 and Jet A profile reported that there were limited data on the toxicity of JP-5, JP-8, or Jet A fuels in humans; a single study[20] in humans exposed to JP-8 fuel reported an inverse association between aliphatic hydrocarbons in exhaled breath and serum levels of luteinizing hormone (LH). However, exposure to JP-8 was not associated with higher odds of menstrual disorders. This study has already been discussed above.[20]

The Institute of Medicine (IOM) produced a report to assist the US Veterans Affairs and Congress evaluate the scientific literature regarding exposures that may have occurred in the 1990-1991 Gulf War. The IOM appointed a committee with knowledge of toxicology and epidemiology of fuels.[24] The report included a chapter that examined the reproductive and developmental outcomes of exposure to fuels and combustion products. Adverse outcomes for women reviewed were infertility, preterm birth, low birth rate as well as birth defects and childhood cancers. There were no studies of infertility in women and exposure to fuels that met the committee's inclusion criteria.

There were a small number of studies on maternal exposure to fuels and adverse reproductive outcomes among women, a lack of exposure to specific agents/fuels and a possibility of recall bias. The committee concluded that there was inadequate/insufficient evidence to determine whether there is an association between adverse reproductive outcomes and exposure to fuels.

CONCAWE[10] (Conservation of Clean Air and Water in Europe) is an industry based taskforce (Environmental Science for European Refining Industry) that undertook a program of voluntary risk assessments under the framework of the European Union (EU) chemical substances regulations. The European Chemicals Agency (ECHA) refers to the CONCAWE report for the assessment of kerosene and jet fuel. This report is a risk assessment of kerosene and reviews the hazards to human health and the environment. Aviation refuelling operations and aircraft maintenance are two of the activities documented by CONCAWE involving the occupational exposure to kerosene in the form of jet fuels. Their search of the literature through the Biosis database also resulted in a limited number of publications for kerosene exposures during military aircraft operations in the US. In relation to reproductive outcomes, CONCAWE also cited the Reutman et al study[20] in regards to the potential reproductive endocrine effects following exposures to aliphatic and aromatic hydrocarbons.

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart of fuels component the REA literature review, Jan 2000 – May 2017



Solvents

The Evidence Profile and Summary of Evidence focuses on reporting of the agreed specified solvents for this review from within the reported studies, to maintain relevance. These were isopropanol, propylene glycol monomethyl ether, ethyl acetate, acetone, methyl ethyl ketone (oxygenated solvents); ethyl benzene, toluene, xylene (aromatic solvents), and white spirits, (hydrocarbon solvents); and trichloroethylene (halogenated solvent). The reported studies may have used synonymous terms that are replicated here, or the studies may also have investigated associations for other solvents in that class that are referred to only in describing the study.

Figure 2 shows that the search yielded 8,623 records with 62 records identified through additional sources, with 5,498 records remaining after removal of duplicates. After title/abstract review, 145 full-text records were identified for further review. Information on papers or guidelines/reports which had a full screen is presented in Appendix 4.

From all the sources searched, for the specified solvents a total of 27 records met the inclusion criteria and are included in the final report of articles. Of these, 13 were scientific peer review publications,[20, 26-37] two were peer review publications summarising or updating guidelines findings,[38, 39] and the other 12 were government agency or other independent scientific body reports or risk assessments (guidelines/reports) that had reviewed and synthesised literature and included a peer review process.[24, 40-51]

The publications are grouped under the broad adverse reproductive health outcomes areas of menstrual disturbances,[20, 26-29] infertility,[30] and adverse birth outcomes.[31-37] The search did not identify any studies that reported exposure to solvents and premature ovarian failure (POF) or early onset menopause. Whilst the studies assessed occupational exposure to solvents, only one study was conducted in a military population.[20]

A summary of the studies is found in the evidence profile presented in Appendix 3 in detail.

There were several studies identified through the search in which reproductive health effects have been investigated in relation to organic solvent exposure in general. These studies are described in Table 7: Studies mentioning organic solvents in Appendix 3. In these studies the participants were categorised by exposure to any organic solvent or to unspecified organic solvents. As these data do not relate to the specified solvents of interest to this review they have not been included in the main evaluation. We present them for completeness.

Observational studies' papers

Five studies reported findings in relation to associations between specified solvents and menstrual disturbances.[20, 26-29]

A cross-sectional study of petrochemical workers in China[26] found that exposure to toluene and xylene were associated with oligomenorrhea (prolonged menstrual cycle length during the previous year) as was exposure to 'all aromatic solvents'. Assuming a linear association, a 7% increase in the odds of oligomenorrhea was associated with one additional year of exposure (presumably to 'all aromatic solvents' though this was not specifically stated). The target population was clearly defined; and all eligible participants were enrolled into the main data collection with a different selection process for urine sampling, the results of the latter were not reported in this paper. Menstrual pattern and exposure assessment seemed to be collected by standardised but not validated data collection instruments/methods. There was no analysis of differences conducted on non-responders, but 95 exclusions on the basis of inadequate menstrual history or job data were noted. Co-exposures to solvents were reported. Analysis was adjusted for possible confounders although only data on passive smoking was collected and smokers were excluded. Several analyses were conducted including all solvents, and any solvents, including dose response and by length of work, and by specific solvents.

A cross-sectional study of workers in a LCD manufacturing plant in Taiwan, a high tech industry that used many organic solvents in the fabrication process, found that short menstrual cycle length was more common amongst workers in the panel and module fabrication areas of the plant compared with array fabrication workers or office workers. No significant differences in risk were observed for long menstrual cycles.[27] The target population was clearly defined and exclusions were defined. No probability sampling method was used as all those exposed were invited to take part and the response rate overall was high, reported as 94% in the abstract and 93% in the results. A questionnaire was used to assess participant information including menstrual cycle and was standardised, but no indication of its validation was provided. Exposure data measurement via air sampling appeared validated but some aspects such as the number of days the air was sampled was not reported. The risks and exposure were assessed by area, i.e. array, panel, module fabrication area, and although the levels of exposures were reported by area the risks based on specific solvents were not assessed. A long list of possible solvents was reported, some with no detectable levels. Duration of exposure was not reported. Analysis of non-responders was not reported.

A further aspect of the study of workers in a LCD manufacturing plant[27] was analysis of urinary metabolites of sex steroids in fabrication workers to characterise their menstrual cycles.[28] Compared to the work array area, the panel area work was significantly associated with higher levels of follicular stimulating hormone (FSH); and lower levels of estrone conjugates (E1C) (early follicular phase) and lower levels of E1C (periovulatory phase). The reasons for discrepancies in the panel group were unclear, and further studies of individual exposure assessment were considered important in clarifying the relationships. Compared to the work array area group, the module area group was significantly associated with higher levels of E1C and progesterone metabolite pregnanediol-3-glucuronide (PdG) levels in the early follicular phase and in the periovulatory phase and higher levels of E1C, PdG and FSH levels in the luteal phase. Of the 178 workers recruited for the study, only 94 workers could be analysed on early morning urine samples, with 63 workers dropping out during the month of urine collection or who were ineligible or excluded due to missing data. Analysis of those who dropped out or were excluded, was not reported. The methods of urinalysis were reported. A strength of the study was the comparison of three groups with different exposures, however within the range of volatile organic compounds measured many were very low or not detectable, and the exposure assessment would have been strengthened if exposure had been measured over several days. As previously stated there were multiple exposures and analysis was conducted by work area not by individual exposure.

In addition to fuel exposure in the USAF personnel (discussed previously), Reutman et al[20] considered solvent exposure in relation to reproductive endocrine effects and endpoints predictive of non-conceptive menstrual cycles measured using urinary endocrine markers in a study in which data was collected in 170 women from 10 USAF bases, using a questionnaire and urine samples. Internal doses of aliphatic and aromatic hydrocarbons were estimated from exhaled breath samples collected from 63 participants. Participants who provided urinary endocrine and breath samples were compared. Neither total BTEX (benzene, toluene, ethylbenzene, and *m,p,o*-xylenes) nor toluene analysed as continuous variables were significantly associated with any of the hormone levels (preovulatory luteinizing hormone (LH), mid-luteal phase pregnanediol 3-glucuronide (Pd3G), mid-luteal estrone 3-glucuronide ($E_1$3G), follicle phase (Pd3G)). Toluene exposure approached statistical significance with pre-ovulatory LH when analysed in a model together with the aliphatic hydrocarbons (C_6-C_{16}) and age. The analytical method for the breath testing was referenced. A number of solvents were reported and co-exposures of solvents (and fuels) would have occurred; the separation of the effects of specific solvents was not ascertained. The assessment of the study overall and its generalisability to our study population of interest is reported previously in the jet fuels section of the Summary of Evidence.

A retrospective cross-sectional study of petrochemical workers in China assessed self-reported menstrual cycle length and exposures by questionnaire, including to exposure solvents such as toluene and the relationship with an abnormal menstrual cycle length.[29] There were several limitations in this study. The definition of abnormal menstrual cycle length included both long and short cycles and these were not differentiated in the analyses. Whilst the target population was defined, little information was provided to describe recruitment and the exposure assessment was based on self-report. A limitation in presentation of results was that data on effect estimates was not presented for exposures other than benzene, but rather it was stated that the odds ratio for the relationship between toluene exposure and abnormal menstrual cycle length was the only exposure to be greater than that of benzene. Generalisability of the study population to the study population of interest in our study is likely to be limited.

One study was identified that assessed solvents in relation to measures of fertility[30] and urine glycol ether metabolites in relation to time to pregnancy (TTP) as a measure of fertility. This was part of the PELAGIE cohort study. 2-MPA, a metabolite of methoxypropanol (propylene glycol methyl ether or PGME), one of eight urinary metabolites investigated, was not associated with a longer TTP. The target population in this study was well defined. For cost reasons, only a random sample of the study population, a cohort of pregnant women, had urine samples collected and analysed, and occupational status was not one of the criteria for selection. The questionnaire was standardised but no indication was provided of its validation, however the urinalysis analytical method was referenced. Details of the cohort including sampling and responders was referred to in another paper.[31] The study conducted various sensitivity analyses. Urinalysis for quantitative exposure assessment was a strength of the study, but it was not clear how much the exposure may have been due to occupational sources or cosmetic/domestic exposures. The generalisability to our study population is limited.

Seven studies were identified that investigated the association between exposure to specified solvents and birth defects.[31-37]

The PELAGIE cohort study of 3421 women in France also investigated congenital malformations among live births, stillbirths and medical terminations and urinary concentrations of 10 metabolites of glycol ethers in a nested case control study of 79 cases and 580 controls.[31] Detection of some glycol ether metabolites (of interest in this study was 2-MPA, a metabolite of PGME, which was associated with major malformations and urinary tract malformations) and of trichloroacetic acid and trichloroethanol in urine which were

associated with major malformations and limb malformations. The cohort study population was clearly identified, although the study sample of participants were recruited from around 30% of original private and hospital practitioners in the study area. A relatively high percentage (80%) participated in the cohort study, while the nested case control study with urinary biomarkers and the number of cases of malformations were limited by small numbers; but the authors considered that these findings identified work situations that require further investigation. Data on exposure were collected by several measures, self-report of occupation since pregnancy began, a job exposure matrix (JEM), and urinalysis in the nested case control study, and occupational exposure was collected prior to the outcome, decreasing the risk of bias. Urine sampling as an objective measure was a strength of the study, but whether the one-off urine sample was typical of the exposure period was not possible to assess. It is likely that most women in the general community would be unexposed to solvents so there may be some dilution of the observed effect in the cohort.

A case control study in the US National Birth Defects Prevention Study investigated the association between exposure to aromatic solvents, chlorinated solvents and Stoddard solvent (a specified solvent of interest in this study) during early pregnancy and neural tube defects (NTDs) and orofacial clefts (OFCs).[32] Maternal exposure to Stoddard solvent was not associated with any NTD or with NTD phenotypes (anencephaly, spina bifida, encephalocoele) although the number of cases of phenotypes of NTDs involved in this section of the analysis was limited. There were no significant associations between exposure to Stoddard solvent and any OFC or phenotypes (cleft palate or cleft lip with or without cleft palate). The target population was clearly defined and exclusions were stated, and there was a participation rate of 70%. The mothers of cases and controls differed on some factors such as body mass index >30 kg/m^2 (obesity) but analyses were adjusted for possible confounding factors. Non-malformed live births controls were randomly sampled using birth certificates or hospital records from the same base population as cases.

In the exposure assessment, job history was collected after birth with the potential for recall bias and difficulty in blinding as to case status. Exposure was classified (case blind) on several categories of probability of exposure (<10%, 10-49%, 50-89%, ≥90%); with the comparison group defined as those with (0) (unexposed) and the exposed group including all other categories. Sensitivity analyses were conducted restricting the exposed group to women with at least one job with an estimated probability of exposure of greater than or equal to 10% for an individual solvent within each solvent class. The ‘exposed’ group was therefore likely to have included women who were probably not exposed. The level of exposure was not defined. Although prevalence estimates of exposure to specific solvents

were presented for chlorinated solvents including trichloroethylene, odds ratios for association of trichloroethylene specifically with birth defects were not presented.

In further study of data from 2886 mothers and their infants (control population)[33] from the National Birth Defects Prevention Study[32] described above, the relationship between probability of exposure to solvents and small for gestational age birthweight was assessed.[33] Among women with any probability of exposure (exposure probability >0) during the month before conception or pregnancy, maternal exposure to Stoddard solvents was not associated with small for gestational age (SGA). In analysis restricted to the sample of women with ≥ 50% probability of exposure, the ORs could not be estimated for Stoddard solvent as the number of cases was n=0. As was undertaken in this paper, a sensitivity analysis restricted to a probability of exposure ≥ 50% would lessen the likelihood of inclusion of those who were probably unexposed, but also lessened the available number of participants for analysis.

A case control study nested in the National Birth Defects Prevention Study, assessed the relationship between any solvent, aromatic solvents, chlorinated solvents and Stoddard solvent and risk of congenital heart defects.[34] It used two independent exposure assessment classifications, a literature based approach and an expert consensus-based approach. The two exposure assignment approaches yielded different exposure prevalences. The specified solvent which was of interest in this study was Stoddard solvent. Based on the expert consensus-based approach, Stoddard solvent was not associated with any congenital heart defect or categories of congenital heart defects (some risks could not be estimated due to n=0 cases). According to the literature-based approach, Stoddard solvent exposure was associated with d-transposition of the great arteries, right ventricular outflow tract (RVOT) obstruction defects, and pulmonary valve stenosis (OR 2.1; 95% CI 1.1-3.8).

When analysis was restricted to mothers with at least one job rated as exposed with 50% or greater probability (42% cases; 33% controls), there were associations of Stoddard solvent exposure with any CHD, septal defects, perimembranous ventricular septal defect (VSD), and atrial septal defects; and the effect estimates of the odds ratios of the association of Stoddard solvent exposure with RVOT obstruction defects and pulmonary valve stenosis increased in magnitude. The target population in this study was well defined and exclusions stated. Job history was collected after birth with the potential for recall bias. Exposure assessment for analysis was based on the probability of exposure, and the base analysis appeared to be with the comparison group defined as those with (0) (unexposed) probability exposure. Sensitivity analyses were conducted to restrict the exposed group to those with >50% probability of exposure. The numbers of cases for some outcomes were small and

multiple exposures were considered. The capacity to attribute findings to specific exposures was limited.

A case control study of maternal occupational exposure to oxygenated, chlorinated, and petroleum solvents was associated with an increased risk of cleft lip/palate (CL/P) or cleft palate (CP) although not all the odds were statistically significantly increased.[35] Although specified exposures were not used in the analysis, each of the overall categories of solvents included solvents of relevance to this study, e.g. petroleum solvents, aliphatic alcohols (including isopropanol), glycol ethers (including PGME), aliphatic aldehydes, esters, ketones (including MEK) and acetone, and chlorinated solvents (including TCE). The risk of oral clefts increased linearly with level of exposure within the three subgroups of oxygenated solvents that were considered. However, the small number of subjects and multiple comparisons that were made were acknowledged by the authors, with a suggestion that the results be interpreted with caution. The study population of cases and controls were well defined and exclusions stated. Controls were hospital based, children who were recruited from the same or neighbouring hospitals as cases, hospitalised for a disorder other than birth defect, genetic disease or cancer, and frequency matched to cases. Mothers of cases (CL/CP cohort) and controls differed on some factors such as alcohol consumption, 19.5% cases consumed alcohol in the first trimester of pregnancy compared with 12.7% controls. Analyses were adjusted for possible confounding factors. Exposure assessment through interview then expert rating was standardised but not validated. A small number of cases and a generally low level of exposure was a limitation but analysis was enhanced through trend tests in exposure analysis.

A case referent study compared occupational exposures in 100 women with babies born with orofacial clefts (cleft lip, cleft palate) and 751 mothers of healthy referent births from a multicentre European study.[36] In a model, occupational exposure to aliphatic aldehydes and glycol ethers remained in the model ($p \leq 20\%$) with cleft lip with/without cleft palate and trichloroethylene remained in the model ($p \leq 20\%$) for cleft palate. Toluene and mineral oil exposures were not significantly associated with oral clefts. The target population in this study was clearly defined, although only 63% of eligible cases were interviewed. The case referent population of mothers of healthy referent births were obtained from the general population and hospital sources, and the participation rate was not clear. Comparisons of responders and non-responders was not reported. Exposure assessment of jobs was coded by an industrial hygienist (case blind), but classification of exposure by non exposed or exposed by either frequency or probability meant that there was considerable variability

within the exposed group. Multiple exposures were considered and the number of cases were small, and the results needed to be interpreted with caution.[36]

A prospective cohort study of self-reported pregnancy outcomes and maternal exposure assessment found no association between pregnancy duration or miscarriages and maternal exposure to xylene or acetone.[37] These findings were reported in the context of a study of a structured employee medical program in Germany. Some elements of the program such as when the reporting of pregnancy or the gestational ages at which this took place that may have impacted on the study were not reported. It is not clear whether early miscarriages would have been captured by the study. Outcomes and exposure assessment were based on self-report, and likely standardised but not validated. The predominantly laboratory-based women were likely to have low rather than high exposure levels, and they were assessed and their job potentially changed on reporting of pregnancy. Analysis of non-responders was not reported, it is possible that some may have left without reporting pregnancy.

Guidelines or Reports

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

In 2001, the Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands reviewed xylene and toluene in 2001 and evaluated the effects on reproduction with a view to recommendation for classification according to the guidelines of the European Union.[41] The Committee concluded for toluene, that available data were not sufficient to assess its effects on human fertility and draw any conclusions. For developmental toxicity, the committee recommended toluene be classified in category 3 (substances which cause concern for humans owing to possible developmental effects). For xylene, relevant human data was lacking therefore the committee recommended not to classify it for effects on fertility. For developmental toxicity, the committee recommended xylene be classified in category 3 (substances which cause concern for humans owing to possible developmental effects).

In 2008, the Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands[40] reported on Occupational exposure to organic solvents: effects on human reproduction. The peer-reviewed report was prepared for the Ministry of Social Affairs and

Employment, The Netherlands, and provided advice on possible effects on reproduction (i.e. effects on male and female fertility, pregnancy and development effects in offspring) and occupational exposure to organic solvents including, toluene, xylene and acetone. The developmental effects considered included spontaneous abortion, birth weight, and congenital malformations. The Committee concluded overall that available data indicated an association between women's exposure to toluene and spontaneous abortion; there was insufficient evidence regarding an association between women's exposure to toluene and developmental effects or malformations. In relation to xylene, the Committee concluded that available evidence supported a weak association between women's exposure to xylene and spontaneous abortion; there was insufficient evidence regarding an association between women's exposure to xylene and developmental effects or malformations. The Committee concluded that available evidence does not suggest any association between women's exposure to acetone and effects on female fertility and developmental effects.

In 2003, the Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands evaluated the effects on reproduction of trichloroethylene exposure with a view to recommending a classification according to the guidelines of the European Union.[42] For effects on fertility, trichloroethylene was not recommended to be classified in relation to effects on fertility because of a lack of sufficient human data, and sufficient animal data which showed that no classification was indicated. For developmental toxicity, the Committee recommended trichloroethylene be classified in category 2 (substances which should be regarded as if they cause developmental toxicity for humans).

In 2015, the Agency for Toxic Substances and Disease Registry (ATSDR), USA prepared a Draft Toxicological Profile for Toluene.[43] This profile reported that there was inadequate data to suggest acute or repeated exposure to toluene may have reproductive effects in humans. There was limited evidence to indicate maternal occupational exposure to toluene is associated with an increased incidence of spontaneous abortion or decreased fecundity in females. It highlighted that high levels of toluene exposure can be toxic to the developing foetus; one study reported that a lower level of occupational exposure to toluene may also increase the risk of central nervous system anomalies and neural tube closure defects. This was noted to be a Draft report for comment, a final report was not identified.

In 2007, the ATSDR prepared a Toxicological Profile for Xylene.[44] The report indicated that available studies of developmental or reproductive toxicity from occupational exposure to xylenes were not definitive because of the small number of subjects and/or concurrent

exposure to other chemicals. Very little information was found to be available on chronic health effects, including reproductive health effects.

In 2014, the ATSDR prepared a Draft Toxicological Profile for Trichloroethylene.[51] In a summary of the health effects, the male reproductive system and developing foetus were two of the identified potential targets of trichloroethylene toxicity. Limitations of assessment of the epidemiological evidence in humans of relationship between occupational exposure to trichloroethylene and adverse developmental effects included potential concurrent exposures to other chemicals (unspecified). The profile identified that case-control studies involved a rather small number of cases, and that some epidemiological studies related to maternal exposure to trichloroethylene via environmental sources such as drinking water in which exposure to other potential contaminants was a recognised limitation in exposure assessment.

The U.S. National Academies assessed the human health risks of trichloroethylene, although not all the evidence came from occupational exposure studies.[45] The Committee identified those end points for which animal and human evidence generated the greatest level of plausibility; these end points included impaired intrauterine growth, cardiac teratogenesis, and altered spermatogenesis. The Committee considered that although the evidence suggested that trichloroethylene can generate such effects the lowest-observed-adverse-effect level of human risk assessment remains unclear, the combined human and animal evidence generated to date did not reach levels of reasonable plausibility to indicate that other reproductive or developmental end points are associated with exposure to trichloroethylene.

In 2011, U.S. Environmental Protection Agency (EPA), National Center for Environmental Assessment presented a Toxicological Review of Trichloroethylene,[46] and reported that available studies showed maternal exposure to trichloroethylene can result in negative reproductive outcomes such as reduced fertility (as measured by TTP), incidence of fecundability (measured by TTP), amenorrhea, menstrual cycle disturbances and abnormal cycle length. An evaluation of the human studies, taking the overall weight and strength of the evidence into account, indicated that there is a potential for adverse developmental outcomes associated with pre- and/or postnatal trichloroethylene exposures.

Chiu et al.[39] summarized the main findings and scientific issues in relation to the human health effects of trichloroethylene (including developmental cardiac toxicity) in the U.S. EPA's toxicological review.[46] The review reported that cardiac defects have been associated with

exposure to trichloroethylene. In addition, other developmental outcomes, including embryonic foetal mortality and prenatal growth inhibition, were found to be associated with trichloroethylene exposure. It was noted that interpretation of human epidemiological data on trichloroethylene exposure has been controversial, as many studies were limited by small number of cases and methodological limitations. However, the data showed associations with a range of trichloroethylene related cardiac defects but lacked adequate statistical power to identify any particular type of defect that may be more susceptible to trichloroethylene exposure. The report, citing the National Research Council (2006) report, noted that elevation of cardiac malformations with similar relative effect sizes of 2 to 3-fold (with some significant findings) was associated with exposure to trichloroethylene. Overall, this review[39] summarised the findings that exposure to trichloroethylene: i) has strong evidence for male reproductive toxicity, ii) suggestive evidence for female reproductive toxicity, iii) strong evidence (based on weakly suggestive epidemiological studies) for foetal cardiac malformations.

In a peer review publication, Makris et al.[38] published a review evaluating potential effects of trichloroethylene and/or its oxidative metabolites (dichloroacetic acid and trichloroacetic acid) on cardiac development. This study also evaluated two additional epidemiological studies, i.e. Fornad et al.[52] and Ruckart et al.[53] that were not included in the EPA's 2011 report, and concluded that epidemiological studies demonstrate some support for the possible relationship between maternal exposure to trichloroethylene and cardiac birth defects. This conclusion is consistent to those discussed in the EPA 2011 report.

The World Health Organization IARC Monographs on the Evaluation of Carcinogenic Risks to Humans evaluates industrial chemicals,[47] predominantly for an evaluation of carcinogenic risks and studies of cancer in humans. Other studies relevant to an evaluation of carcinogenicity and its mechanisms are considered. Volume 77 of the monographs critically reviewed data on carcinogenicity for ethylbenzene exposure. However, the working group concluded that no studies were found in relation to human reproductive or developmental effects of ethylbenzene.

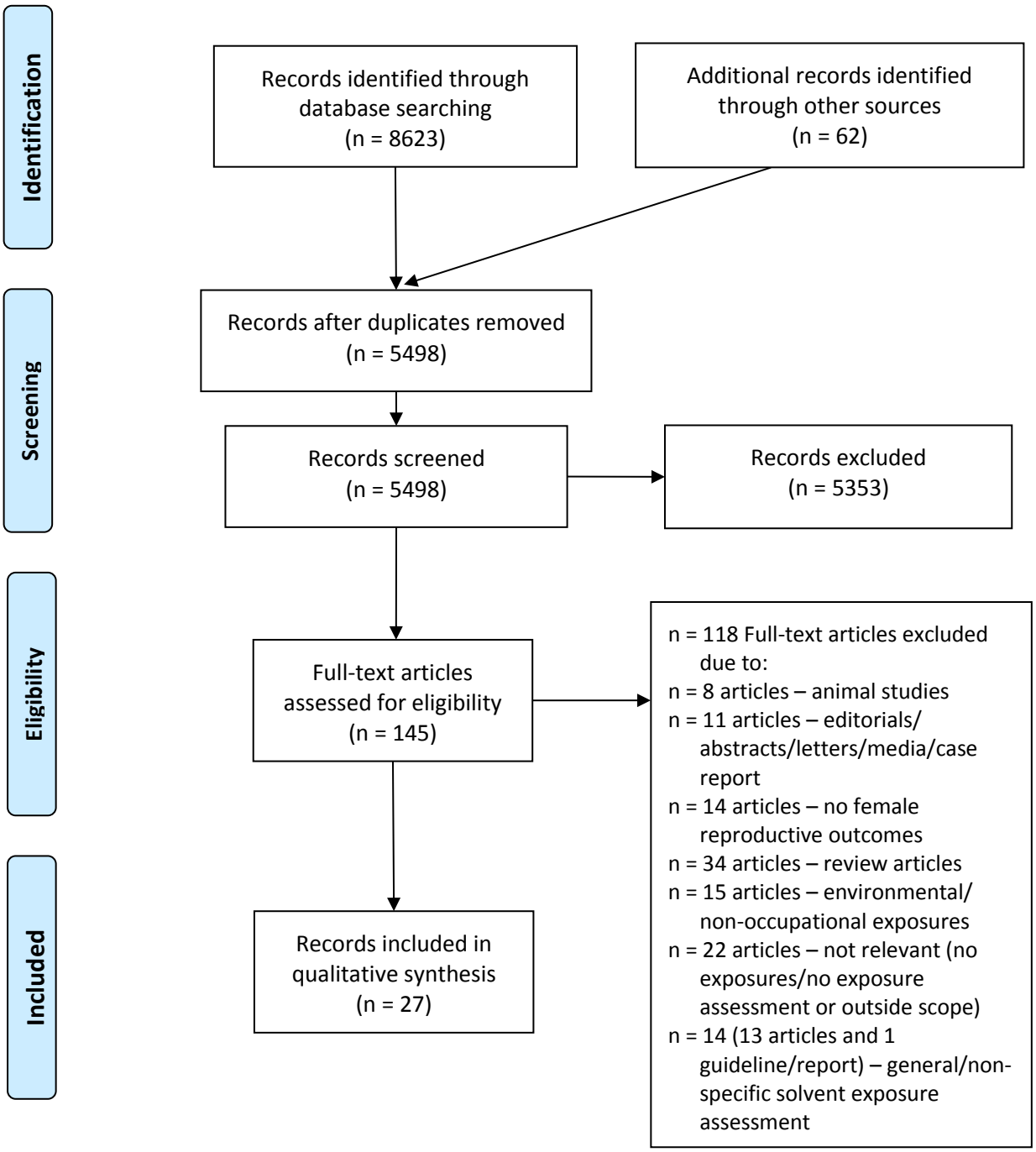
In 1994, the U.S. ATSDR prepared a Toxicological profile for acetone.[48] We would note that the studies referred to in the report are very early and exposures and their controls and methods of assessment are likely to have changed over time. No other toxicological profiles for acetone were identified in the search period of this Evidence Profile. The Toxicological profile reported that no studies were located regarding reproductive and developmental effects in humans following dermal or oral exposure to acetone. The report concluded that

the relevance of the reproductive and developmental effects to humans in relation to exposure to acetone is unknown, and there was insufficient data to sufficiently examine these end points in humans.

The ATSDR prepared a Toxicological profile for 2-butanone (methyl ethyl ketone (MEK)) in 1992.[49] This was included as no toxicological profiles for 2-butanone were identified in the search period of this Evidence Profile, however we would note that the studies referred to in the report are consequently very early and exposures and their controls and methods of assessment are likely to have changed over time. The Toxicological profile reported that no studies were located regarding reproductive or developmental effects in humans following inhalation, oral or dermal exposure to 2-Butanone, and no concluding remarks in relation to reproductive or developmental effects were located in the report.

The Institute of Medicine of the National Academies in a review in 2003 focused on evaluating long term adverse health outcomes of exposures during Gulf War, and included a review of the literature in relation to reproductive and developmental effects of exposure to solvents and mixture of solvents that were considered.[50] The committee concluded from its assessment of the epidemiological literature that there was inadequate/insufficient evidence to determine whether an association exists between exposure to specific solvents under review or solvent mixtures and male or female infertility after cessation of exposure; or whether an association exists between maternal or paternal preconception exposure to specific solvents under review or solvent mixtures and spontaneous abortions, other adverse pregnancy outcomes, and congenital malformations.

Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of solvents component the REA literature review, Jan 2000 – May 2017



Discussion

The aim of this project was to conduct a literature review of adverse reproductive health outcomes on service women from their occupational exposure to MATFs (referred to as jet fuels) and specified solvents used in the Australian military, with a main focus on evidence from human studies.

There was a limited number of observational studies identified that investigated the relationship between jet fuels and the specified solvents and each of the adverse reproductive health outcomes in women. The Evidence Profile and Summary of Evidence provide further detail that should be considered in relation to these studies, in particular limitations or strengths in relation to the evidence, but in the interest of summarising some findings of the studies the following is provided.

One study investigated the potential effects of low-dose hydrocarbons in fuel (primarily stated as JP-8) on menstrual cycle function relating to conception and found that preovulatory luteinising hormone (LH) levels were lower in otherwise healthy reproductive age women who had higher internal doses of aliphatic hydrocarbons (HCs), as measured by exhaled breath levels, suggesting that exposure has the potential to impact fertility.[20] A further study finding was that jet fuel exposure was not statistically significantly associated with dysmenorrhea in fuel handlers.[23] Reported exposure to petroleum products was not associated with reported adverse live-birth outcomes of low birth weight, preterm birth, small for gestational age, birth defect, or foetal distress,[21] and reported exposure to aliphatic hydrocarbons was not associated with congenital anomalies of conotruncal heart defects, limb deficiencies or oral cleft defects.[22] The Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP) found no evidence of an increased risk in female Deseal/Reseal personnel or female partners of male Deseal/Reseal personnel of miscarriage or stillbirth, or of reported difficulties getting pregnant or seeing a fertility specialist.[2]
A limited number of epidemiological studies for the relationship between jet fuel exposure and adverse reproductive effects in women was acknowledged in the included guidelines/reports in relation to an evidence base.

Neither total BTEX nor toluene were significantly associated with any of the hormone levels of menstrual cycle function relating to conception in USAF employees.[20] Exposure to xylene was associated with oligomenorrhea in petrochemical workers in China.[26] Toluene exposure was reportedly associated with abnormal menstrual cycle length in another study of Chinese petrochemical workers.[29] In two separate studies based on a French cohort study, 2-MPA, a

metabolite of PGME, was not associated with a longer TTP[30] but was associated with major malformations and urinary tract malformations.[31]

Maternal exposure to Stoddard solvent was not associated with any NTD or with NTD phenotypes although for the phenotypes of NTDs the number of cases was small.[34] There were no significant associations between exposure to Stoddard solvent and any orofacial cleft malformations or phenotypes (cleft palate or cleft lip ± cleft palate)[32] or association with SGA.[33] One study reported that Stoddard solvent was not associated with any congenital heart defect (CHD) or categories of CHDs based on one exposure assessment methodology but that exposure was associated with d-transposition of the great arteries, RVOT obstruction defects, and pulmonary valve stenosis based on an alternative exposure assessment methodology.[34] Occupational exposure to trichloroethylene was non-significantly associated with cleft palate.[36] Toluene and mineral oil exposures were not significantly associated with oral clefts.[36] A prospective cohort study found no association between maternal exposure to xylene or acetone and pregnancy duration or miscarriages.[37]

The guidelines/reports that were included for the specified solvents varied in availability of epidemiological studies for an evidence base for the relationship between the specified solvents and adverse reproductive effects in women, generally considered as reproductive and developmental effects. The emphasis was on guidelines/reports published since 2000, but none were identified as published during this period for some specified solvents and earlier guidelines/reports were included for completeness.

Overall limitations of individual studies of the association between jet fuel or specified solvent exposure and adverse female reproductive health outcomes included the small numbers of cases for adverse reproductive health outcomes, limitations in exposure assessment or in health outcome assessment such as in self-reported outcomes, recall bias, and co-exposure with other chemical(s) or solvent(s) or fuel exposures at the workplace which made it difficult to attribute any effect to the specified solvent or jet fuel.

The reporting of outcomes varied, from being based on self-report to hospital records or birth defects registries. Exposure assessment varied from self-report to hygienist classified and use of JEMs to objective measurements e.g. of metabolites; and categorisation of exposure or probability of exposure varied between studies. Commonly, assessment of outcomes and exposures was undertaken in a standardised, but not validated, manner. Limitations of exposure assessment in studies included self-report of exposure, estimation of probability of exposure and inclusion of any or very low probability of exposure with high probabilities of

exposure and women with varying levels of exposure being grouped together and potential misclassification of exposure status, exposure status assessed by area group in a work place, and the potential for recall bias.

To maintain relevancy, this Rapid Evidence Assessment literature review was based on an agreed selection of relevant jet fuels and specified solvents and adverse reproductive health outcomes. Within the epidemiological studies considered, a number of solvents were reported and co-exposures to other solvents, and fuels in some studies, would have occurred in the workplace; the separation of the effects of specified solvents in assessment of the association with adverse reproductive health effects is difficult. In other studies, that were identified, more general solvent exposure was used as the exposure metric for assessment with adverse reproductive health effects.

Overall, there was a limited body of literature on each of the specific jet fuels and specified solvents and the adverse reproductive health outcomes under consideration in this review. The individual epidemiological studies relevant to jet fuels and to specified solvents provided limited evidence of associations in relation to the adverse reproductive health outcomes under consideration. It was difficult to establish more definitive conclusions without a more substantial body of evidence. Furthermore, there were no studies identified that investigated POF or early onset menopause, and only one study identified that investigated the relationship between solvents and fertility.

Although the effects of occupational exposure of service women to jet fuels and specified solvents used in the Australian military was of prime interest, the search was not restricted to articles that assessed occupational exposures in women in military services. This would have considerably limited the number of articles for consideration and occupational exposures to the jet fuels or specified solvents that occurred in other occupational groups were also considered relevant to adverse reproductive health outcomes. However, the generalisability of the findings may be less given the nature of industries and ethnicity of participants. Furthermore, the range of co-exposure of fuels and/or solvents that they may have experienced were likely different from exposures of service women in the Australian military. There were a very limited number of studies that were conducted in military populations.

Part of the evidence profile that was built up was based on high quality guidelines or reports identified through the literature. These were incorporated into the inclusion criteria as these sources that had utilised systematic reviews, peer review processes and evaluation of evidence to consider the effects of jet fuels and specified solvents on adverse reproductive

health outcomes. Through the search of the grey literature we identified publicly available independent medical scientific advisory committee reports, toxicological profiles, or risk assessments assessing health outcomes of jet fuels or kerosene and specified solvents. In some of these reports, the conclusions identified that there was limited evidence for an association between the specific fuel or solvent under consideration and adverse reproductive health outcomes in women based on available, often very limited data but often included *in vitro* and animal as well as human data.

Strengths and limitations

This REA searched multiple databases relevant to medical, scientific and toxicological literature over a 17 year period back to January 2000. Key peer review publications published prior that were identified through the search were sourced and reviewed for inclusion/exclusion within the parameters of the review. Further, the REA sourced high quality guidelines/reports relevant to the topic.

Limitations of the REA include: the omission of possibly relevant papers that were published prior to or after the defined search period; the omission of non-English language papers; and reference lists of included papers were not fully hand searched to find other relevant studies, as would usually be done in a full systematic review.

Implications

This REA has identified peer reviewed published and high quality guideline/report evidence available in relation to the effects of jet fuels and specified solvent exposure and adverse human female reproductive outcomes. The Summary of Evidence and Evidence Profile does highlight where associations between occupational exposure to jet fuels and/or specified solvents and adverse reproductive outcomes have been reported and the strengths or limitations in relation to these. There were no studies identified that considered the outcomes of POF or early onset menopause, and only one study identified as investigating the relationship between the specified solvents and fertility. Limited epidemiological evidence was available for the research question for women in military settings. The implications for occupational exposures for women in the military needs to be considered in the light of the findings of studies and the limitations of the evidence.

Conclusion

This REA summarised the literature in relation to some specific adverse reproductive health outcomes among women including adverse fertility and pregnancy outcomes following occupational exposure to jet fuels and specified solvents of most relevance to the military. Whilst the body of literature on reproductive health effects following exposure to fuels and solvents *per se* is quite extensive, however the number of epidemiological studies and evidence identified which investigated exposure to jet fuels and to the specified solvents and these adverse reproductive health outcomes was relatively limited. There were no studies identified that investigated jet fuels and the specified solvents and POF or early onset menopause. The individual epidemiological studies relevant to jet fuels and to specified solvents provided limited evidence of associations in relation to the adverse reproductive health outcomes under consideration.

Overall, it was difficult to reach more definitive conclusions based on the individual epidemiological studies and overall body of evidence identified in the REA on the associations between exposure to jet fuels or the specified solvents and adverse reproductive health outcomes. It was difficult to establish more definitive conclusions without a more substantial body of evidence. This REA does however provide Department of Veterans' Affairs and Department of Defence with a summary of the available evidence for consideration in relation to occupational exposures and preventive measures in relation to women in the military.

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Appendix 1

Population Exposure Comparison Outcome (PECO) Framework

The question was formulated within the PECO framework as described in the REA.[14] The Application of a PECO framework helps to structure, contain and set the scope for the research question.

The proposed research questions were:

1. Is there an association between occupational exposure to MATFs and adverse reproductive outcomes including
    - adverse fertility and pregnancy outcomes:
        - early foetal loss,
        - still birth,
        - miscarriage,
        - foetal malformations or congenital anomalies,
        - pre-term birth,
        - intra-uterine growth retardation,
        - low birth weight,
        - neonatal death;
        - reduced fertility;
        - not achieving desired family size;
    - Premature Ovarian Failure (POF) and early onset menopause.

Table 2: PECO Framework and Research questions in PECO format

P Patient, Problem, Population	**E** Exposure	**C** Comparison (population) (optional)	**O** Outcome
Reproductive Age - 18 years–55 years age Gender – female Employment status – employed or previously in defence or military related forces	Exposure – MATFs Jet fuels: JP-4, JP-5, JP-7 JP-8, Jet A, Jet A-1, Jet B, F34 and F44. Specified solvents: ethyl acetate, ethyl benzene, toluene, xylene, acetone, isopropanol, methyl ethyl ketone, propylene glycol monomethyl ether, white spirit and trichloroethylene.	Not exposed to MATFs in defence or military related forces General population Note: An Intervention can be examined without alternatives, and in some cases, there may not be an alternative.	Adverse reproductive health outcomes: – ○ Adverse fertility and pregnancy outcomes: early foetal loss, still birth, miscarriage, foetal malformations or congenital anomalies, pre-term birth, intra-uterine growth retardation, low birth weight, neonatal death; reduced fertility; not achieving desired family size; ○ Premature Ovarian Failure (POF) and early onset menopause

Research questions in PECO format:
In adult females of reproductive age who are or who have been employed in defence or military related forces, is exposure to MATFs associated with an increased risk of adverse reproductive health outcomes compared with adult females employed or previously employed in defence or military related forces or in the general population who have not been exposed. In adult females of reproductive age who are or who have been employed in defence or military related forces, is exposure to specified solvents associated with an increased risk of adverse reproductive health outcomes compared with adult females employed or previously employed in defence or military related forces or in the general population who have not been exposed.

Appendix 2

Example search strategy

The following is an example of the search Strategy conducted in the Medline Database(s): Ovid MEDLINE(R), Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy: 05 May 2017

#	Searches	Results
1	exp Reproductive Medicine/	21237
2	exp Reproductive Health/	2058
3	exp Reproduction/	1023323
4	"Reproduct*".mp.	251514
5	exp Fertility/	36576
6	exp Infertility/	60650
7	exp Infertility, Female/	26815
8	("fertilit*" or "infertilit*").mp.	151110
9	subfertility.mp.	2904
10	"fecund*".mp.	11494
11	exp Reproductive Techniques/	134845
12	exp pregnancy/	831510
13	exp Pregnancy Complications/	394616
14	exp Infant Mortality/	28542
15	exp Fetal Mortality/	459
16	(foetal or fetal or foetus or fetus or infant* or perinatal*).mp.	1468719
17	stillbirth*.mp.	11519
18	"miscarriage*".mp.	11295
19	"abortion*".mp.	86974

#	Searches	Results
20	"pregnan*".mp.	921388
21	exp "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"/	1117053
22	"Congenital*".mp.	292405
23	"prenatal".mp.	151853
24	exp Premature Birth/	10039
25	exp Infant, Premature/	48934
26	("prem* birth*" or "prem* deliver*" or "premature labo#r*").mp.	16408
27	exp Infant, Low Birth Weight/	30607
28	exp Growth Disorders/	30108
29	exp Fetal Development/	83955
30	exp Fetal Weight/	1488
31	exp Birth Weight/	38028
32	"*growth retardation".mp.	27673
33	"IUGR".mp.	4966
34	"low birth weight".mp.	36779
35	exp Libido/	4570
36	Libido.mp.	7310
37	exp Time to Pregnancy/	104
38	"conception".mp.	27317
39	exp Menstruation Disturbances/	26922
40	("menstrual*" or "menstral").mp.	42223
41	"family size".mp.	5127
42	exp Primary Ovarian Insufficiency/	2135
43	"Ovarian Failure".mp.	3491
44	exp Menopause, Premature/	905

#	Searches	Results
45	exp Menopause/	53164
46	("menopause" or menstruat* or "menopausal").mp.	83450
47	((Aviation or jet* or aircraft*) and fuel*).mp.	920
48	matf*.mp.	40
49	exp Kerosene/	704
50	Keros#ne.mp.	1570
51	Kerosene*.mp.	1561
52	exp Petroleum/	14056
53	exp Fuel Oils/	1295
54	petroleum distillate*.mp.	135
55	("JP4" or "JP-4" or "Nato F-40" or "MIL-DTL-5624").mp.	71
56	Petroleum Naphtha.mp.	10
57	(JP5 or JP-5).mp.	67
58	"Aviation Keros#ne".mp.	14
59	"Avtur".mp.	0
60	(JP7 or JP-7 or "Mil-DTL-38219").mp.	11
61	(JP8 or JP-8 or "JP-8+100" or "Mil-DFL-83133").mp.	244
62	"Fuel System Icing Inhibitor".mp.	1
63	("Civilian Jet A" or "Jet A").mp.	156
64	("Civilian Jet A-1" or "Jet A-1").mp.	16
65	"Jet B".mp.	1
66	("F34 Avtur" or "Fuel F34").mp.	0
67	("F44 Avcat" or "Fuel F44").mp.	0
70	exp Military Personnel/	35485
71	exp Veterans/	13192

#	Searches	Results
72	exp "United States Department of Veterans Affairs"/	6542
73	exp Military Medicine/	28519
74	exp Naval Medicine/	9472
75	exp Occupational Health/	30122
76	exp veterans health/	773
77	Defence.mp.	24309
78	"servicewom#n".mp.	73
79	(military* or service personnel or service member* or veteran* or combat* or soldier* or militaries or active duty or deployed* or deployer* or deployment* or postdeploy* or predeploy* or redeploy* or nondeploy* or non-deploy* or post-deploy* or pre-deploy* or re-deploy* or troop* or air force* or sailor* or submariner* or armed force* or army or navy or marine corps or uniformed service* or coast guard or coastguard or reservist or reserves or national guard or defen?e force*).mp.	185969
80	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46	3343861
81	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67	15756
82	69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78	242255
83	80 and 81	884
84	Limit 83 to (english language and yr="2000 -Current")	435
85	80 and 81 and 82	23
86	limit 85 to (english language and yr="2000 -Current")	0

Appendix 3

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

Table 3: Evidence Profile: Observational studies – jet fuels

Authors & Year	Study design	Country	Study pop^{n} and sampling methodology	Study Group (*N*)	Comparison Group (*N*)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Reutman et al. (2002)	Cross-sectional study. Data collected by: telephone and in person interview, self-report via diary entry, exhaled breath, and urine sample analysis	USA	Female United States Air Force (USAF) employees: civilian and active military female personnel at 10 USAF bases were screened for age, medication use, medical diagnoses, and surgical procedures. Non-smokers were targeted. (N=335)	Completed questionnaire and daily diaries N=170 (51%) Subgroup: Endocrine data and provided urine samples (n=100) Subgroup: Endocrine and breath analysis data (n=63 breath samples)		Reproductive endocrine endpoints predictive of non-conceptive menstrual cycles measured using urinary endocrine markers: • Preovulatory luteinizing hormone (LH) • mid-luteal phase pregnanediol 3-glucuronide (Pd3G) • mid-luteal estrone 3-glucuronide($E_1$3G) • follicle phase Pd3G. Menstrual cycles were calculated from diary records. Morning urine samples were collected daily. Urinary endocrine measurements and menses dates were used to derive the endocrine endpoints.	Internal doses of aliphatic and aromatic hydrocarbons (HCs) from fuels and solvents (reported in Tables 2 & 3) measured by post-shift exhaled breath analysis for exposure to aliphatic (C_6-C_{16}) and aromatic (BTEX) HC levels. Exposure characterised as low versus high exposure groups for C_6-C_{16} and BTEX based on the median. Reported exposure to fuels (not clearly stated but indirectly reference made to JP-8 predominance in introduction) (and solvents) and job titles/codes collected and compared.	Age: 18-42 y Female
Findings: There was no significant (p≤0.05) difference in endocrine levels between self-reported exposed versus non-exposed participants when examined bivariately or in multivariable regression models including potential confounders and covariates. Urinary preovulatory LH mean levels (unadjusted) were significantly lower (p=0.01) in the high versus low aliphatic HC exposure group (mean ± SD 15.4±8 versus 22.6± 12.0 mIU/mgCr) respectively. For mid Pd3G, mid $E_1$3G and follicle phase Pd3G there were no significant differences in the mean endocrine levels (unadjusted) in the high versus low aliphatic HC exposure group (high 10.5± 7.4 versus low 10.0± 6.3), (24.9± 13.1 versus 27.2± 13.6) and (1.2± 0.8 versus 1.2 ± 0.7) respectively. For BTEX, the urinary preovulatory mean LH levels (unadjusted) were also significantly lower in the high exposure group (15.8± 8.2 versus 22.0± 12.2 mIU/mgCr). For BTEX there								

Authors & Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (*N*)	Comparison Group (*N*)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
were no significant differences between the high and low exposure groups for the other three endocrine markers. Adjusted regression analysis of the four endocrine outcomes separately showed that preovulatory LH levels were significantly lower β= -7.34 (p=0.007) in women whose total aliphatic HC levels were above the median (high dose). Reported hours of exposure were consistent with job categories (women in fuel handling, flight line and maintenance jobs reported more exposure than 'non-exposed' jobs) but were similar for women with high and low levels of aliphatic and BTEX HCs in exhaled breath and some possible explanations were considered.								
Hourani & Hilton (2000)	Case–control study. Mailed questionnaire sent as a reproductive health survey	USA	All pregnant Navy active duty women, who, based on hospital records, visited an inpatient/ outpatient obstetric clinic at any of three Navy hospitals (San Diego, Portsmouth, Jacksonville, to enable large numbers and aviation occupations) Jan to Oct 1993 (N=3099)	Response rate 56% among reached, 38% among target subjects. Women >30 y with a hospitalised foetal death outcome under-represented. So analyses restricted to women whose pregnancy in 1993 resulted in a live birth and who had none or any of five outcomes (n=1032)	Civilian beneficiaries identified from San Diego clinic N=109 (Response rate 66% among reached, 49% among targeted) included in initial analyses	Mother reported adverse live–birth outcomes: • low birth weight (<2500g at birth) • preterm birth (<37 weeks gestation) • small for gestational age (yes/no) • birth defect (yes/no) • foetal distress prior to or during delivery (yes/no) Cases: defined as women with ≥1 of five adverse outcomes. Controls: women with none of the adverse outcomes	Exposures included: • Duty station at pregnancy inception (ship vs shore) • Mother or father had spent time in Persian Gulf since 1990 • Mother-reported maternal and paternal occupational and environment exposures (yes/no) in 3 months preceding conception including: petroleum products (eg jet fuel and diesel fuel). Level of exposure and route of exposure was not documented. • Other variables including demographics, maternal medical history, and lifestyle factors	Age: 17-44 y Female
Findings: Active duty women were significantly more likely than civilian beneficiaries to report exposure to petroleum products (χ^2=10.7, p < 0.002), solvents (χ^2=30.8, p < 0.001), heavy metals and some lifestyle factors, more likely to experience preterm labour during pregnancy (χ^2=4.2, p <0.05), but did not differ on live-birth outcomes; and were excluded from further analyses. Solvents and petroleum products were the second most frequently reported exposures in the workplace for both mothers and fathers. Pesticides and solvents were second most frequently reported exposures at home. No outcome variables were associated with solvent, shipboard duty or Persian Gulf duty in unadjusted OR. Maternal exposure to petroleum products at home was the only exposure variable related to low birth weight (unadjusted OR 2.4; 95% CI 1.03-5.56). No association between reported exposure to petroleum products (and solvents) in multivariate regression models controlling for maternal demographic, lifestyle and health variables. Only a single exposure variable, paternal but not maternal occupational exposure to pesticides, was associated with OR > 2 of preterm delivery. No evidence of association of adverse live-birth outcomes considered with reported exposure to petroleum products or solvents in this group of Navy military women.								

Authors & Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (*N*)	Comparison Group (*N*)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
DVA (2004)	Self-reported Reproductive questionnaire administered in the Study of Health Outcomes in Aircraft Maintenance personnel (SHOAMP)	Australia	Female F-111 Deseal/Reseal (DSRS) workers and female partners of male study participants who reported pregnancies during the five posting periods over 1975-1999. Reproductive Questionnaire included in invitation package and males instructed to forward to current or past female partner for completion. Female DSRS personnel (n=24) and female partners of male DSRS personnel (n=767) for analysis	DSRS Exposed (n=293 respondents)	Technical personnel posted at RAAF base Richmond (NSW) (n=294 respondents). Other personnel (non-technical) posted at Amberley base (n=204 respondents)	Reproductive health outcomes referenced to a posting date: • Outcome of pregnancies during the period of F-111 DSRS • For any pregnancies recorded, if there were reported difficulties getting pregnant and if reported seeing a specialist Analysed in female participants or partners only as: • Pregnancy result (live birth vs other incl. still birth or miscarriage) Also asked about age at conception, lifestyle factors during pregnancy, male partner rank and posting	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
SHOAMP personnel were exposed to a number of materials, some at low levels and others at higher levels. The exposures varied in the different programs over the years. There was exposure to a number of solid and liquid materials. These included: jet fuels JP A1, JP 4 and JP 8, from mopping out the tanks prior to desealing; desealants which contained dimethyl acetamide, thiophenol and an aromatic solvent; Sealants; Alkaline detergent washes which contains glycol ethers and thiophenol residues; a range of solvents eg MEK, naphtha, ethyl acetate, isopropanol eg for cleaning the surfaces; metal surface protector including toluene, xylene, isopropanol; epoxys and primers. *SHOAMP had 4 programs: Program 1 (1975-1982), Wing program (1985-1992), Program 2 (1990-1993) and Spray seal (1996-1999) 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								

Authors & Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (*N*)	Comparison Group (*N*)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
few participants. 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).								
Findings: N=552 total females included in analysis who reported pregnancies within exposure period of interest. N=1327 total 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% of births) and exposed group (20% of births). 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, CL0.65-1.3) 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) 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) There was no dose repose relationship for mild, moderate or prolonged exposure (p=0.99). Formal analysis was not possible for pregnancy outcomes regarding difficulties getting pregnant and visits to a specialist for fertility problems as key confounders such as maternal age at the time 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. **Conclusions:** There was no evidence of an association in female DSRS personnel or partners of male DSRS personnel and miscarriage or stillbirth, or in reported difficulties getting pregnant or seeing a fertility specialist.								
Shaw et al (2003)	Case- control study Data collected by: telephone interview	USA	All women residing in the California counties (1987-1989) that had infant and foetal deaths ≥20 weeks and listed anomalies diagnosed within the first birthday (N=552,601)	Cases: mothers of 662 CLP and CP cases, 207 conotruncal defect cases, 165 limb deficiency cases (n=) mothers with periconceptional occupational exposure	Controls: mothers of 972 control infants with no major congenital anomalies randomly selected from all infants born in same area and time	Risk of congenital anomalies: • Cleft palate (CP) • Cleft lip with or without CP (CLP) • Conotruncal heart defects • Limb deficiencies Case eligibility determined by a clinical geneticist reviewing medical records information. CP or CLP with no other major anomaly were categorised as isolated CP or CLP cases; with one accompanying major anomaly as multiple CP or CLP cases	Exposure assigned based on an industrial hygienist assessment of periconceptual (1 m before to 3 m after conception) occupational tasks and assigned to *a priori* defined exposure categories as likely, maybe or not exposed to 74 chemical agent groups and nine 'end-use' groups, including aliphatic hydrocarbons(C_1-C_4) and (C_5-C_{12}) as groups (i.e. kerosene)	Age: Foetus ≥ 20 weeks and up to 1 yr Mother's age range not stated but reference range <20->39y [54]

Authors & Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (*N*)	Comparison Group (*N*)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Findings: Analyses limited to women who reported working during the periconceptual period. OR of 1.5 or greater (based on a minimum 10 exposed cases and controls combined) were observed for a relatively small number of all possible exposure-anomaly comparisons. Isolated CP (n=6) cases OR 2.2 (95% CI 0.9-5.7) and multiple CP (n=2) cases OR 1.5 (CI 0.5-7.0) (n=17 controls) were observed for maternal exposures to aliphatic HC (C_1-C_4). Conotruncal heart (n=14) cases OR 1.6 (95% CI 0.8-3.3) and limb (n=9) cases OR 1.6 (CI 0.7-3.8) (n=35 controls) were observed for maternal exposures to aliphatic HC (C_5-C_{12}). **Conclusions:** OR 1.5 was observed for a small number of exposure-defect comparisons and in association with maternal exposure to aliphatic hydrocarbons these were statistically non-significant, but the number of cases were small. Although potential associations were observed, most results suggested that maternal occupational exposures to a variety of chemicals did not contribute substantially to the risk of conotruncal heart defects, limb deficiencies or oral cleft defects in the study population.								
Gordley et al (2000)	Cross-sectional study. Par Data collected by: in person interview, self-report via diary entry. Urinalysis collection referred to as part of expanded study data collection	USA	Female United States Air Force (USAF) employees: civilian and active military female personnel at 10 USAF bases participating in an expanded study investigating hormonal effects of exposure to jet fuel in women were screened for age, medication use, medical diagnoses, and surgical procedures. (N=170)	Completed questionnaire and daily diaries N=170 (51%)		Menstrual abnormalities: • Abnormal cycle length: intervals <24 or >35 days • Hypermenorrhoea: menses excessive in duration (>7days) or amount of menstrual bleeding reported as 'heavy' • Primary dysmenorrhea: derived from responses to questions "did you miss work..need to lie down..due to [menstrual or premenstrual] symptoms?"	Fuel exposure defined by self-report of having a job either handling or not handling fuel such as aircraft maintenance and refuelling operations Job stress measured by Job Content Questionnaire (JCQ) developed by Karasek et al. Life events measure by Life Events Questionnaire (LEQ) Data on age, marital, education, smoking, passive smoke, race or ethnicity, military vs civilian employment status, occupational jet fuel exposure	18-41 y Female
Findings: Fuel handling reported by n=66, 38.8% participants. No significant differences between fuel and non fuel handlers with respect to the stress factors. Job strain was not significantly associated with any of the menstrual outcomes. 40.9% (n=26) of fuels handlers and 26.0% (n=27) of non fuel handlers had dysmenorrhoea. Fuel handling: non statistically significant association with dysmenorrhoea (n=53) OR 1.83, 95% CI 0.90-3.70, coefficient 0.60; abnormal cycle length (n=20) OR 0.27 (0.08-1.06), coefficient -1.24.								

Table 4: Evidence Profile: Guidelines/Reports – jet fuels

Authors & Year	Country	Title and scope	Exposure(s) route	Reproductive and Developmental Effects	References
Agency for Toxic Substances and Disease Registry (ATSDR) (2017)	USA	Toxicological profile for JP-5, JP-8 and Jet A Fuels. The profile was prepared in accordance with guidelines developed by ATSDR and the US Environmental Protection Agency (US EPA). 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 substances' toxicological properties and the pertinent literature is presented but described in less detail than key studies. The focus of the profiles is on health and toxicological information. The health effects section and human studies findings were considered in relation to this Evidence Profile		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.	
			Inhalation	One study reporting 170 military and civilian women in occupations involving fuel handling found that women did not have significantly higher odds of menstrual disorders in adjusted analyses. Exposure was characterized by measuring aliphatic hydrocarbons (total C_6–C_{16}) and total benzene, toluene, ethylbenzene, and xylene in exhaled breath. The study found a significant (p=0.007) reverse association between preovulatory LH and breath aliphatic hydrocarbons, the mechanism by which this could occur was unknown. Although not clearly stated, the assumption appears to be that the exposure was mainly to JP-8 although other products such as a gasoline, diesel fuels, and the combustion products were not completely ruled out. No studies were located regarding developmental effects in humans after inhalation exposure to JP-5, JP-8, or Jet A fuels.	Army 2001[55]; Reutman et al. 2002[20] as reported above
			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.	
			Dermal	No studies were located regarding reproductive effects or developmental effects in humans 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 have evaluated neurologic, reproductive, genotoxic, or carcinogenic end points following inhalation exposure. Single studies in humans exposed to JP-8 fuel reported an inverse association between aliphatic hydrocarbons in exhaled breath and serum levels of LH. However, exposure to JP-8 was not associated with higher odds of menstrual disorders.					

Authors & Year	Country	Title and scope	Exposure(s) route	Reproductive and Developmental Effects	References
Agency for Toxic Substances and Disease Registry (ATSDR) (1995)	USA	Toxicological profile for Jet Fuels JP-4 and JP-7. The profile was prepared in accordance with guidelines developed by ATSDR and the US EPA and in support of Department of Defense needs. An ASTDR toxicological profile succinctly characterises the toxicological and adverse health effects information for the toxic substances of the profile. The profile identifies and reviews the key literature (that has been peer reviewed) of a substances' toxicological properties and the pertinent literature is presented but described in less detail than key studies. The focus of the profiles is on health and toxicological information. The health effects section and human studies findings were considered in relation to this Evidence Profile.		Health effects: No long term epidemiological studies were located regarding exposure to JP-4.	
			Inhalation	No studies were located regarding reproductive effects or developmental effects in humans after inhalation exposure to JP-4 and JP-7.	
			Oral	No studies were located regarding reproductive effects or developmental effects in humans after oral exposure to JP-4 and JP-7.	
			Dermal	No studies were located regarding reproductive effects or developmental effects in humans after dermal exposure to JP-4 and JP-7.	
Findings: This profile located no studies reporting reproductive effects or developmental effects in humans after exposure to JP-4 and JP-7.					
Institute of Medicine (IOM) (2005)	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 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 to the Gulf War.	Fuels. The Committee found that there was a lack of exposure information for individual veterans.	Reproductive and developmental outcomes of interest included infertility, preterm birth and low-birth rate, birth defects and childhood cancers. No studies of infertility in women and exposure to fuels met the committee's inclusion criteria. No studies reported for spontaneous abortion in veterans or that included occupational exposures.	
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 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.					
CONCAWE (2007)	Belgium	Human exposure information for European Union (EU) substance risk assessment of kerosine.	Inhalation	The taskforce discussed the Reutman et al. study [20] of potential reproductive effects of low dose HCs encountered	Reutman et al. 2002[20] as

Authors & Year	Country	Title and scope	Exposure(s) route	Reproductive and Developmental Effects	References
		The activities considered included the manufacture, distribution and use of petroleum production collectively known as kerosines. The assessment was noted to be applicable to products blended with these refinery products, in particular aviation fuel, (jet fuel), automotive fuel etc. CONCAWE is an industry based taskforce that undertook a program of voluntary risk assessments under the framework of the EU chemical substances regulations.		by female US Air Force personnel and changes to urinary hormone levels.	reported above
			Dermal	There is no reported studies or discussion on reproductive effects following dermal exposure.	
Findings: The taskforce concluded that worker exposure levels for kerosines were generally low, there were a wide range of control measures in place and occurrences of elevated exposure appear to be infrequent. Some studies reported in the literature showed higher exposure levels (i.e. maintenance workers).					
National Research Council (NRC) (2001)	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	No human studies have been conducted to assess female reproductive or developmental toxicity caused by exposure to JP-8 or any other ketone-based fuel.	
Findings: There were no human data on the effects of JP-8 on female reproduction.					
National Research Council (NRC) (2003)	USA	Toxicological assessment of jet propulsion fuel 8. The NRC assigned this project to the Committee on Toxicology (COT), which assembled the Subcommittee on Jet-Propulsion Fuel 8 to prepare this report/assessment.	Not applicable	No studies were found that examined the potential for developmental toxicity or adverse reproductive effects of JP-8 or other jet fuels in women.	
Findings: As the data were scarce and the military personnel were occupationally exposed to JP-8, the subcommittee recommended that experimental animal studies be conducted to determine reproductive and developmental toxicity potential of JP-8.					

Table 5: Evidence Profile: Observational studies - solvents

Menstrual cycles

Authors and Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Cho et al. (2001)	Cross-sectional study. Data collected: Questionnaire on menstrual pattern; and daily urine collection for childbirth permission (CBP) seeking group; and/or those enrolled at marriage health examination (MHE)	China	Petrochemical workers obtaining CBP from local family planning office before having a baby (20 to 40 years, no previous marriage, no previous clinical pregnancy, no diagnosed gynaecological or endocrine disease) N=1,510 (enrolled)	Petrochemical workers n=1,408 including n=338 CBP enrolment group that had urine collection and worked in one of nine selected production facilities		Menstrual pattern: • Oligomenorrhea - average cycle length >35 days during the previous year • Average cycle length, longest and shortest cycle length, average duration of bleeding, perceived irregularity, intermenstrual spotting, and perimenstrual symptoms	Industrial hygienist evaluated exposure at workshop level to organic solvents (benzene, styrene, toluene, or xylene) [presence or absence]. Other variables collected: age, BMI, enrolment group, smoking, exposure to other solvents, parity, presence of indoor coal combustion and cooking oil fumes, alcohol consumption, diet, use of herbal medicines, noise, heavy lifting, exertion, perceived work stress, rotating shift work, and education	20–34.5 y Female
Findings: Prevalence of oligomenorrhea by solvent exposure groups: 12.9% [toluene], 14.1% [xylene], 9.3% [benzene+toluene], 6.9% [benzene+toluene+styrene], 9% [benzene+ toluene+xylene] and 16.3% [benzene+ toluene+xylene+styrene]. Prevalence of oligomenorrhea: 7.7% (MHE group) and 13.1% (CBP group) [unexposed]; 9.3% (MHE group) and 17.1% (CBP group) [exposed]. Exposure to “all aromatic solvents” was associated with oligomenorrhea OR 1.76 (95% CI 1.08-2.82), compared with unexposed group. Exposure to toluene and xylene were associated with oligomenorrhea: OR1.43 (95% CI 0.93-2.17) non-statistically significantly [toluene]; OR 1.63 (95% CI 1.04-2.53) [xylene]; OR 1.76 (95% CI 1.08-2.82) [all aromatic solvents]. A 7% increase in the odds of oligomenorrhea was associated with 1 additional year of exposure, assuming a linear association. Authors concluded exposure to organic solvents was associated with a trend toward increased frequency of oligomenorrhea.								
Lin et al. (2013a)	Cross-sectional study. Data collected:	Taiwan	Premenopausal workers (with 1 year	n=622 completed questionnaire,		Menstrual cycle length • abnormal if <24 or >35 days	Exposure to VOCs including toluene, *m/p* xylene, ethyl acetate, ethylbenzene and acetone assessed	18-44 y Female

Authors and Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Questionnaires on menstrual cycle characteristics, risk factors; Hand held volatile organic compound (VOC) monitors for chemical exposures		employment) undergoing annual health examinations at a liquid crystal display (LCD) manufacturing plant in 2002 N=666	response rate =93%; n=288 for analysis sample after exclusions		• short <24 days • long >35 days Abnormally heavy flow: • use of >8 sanitary towels daily	with hand-held VOC monitors with 24h canister sampling in office (reference group) and each fabrication area (array, panel, module) which result in different levels of VOC exposure. Other variables collected: demographics, BMI, working history/pattern, medical and reproductive history, alcohol, tobacco, exercise	
Findings: Measured levels of VOCs (in ppb) [canister sampling] were: i) toluene 20.6 [office], 7.5 [panel], 11.1 [module], 20.8 [array]; ii) *m/p* xylene 3.2 [office], 1.7 [panel], 1.1 [module], 6.9 [array]; iii) ethylbenzene 0.9 [office], 0.6 [panel], 0.7 [module], 4.6 [array]; ethyl acetate 1.5 [office], 1.8 [panel], 2.0 [module], 2.6 [array]; and acetone 15.4 [office], 592 [panel], 2283 [module], 58.9 [array]. Concentrations were well below the occupational exposure limits. Short cycle length was more common amongst the panel (17%) and module (22%) groups, ii) these groups also showed increased odds of a shorter menstrual cycle (OR 7.68; 95% CI 1.51–39.15) [panel] (OR 8.38; 95% CI 1.72–40.95) [module] but not array group (OR 0.73 95% CI 0.07-7.76) compared with office group. No significant difference in risk were observed for long menstrual cycles. Authors conclusions – possible link between repeated exposure to multiple organic solvents such as ethanol and acetone and increased prevalence of short menstrual cycles in premenopausal women.								
Lin et al. (2013b)	Cross-sectional study. Data collected: self-administered questionnaire; Morning urine sample collected for at least one menstrual cycle	Taiwan	Female employees (at least one year of employment) at an LCD manufacturing plant; pre-menopausal women. 2002	N=178 recruited; n=94 (excluding drop-outs) analysed from 3 subgroups (work areas): array n=23, panel n=53 and module n=18		Daily urinary metabolites of sex steroid hormones: estrone sulphate and estrone glucuronide (estrone conjugates) (E1C); progesterone metabolite pregnanediol-3-glucuronide (PdG); and total urinary follicle-stimulating hormone (FSH). Menstrual diary records, urinary endocrine measurements and menses phases (early follicular, periovulatory and luteal) were used to derive the endocrine endpoints.	Exposure measured with VOC, e.g. toluene, xylene, ethyl benzene, ethyl acetate, acetone, isopropyl alcohol, etc. monitors in working areas, and 24 hour canister collection.	<30 years to >45 y Female

Authors and Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Findings: Mean FSH, E1C and PdG urinary concentrations were significantly higher in the module group than any other work area groups [early follicular phase]. E1C and PdG urinary concentrations in the module group were significantly higher than any other groups [periovulatory phase]. E1C concentrations in the panel group were lower but FSH concentrations in the module group were higher than other groups [luteal phase]. Compared to the work array area group, the module area group was significantly associated with i) higher levels of E1C and PdG levels (β (95% CI)): 12.55 (8.49, 16.61); 0.53 (0.29, 0.77), respectively [early follicular phase], and ii) β (95% CI): 11.93 (6.21, 17.65); 0.53 (0.29, 0.77) respectively [periovulatory phase], and ii) higher levels of E1C, PdG and FSH levels (β 95% CI): 9.29 (4.92, 13.66); 1.01 (0.42, 1.60); and 1.48 (0.81, 2.15) respectively [luteal phase]. Compared to the work in array area, the panel area work was significantly associated with higher levels of FSH; β (95% CI): 0.89 (0.07, 1.71) and lower levels of E1C -4.49 (-7.90, -1.08) [early follicular phase] and significantly lower levels of E1C -5.16 (-9.16, 0.71) [periovulatory phase]. Analyses were adjusted for age, BMI, education, smoking, alcohol, working patterns.							
Reutman et al. (2002)	Cross-sectional, Cross-sectional study. Data collected by: telephone and in person interview, self-report via diary entry, exhaled breath, and morning urine sample analysis	USA	Female United States Air Force (USAF) employees: civilian and active military female personnel at 10 USAF bases were screened for age, medication use, medical diagnoses, and surgical procedures. Non-smokers were targeted. (N=335)	Completed questionnaire and daily diaries N=170 (51%) Subgroup: Endocrine data and provided urine samples (n=100) Subgroup: Endocrine and breath analysis data (n=63 breath samples)		Reproductive endocrine endpoints predictive of non-conceptive menstrual cycles measured using urinary endocrine markers: • Preovulatory luteinizing hormone (LH) • mid-luteal phase pregnanediol 3-glucuronide (Pd3G) • mid-luteal estrone 3-glucuronide($E_1$3G) • follicle phase Pd3G. Menstrual cycles calculated from diary records. Morning urine samples were collected daily. Urinary endocrine measurements and menses dates were used to derive the endocrine endpoints.	Exhaled breath samples (N=63) analysed for internal doses of aromatic (benzene, toluene, ethyl benzene and *m, p, o*-xylene, BTEX) and aliphatic (C_6-C_{16}) hydrocarbons. Exposure characterised as low versus high exposure groups for C_6-C_{16} and BTEX based on the median. Other variables collected: included socio-demographics, BMI, alcohol, coffee, caffeine, smoking, history of illness, second-hand smoke, job strain, hours/shifts worked, reproductive and menstrual histories.	18-42 years Females
Findings: Breath levels (ppb) in exposed groups (mean±SD): toluene=1.3±2.2 [low], 9.0±12.3 [high]; ethylbenzene=1.0±0.5 [low], 3.0±6.9 [high]; *m, p*-xylene=0.8±1.2 [low], 37.3±85.6 [high]; *o*-xylene=1.0±2.0 [low], 11.3±15.0 [high]. No significant difference in endocrine levels between self-reported exposed vs non exposed participants in adjusted regression models. Multiple regression of BTEX and endocrine outcomes: β = -4.61 (p=0.10) [pre-ovulatory LH]; β = -0.10 (p=0.34) [follicular Pd3G]; β = -3.59 (p=0.08) [mid-luteal Pd3G]; β = -2.73 (p=0.32) [midluteal E13G].								

Authors and Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Total BTEX nor toluene analysed as continuous variables were not significantly associated with any of the hormone levels. Toluene exposure approached statistical significance, β = -0.19, p=0.058 with pre-ovulatory LH exposure when analysed in a model together with the aliphatic hydrocarbons (C_6-C_{16}) and age.								
Thurston et al. 2000	Retrospective cross-sectional study 1993 Data collected: Questionnaire administered to worker asked about menstrual outcomes, petrochemical exposure, working conditions.	China	Women who worked for a petrochemical company with 17 production plants and institutes	Completed questionnaire (after exclusions) N=3,343		Abnormal menstrual cycle length (AMCL): • an average menstrual cycle length >35 days or <21 days	Self-reported exposure to benzene, gasoline, toluene including number of years exposed and coded as exposed or not exposed Additional data collected on: ergonomic factors, noise levels, age, BMI, green tea consumption, contraception use, exposure to passive smoke, history of pregnancy or menstrual problems, or diseases associated with menstrual disorders	20-44 years Female
Findings: Key exposure of interest as reported was benzene. Benzene exposure for ≤ 7 years exposure OR 0.79 (95% CI 0.55-1.13); for >7 years exposure OR 1.71 (95% CI 1.27-2.31) Toluene: no exposure 325/3285 (9.9%) AMCL; 1-9 years 2/28 (7.1%) AMCL; 10+ years exposure 6/30 (20%) In separate logistic regression models in which years of exposure to a particular chemical (hydrogen sulfide, lime dust, acid, manganese, ammonia, gasoline) was substituted for years of exposure to benzene, only the odds ratio for toluene was larger than for benzene when each was put in linearly (data not included in the paper).								

Fertility

Authors and Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Garlantézec et al. (2013)	Cohort study. Data collected by: self-administered questionnaire by mail and	France	Pregnant women between 2002 and 2006 in 3 districts of Brittany;	3,421 pregnant women in PELAGIE Study		Time to pregnancy (TTP) as a measure of fertility: • TTP = time length (months) that the women required to become	Urinary measurements of exposure to glycol ethers (GEs) and their main urinary metabolites: eight alkoxycarboxylic acids [methoxyacetic acid (MAA), methoxyethoxyacetic acid (MEAA),	<25 to ≥35 y Female

Authors and Year	Study design	Country	Study pop[n] and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	urine sample (1st morning void)		recruited by gynaecologists, obstetrics, or ultrasonographers at visits for prenatal care before 19 weeks of gestation and followed through the end of pregnancy	Random subset of women with urine analysis, n=609; TTP was available for 519 of these subjects (85%)		pregnant	ethoxyacetic acid (EAA), ethoxyethoxyacetic acid (EEAA), 2-butoxyacetic acid (BAA), *n*-propoxyacetic acid (PAA), phenoxyacetic acid (PhAA), and 2-methoxypropionic acid (2-MPA)* were measured. Potential covariates included paternal occupational exposure to solvents evaluated according to job-exposure matrix. Other variables included demographics, diet, and life style, contraceptive use, reproductive history, and fertility medication *2-MPA noted to be a metabolite of minor β isomer of PGME or methoxypropanol	
Findings: Median TTP = 3 months (Quartile 1-Quartile 3, 2-7 months). Glycol ether metabolites detected in 6% (for ethoxyacetic acid) to 93% (for BAA and PhAA) and MEAA in more than 50% of women's urine. Highest median level of PhAA: 0.48 mg/L. Fecundability non significantly increased with PAA detection fecundability OR (fOR) 1.30; 95% CI 0.94-1.80. PhAA was only metabolite significantly associated with longer TTP: fOR 0.82; 95% CI 0.63-1.06 for Q2 and Q3 combined and fOR OR 0.70; 95% CI 0.52-0.95 for Q4 level concentration of PhAA (≥1.38 mg/L) vs Q1 concentration (<0.14 mg/L). A statistically significant dose response trend: Fecundability decreased with increase in PhAA level (p-trend 0.02) – for a 1 mg/L increase in PhAA = 0.95, 95% CI 0.90-1.00. EEAA detection was significantly associated with a longer TTP among primiparous women. *2-MPA was not associated with a longer TTP OR 1.10; 95% CI 0.69-1.75.								

Pregnancy outcomes

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Cordier et al. (2012)	Cohort, and nested case–control study.	France	Cohort of pregnant women	N=3,421 [cohort]	N=580 controls [nested case–	Congenital malformations: • in live births diagnosed by paediatricians;	Self-reported occupational exposure during pregnancy assessed [none, occasional, regular] from a JEM.	<20 to >35 y Female

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Data collected: Questionnaire on demographics, occupation and exposures; maternity hospital records on pregnancy outcomes [cohort] Early pregnancy maternal urinary samples for 10 metabolites of glycol ethers and chlorinated solvents		recruited at prenatal care visits (2002–2006) in three districts of Brittany (N=3399 pregnancies) 80% participation Chemical analysis of the 79 cases of nonchromosomal nongenetic cases of major malformations (97 total major malformations in cohort)	N=79 cases [nested case–control]	control]	• malformations in foetal deaths and medical pregnancy terminations diagnosed by pathology and karyotype • male genital anomalies later validated by surgery reports within 2 years of follow up	Urine analysis (nested case control) of 79 nonchromosomal, nongenetic major malformations cases for eight alkoxycarboxylic acids as main urinary metabolites of glycol ethers and trichloroethanol (TCOH) and trichloroacetic acid (TCAA) as main urinary metabolites of trichloroethylene and tetrachloroethylene. Other variables collected included socio-demographics, occupation, medical/obstetric history, dietary habits, alcohol, and tobacco use.	
Findings: Regular occupational exposure to solvents in working population 29%; the JEM classified exposed population=18% [medium-exposed], 3% [high-exposed]. Exposure to solvents during hobbies: 13% of controls ORs for oral clefts: OR = 4.3, 95% CI 1.0–18.2 [regularly exposed vs. nonregularly exposed by self-report]; OR 12, 95% CI 2.3–60 [exposed vs. nonexposed by the JEM] OR for urinary tract malformations: OR 2.2, 95% CI 0.6–7.3 [regularly exposed vs. nonregularly exposed, self-report]; and OR 3.0, 95% CI 0.9–9 [exposed vs. nonexposed, the JEM], OR for male genital malformations: OR 3.6, 95% CI 1.1–12 [regularly exposed vs. nonregularly exposed, self-report]; and OR 2.11 95% CI 0.6–7.3) [exposed vs. nonexposed, the JEM]. No association for solvent exposure during hobby activities and the risk of major malformations. Detection of TCAA, TCOH and 2-MPA in controls = 7.2 %, 5.9% and 5.2% respectively. Detection of TCAA and TCOH (≥0.01 mg/L) and 2-MPA (≥0.05mg/L) were associated with higher risk of malformations, some statistically significantly – i) TCAA (n=7 cases) OR 2.1, 95% CI 0.9-4.9) [major malformations] and (n=5 cases) OR 8.0 95% CI (2.5-25.9) [limb malformations]; ii) TCOH (n=7 cases) OR 3.3, 95% CI 1.3-8.3 [major malformations] and (n=3 cases) OR 5.8 95% CI 1.4-23.6) [limb malformations]; iii) 2-MPA (n=8 cases) OR 2.9 95% CI (1.2-6.8) (major malformations), (n=2 cases) OR 5.3 95% CI (1.0-27.2) (urinary tract malformations) Authors' conclusions: Detection of some glycol ether metabolites (of interest in this study 2-MPA) and of trichloroacetic acid and trichloroethanol in urine was associated with oral clefts and of urinary tract and limb defects. Results based on urinary biomarker are limited by small numbers but identify work situations that require further investigation.								
Desrosiers	Case-control	USA	Participants of	Employed	Employed	NTDs [anencephaly, spina	Self-reported job history coded by	<20

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
et al. (2012)	study Data collected: Birth defects surveillance programs identified cases of neural tube defects (NTDs) and orofacial clefts (OFCs)		population-based National Birth Defects Prevention Study: Mothers of the infants with NTDs OFCs delivered 1997-2002 (N=1,674 and mothers of non-malformed infants (N=5,941, employed for ≥1m from 3 m preceding estimated date of conception through date of delivery	mothers of cases of NTDs and OFCs (live births, and foetal deaths >20 w gestation and prenatally diagnosed elective terminations at most sites) n=1674 [n=511 NTDs cases, n=1,163 OFC cases]	mothers of non-malformed live birth infants [n=2,977 controls] Controls identified and randomly selected through birth certificates or hospital records	bifida and encephalocele] and OFCs [cleft lip, cleft palate and cleft palate alone] Clinical geneticists reviewed medical records to confirm case eligibility; eligible case further classified by clinicians as having one isolated major congenital anomaly, multiple major anomalies or anomalies representing a complex developmental syndrome Women with family history of NTD/OFCs and pregestational diabetes excluded from analyses	occupation and industry and assessed for exposure to 10 solvents -organic solvents (including benzene, xylene, toluene), chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, trichloroethylene, 1,1,1-trichlorothane), Stoddard solvent (mineral/white sprits) - estimated by industrial hygienist review Other variables: demographics, mother's job title, job task/duties, chemical/machine handling at work, hours/days worked per week, etc.	to ≥36 y Female
Findings: Probability of exposure for each reported job was estimated as 0 (unexposed), <10%, 10-49%, 50-89% and ≥90%. For Stoddard and aromatic solvents over 90% of exposed mothers worked in at least one job with estimated exposure probability of ≥10%, however for chlorinated solvents, this proportion was only 30%. Data not presented for other exposure probability categories in analyses. Of all women rated as exposed to any solvent during periconceptual period, nearly 85% were exposed to more than one solvent (data not shown). Prevalence of occupational exposure to any organic solvent: 8.2% (control mothers), 13.1% (NTD case mothers), 9.6% (OFC mothers). Prevalence of any solvent exposure was higher in mothers of spina bifida (14.4%) and encephalocele (16.4%) than those of anencephaly 98.4%); exposure prevalence did not differ across OFC mothers. Maternal exposure to chlorinated solvents associated with NTDs (OR 1.96, 95% CI 1.34-2.87) but not with aromatic solvents (OR 0.75, 95% CI 0.36-1.55) or Stoddard solvent (OR 0.63, 95% CI 0.33-1.23). The association was stronger for spina bifida (OR 2.26, 95% CI 1.44-3.53) and encephalocele (OR 2.22, 95% CI 0.84-5.82) than for of anencephaly (OR 1.25, 95% CI 0.58-2.71). No significant difference in effects for NTD phenotypes (p=0.36). No significant associations of any solvent class and OFC.								
Desrosiers et al. (2015)	Controls from a case-control study (multisite, population-based) used to investigate risk factors for	USA	Participating mothers of National Birth Defects Prevention Study (NPDPS),	NPDPS controls – unmatched (non-malformed, live born infants from same		SGA as a surrogate for foetal growth restriction (FGR) • SGA = birth weight < 10th centile for a given gestational age at delivery in weeks;	Self-reported job history coded by occupation and industry and assessed for exposure to 10 solvents -organic solvents (including benzene, xylene, toluene), chlorinated solvents (carbon tetrachloride, chloroform, methylene	<20 to ≥36 y Females

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	major congenital malformations and other adverse pregnancy outcomes Data collected: telephone interview		during 1997-2002. NPDPS control mothers were the subjects in this study. N=2,886 eligible mother-infant pairs	geographical/ temporal base population as cases in NPDPS). N=2,861 mother-infant pairs - of these n=230 infants were classified as SGA		Data on infants sex and gestational age obtained from birth certificate/medical record Restricted analysis of birthweight to term births	chloride, perchloroethylene, trichloroethylene, 1,1,1-trichlorothane), Stoddard solvent (mineral/white sprits) - estimated by industrial hygienist review Probability of exposure estimated mothers to be exposed to a particular solvent if any of her jobs during pregnancy or month before conception classified as exposed (exposure probability >0) and unexposed (exposure probability=0). Other variables collected: demographics, mother's employment at time of, during pregnancy and before conception, job title, job task/duties, chemical/ machine handling at work, hours/days worked, etc.	
Findings: Prevalence of occupational exposure to organic solvents: 8.4% (mothers of non-SGA infants) and 10.1% (mothers of SGA infants). Exposure prevalence (regardless of SGA categorization): chlorinated solvent(s) (7.9% of SGA infants; 7.2% of non-SGA infants), 3% or fewer women were exposed to Stoddard/aromatic solvents. The number of women with ≥50% probability of exposure were none (Stoddard solvents), six (chlorinated solvent(s), six (aromatic solvent(s). Among women with any probability of exposure during the month before conception or pregnancy, maternal exposure to any solvent(s) was not associated with SGA (OR 1.16, 95% CI 0.73-1.83). Exposure to chlorinated solvents and Stoddard solvents were not associated with SGA (OR 1.03, 95% CI 0.62-1.71; OR 0.98, 95% CI 0.44-2.18, respectively). Exposure to aromatic solvents associated with a non-significant increase in odds of SGA (OR 1.60, 95% CI 0.71-3.58), likely driven by assessed exposure to toluene and xylene. In analysis restricted to the sample of women with ≥ 50% probability of exposure, ORs = 1.71, 95% CI 0.86-3.40 [any solvents]; 1.70, 95% CI 0.69-4.01 [chlorinated solvent(s)]; 1.87, 95% CI 0.78-4.50 [aromatic solvent(s)]. This was not estimated in relation to Stoddard solvent as the number of cases was n=0. Maternal exposure to any solvent/solvent class was not associated with a meaningful effect on distribution of term birthweight. Authors' conclusions: women in the study population assessed to have a higher probability of workplace exposure to chlorinated and aromatic solvents had a small increase risk for delivery a growth restricted infant, although effect estimates were based on small numbers and imprecise (and were not statistically significant).								
Gilboa et al. (2012)	Case-control study. (The National Birth Defects Prevention Study)	USA	Mothers of infants with simple and isolated CHD cases and control infants delivered from	Mothers of infants with simple and isolated CHD; response rate 69%; cases had at least	Randomly selected mothers of infants without major birth defects from birth	CHD status –confirmed by echocardiography, cardiac catheterization, surgery, or autopsy, and diagnostic information was assessed by the experts in paediatric cardiology and clinical	Exposure assessment: • Reported job history (full/part-time) for ≥1 month from 3 months before conception through the end of pregnancy • Job coded for occupation and industry	<20 years to ≥35 y Female

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Data collected by: telephone interview, self-reported information on maternal occupational exposure to organic solvents		1997 to December 2002; worked in paid/volunteer/ military service (part/full time); living in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York and Texas (N=4,998)	one of over 30 eligible birth defects and were live born, still born, or electively terminated; cases N=2,047	certificates or hospital records; response rate 67%; control were live born infants without major birth defects; control N=2,951	genetics CHD status types: • Simple cardiac defects: hypoplastic left heart syndrome or tetralogy of Fallot • Complex cardiac defects: ventricular septal defects (VSDs) and pulmonary valve stenosis • Extracardiac defects: isolated CHD (no extracardiac defects); multiple CHD (multiple extracardiac defects)	• Two independent exposure assessment strategies: i) Consensus-based and ii) a literature-based approach for exposure assessment of: chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, 1,1,1-trichloroethane/ trichloroethylene) aromatic solvents (benzene, toluene, xylene) and Stoddard solvents Other variables including demographics, exposures (nutritional, behavioural and occupational), medication use before and during pregnancy	
Findings: The two exposure assignment approaches yielded different exposure prevalences. Expert consensus-based approach estimated nearly 4% controls and 5% cases exposed to any solvent during periconceptual period; literature-based approach estimated nearly 8% controls and 10% cases exposed to any solvent. Among controls rated as exposed (consensus-based approach) (N=110), considered exposed to only chlorinated solvents (66%), only Stoddard solvent (8%), both solvents (26%). Among controls rated as exposed (literature-based approach) (N=240), considered exposed to only chlorinated solvents (50%), only aromatic solvents (9%), only Stoddard solvent (6%). The rest, 35% (n=85) estimated exposed to ≥2 classes of solvents. Expert consensus-based approach: Any solvent and chlorinated solvents exposures were both associated with perimembranous ventricular septal defects (VSDs) (any solvents OR 1.6; 95% CI 1.0-2.6; chlorinated solvents; OR 1.7; 95% CI 1.0-2.8). Literature-based approach: Any solvent exposure with aortic stenosis OR 2.1; 95% CI 1.1-4.1; and Stoddard solvent exposure with d-transposition of the great arteries OR 2.0, 95% CI 1.0-4.2, right ventricular outflow tract (RVOT) obstruction defects OR 1.9, 95% CI 1.1-3.3 and pulmonary valve stenosis OR 2.1; 95% CI 1.1-3.8. When analysis was restricted to exposed mothers with at least one job rated as exposed with 50% or greater probability (42% cases; 33% controls), the associations were: any solvent exposure with CHD OR 1.4, 95% CI 1.0-1.9 and septal defects OR 1.5, 95% CI 1.0-2.3; and Stoddard solvent exposure with any CHD OR 2.8, 95% CI 1.3-6.2, septal defects OR 3.1, 95% CI 1.2-8.0, perimembranous VSD OR 3.7, 95% CI 1.1-12.2, and atrial septal defects OR 3.8, 95% CI 1.2-12.6. The ORs for association of Stoddard solvent exposure with RVOT obstruction defects and pulmonary valve stenosis were OR 4.6, 95% CI 1.4-15.3 and OR 4.2, 95% CI 1.1-16.2, respectively.								
Chevrier et al. (2006)	Case-control study Data collected: mothers of cases and	France	Cases and controls, recruited from seven hospitals 1998-2001.	Cases = a child diagnosed with cleft lip and/or cleft palate) n=240 [164	Controls: children with no birth defect, cancer/geneti	• Cleft lip with/without cleft palate (CL/P) • Cleft palate only	Mothers interviewed and asked to describe occupational tasks for job during first trimester. Expert chemist blinded to case-control status evaluated each	<30 to >35 y Female

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	controls were interviewed using a structured questionnaire		Cases recruited from maxillofacial surgery departments; controls recruited in the same hospital (matched with case for sex, age, mother's geographic origin and residence)	children with cleft lip with/without cleft palate (CL/P); 76 with cleft palate only (CP)	c disease but hospitalised for treatment of some other disorder, such as respiratory/ urinary) or need for minor surgery, n=236 controls		mother's exposure to 22 classes of agents, including: organic solvents (e.g. oxygenated solvents, chlorinated solvents and petroleum products, as well as lead compounds and non-ionising and ionising radiation. Other variables collected: sociodemographics, mother's medical and obstetric history, family history of oral clefts and other congenital anomalies, exposure to x rays and surgery during pregnancy, alcohol, tobacco, occupational tasks, etc.	
Findings: There were more boys in the CL/P (70%) cases, and the sex ratio was balanced in the CP group. Maternal occupational exposure to oxygenated, chlorinated, and petroleum solvents was associated with an increased risk of CL/P or CP although not all the unadjusted odds were statistically significantly increased: OR 1.76, 95% CI 1.1-2.9 (CL/P) and OR 1.42, 95% CI 0.7-2.7 (CP) [oxygenated solvents] OR 1.76, 95% CI 1.0-3.1 (CL/P) and OR 1.56, 95% CI 0.8-3.0 (CP) [aliphatic alcohols] OR 1.88, 95% CI 1.1-3.5 (CL/P) and OR 1.5, 95% 0.7-3.2 (CP) [glycol ethers] OR 1.74, 95% CI 1.0-2.9 (CL/P) and OR 1.82, 95% CI 1.0-3.5 [aliphatic aldehydes, esters, and ketones] OR 9.45, 95% CI 2.5-35.3 (CL/P) and OR 3.78, 95% CI 0.7-20.7 (CP) [chlorinated solvents] OR 3.64, 95% CI 1.5-8.8 (CL/P) and OR 1.21, 95% CI 0.3-4.9 (CP) [petroleum solvent]. No significant change in these associations after adjusting for maternal smoking status, alcohol consumption, and dietary folate intake during the first trimester. Significant increasing linear trends were observed for the association between CL/P and level of exposure to aliphatic alcohols (p trend=0.02), glycol ethers (p trend=0.009), some types of aliphatic aldehydes, ketones, or esters (p trend=0.02), and petroleum solvents (p trend=0.005). Similar but not significant trends in the CP group were observed when there were enough subjects. The risks association between the exposure to oxygenated solvents alone (N=33) (when women exposed to chlorinated or petroleum solvents excluded) and CL/P or CP remained elevated but no longer significant: OR 1.44, 95% CI 0.8-2.4 [CL/P] and OR 1.47, 95% CI 0.8-2.8 [CP]. Authors' conclusions: Results of the study suggest that maternal occupational exposure to organic solvents may be associated with the risk of CL/P and CP, however small number of subjects and multiple comparisons require that results be interpreted with caution.								
Lorente et al. (2000)	Case- referent study	Europe (France,	Mothers who worked during	Mothers of babies with oral	Mothers of healthy	Cleft lip and cleft palate, as coded locally according to the	An industrial hygienist, blinded to case-referents, estimated exposure	≤24 to ≥35 y

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Data collected by: interview questionnaire, and European congenital malformation registries used to identify cases between 1989 and 1992 Case: any product of conception with major congenital malformation diagnosed prenatally or during perinatal period (0-6 days)	Scotland, The Netherlands, and Italy)	the first trimester of pregnancy, recruited N=851	clefts, cases recruited from hospitals (France and Italy) and general populations (The Netherlands and Scotland); N=100 (63% eligible cases participated)	referent babies [the next child born without malformation (for hospital-based cases), a child born on same date and same town (for population-based cases)] N=751	British Paediatric Association Classification of Diseases	status of women (based on questionnaire data): i) route of exposure (inhalation, cutaneous, both), ii) levels of exposure (low, medium, high), iii) frequency <5%, 5-50%, >50% of worktime) iv) reliability of assessment (possible, probable or certain exposure) Other variables collected: demographics, mother's medical and obstetric history, use of medication, occupation, occupational activities, etc.	Female
Findings: Only 14% and 6% women worked in service industries and production, respectively. Service women had highest ORs for each type of cleft. Cleft palate only was associated with maternal occupation as hairdressing (OR 5.1, 95% CI 1.0-26.0) and housekeeping (OR 2.8, 95% CI 1.1-7.2). Occupational exposure to the following chemicals of relevance to this study were non significantly associated with orofacial clefts in a model: aliphatic aldehydes (OR 2.1, 95% CI 0.8-5.9) and glycol ethers (OR 1.7, 95% CI 0.9-3.3) for cleft lip with/without cleft palate; and trichloroethylene (OR 6.7, 95% CI 0.9-49.7) for cleft palate only. Toluene and mineral oil exposures were not significantly associated with oral clefts. The analyses were adjusted for centre, maternal age, mother's socio-economic status, urbanisation, and country of origin.								
Frey et al. (2015)	Prospective cohort Data collected: Questionnaire - at the time of pregnancy report, end of pregnancy, and 1 year later	Germany	Female employees (childbearing age) at a chemical company (2003-2010), N=6,332; Eligible: women with announced pregnancy with expected date	Women with pregnancy documented N=1,402 [live births, N= 1,430]		Pregnancy outcomes: (self –reported) • Pregnancy duration • Preterm birth (<37 weeks) • Miscarriages	Self –reported exposure (i.e. handling of chemical) during the 3 months before conception and during the first trimester. Other variables collected: work type, work load (physical), working hours per week, disease history, medication/supplements during pregnancy, partner's age at conception, smoking and alcohol intake, education, etc.	16-45 y Female

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
			of delivery 2003-2011 n=1342 (21%) Pregnancy documentation program (86% of those)					
Findings: No association between maternal exposure to xylene or acetone and pregnancy duration or miscarriages; β (95% CI): -0.05 (-0.79 to 0.69) [n=20, xylene and pregnancy duration]; 0.02 (-0.29 to 0.33) [n=131, acetone and pregnancy duration], and [n=11, OR 0.97, 95% CI=0.48-1.98 [acetone and preterm birth]. [n=2, OR not applicable because of limited number of cases xylene and preterm birth].								

Table 6: Evidence Profile: Guidelines/Reports - solvents

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2008)	The Netherlands	Occupational exposure to organic solvents: effects on human reproduction The peer-reviewed report was prepared for the Ministry of Social Affairs and Employment, The Netherlands, providing advice on possible effects on reproduction (i.e. effects on male and female fertility, pregnancy and development effects in offspring) and occupational exposure to organic solvents including, toluene, xylene and acetone. The development effects mainly included spontaneous abortion, birth weight, and congenital malformations. The classification for fertility and development – category 1 [known to impair human fertility (risk phrase (R) R60)/developmental toxicity (R61)], category 2 [should be regarded as if they affect human fertility (R60)/ developmental toxicity (R61)], category 3 [cause concern for human fertility (R62)/ developmental toxicity (R63)], and no classification – were done according to the European Union guidelines.	Toluene The Dutch Expert Committee on Occupational Standards (2001) recommended for toluene no classification for effects on fertility. The committee recommended toluene as a category 3 - substance causing concerns for humans in relation to possible developmental effects.[56]	Fertility: four studies were included to assess the effects of exposure to toluene on female fertility.[20, 26, 57, 58] No evidence of association between exposure to toluene: i) and effects on endocrine hormones, luteinizing hormone and follicle stimulating hormone,[20, 58] [experimental study and cross-sectional study] ii) and oligomennorrhoea[26] [cross-sectional study]. Conclusion of the committee: no indication for an association between maternal exposure to toluene and fertility effects. Developmental effects: eight studies were included to assess the effects of exposure to toluene on infant development. Spontaneous abortion: a significant association between maternal exposure to toluene and spontaneous abortion (cross-sectional study and nested case control study).[59, 60] No such significant effect was observed (except for shoe workers) [61-63] Conclusion of the committee: available evidence indicates an association between maternal exposure to toluene and spontaneous abortion. Birth weight: two studies were included to assess the effects of exposure to toluene on birth weight. No evidence for association between of exposure to toluene containing solvent and birth weight (individual compounds not assessed).[64] Significant reduced birth weight was associated with exposure to solvents [individual compounds not assessed].[65] Conclusion of the committee: there was limited human data available to assess the association between toluene and birth weight. Malformations: A single study provided no evidence for association between of exposure to toluene containing solvent and malformations.[59] Conclusion of the committee: there was limited human data available to assess this association.	Cho et al.[26]; Sallmén et al.[57]; Luderer et al.[58]; Reutman et al. [20] Taskinen et al. (a)[59]; Ng et al (a).[60] Lindbohm et al.[61] Xu et al.[62]; Taskinen et al. (b)[63] Chen et al.[64]; Ha et al.[65]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
			Xylene The Committee for Compounds Toxic to Reproduction (2001) did not classify xylene in regard to its effects on fertility. The committee recommended for xylene to be classified as a category 3 - substance.	Fertility: seven studies were included to assess the effects of exposure to xylene on female fertility.[20, 26, 57, 61, 66-68] Exposure to xylene, along with other solvents, i) was associated with oligomenorrhoea,[26] yet its relevance to female fertility is unclear; ii) was not associated with endocrine hormones, luteinizing hormone and follicle stimulating hormone [cross-sectional study].[20] No association between exposure to xylene and prolonged time to pregnancy [case-control study].[57] Conclusion of the committee: limited data available limits drawing any conclusions regarding xylene exposure and its effects on female fertility. Developmental effects: nine studies were included to assess the effects of exposure to toluene on infant development.[59, 61, 63-65, 69-72] No significant association was shown between maternal xylene exposure and spontaneous abortion [population or industry based studies].[61, 63, 71, 72] Weekly handling of xylene for 3-5 times showed increased risk of spontaneous abortion [case-control].[59] Significant association between solvent exposure and spontaneous abortion was observed.[61] Two cohort studies on women in semiconductor industry provided inconsistent findings[70, 71] – one showing higher risk of spontaneous abortion with intermediate and high exposure to xylene, and the other showing no association. Conclusion of the committee: available data suggests an association (but weak) between spontaneous abortion and exposure to xylene. Birth weight: two studies were included to assess the effects of exposure to xylene on birth weight. No evidence for association between exposure to xylene containing solvent and birth weight [individual compounds not assessed].[64] Significant reduced birth weight was associated with exposure to solvents [individual compounds not assessed].[65] Conclusion of the committee: there was limited human data available to assess this association and draw any conclusion.	Cho et al.[26]; Sallmén et al.[57]; Reutman et al.[20]; Lindbohm et al.[61]; Xiao et al.(a)[66]; Xiao et al.(b)[67]; Hanaoka et al.[68]; Taskinen et al. (a)[59]; Lindbohm et al.[61] ; Taskinen et al. (b)[63]; Chen et al.[64]; Ha et al.[65]; Taskinen et al. (c)[69]; Swan et al.[70]; Correa et al.[71]; Windham et al.[72] Chen et al.[64]; Ha et al.[65]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				Malformations: the committee concluded that no human data was available to assess this association and draw any conclusion.	
			Acetone The Committee for Compounds Toxic to Reproduction (2001) did not evaluate the association between exposure to acetone and effects on female fertility and development.	Fertility: Only one study [cohort] was included to assess the effects of exposure to acetone on female fertility among laboratory workers.[73] A significant association was observed between prolonged time to pregnancy and exposure to acetone. However, this finding is doubtful if the association was specific to exposure to acetone. Conclusion of the committee: available data are not sufficient to assess this association and draw any conclusion. Developmental effects: two studies were included to assess the effects of acetone on development.[59, 74] Both studies showed that spontaneous abortion was not associated with maternal exposure to acetone. Conclusion of the committee: available data do not suggest any association between women's exposure to acetone and developmental effects.	Wennborg et al.[73] Axelsson et al.[74]; Taskinen et al. (a)[59]
Findings: Conclusion of the committee: i) available data indicates an association between women's exposure to toluene and spontaneous abortion; insufficient evidence regarding an association between women's exposure to toluene and developmental effects or malformations; ii) available evidence supports for a weak association between women's exposure to xylene and spontaneous abortion; insufficient evidence regarding an association between women's exposure to xylene and developmental effects or malformations; iii) available evidence does not suggest any association between women's exposure to acetone and effects on female fertility and developmental effects.					
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2001)	The Netherlands	Toluene – Evaluation of the effects on reproduction, recommendation for classification. The peer-reviewed reports (for toluene and xylene) were prepared for the Ministry of Social Affairs and Employment, the Netherlands, providing with the advice regarding classifying potentially toxic effects of occupational exposures to toluene or xylene. The classification for fertility and development) – category 1 [known to impair human fertility (R60)/developmental toxicity (R61)], category 2 [should be regarded as if they affect human fertility (R60)/ developmental toxicity (R61)],	Toluene	Fertility/endocrine effects: Six studies that involved women's occupational exposure to toluene or mixture of organic solvent containing toluene were included.[57, 58, 75-78] No significant effects on luteinizing hormone,[58] or incidence of menstrual disorders[60] and exposure to toluene was found. Reduced fecundity in women with low daily toluene exposure was reported by a study;[78] while no effect on fecundity was demonstrated by another study.[57] Conclusion of the committee: available data are not sufficient to assess fertility and draw any conclusion.	Ng et al. (b)[75]; Svensson et al. (a)[76]; Svensson et al. (b)[77]; Sallmén et al.[57]; Luderer et al.[58] ; Plenge-Boenig et al.[78] Holmberg;[79] Holmberg et al.[80]; Kurppa et al.[81]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		category 3 [cause concern for human fertility (R62)/ developmental toxicity (R63)], and no classification – were done according to the European Union guidelines. Xylene – Evaluation of the effects on reproduction, recommendation for classification.		Developmental effects: Fifteen studies that involved women's occupational exposure to toluene or mixture of organic solvent containing toluene were included.[61, 63, 75, 79-89] Developmental effects evaluated included were congenital malformations, spontaneous abortions, preterm delivery, growth retardation, perinatal death, birth weight and other growth parameters (e.g. microcephaly, wide nasal bridge, blunt fingertips, etc.). Some of the studies found maternal exposure to toluene affecting infant's developmental outcomes. Conclusion of the committee: Limited human data precludes the classification of toluene for effects on fertility. Toluene was recommended to be classified as a category 3 – substance causing concern for developmental toxicity.	Toutant & Lippman[82] ; Hersch et al.[83]; Hersch[84] ; Taskinen et al. (b)[63]; McDonald et al.[85]; Goodwin et al.[86]; Lindbohm et al.[61]; Wilkins-Haug & Gabow[87]; Ng et al. (b)[75] ; Arnold et al.[88] ; Pearson et al.[89]; Taskinen et al. (a)[59]
			Xylene	Time to pregnancy: Only one study that involved women's occupational exposure to xylene or mixture of organic solvent containing xylene was included.[57] Conclusion of the committee: lack of relevant data, xylene was recommended not to be classified for effects on fertility. Developmental effects: Eight studies that involved women's occupational exposure to xylene or mixture of organic solvent containing xylene were evaluated.[59, 61, 63, 69, 72, 79-81] Of them, some found positive association while other found no association between maternal exposure to xylene/mixture of solvent containing xylene and developmental effects on infants. Conclusion of the committee: xylene was recommended to be classified as category 3 (substance causing concern for human in relation to possible developmental toxic effects).	Sallmén et al.[57] Holmberg[79]; Holmberg et al.[80] ; Kurppa et al.[81]; Taskinen et al.(b) [63]; Lindbohm et al.[61]; Taskinen et al (a).[59]; Taskinen et al.(c)[69]; Windham et al.[72]
Findings: For toluene, available data are not sufficient to assess its effects on human fertility and draw any conclusion. For developmental toxicity, the committee recommended toluene be classified as category 3 (substance causing concern for human in relation to possible developmental effects). The committee recommended toluene to be classified as a category 3 –					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
substance causing concern for developmental toxicity. For xylene, relevant human data is lacking therefore the committee recommended not to classify it for effects on fertility. For developmental toxicity, the committee recommended xylene be classified as category 3 (substance causing concern for human in relation to possible developmental effects).					
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2003)	The Netherlands	Trichloroethylene – Evaluation of the effects on reproduction, recommendation for classification. The peer-reviewed report was prepared for the Ministry of Social Affairs and Employment, the Netherlands, providing with the advice regarding classifying potentially toxic effects of occupational exposures to toluene or xylene. The classification for fertility and development) – category 1 [known to impair human fertility (R60)/developmental toxicity (R61)], category 2 [should be regarded as if they affect human fertility (R60)/ developmental toxicity (R61)], category 3 [cause concern for human fertility (R62)/ developmental toxicity (R63)], and no classification – were done according to the European Union guidelines.	Trichloroethylene	Time to pregnancy: only one study that involved maternal occupational exposure to ttrichloroethylene in a mixture of organic solvent was included.[57] Incidence density ratios (trichloroethylene exposed) = 1.21 (95% CI 0.73-2, low exposure); 0.61 (95% CI 0.28-1.33, high exposure). Conclusion of the committee: human data are scare, and trichloroethylene was not recommended to be classified in relation to effects on fertility. Developmental effects: Four studies that involved maternal occupational exposure to trichloroethylene or mixture of organic solvent containing trichloroethylene were included.[59, 61, 72, 81] Two studied that included maternal exposure to trichloroethylene via drinking water contamination were also included.[90, 91] Epidemiological studies did not find any significant association between exposure to trichloroethylene and developmental effects.[59, 61, 81] Significantly higher incidence of spontaneous abortion in trichloroethylene was reported by a study.[72] Incidence of congenital heart diseases were found to have association with maternal consumption of trichloroethylene-contaminated drinking water [exposure poorly defined].[90] Incidence of oral cleft, central nervous system and neural tube defects were also found to have association with maternal consumption of trichloroethylene-contaminated drinking water [few cases, exposure misclassification].[91] Conclusion of the committee: based on animal data, the committee recommended that trichloroethylene be classified as category 2 (substance that should be regarded as if they cause developmental toxicity in humans)	Sallmén et al.[57] Kurppa et al.[81]; Lindbohm et al.[61]; Windham et al.[72]; Taskinen et al (a).[59]; Goldberg et al.[90] ; Bove et al.[91]
Findings: For effects on fertility, trichloroethylene was not recommended to be classified in relation to effects on fertility on the basis of a lack of sufficient human data, and sufficient animal data					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
which show that no classification is indicated. For developmental toxicity, trichloroethylene should be classified as category 2 (substance that should be regarded as if they cause developmental toxicity in humans)					
Agency for Toxic Substances and Disease Registry (ATSDR) (2015)	USA	Draft Toxicological Profile for Toluene The profile was prepared in accordance with guidelines developed by ATSDR and the US Environmental Protection Agency (EPA) and in support of Department of Defense needs. An ASTDR toxicological profile characterises the toxicological and adverse health effects information for the toxic substances of the profile. The profile identifies and reviews the key literature (that has been peer reviewed) of substances' toxicological properties and the pertinent literature is presented but described in less detail than key studies. The focus of the profiles is on health and toxicological information. The health effects section and human studies findings were considered in relation to this Evidence Profile.	Toluene	Reproductive effects: Current evidence is not adequate to suggest that acute or repeated inhalation exposure to toluene may have reproductive effects in humans. Nevertheless, the profile reported that limited evidence exists to indicate that maternal occupational exposure to toluene may result in an increased incidence of spontaneous abortion or decreased fecundity in females. Numerous studies evaluating blood levels of reproductive hormones in repeatedly exposed populations have not provided consistent and strong evidence for exposure related health effects. Developmental effects: several studies reported birth defects in children born following maternal exposure to inhaled toluene during pregnancy. The evidence suggested that high level of toluene exposure can be toxic to the developing foetus. Further, a lower level of occupational exposure to toluene may also increase risk for central nervous system anomalies and neural tube closure defects.	
Findings: This profile reported that there was inadequate data to suggest that acute or repeated exposure to toluene may have reproductive effects in humans; also, limited evidence indicates maternal occupational exposure to toluene is associated with an increased incidence of spontaneous abortion or decreased fecundity in females. It highlighted that that high levels of toluene exposure can be toxic to the developing foetus; one study reported that a lower level of occupational exposure to toluene may also increase risk for central nervous system anomalies and neural tube closure defects. A final report of this draft publication could not be identified.					
Agency for Toxic Substances and Disease Registry (ATSDR) (2007)	USA	Toxicological Profile for Xylene An ASTDR toxicological profile characterises the toxicological and adverse health effects information for the toxic substances of the profile. The profile identifies and reviews the key literature (that has been peer reviewed) of substances' toxicological properties and the pertinent literature is presented but described in less detail than key studies. The focus of the profiles is on health and toxicological information. The health effects section and human studies	Xylene	Reproductive effects: a few epidemiological studies reported significant increase in odds of spontaneous abortions or prevalence of oligomennorhea among the females exposed to xylene (together with other organic solvents). No studies were found that examined reproductive effects in humans due to oral exposure to mixed xylene or individual isomers. Developmental effects: limited data suggested a possible association between solvent exposure (unspecified) and developmental toxicity. Available	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		findings were considered in relation to this Evidence Profile.		studies involved simultaneous occupational exposure to other solvents, including xylene, and involved a small number of human subjects (N=9-61 subjects). No studies were located that examined developmental effects in humans due to oral exposure to mixed xylene or individual isomers. No studies were located that examined developmental effects in humans due to dermal exposure to mixed xylene or individual isomers. However, occupational dermal exposure to xylene was likely as reported by a few studies.	
Findings: Although human data indicated a possible relationship between maternal exposure to solvent (unspecified) exposure) and adverse developmental effects, the data was considered limited for assessing the relationship between occupational exposure to xylene and developmental effects, as available studies involved concurrent exposure to other solvents in addition to xylene. Available studies of developmental or reproductive toxicity from occupational exposure to xylenes were not definitive because of the small number of subjects and/or concurrent exposure to other chemicals. Very little information was found to be available on the chronic health effects, including reproductive health effects, of xylene exposure in humans.					
Agency for Toxic Substances and Disease Registry (ATSDR) (2014)	USA	Draft Toxicological Profile for Trichloroethylene An ASTDR toxicological profile succinctly characterises the toxicological and adverse health effects information for the toxic substances of the profile. The profile identifies and reviews the key literature (that has been peer reviewed) of substances' toxicological properties and the pertinent literature is presented but described in less detail than key studies. The focus of the profiles is on health and toxicological information. The health effects section and human studies findings were considered in relation to this Evidence Profile.	Trichloroethylene	Reproductive effects: occupational exposure to unspecified level of trichloroethylene (with concomitant exposure to other chemicals) and increase in miscarriage in nurses has been reported.[92] Inconsistent findings have been reported regarding maternal exposure to trichloroethylene and spontaneous abortions. One study showed a higher rates of spontaneous abortions were observed amongst trichloroethylene and other solvents exposed (occupational and non-occupational) women[72]; while other showed no significant effects.[61] Overall, these studies indicate a potential association between exposure to organic solvent (including trichloroethylene) and reduced fertility, menstrual cycle disturbances or amenorrhoea.[57] No significant association was observed between the exposure and time to pregnancy. Developmental effects: Inconsistent findings have also been reported regarding maternal exposure to trichloroethylene and malformations in babies. No increase in malformations in babies was reported	Corbett et al. 1974[92]; Windham et al.[72]; Sallmén et al.[57] ; Lindbohm et al.[61] Tola et al.[93]; Yauck et al.[94] ; Forand et al.[52]; Bove et al.[91] ;

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				in mothers occupationally exposed to unspecified level of trichloroethylene.[93] No significant risk of congenital heart defects (CHDs) born to mothers aged <38 years exposed to trichloroethylene, compared to unexposed ones. The risk increased with increasing mothers' age (≥ 38 years), OR 6.2, 95% CI 2.6-14.5; suggesting maternal age at delivery may influence risk of CHDs in babies born to trichloroethylene exposed women.[94] Adjusted rate ratios for low birth weight (rate ratio 1.36, 95% CI 1.07-1.73), small for gestational age (rate ratio 1.23, 95% CI 1.03-1.48), term low birth weight (rate ratio 1.68, 95% CI 1.2-2.34), cardiac defects (rate ratio 2.15, 95% CI 1.27-3.62) and conotruncal defects (rate ratio 4.91, 95% CI 1.58-15.24) were higher amongst babies born to women exposed to trichloroethylene and tetrachloroethylene in indoor air contamination.[52] An association between trichloroethylene levels (contaminated drinking water) and oral clefts, central nervous system defects, neural tube defects, major cardiac defects[91] or chromosomal anomalies. An association was also found between elevated level of trichloroethylene in drinking water and CHD (amongst the child born to exposed mothers) before conception/1st trimester.[90] No significant association was reported between trichloroethylene in drinking water and birth weight.[95] No elevated adverse pregnancy outcomes (including congenital defects) were noted amongst to trichloroethylene and other solvents in drinking water exposed populations.[96] No studies were located in relation to reproductive or developmental effects in humans due to dermal exposure to trichloroethylene.	Goldberg et al.[90] ; Rodenbeck et al[95]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Findings: Summary of health effects: the male reproductive system and developing foetus were two of the identified potential targets of trichloroethylene toxicity. Limitations of assessment of the epidemiological evidence in humans of relationship between occupational exposure to trichloroethylene and adverse developmental effects included potential concurrent exposures to other chemicals (unspecified). Case-control studies involved rather small number of cases. Some epidemiological studies related to maternal exposure to trichloroethylene (via environmental sources such as drinking water in which exposure to other potential contaminants was a recognised limitation in exposure assessment. No final report of this draft publication was identified.					
National Research Council; Division on Earth and Life Studies; Board on Environmental Studies and Toxicology; Committee on Human Health Risks of Trichloroethylene (2006)	USA	Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues. The National Research Council, the research arm of the National Academy of Sciences, Engineering and Medicine, produces reports that influence policies, inform public opinion, and advance the knowledge of science, engineering and medicine.	Trichloroethylene	A number of human studies, mainly community-based[91, 94, 95, 97-101] were included to discuss reproductive and developmental effects of trichloroethylene. Some of these studies found significant association between exposure to trichloroethylene and adverse reproductive and developmental effects, while others did not. The report noted that some of these studies had limitations mainly related to ascertainment of exposure and/or outcome and small sample size. The committee suggested that for developmental effects, there is substantial evidence that trichloroethylene in drinking water might cause impaired intrauterine growth at environmentally relevant levels. Furthermore, the committee also identified that impaired intrauterine growth and cardiac teratogenesis have greatest level of plausibility (based on human and animal evidence) to be affected by trichloroethylene exposure.	Lagakos et al.[97]; Yauck et al.[94]; Sonnenfeld et al.[98]; Deane et al.[99]; Wrensch et al.[100]; Swan et al.[101]; Bove et al.[91]; Rodenbeck et al.[95]
Findings: The Committee identified those end points for which animal and human evidence generated the greatest level of plausibility; these end points included impaired intrauterine growth, cardiac teratogenesis, and altered spermatogenesis. The Committee considered that although the evidence suggested that trichloroethylene can generate such effects the lowest-observed-adverse-effect level of human risk assessment remains unclear. The combined human and animal evidence generated to date does not reach levels of reasonable plausibility to indicate that other reproductive or development mental end points do have an association with trichloroethylene.					
U.S. Environmental Protection Agency (EPA), National Center for Environmental Assessment	USA	Toxicological Review of Trichloroethylene The report provides scientific support and rationale for the hazard and dose-response assessment in relation to chronic exposure to trichloroethylene. In relation to human studies (occupational and community-based), the report	Trichloroethylene (TCE)	Fertility effects: three studies were included and discussed in the reported in relation to female infertility effects due to occupational/community exposure to TCE.[57, 61, 102] In relation to menstrual cycle disturbance, four studies/reports were included and discussed.[102-105]	Sallmén et al.[57]; Lindbohm et al.[61] ; ATSDR[102] ; Zielinski[103] ; Bardodej & Vyskocil[104]; Sagawa et al.[105]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
(2011)		reviewed both male and female reproductive effects, and prenatal developmental outcomes.		Developmental effects: three occupational,[59, 61, 72] eleven community-based studies/reports[90, 91, 95, 97, 102, 106-112] were included and discussed in the report. These studies/reports evaluated prenatal/postnatal developmental outcomes in infants such as spontaneous abortion, perinatal death, decreased birth weight, small for gestational age (SGA), postnatal growth, congenital malformations (e.g. cleft lip or cleft palate), and developmental neurotoxicity and immunotoxicity associated with the maternal exposure to TCE.	Taskinen et al.[59]; Lindbohm et al.[61] ; Windham et al.[72] ; Lagakos et al.[97] ; ATSDR[102]; Goldberg et al.[90] ; Bove et al.[91] ; Bove[106] ; ATSDR (a)[107] ; ATSDR (b)[108] ; Rodenbeck et al.[95]; ATSDR[109] ; ATSDR[110] ; ATSDR[111] ; U.S.GAO[112]
Findings: Available studies show that maternal exposure to trichloroethylene can result in negative reproductive outcomes such as reduced fertility, as measured by time to pregnancy incidence of fecundability (measured by time to pregnancy), amenorrhea, menstrual cycle disturbances and abnormal cycle length. An evaluation of the human studies, taking the overall weight and strength of the evidence into account, indicate that there is a potential for adverse developmental outcomes associated with pre- and/or postnatal trichloroethylene exposures. Chiu et al.[39] summarized the main findings and scientific issues in relation to the human health effects of trichloroethylene (including developmental cardiac toxicity) in the US EPA's toxicological review. The review reports that cardiac defects have been associated with exposure to trichloroethylene. In addition, other developmental outcomes, including embryonic/foetal mortality, prenatal growth inhibition were also found to be associated with trichloroethylene exposure. The report further states that interpretation of human epidemiological data on ECE exposure has been controversial, as many of them were limited by small number of cases, and methodological limitations. Nevertheless, the data provide a range of trichloroethylene-related cardiac defects, but lack adequate statistical power to identify any particular type of defect that may be more susceptible to trichloroethylene exposure. The report, citing National Research Council (2006) report, noted that elevation of cardiac malformations with similar relative effect size of 2-3-fold (with some significant findings) was associated with the exposure to TCE. Overall, this review (Chiu et al) summarises that that exposure to TCE: i) has strong evidence for male reproductive toxicity, ii) suggestive evidence for female reproductive toxicity, iii) strong evidence (based on - weakly suggestive epidemiological studies) for foetal cardiac malformations. These findings are consistent to those discussed in the EPA report. Makris et al.[38] published a review evaluating potential effects of trichloroethylene and/or its oxidative metabolites (dichloroacetic acid and dichloroacetic acid) on cardiac development. This study also evaluated two additional epidemiological studies (Fornad et al.;[52] Ruckart et al.[53]) that were not included in the EPA's 2011 report, and concluded that epidemiological studies demonstrate some support for the possible relationship between maternal exposure to trichloroethylene and cardiac birth defects. This conclusion is consistent to those discussed in the EPA report.					
World Health Organization - International Agency for	France	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 77 Some industrial chemicals – Ethylbenzene	Ethylbenzene	Reproductive and developmental effects: No studies were reported to be available to the working group in relation to reproductive or	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Research on Cancer (IARC) (2000)		The IARC evaluates human carcinogenic risks associated with exposures to chemical, biological and physical agents. Whilst the focus is on an evaluation of carcinogenic risks and studies of cancer in humans, other studies relevant to an evaluation of carcinogenicity and its mechanisms are considered. The monograph critically reviewed data on carcinogenicity for ethylbenzene exposure, and represents expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans.		developmental effects of ethylbenzene	
Findings: The report discussed sources of human (occupational and non-occupational) exposure to ethylbenzene. However, the working group concluded that no studies were found in relation to human reproductive or developmental effects of ethylbenzene.					
Agency for Toxic Substances and Disease Registry (ATSDR) (1994)	USA	Toxicological Profile for Acetone An ASTDR toxicological profile succinctly characterises the toxicological and adverse health effects information for the toxic substances of the profile. The profile identifies and reviews the key literature (that has been peer reviewed) of substances' toxicological properties and the pertinent literature is presented but described in less detail than key studies. The focus of the profiles is on health and toxicological information. The health effects section and human studies findings were considered in relation to this Evidence Profile.	Acetone Inhalation	Reproductive effects: data are limited in relation to inhalation exposure to acetone and reproductive effects -only three studies/reports were included and discussed.[74, 113, 114] Acetone inhalations could possibly have effect on shortening of the menstrual cycle. No statistically significant difference in reproductive effects was observed in women exposure to solvents (including acetone), compared to non-exposed. Developmental effects: data are limited in relation to inhalation exposure to acetone and developmental effects - only two studies/reports were included and discussed.[114, 115] No statistically significant differences in the incidences of miscarriage, prenatal death arte, or malformations were observed in women exposure to solvents (including acetone), compared to non-exposed.	Stewart et al.[113]; Nizyaeva[114]; Axelsson et al.[74]
			Oral exposure	No studies were found regarding reproductive and developmental effects in humans following oral exposure to acetone.	Nizyaeva[114]; Axelsson et al.[74]
			Dermal exposure	No studies were located regarding reproductive and developmental effects in humans following dermal or oral exposure to acetone.	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Findings: The relevance of the reproductive and developmental effects to humans in relation to exposure to acetone is unknown, and there is insufficient data to sufficiently examine these end points in humans.					
Agency for Toxic Substances and Disease Registry (ATSDR) (1992)	USA	Toxicological Profile for 2-Butanone [methyl ethyl ketone (MEK)] An ASTDR toxicological profile succinctly characterises the toxicological and adverse health effects information for the toxic substances of the profile. The profile identifies and reviews the key literature (that has been peer reviewed) of substances' toxicological properties and the pertinent literature is presented. The focus of the profiles is on health and toxicological information. The health effects section and human studies findings were considered in relation to this Evidence Profile.	Inhalation Oral exposure Dermal exposure	No studies were located regarding reproductive or developmental effects in humans following inhalation, oral or dermal exposure to 2-Butanone [i.e. methyl ethyl ketone (MEK)].	
Findings: No concluding remarks in relation to reproductive or developmental effects were located in the report.					
Institute of Medicine of the National Academies (2003)	USA	Gulf War and Health: Vol 2 Insecticides and solvents 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. The focus of this volume was on long term adverse health outcomes of exposures during Gulf War, and included review of the literature in relation to reproductive and developmental effects of exposure to solvents and mixture of solvents were considered.	Organic solvents. Studies considered specific solvents and mixtures of solvents.	Reproductive and developmental outcomes of interest included those related to preconception (sperm morphology, hormonal changes, infertility), during pregnancy (foetal loss) or as congenital malformations.	
Findings: The committee concluded from its assessment of the epidemiological literature, that there was inadequate/insufficient evidence to determine whether an association exists between exposure to specific solvents under review or solvent mixtures and male or female infertility after cessation of exposure. The committee concluded from its assessment of the epidemiological literature, that there was inadequate/insufficient evidence to determine whether an association exists between					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
maternal or paternal preconception exposure to specific solvents under review or solvent mixtures and spontaneous abortions or other adverse pregnancy outcomes. The committee concluded from its assessment of the epidemiological literature, that there was inadequate/insufficient evidence to determine whether an association exists between maternal or paternal preconception exposure to specific solvents under review or solvent mixtures and congenital malformations.					

Table 7: Studies mentioning organic solvents

Studies that assessed or analysed general organic solvent exposure

Reference	Type of study	Population	Exposure	End point investigated
Ahmed & Jaakkola 2007 [116]	Cohort	Children from 2 hospitals	Solvent exposure at work before and during pregnancy	Low birth weight, small for gestational age, preterm delivery
Birks et al 2016 [117]	Cohort	13 European cohorts meta-analysis	Organic solvents based on job title	Birth weight, term low birth weight, length of gestation, preterm delivery
Brender et al 2002 [118]	Case-control	Mexican American mothers and fathers	Self-reported solvents, glycol ethers	Neural tube defects
Garlantézec et al 2009 [119]	Population-based cohort	Pregnant women from 3 districts in Brittany, France	Self-reported and job exposure matrix (JEM) assessed solvents	Congenital malformations
Kuehl & Loffredo 2006 [120]	Case-control cohort	Maryland and DC	Mothers' self-reported miscellaneous solvent exposure	Hypoplastic left heart malformation
Qin et al 2017 [121]	Exposed and unexposed mother/infant pairs	Mothers from Chinese Petrochemical Company	Organic solvents	Maternal/infant gene polymorphisms and gestational age
Sallmén et al 2006 [122]	Cross-sectional	Families of male pesticide applicators	Self-reported painting, gasoline, other solvents	Subfertility
Sallmén et al 2008 [123]	Cohort	Shoe manufacturing workers	Measured workplace data on organic solvent exposure	Fertility including time to pregnancy
Testud et al. 2010 [124]	Prospective follow up study of cases and controls	Requests for risk assessment to Lyon Poison Centre	Occupational exposure to organic solvents	Pregnancy outcome, variety
Till et al 2001 [125]	Cohort	Mothers who contacted Motherrisk Program	Organic solvents including aromatic, aliphatic, halogenated, alcohols, ketones, PaHs, glycols, and ethers	Offspring visual functioning
Wennborg et al 2001 [73]	Retrospective cross-sectional questionnaire	Female biomedical laboratory work vs non-lab workers	Self-reported solvents in general, acetone, benzene, chloroform, diethyl ether	Time to pregnancy
Wennborg et al 2005 [126]	Retrospective cross-sectional questionnaire	Female biomedical laboratory work vs non-lab workers	Self-reported solvents in general, benzene	Congenital malformations
Zhu et al 2006 [127]	Cohort	Female laboratory technicians	Organic solvents from JEM	Pregnancy outcomes (preterm birth, small for gestational age, "major" malformations)

Appendix 4

Table 8: Selection of papers and guidelines/reports which had a full title screen – jet fuels

Authors & Year	Title	Comments	Include	Reason for exclusion
Balise et al 2016	Systematic review of the association between oil and natural gas extraction processes and human reproduction.	Systematic literature review of oil and gas extraction. Rated reproductive endpoints. Occupational and residential exposures. Male and female endpoints. (similar petroleum industry) However is not specific to MATF fuels.	No	Not MATF
Berg, JS 2000	Early menopause presenting with mood symptoms in a student aviator.	Case study of one individual with early menopause. Discussed the psychiatric history of the student pilot. There was a diagnosis of premature ovarian failure, however there was no history of exposure to toxins or fuel leaks during flight training. No MATF Exposure.	No	No exposure
Buonanno et al 2012	Occupational exposure to airborne particles and other pollutants in an aviation base.	Article reviewed occupational exposure to airborne particulates in a jet engine airport. Utilized environmental monitoring to report occupational exposures. Measured particulates PM2.5 and reviewed PAHs. Had monitoring data at 2 receptor sites and personnel monitoring data. No association with reproductive health outcomes.	No	No reproductive outcomes
Cavallo, D 2009	Occupational exposure in airport personnel: Health risks	Chapter 5 of this book titled Airports: Performance, Risk and Problems are a review article. Discussion of occupational exposures to airport personnel. Discussed exposures of chemical pollutants (air pollutants from fuel combustion) and physical agents (noise, cosmic radiation). Reproductive disorders associated with heavy metals only. Tabulated studies of fuels, civilian fuels Jet A, and PAHs had no observed female reproductive effects. One study was cited regarding male reproductive effects of fuel exhaust and solvents (Lemasters et al 1999). Talks about genotoxicity (SCE). No female reproductive health outcomes relating to MATF fuels.	No	Male study
Chevrier, C 2006	Occupational exposure to organic solvent mixtures during pregnancy and the risk of non-syndromic oral clefts	Maternal exposures to solvents & petroleum. Maternal occupations were mostly to solvent exposures. No military fuels. Use for solvents and references for paternal exposures	No	Solvent and male study
Dalbey et al 2014	Subchronic and developmental toxicity of aromatic extracts	Animal study on developmental toxicity for aromatic distillates. Has NOELs on paraffins.	No	Animal study

Authors & Year	Title	Comments	Include	Reason for exclusion
DelRaso, NJ 2015	Air Force Research Laboratory Integrated Omics Research	Has identified biomarkers of toxicity as a preclinical indicator. Identified Jet fuel exposures. No reproductive outcomes discussed.	No	No reproductive outcomes
Edwards et al 2005	The metabolism of nonane, a JP-8 jet fuel component, by human liver microsomes, P450 isoforms and alcohol dehydrogenase and inhibition of human P450 isoforms by JP-8.	Discussion on the metabolite "2-nonanol" of JP-8 and its effects on hormones testosterone and estradiol, uses human liver microsomes and P450 Isosomes and mechanism. An animal study	No	Animal study
Espinoza, LA 2003	Macroarray analysis of the effects of JP-8 jet fuel on gene expression in Jurkat cells	Mechanisms of cytotoxicity due to JP-8. No reproductive outcomes.	No	No reproductive outcomes
Figà-Talamanca et al 2006	Occupational risk factors and reproductive health of women	Non-systematic review article- Occupational exposures of petrochemicals and solvents. Literature review (15 years) has additional references. Authors cite 2 studies with spontaneous abortion and reduce birth weights following exposures to petrochemicals. Follow up cited references Xu et al and Ha et al. (Petrochemical references & useful for solvents)	No	Review article
Fowles et al 2016	Assessment of petroleum streams for thyroid toxicity	Reviewed toxicological data on chemically complex petroleum streams and effects on the thyroid gland (Thyroid affects reproductive hormones). Naphthenic solvents also utilized animal studies and states they found no human data. JP-8 and kerosene referred to animal data.	No	Animal study
Gordley et al 2000	Menstrual disorders and occupational, stress, and racial factors among military personnel	Study of menstrual abnormalities as part of a wider study of hormonal effects in USAF female personnel	Yes	
Gregg et al 2006	A review of analytical methods for the identification and quantification of hydrocarbons found in jet propellant 8 and related petroleum based fuels	History of all the fuels JP-1 through to JP-8. Reviewed sampling techniques and analytical methods. Brief discussions of health effects, no reproductive health outcomes	No	No reproductive outcomes
Henley, M 2014	Health assessment of gasoline and fuel oxygenate vapors: Generation and characterization of test materials	Study on gasoline and gasoline containing fuel oxygenates. Not specific to Jet fuels.	No	No MATFs
Hood E 2002	Reproduction disruption: Hydrocarbons may affect menstrual cycle. (Science Selections)	Summary article of the Reutman et al study which discussed potential reproductive effects. Refer directly to Reutman article.	No	Review article
Hood, DB 2009	Polycyclic aromatic hydrocarbons: Exposure from emission products and from terrorist attacks on US targets -	Chapter in Book reports PAHs released from the World Trade Centre attack. Review of combustion of jet fuel due to impact. Epidemiological study, reported different cohorts that	No	Environmental exposure

Authors & Year	Title	Comments	Include	Reason for exclusion
	implications for developmental central nervous system toxicity	have been impacted by 911. Main cohort was pregnant woman and birth outcomes. Prenatal exposure to PAHs, dust etc. Reported air particulates and other environmental exposure emissions from the terrorist attack.		
Hourani, L 2000	Occupational and environmental exposure correlates of adverse live-birth outcomes among 1032 US Navy women	1000 US navy personnel self-report adverse live birth outcomes. Survey requested maternal and paternal data. Reported exposures to petroleum products (jet fuels and diesel fuel) and solvents and other occupational exposures. Looked at information from women with a pregnancy in 1993.	Yes	
Jackman et al 2002	DNA damage assessment by comet assay of human lymphocytes exposed to jet propulsion fuels	DNA damage using comet assay looking at human lymphocytes and jet fuels. Not specific to reproductive outcomes.	No	No reproductive outcomes
Johanson, G 2000	Toxicity review of ethylene glycol monomethyl ether and its acetate ester	Review on the toxicity of EGME, the anti-icing agent in Jet fuel JP-8. Male effects, female effects and teratogenicity discussed. Not looking at breaking down the fuels at this stage to individual constituents	No	Outside scope: Individual constituent of the fuel
Kerr, MA 2000	Parental occupational exposures and risk of neuroblastoma: A case-control study (United States)	Parental exposures and neuroblastomas in children. Chemical exposures in benzene, petroleum solvents and xylene. Study population 1976-1987 in New York. Childhood outcomes (ie cancers) are outside the scope of this study.	No	Outside scope
Kim et al 2006	A dermatotoxicokinetic model of human exposures to jet fuel	Toxicokinetic model following dermal exposure to JP-8, looks at systemic circulation. Simulations conducted on blood naphthalene levels and dermal exposure to JP-8. No data on reproductive end points	No	No reproductive outcomes
Lawson et al 2003	An occupational reproductive research agenda for the third millennium. (Workgroup Report)	Discussion Paper: The objectives of the article were to recommend future directions in occupational reproductive health research. Identified that 4000 chemicals have been evaluated in model species for reproductive toxicity potential by the US EPA, and discussed the mammoth task of reviewing the remaining 80,000 chemicals in commerce. Discussed different human biomarkers and other genetically engineered cells and assays to be able to quickly screen these chemicals for endocrine disruption. No fuels or solvents of interest are in the tabulated list of known human developmental toxicants or human adult reproductive toxicants. Has cited Reutman 2002 using menstrual function studies with jet fuel exposures and Gold et al 1995 in the semiconductor industry. Useful ref NIOSH, US EPA and NIEHS	No	Review article

Authors & Year	Title	Comments	Include	Reason for exclusion
Lei et al 2015	Overview of emerging contaminants and associated human health effects	Review Paper on contaminant products like perfluorinated compounds, water disinfection products and gasoline additives. Reported cancer and reproductive risks. Gasoline additives reviewed benzene, 1,3 butadiene and methyl tert butyl ether(MTBE). Genotoxicity mentioned. Inhalational exposures and animal study with testicular cancer the endpoint for MTBE. Not relevant to military fuels or solvents.	No	No MATFs
MacDonald et al 2010	Occupational health and safety assessment of exposure to jet fuel combustion products in air medical transport	Reviews occupational exposures. Measured/ analysed exposures to jet fuels and the combustion products. Air monitoring and sampling conducted. No mention of reproductive endpoints	No	No reproductive outcomes
Maiyoh et al 2015	Effects and mechanisms of kerosene use-related toxicity	Review paper of kerosene. Occupational and Residential exposures. Neurotoxicity discussed. Animal studies suggest endocrine effects. review some references: Chilcott 2006 (based on animal studies), Koschier 1999(middle distillates) and Bunin et al 1994 (Children cancer group)	No	Review article
Mattie et al 2011	Past, present and emerging toxicity issues for jet fuel	Discussions of JP4, skin irritation, neurotoxicity and nephrotoxicity. Rats study renal carcinogenicity. Discussion of JP-8 animal studies. The developmental and reproductive section also refers to animal studies. Had references for animal studies.	No	Animal study
McDougal & Rogers 2004	Local and systemic toxicity of JP-8 from cutaneous exposures	Discussed JP-8 and toxicity to skin. Author made reference to one study (LeMasters 1999) regarding sperm quality in men. Other animal studies. References: ATSDR (1998), NRC Tox Ass of Jet Fuel Vol 8 (Subcommittee on JP-8 Committee on Toxicology) (2003)	No	Review article
McKee et al 2014	The toxicological effects of heavy fuel oil category substances	Heavy fuel oils, animal studies: Development toxicology studies via derma route	No	No reproductive outcomes
McKee et al 2014	Characterization of the noncancerous hazards of gas oils	Gas oils, not fuels	No	No MATFs
McKinney, PA 2008	The UK Childhood Cancer Study: Maternal occupational exposures and childhood leukaemia and lymphoma	Article discussed occupational maternal exposures and childhood leukemias. Childhood outcomes (i.e. cancers) are outside the scope of this study.	No	Outside scope
Ortega-García, JA 2012	Congenital fibrosarcoma and history of prenatal exposure to petroleum derivatives	4 cases of congenital fibrosarcoma, mothers worked in a gas station during pregnancy. Exposures are petroleum derivatives for gas station. Childhood outcomes (i.e. cancers) are outside the scope of this study.	No	Outside scope

Authors & Year	Title	Comments	Include	Reason for exclusion
Patterson et al 2013	Peer consultation on relationship between PAC profile and toxicity of petroleum substances	Consultation of peer specialists and discussion on PACs and development/ reproductive toxicity from repeat dose dermal toxicity studies	No	Review article
Pleil et al 2000	Personal exposure to JP-8 jet fuel vapours and exhaust at air force bases	The article reviewed personal exposures and measurements via sampling techniques. No association of Reproductive outcomes.	No	No reproductive outcomes
Reutman SR 2002	Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures	Low dose exposure & potential reproductive endocrine effects JP 8 & solvents Study female US personnel Effects on menstrual cycle function specific endocrine end points	Yes	
Ritchie GD 2003	Biological and health effects of exposure to kerosene-based jet fuels and performance additives	Performed risk assessment on fuels & their additives. Authors discuss 2 published studies: male sperm parameters (LeMasters1999) and developmental study of childhood tumours (Bunin1994). The 2 articles have been discussed elsewhere. There are animal studies on reproductive and developmental toxicology.	No	Risk assessment use for solvent assessment
Thurston et al 2000	Petrochemical exposure and menstrual disturbances	Looked at short menstrual cycles and occupational exposure to solvents and to petrochemicals, Population is female workers in a large petrochemical plant in China. Retrospective study with a questionnaire of menstrual disturbances in 1993. Use for Solvent Toluene	No	Use for solvents
Van DP 2010	A literature review of air medical work hazards and pregnancy	Literature review investigated pregnancy risks, exposure to vibration, noise altitude fatigue and jet fuel. Uses Material Safety Data Sheets (MSDS) in regards to benzene, toluene and xylene, animal studies. Mentions one study of US air force personnel exposed to JP-8 and Jet A. (Reutman et al 2002). Animal Studies and NOELs(rats)	No	Review article
Vulimiri 2011	Reproductive and developmental toxicology: Toxic solvents and gases	Literature Review: Solvents, kerosene and jet fuels. The target organs are lungs and skin. Study on sperm parameters and JP 4 & 8 (LeMasters1999) and intrauterine exposures and risk of brain tumours (Bunin et al 1994).ATSDR 1995 has no reproductive effects in humans for fuels JP-4 & JP-7. Authors comment on limited assessments of reproductive & developmental toxicity risk to humans. Has references to animal studies (1991, 93 & 97) and solvents	No	Review article
Weinhold B 2012	More chemicals show epigenetic effects across generations	Animal study - Rat study using 3 generations	No	Animal study

Authors & Year	Title	Comments	Include	Reason for exclusion
Yang Y 2013	An epidemiological study of reproductive health in female civil aviation employees	Epidemiological study of reproductive health effects. Looks at Flight attendants in China. Questionnaire, not specific to fuel/solvents exposure	No	No MATFs
Grey literature or additional records				
Araneta et al 2004	Conception and Pregnancy during the Persian Gulf War: The risk to Women veterans.	Epidemiological study compares Gulf War exposed pregnancies with non deployed veterans. Discusses briefly exposure from possible reproductive toxicants from oil fires, pesticides and decontaminating agent used in the Gulf war. Oil well fires and smoke from the fires would be environmental exposures. Oil fires and soil samples contained arsenic, benzene, BaP, toluene, xylene and other reproductive toxicants. Not specific to Military fuels	No	Environmental exposures
ATSDR 1995	Toxicological Profile for Jet Fuels JP-4 and JP-7	US Public Health government document that reviewed exposures based on inhalational, oral and dermal exposures of jet fuels JP-4 and JP-7.	Yes	
ATSDR 2017	Toxicological Profile for JP-5 JP-8 and Jet A fuels	US Public Health government document that reviewed exposures based on inhalational, oral and dermal exposures of jet fuels JP-5, JP-8 and Jet A. Reproductive section refers to the Reutman study (2002). No studies reported for the oral and dermal exposure route.	Yes	
Axelsson G & Rylander R (1989)	Outcome of pregnancy in women engaged in laboratory work at a petrochemical plant	The study was on women working in a laboratory at a Swedish petrochemical plant. The reproductive health outcome of concern was miscarriage. Chemical substances used at this laboratory were phosphates, perborates and some aromatic solvents, carbon tetrachloride and radioactive isotopes. Not specific to MATF fuels or solvents or interest.	No	No MATF exposures
Bowling FG 2014	Report on the general molecular investigations into the jet fuel and solvent exposure in the DeSeal/ReSeal programme	Report reviewed cellular toxicity of the fuel and solvents and used a biological approach. Contains male erectile dysfunction	No	Male study
Bunin et al 1994	Risk factors for astrocytic glioma and primitive neuroectodermal tumour of the brain in young children	Study looks at gestational risk factors and the possibilities of childhood brain tumours. Maternal exposures to Nitroso compounds and Kerosene in the home environment. Increased risk for astrocytoma and the use of kerosene.	No	No occ exposure

Authors & Year	Title	Comments	Include	Reason for exclusion
IOM Committee on Gulf War and Health (2005)	Gulf War and Health: Volume 3. Fuels, Combustion Products, and Propellants Ch7: Reproductive and Developmental Outcomes	Literature Review: Studies investigating reproductive effects on service in the Gulf War. Outcomes of interest include infertility, preterm birth and low birth rate as well as birth defects and childhood cancers. Most studies were on birth defects, however, none were analysed as to whether the effects were due to chemical exposures. A review on paternal and maternal exposure to fuels. Studies report infertility, spontaneous abortion, childhood leukaemia neuroblastoma and Prader-Willi syndrome. Authors concluded limited evidence for these outcomes. Also contains paternal exposures	Yes	
CONCAWE 2007	Human exposure information for EU substance risk assessment of kerosine	Risk Assessment performed for the EU chemical substances regulations. Vast number of exposures documented for military personnel (Aviation refuelling operations and aircraft maintenance). Has measured biomonitoring results. Documents occupational exposure limits for kerosines. Has a small section on Reproductive toxicity. Uses the Reutman study for potential reproductive endocrine effects.	Yes	
Dept of Veterans Affairs (DVA) 2004	Report on the general health and medical study Vol 5	Health study looked for a link between exposures F111 Deseal/Reseal Program and birth defects. Female Reproduction section in the Chapter 14. (Reference Tas S et al 1996 Male study)	Yes	
Doyle et al 2006	Reproductive health of Gulf War veterans.	Review Article: Reproductive health from first Gulf War. Female & male veterans were included in review. The studies grouped birth defects, foetal death, and infertility. No studies examined risk of particular exposures. No mention of MATF fuels Review other references in journal. Congenital malformations in children of male veterans	No	Review article
Kang et al 2001	Pregnancy outcomes among US Gulf War veterans: A Population based survey of 30,000 veterans.	Gulf War veterans subjected to a variety of environmental exposures. The study aims to estimate and compare the rates of spontaneous abortions, still births, preterm births and birth defects between Gulf veterans and non- Gulf veterans. No exposures mentioned to fuels or solvents	No	No MATFs

Authors & Year	Title	Comments	Include	Reason for exclusion
Kang et al 2000	Pregnancy outcomes among US women Vietnam veterans.	US Congress mandated comprehensive health study on women Vietnam veterans. The report deals with reproductive health outcomes. Exposures to Agent Orange and links to spina bifida and anencephaly. Cohort study of 8280 women. No specific exposures. Exposures pooled together to call it "Vietnam experience". Nothing specific to fuels or solvents. Contains study on male veterans.	No	No MATFs
Katon et al 2017	Deployment and adverse pregnancy outcomes: Primary finding and methodological considerations	Retrospective cohort study characterising pregnancy outcomes in Iraq. Outcomes included preterm births, low birth weights and macrosomia. Study concentrated on the association of deployment with adverse pregnancy outcomes among women veterans. No mention of MATF fuels or solvent exposure. Contains 3 references on exposures/ conditions.	No	No MATFs
Kozumbo WJ 2010	Air Force Related Jet Fuel Toxicology Research (1991-2010)	Chapter 1 from the Book: Jet Fuel Toxicology. Reviews potential toxic effects as a result of jet fuel exposure in particular JP-8. Unable to access. Available table of contents referred to NRC reports.	No	Unable to readily access
Koschier F 1999	Toxicity of middle distillates from dermal exposure.	Reproductive / Developmental toxicity has been analysed using animal studies	No	Animal study
National Research Council 2001	Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity	NRC to conduct reproductive and Developmental assessment of chemicals for the US Navy. JP-8 is evaluated in the Appendix A.	Yes	
National Research Council 2003	Toxicological Assessment of Jet Propulsion Fuel 8	Chapter 9 reviews studies on potential reproductive and developmental toxicity of JP-8. Has found NO studies that examined the potential for developmental toxicity or adverse rep effects of JP-8 or other jet fuels on women. One study examined reproductive effects on men. Male study refers to "LeMasters et al 1999". Several studies on experimental animals.	Yes	
National Research Council 2011	Acute Exposure guidelines for selected Airborne Chemicals Vol 10	Assessment of Acute Exposure Guideline Levels for Hazardous Substances (AEGLs) for identified high-priority chemicals. Assessment of AEGLs on JP5 and JP8 and methyl ethyl ketone included as appendices. In relation to jet fuels developmental and reproductive effects, reported that no studies regarding human exposure and aspects of developmental toxicity were located in the published literature and methyl ethyl ketone included animal studies	No	No data on female reproduct-ive outcomes or based on animals studies

Authors & Year	Title	Comments	Include	Reason for exclusion
Oakes et al 2005	Final report on research into the toxicological effects of chemicals used in F111 Deseal/Reseal programs	Exposure was specific to SR51 and it looked at animal exposure and memory loss.	No	No Female Reproduct-ive outcomes
O'Connor MC 1999	Is active duty hazardous for pregnant ADF servicewomen?	Short article reviewing servicewomen in the ADF. Discussed studies of US servicewomen and preterm delivery and also a Navy study. Provided 5 reasons why active servicewomen might incur higher rates of complications. One is Toxic exposures. This study found as association between exposure to or5ganic solvents and hypertensive disorders during pregnancy. No relevant to fuel. Marked relevant to obtain reference for solvents.	No	No MATFs
Pierce et al 1999	Health Care utilization and satisfaction concerning gender specific health problems among military women.	Paper provides baseline health information on a sample of military women serving in the Gulf War. Not relevant	No	Not relevant
Savitz et al 1989	Effect of parent's occupational exposures on risk of stillbirth, preterm delivery and small for gestational age infants.	Reviews industries like textile and agriculture. Still birth caused by ionizing radiation or cigarette smoke, anaesthetic gases, lead or cadmium. Not relevant to fuels or military	No	No MATFs
Shaw et al 2003	Maternal occupational chemical exposures and biotransformation Genotypes as risk factors for selected congenital anomalies	A case controlled study investigating occupational exposures and increased risks of infants with Cleft palate and cleft lip, conotruncal heart defects or limb deficiencies. Female exposures. Chemical exposures broken down to aliphatic hydrocarbons (Kerosene are Aliphatic)	Yes	
Xu et al 1998	Association of petrochemical exposure with spontaneous abortion.	Retrospective epidemiological study that looks into petrochemical exposure and spontaneous abortion. Chemical exposure to benzene, gasoline and hydrogen sulfide. Large petrochemical plant in Beijing, China. Specific chemical exposures reviewed include benzene, styrene, toluene xylene ethylene, and ethylbenzene. Levels sampled were low as TWA was low. Not specific to fuels	No	No MATFs

Table 9: Selection of papers and guidelines/reports which had a full title screen - solvents

Authors & Year	Title	Comments	Include	Reason for exclusion
Ahmed & Jaakkola 2007	Exposure to organic solvents and adverse pregnancy outcomes	Population based study in Finland, occupational exposures to solvents and adverse pregnancy outcomes	No	General occupational solvent exposure assessment and/or reporting
Akdeniz et al 2013	Health risk assessment of occupational exposure to hazardous volatile organic compounds in swine gestation, farrowing and nursery barns	Calculation of emission rates and quantification of cancer and hazard risks of eight VOCs (phenol, p-cresol, o/m-cresol, benzene, toluene, ethylbenzene, o-xylene, and m/p-xylene) most likely emitted from swine buildings and expose livestock producers, using Mote Carlo simulation. Reproductive risks not specifically assessed	No	No reproductive health outcome
Axelrod et al 2001	It's time to rethink dose: the case for combining cancer and birth and developmental defects	Editorial on rationale for combining the epidemiological assessment of some cancer, some birth defects and some development defects that may be associated with exposures that take place early in life during critical window periods. Included some discussion of paternal exposures	No	Editorial
Baccarelli & Bollati 2009	Epigenetics and environmental chemicals	Review of current evidence from in vitro, animal and human studies for epigenetic mechanisms that can mediate the effects of environmental chemicals. Trichloroethylene referred to but animal study only.	No	Review
Bajeux et al 2014	Perinatal exposure to solvents and wheezing eczema and food allergies at age 2.	Study of mother-child pairs in the PELAGIE cohort assessed effects of maternal occupation and prenatal and postnatal solvent exposures on wheezing, eczema or food allergies assessed at 2 years age	No	No reproductive endpoints
Barton & Clewell 2000	Evaluating noncancer effects of trichloroethylene: Dosimetry, mode of action, and risk assessment	Review- Acute effects on humans, Animal studies	No	Review article
Bhattacharya & Keating 2011	Ovarian metabolism of xenobiotics	Review of mechanistic events in relation to metabolism of three chemicals that can induce premature ovarian failure, including trichloroethylene, with a focus on events occurring in the ovary. Evidence presented predominantly animal studies.	No	Not relevant and review article
Bhattacharya & Keating 2012	Impact of environmental exposures on ovarian function and role of xenobiotic metabolism during ovotoxicity	Review of mechanistic events in relation to metabolism of three chemicals that can induce premature ovarian failure, including trichloroethylene, with a focus on	No	Not relevant and review article

Authors & Year	Title	Comments	Include	Reason for exclusion
		events occurring in the ovary, and enzymes involved in bioactivating and detoxifying these chemicals. Evidence presented predominantly animal studies. Similar to another paper by these authors.		
Bharti 2003	Intrauterine cerebral infarcts and bilateral frontal cortical leukomalacia following chronic maternal inhalation of carburetor cleaning fluid during pregnancy	One case report regarding solvent abuse to carburetor fluid.	No	Non-occupational exposure
Birks et al 2016	Occupational exposure to endocrine-disrupting chemicals and birth weight and length of gestation: a European meta-analysis	Large population, 13 European cohorts & meta-analysis of chemicals including solvents (toluene, xylene & TCE). Assessed organic solvents based on job title	No	General occupational solvent exposure assessment and/or reporting
Bolden et al 2015	New look at BTEX: Are ambient levels a problem	Review article. Includes references for Toluene, ethyl benzene and xylene	No	Review article
Boldenow et al 2015	The trichloroethylene metabolite S-(1,2-dichlorovinyl)-L-cysteine but not trichloroacetate inhibits pathogen-stimulated TNF-α in human extraplacental membranes in vitro	In vitro study of metabolites of trichloroethylene and immune response of extraplacental membrane in relation to infection	No	Not relevant
Bondy & Campbell 2005	Developmental neurotoxicology	Min-review of neurodevelopmental consequences of contact with various neurotoxic agents including metals, solvents (focussed on alcohol and foetal alcohol syndrome), pharmaceutical agents and natural products	No	Not relevant and review article
Bove et al 2002	Drinking water contaminants and adverse pregnancy outcomes: A review	A qualitative review of chlorinated products including trichloroethylene in drinking water	No	Non-occupational exposure
Bowen & Hannigan 2006	Development toxicity and prenatal exposure to toluene	Mini-review focusing on developmental toxicity of voluntary inhalation and inhalant abuse of toluene	No	Non-occupational exposure
Boyer et al 2000	Trichloroethylene inhibits development of embryonic heart valve precursors in vitro	Chick-AV canal culture model : Animal In vitro study	No	Animal study
Boyle et al 2016	Assessment of exposure to VOCs among pregnant women in the National Children's Study	A US longitudinal child study measuring VOC exposure and urinary metabolite samples and relationship to sources of exposure including smoking. No occupational exposure specifically	No	Non-occupational exposure , no adverse reproductive outcome assessment

Authors & Year	Title	Comments	Include	Reason for exclusion
Brender et al 2002	Parental occupation and neural tube defect-affected pregnancies among Mexican Americans	Case control study in Mexican-American women with neural tube defect-affected pregnancies; and control women who were study-area residents who delivered normal babies during the same period. Interviewed about maternal and paternal occupations and work exposures during the periconceptional period.	No	General occupational solvent exposure assessment and/or reporting
Brent 2001	The cause and prevention of human birth defects: what have we learned in the past 50 years?	Review article on human birth defects and teratogens	No	Review article
Brouwers et al 2009	Occupational exposure to potential endocrine disruptors: further development of a job exposure matrix	Description of development of a more up to date job exposure matrix (JEM) for estimating occupational exposure to potential endocrine disruptors based on a previous JEM (van Tongeren et al, 2002)	No	No reproductive health outcome Not relevant
Bukowski 2014	Critical review of the epidemiologic literature regarding the association between congenital heart defects and exposure to trichloroethylene	Review article of the epidemiologic literature of TCE and congenital malformations including varied sources of exposures. An occupational study post 2000 Gilboa (2012) is reviewed	No	Review article
Bukowski J 2001	Review of the epidemiological evidence relating toluene to reproductive outcomes	Review relating to toluene exposures. Occupational exposures of toluene have been associated spontaneous abortion, congenital malformations and reduced fertilities. Epidemiological studies reviewed and occupational exposures were based on 1980's -90's	No	Review article
Callan et al 2016	Changes in developmental body weight as a function of toluene exposure	A systematic review and meta-analysis on animal studies	No	Animal study
Carelli et al 2007	Grand rounds: Could occupational exposure to n-hexane and other solvents precipitate visual failure in Leber hereditary optic neuropathy?	One case of a 27 year old man with loss of central vision.	No	Not relevant
Chabert et al 2016	Lack of information received by a French female cohort regarding prevention against exposure to reprotoxic agents during pregnancy.	Cohort study investigated information pregnant women received regarding possible exposures to five reprotoxic agents during their pregnancy (bisphenol A, toluene, n-hexane, cis-chloroallyl-triaza-azonia-adamantane-chloride (cis-CTAC) and O-phenyl-phenol). Collected data on occupation and sociodemographics by questionnaire	No	No reproductive endpoints
Chapin et al 2004	Off to a good start: the influence of pre- and periconceptional exposures, parental	Discussion paper, no specific exposure to solvents of interest	No	Review article

Authors & Year	Title	Comments	Include	Reason for exclusion
	fertility and nutrition of childrens health			
Chevrier et al 2006	Occupational exposure to organic solvent mixtures during pregnancy and the risk of non-syndromic oral clefts	Case control study investigating association between maternal occupational exposures to mixtures of organic solvents (oxygenated solvents, chlorinated solvents and petroleum solvents) during pregnancy and risk of non-syndromic oral clefts	Yes	
Cho et al 2001	Effects of exposure to organic solvents on menstral cycle length	Cross sectional study investigating organic solvent exposure and menstrual disturbance.	Yes	
Ciarrocca et al 2012	Assessment of occupational exposure to benzene, toluene and xylenes in urban and rural female workers	Evaluated occupational exposure levels to BTXs in urban air in female workers (traffic policewomen, police drivers) compared to female workers in a rural area (roadwomen); used environmental monitoring of BTXs and biological monitoring of blood benzene, t,t-MA and S-PMA at the end of work shifts	No	No reproductive outcome
Cordier et al 2012	Exposure during pregnancy to glycol ethers and chlorinated solvents and the risk of congenital malformations	Case control study of prenatal exposure to glycols and chlorinated solvents, including trichloroethylene	Yes	
Costa et al 2002	Developmental neurotoxicity: Do similar phenotypes indicate a common mode of action? A comparison of fetal alcohol syndrome, toluene embryopathy and maternal phenylketonuria	Paper briefly reviewing features of foetal alcohol syndrome, abuse of toluene and toluene embryopathy (foetal solvent syndrome), and phenylketoneuria; and possible modes of actions. Does not consider occupational toluene exposure	No	Non-occupational exposure
Crinnion 2009	Maternal levels of Xenobiotics that affect fetal development and childhood health	Review paper. Refers to 3 references from 1979-1987	No	Review article
Cruz et al 2000	Effects of volatile solvents on recombinant N-methyl-D-aspartate receptors expressed in Xenopus oocytes	Solvent abuse as an inhalant and animal study on female frogs	No	Non-occupational exposure
Ramakrishnan et al 2013	Evaluating the effects of maternal exposure to benzene, toluene, ethyl benzene, and xylene on oral clefts among offspring in Texas: 1999-2008	Study evaluated association between estimated maternal exposure to environmental levels (residential exposure) of BTEX during pregnancy and the risk of oral clefts among offspring in Texas 1999–2008	No	Non-occupational exposure
Desrosiers et al 2012	Maternal occupational exposure to organic solvents during early pregnancy and risks of neural tube defects and orofacial clefts	Population based case control study of women with births with congenital anomalies and association with exposures to solvents	Yes	

Authors & Year	Title	Comments	Include	Reason for exclusion
Desrosiers et al 2015	Assessed occupational exposure to chlorinated aromatic and Stoddard solvents during pregnancy and risk of fetal growth restriction	Population based case control study of women in the National Birth Defects Prevention Study with congenital anomalies and association with exposures to any and specific classes of solvents	Yes	
Faber et al 2008	Review of reproductive and developmental toxicity studies with isopropanol	Review of reproductive and development toxicity studies for isopropanol in male and female rats	No	Animal study
Figà-Talamanca 2000	Reproductive problems among women health care workers: Epidemiologic evidence and preventive strategies	Review of reproductive effects of occupational exposures in female health care workers. Solvent and disinfectant exposures were a limited part of the review. Discussed possible preventive strategies overall	No	Review article
Figà-Talamanca et al 2006	Occupational risk factors and reproductive health of women	Review article summarizes epidemiological evidence of occupational exposures, including chemical exposures (including solvents) and adverse reproductive outcomes	No	Review article
Figà-Talamanca et al 2001	Occupational exposures to metals solvents and pesticides: Recent evidence on male reproductive effects and biological markers	Review of epidemiological studies in occupational settings on relationship between exposures to chemical agents and male reproductive function	No	Male reproductive function review
Forouzanfar et al 2015	Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013	Global burden of disease study, mentions risk factors for occupational exposure to trichloroethylene. No reproductive endpoints, only mortality.	No	No reproductive endpoints
Frey et al 2015	Pregnant employee protection program in a large chemical company	Pregnancies at BASF were studies with specific maternal exposures.	Yes	
Garlantézec et al 2009	Maternal occupational exposure to solvents and congenital malformations: a prospective study in the general population	Prospective cohort study to investigate maternal exposure to solvents on risk of congenital malformations, the French PELAGIE cohort.	No	General occupational solvent exposure assessment and/or reporting
Garlantézec et al 2011	Industrial and technical workers are not the only workers exposed to solvents	Reply to letter to editor in relation to one of their studies and describing the exposure assessment in relation to occupations	No	Letter
Garlantézec et al 2013	Urinary Glycol Ether metabolites in women and time to pregnancy: the PELAGIE cohort	Study looked at glycol ethers including PGME, the urinary metabolites and time to pregnancy	Yes	
GBD 2013 Risk Factors	Global, regional, and national comparative risk assessment of 79	Risk factor quantification for the Global Burden of Disease (GBD) Study and Risk Factors study 2013	No	No reproductive endpoints

Authors & Year	Title	Comments	Include	Reason for exclusion
Collaborators	behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013	update of the GBD, compared with the GBD 2010, six new risk factors were included including occupational exposure to trichloroethylene. This did not include any assessment of association with reproductive outcomes		
Gentry et al 2002	Application of a physicologically based pharmacokinetic model for isopropanol in the derivation of a reference dose and reference concentration	An interspecies physiologically based pharmacokinetic (PBPK) model describing isopropanol (IPA) and its major metabolite, acetone, was applied to derive reference dose (RfD) and reference concentration (RfC) values for IPA. Endpoints from chronic, developmental, and reproductive toxicity studies were considered for the derivation of RfDs and RfCs	No	Animal study
Gentry et al 2003	Application of a physicologically based pharmacokinetic model for reference dose and reference concentration estimation for acetone	Description of a risk assessment process for acetone based on a 1991 subchronic study and a 1988 inhalational developmental toxicity study on acetone and several toxicological studies on isopropanol, to estimate a Reference Dose and inhalational reference concentration for acetone	No	Not relevant, no reproductive health outcomes
Gentry et al 2003	Evaluation of the potential impact of pharmacokinetic differences on tissue dosimetry in offspring during pregnancy and lactation	Study to develop a methodology to assess, based on chemical/physical properties of a chemical, pharmacokinetic changes that may impact foetal or neonatal susceptibility to adverse effects following exposure (for six chemical classes including isopropanol)	No	Not relevant
Gilboa SM 2010	Maternal occupational exposure to organic solvents and congenital heart defects: Results from the national birth defects prevention study	Study examining an interspecies physiologically based pharmacokinetic (PBPK) model for IPA and its major metabolite, acetone, to derive reference doses and reference concentration values for IPA. Adult PBPK models for rats and humans extended to simulate exposure to IPA during pregnancy and estimate internal dose metrics	No	Not relevant
Gilboa et al 2012	Association between maternal occupational exposure to organic solvents and congenital heart defects, National Birth Defects Prevention Study, 1997-2002	A population based case control study of congenital heart defects	Yes	
Grandjean & Landrigan 2006	Developmental neurotoxicity of industrial chemicals	Discussion paper recognising 5 substances recognised as developmental toxicants: lead, methylmercury, PCBs and possibly arsenic and toluene	No	Review article
Grandjean &	Neurobehavioural effects	Review of information on developmental neurotoxicity of	No	Review article

Authors & Year	Title	Comments	Include	Reason for exclusion
Landrigan 2014	of developmental toxicity	industrial chemicals to update previous 2006 review (noted epidemiological studies have documented six additional developmental neurotoxicants - manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichlolorethane, tetrachlorethylene, and the polybrominated diphenyl ethers. Proposed control measures for neurotoxicity		
Green et al 2005	The relation of occupational organic solvent exposure to symptom reporting in a sample of white and Chinese midlife women	Cross-sectional study of US Chinese and white women aged 40-55 years examining relationship between occupational solvent exposure, broadly assessed, and self-reported menopausal and other symptoms in which a large number of comparisons were made	No	Not relevant
Hammond 2014	Neurologic and reproductive effects of solvents on automotive repair workers: Assessment of exposure for the Bay Area Solvent Study (BASS) 0321	Published abstract referred to exposure assessment for study of neurological and reproductive effects. Did not discuss reproductive findings. Concluded exposures were significantly affected by temporal trends in cleaning methods, composition of materials and work practices.	No	Published abstract
Hardin et al 2004	Trichloroethylene and cardiac malformations	Published letter expressing concerns regarding data in a publication by Johnson et al 2003 and a prior publication in Dawson et al 1993 reporting on cardiac malformations in rats and TCE as a 'specific' cardiac teratogen. Johnson et al's response included in correspondence in same issue	No	Not relevant
Hardin et al 2005	Trichloroethylene and dichloroethylene: a critical review of teratogenicity	Review article of experimental and epidemiological evidence in relation to teratogenicity of trichloroethylene (TCE) and dichlorethylene (DCE). Occupational epidemiological studies were 1992 or earlier or not specific for TCE. Authors concluded weight of evidence does not support hypothesis that TCE or DCE is a selective development toxicant in general or a cardiac teratogen specifically	No	Review
Hidestrand et al 2013	Hypoplastic left heart syndrome (HLHS) risk increased with measured fetal solvent exposure	Poster session abstract. TCT@ACC-i2: Invasive and Interventional Cardiology. Foetal VOC exposure as measured in meconium (foetal stool) samples from term infants with and without HLHS	No	Abstract, not a peer review paper
Hoe 2013	Reproductive health outcome from chemical exposure in a drug laboratory in Malaysia	Conference abstract presenting findings of a risk assessment conducted in a hospital based dangerous drug monitoring lab in Kuala Lumpur using a Qualitative Risk Assessment process	No	Abstract, not a peer review paper

Authors & Year	Title	Comments	Include	Reason for exclusion
Hougaard & Hansen 2007	Enhancement of developmental toxicity effects of chemicals by gestational stress. A review	Review of 36 animal studies investigating if maternal stress may enhance effects of prenatal chemical exposure. Toluene was one of the chemicals considered	No	Review of animal studies
Hruska et al 2000	Environmental factors in infertility	Review article on associations of cigarette smoke, alcohol, occupational exposures, environmental exposures and infertility. Occupational exposure references to toluene & solvent mixtures prior to 2000	No	Review article
Hsieh 2005	Prolonged menstrual cycles in female workers exposed to ethylene glycol ethers in the semiconductor manufacturing industry	Investigated exposure of ethylene glycol ether	No	Not relevant
Jiang et al 2015	Disruption of cardiogenesis in human embryonic stem cells exposed to trichloroethylene	The study uses human embryonic stem cells to determine cardiac deformities	No	Not relevant
Kassotis et al 2016	Endocrine-disrupting chemicals and oil and natural gas operations: potential environmental contamination and recommendations to assess complex environmental mixtures	Commentary/ review paper. Included brief discussion of occupational exposures and reproductive effects of chemical exposures in the oil/natural gas fracturing industry. Refs included Webb (2014) on reproductive effects of volatile organic compounds in relation to air and water exposure in natural gas/oil operations. Refs on adverse pregnancy outcomes included McKenzie et al. (2014) spatial analysis to evaluate residential proximity to drilling well operations and adverse pregnancy outcomes	No	Review article
Kim et al 2011	Changes in oxidative stress biomarker and gene expression levels in workers exposed to volatile organic compounds	Study evaluated change of oxidative stress biomarker and gene expression levels in workers exposed to VOCs; used urine and blood samples from 21 Korean ship builder workers before and after occupational exposure to VOCs; measured muconic acid (MuA), hippuric acid (HA), mandelic acid (MaA), methyl hippuric acid (MHA) as urinary exposure biomarkers for BTEX, and malondialdehyde (MDA) and 8-hydroxydeoxyguanine (8-OHdG) as oxidative stress biomarkers in all subjects	No	No reproductive end point
Konkel 2014	Birth defects and mothers' proximity to natural gas development. Is there a connection?	News report in a journal of an environmental study findings of proximity of natural gas wells (and possible exposure to benzene, toluene and xylene) in Colorado and mothers who had adverse birth outcomes and those who did not	No	Non-occupational exposure
Kuehl & Loffredo 2006	A cluster of hypoplastic left heart malformation in Baltimore, Maryland	Parental exposure assessment to solvents self-reported through occupational, leisure or residential	No	General occupational solvent

Authors & Year	Title	Comments	Include	Reason for exclusion
		exposure presented as 'miscellaneous solvents', exposures general solvents		exposure assessment and/or reporting
Kumar 2004	Occupational exposure associated with reproductive dysfunction	General non-systematic review on occupational exposures associated with reproductive dysfunction, included toluene, few refs but included males and related to studies pre 2000	No	General review
Kumar & Mishra 2010	Review: Toxicants in reproductive fluid and in vitro fertilization (IVF) outcome	Non-systematic review or compilation of data in relation to role of various toxicants, including TCE, and IVF outcomes and toxicant levels in reproductive fluid (follicular fluid (FF) and seminal plasma). Some refs more relevant to male exposures to TCE	No	General review
Labrèche et al 2003	Characterization of Chemical Exposures in Hairdressing Salons	Measured exposure of the solvents but no association to reproductive endpoints	No	No reproductive outcomes
Lawson et al 2003	An occupational reproductive research agenda for the third millennium	Discussion paper	No	Review paper
Lee et al 2011	Evaluation of the COSHH Essentials model with a mixture of organic chemicals at a medium-sized paint producer	Measured exposure of solvents, conducted modelling, assigning Risk phrases. Use of the model to define Toluene as Hazard band D due to risk phrase R63 (possible risk of harm to unborn child). No quantitative data	No	Not relevant
Lehmann et al 2002	The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells.	Indoor Air exposure of VOC for neonates. No occupational exposure to mothers	No	Non-occupational exposure
Lin et al 2013	Exposure to multiple low-level chemicals in relation to reproductive hormones in premenopausal women involved in liquid crystal display manufacture	Cross sectional study using urinary metabolites to determine association of occupational exposures to VOC and menstrual function	Yes	
Lin et al 2013	Shortened menstrual cycles in LCD manufacturing workers	VOC and reproductive hazard ratings and effects on menstral cycles	Yes	
Lorente et al 2000	Maternal occupational risk factors for oral clefts	Exposures to solvents, i.e. toluene and Trichloroethylene and oral cleft malformations	Yes	
Lumpkin 2015	Chlorinated hydrocarbons In: Hamilton & Hardy's Industrial Toxicology, 6th edition	Book chapter discusses background and uses, physical/chemical properties, environmental fate and bioaccumulation, eco and mammalian toxicology, sources of exposure, industrial hygiene and risk assessment of chlorinated hydrocarbons (including trichloroethylene). Not a systematic review. Noted human data for TCE-induced birth defects are too limited to	No	General review

Authors & Year	Title	Comments	Include	Reason for exclusion
		show a causal link		
Lupo et al 2011	Maternal exposure to ambient levels of benzene and neural tube defects among offspring: Texas, 1999-2004	Article assessed the association of maternal exposures to environmental levels of BTEX and neural tube defects. Included references of neural tube defects and occupational exposures	No.	Non-occupational exposure
Ma et al 2002	Quantitation of exposure to trichloroethylene & the putative proximate cardiac teratogen trichloroacetic acid during human pregnancy	Meeting abstract. Unable to access abstract	No	Abstract
Makris 2000	Retrospective analysis of EPA's developmental neurotoxicity testing battery	Abstract at a conference	No	Review Article
Makwana et al 2010	Exposure to low-dose trichloroethylene alters shear stress gene expression and function in the developing chick heart	Chick embryos - Animal study. References relate to drinking water contaminants causing human congenital cardiac malformations	No	Animal study
Maldonado et al 2003	Occupational exposure to glycol ethers and human congenital malformations	Review paper of toxicological and epidemiological information of generic glycol ethers	No	Review article
Manuela et al 2012	Assessment of occupational exposure to benzene toluene and xylenes in urban and rural female workers	Occupationally exposure of air pollutants with traffic policewomen. Environmental monitoring and biological monitoring conducted. No associated with reproductive effects.	No	No reproductive endpoints
McCanlies EC 2012	Parental occupational exposures and autism spectrum disorder	Occupational exposures assessed through self-report and job history. Outcome was autism spectrum disorder; not classified as a congenital malformation in ICD-10	No	No study defined reproductive endpoint
McKee et al 2015	Characterization of the toxicological hazards of hydrocarbon solvents.	Review/summary of information on the physical/chemical properties and toxicological hazards of hydrocarbon solvents and ways in which information on hazard characterization can be bused for hazard classification and to set occupational exposure limits. Summarise evidence for sexual function and/or fertility, malformations or severe developmental toxicity. Authors report ExxonMobil and Shell International as affiliations	No	Review article
Meyer-Monath et al 2014	Analysis of BTEX and chlorinated solvents in meconium by headspace-solid-phase microextraction gas chromatography coupled with mass spectrometry	Measurements of exposure of VOCs in newborns. Analysis of the first meconium sample	No	Not relevant
Miller et al 2014	Occupational, industrial, and environmental	Chapter in a book that considered specific drug therapies during	No	Review

Authors & Year	Title	Comments	Include	Reason for exclusion
	agents In: Drugs during pregnancy and lactation, 3rd edn	pregnancy and lactation and evidence in relation to exposure to solvent exposure in general and specific solvents including acetone. Not based on a systematic review. Recommendations in relation to avoidance in pregnancy, action if significant exposure, additional diagnostic measures, and workplace measures		
Moro et al 2012	Evaluation of genotoxicity and oxidative damage in painters exposed to low levels of toluene	Biomonitoring study evaluating possible genotoxic effects of low-level exposure to toluene in painters from an industry in Rio Grande do Sul, Brazil. Considered possible effects of confounding by factors such as age, smoking, alcohol consumption and exposure time	No	Not relevant
Niaz et al 2015	A review of environmental and occupational exposure to xylene and its health concerns	Review paper on health effects of xylene. Contains a few references in the reproductive and developmental effects section.	No	Review article
Običan and Scialli 2011	Teratogenic exposures	Review of some teratogenic exposures (pharmaceutical products, recreational drugs including toluene abuse, physical agents e.g. X rays, and infections)	No	Non-occupational exposure and review article
Pak et al 2013	Occupational chemical exposures among cosmetologists. Risk of reproductive disorders	Article to inform nurses and public health professionals about occupational exposures for cosmetologists (particularly hairdressers and nail technicians) including epidemiological studies and interventions to reduce the risks of reproductive disorders in workers. Occupational exposure to toluene considered in relation to nail technicians	No	Review article
Pastino et al 2000	Human variability and susceptibility to trichloroethylene	Review paper on TCE: Acute effects, reproductive effects. Analysis of variability & susceptibility. References ATDSR- TCE 1993 and other references are pre 2000	No	Review article
Qin et al 2017	Low organic solvent exposure and combine maternal-infant gene polymorphisms affect gestational age	Study of association between organic solvent exposure (benzene, toluene, styrene, xylene) and gestational age in mother-infant pairs in Chinese petrochemical plant and effect of polymorphisms of combined maternal-infant metabolic genes	No	General occupational solvent exposure assessment and/or reporting
Ramakrishnan et al 2013	Evaluating the effects of maternal exposure to benzene, toluene, ethylbenzene and xylene on oral clefts among offspring in Texas: 1999-2008	Case Controlled study of residential exposures to BTEX and birth defects (oral clefts). Some references on occupational exposures pre 2000	No	Non-occupational exposure
Red et al 2011	Environmental toxicant exposure during	Brief continuing medical education reference review for acute/chronic	No	Brief review

Authors & Year	Title	Comments	Include	Reason for exclusion
	pregnancy	poisonings in pregnant women, mainly home/occupational environmental toxicants. Non-systematic review		article
Reutman et al 2002	Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures.	Reviews BTEX as the solvent exposures and endocrine markers	Yes	
Rocheleau et al 2011	Inter-rater reliability of assessed prenatal maternal occupational exposures to solvents polycyclic aromatic hydrocarbons and heavy metals.	Rated the National Birth Defects Prevention study, a US population base case control study	No	Review article
Ruder 2006	Potential health effects of occupational chlorinated solvent exposure	Review article with a section on trichloroethylene and discussions for reproductive endpoints. References on epidemiological or occupational exposures pre 2000	No	Review article
Rylander et al 2002	Reproductive outcome among female hairdressers	The study was on a cohort of hairdressers with exposures and association of reproductive outcome. Described likely exposures but no exposure assessment	No	Not relevant
Sallmén et al 2008	Reduced fertility among shoe manufacturing workers	A retrospective study of exposed female shoe manufacturing workers. The study has exposures to toluene, MEK, acetone and IPA. Use time to pregnancy as a measure of fertility.	No	General occupational solvent exposure assessment and/or reporting
Sallmén et al 2006	Fertility and exposure to solvents among families in the Agricultural Health Study	Studied couples with solvent exposure assessment reported in females based on home or work activities >= once per month: painting or using gasoline or other solvents for cleaning hands or equipment. Assessment in men (pesticide applicators) included frequency of the activities. Outcome of subfertility.	No	General occupational solvent exposure assessment and/or reporting
Santiago et al 2017	Benzene poisoning, clinical and blood abnormalities in two Brazilian female gas station attendants: two case reports	2 case studies on exposure to BTX and early pregnancy loss. Characterized cytogenetic, hematological, and immunophenotypic status in two female gas station attendants with benzene poisoning symptoms and benzene poisoning symptoms and miscarriage history.	No	Case report
Sawicka & Dlugosz 2008	Toluene and P-xylene mixture exerts antagonistic effect on lipid peroxidation in vitro	An In vitro model of human placenta mitochondria was used in this study to determine the influence of xylene and toluene on lipid peroxidation	No	Not relevant
Scialli & Gibb 2005	Trichloroethylene exposure and congenital heart defects	Correspondence to editor regarding Yauck et al 2004 paper on residential exposure to trichloroethylene and risk of congenital heart defects	No	Non-occupational exposure
Seeber et al 2005	Changes of neurobehavioral and	Conference abstract on high vs low exposed group and lifetime weighted	No	Abstract

Authors & Year	Title	Comments	Include	Reason for exclusion
	sensory functions due to toluene exposure below 50 ppm?	average toluene exposures and relationship with sensory function, colour discrimination, and auditory thresholds and measures of neuro psychological performance. Reported that evidence for neurobehavioral effects due to long-term toluene exposure below 50 ppm was not established		
Silver et al 2016	Birth defects in infants born to employees of a microelectronics and business machine manufacturing facility	Reported structural birth defects in microelectronics/business machine manufacturing facility matched to state registry. Exposure assessment included metals, chlorinated hydrocarbons, and other hydrocarbons. Association of exposures and outcomes only considered in males because too few female outcomes	No	No reproductive endpoints analysis in females
Simpson & Niebyl 2002	Occupational and environmental perspectives of birth defects Ch7	Chapter in Book Obstetrics: Normal and Problem Pregnancies, Review paper of historical occupational studies. References from 1982	No	Review Paper
Sissell 2003	Study links TCE to male infertility	Chemical Week (website) report of a study at Queens University (Kingston ON) linking TCE to male infertility. TCE detected in semen of males diagnosed with infertility	No	Media report
Sissell 2007	EPA releases candidates for endocrine screening list	Chemical Week (website) report on the Environmental Protection Agency (EPA) release of list of 73 proposed substances to be tested for potential to disrupt the endocrine system; included acetone, atrazinc, chlorpyriros, glycophosate, permethrin and toluene	No	Media report
Smith 2010	Environmentally induced heart malformations	Book chapter discussing assessment tools for study of cardiac teratogens, evidence for selected key cardiac teratogens and mechanisms, including trichloroethylene. Not a systematic review but presented summaries of difficulties of studies and interpretation of evidence in this field. Most cited refs for studies pre 2000	No	Review chapter
Song et al 2011	Cell signaling mechanisms in developmental neurotoxicity	Book chapter describing cell signalling mechanisms by which neurotoxic chemicals can affect the developing nervous system	No	Mechanistic review chapter, not relevant
Stoltenburg-Didinger et al 1990	Neurotoxicity of organic solvent mixtures: embryotoxicity and fetotoxicity	Animal study	No	Animal study
Testud et al 2010	Pregnancy outcome after risk assessment of occupational exposure to organic solvents: A prospective cohort study	Prospective follow up study of pregnant women exposed to chemicals, organic solvents, at workplaces matched with controls exposed to a non-embryotoxic agent. Conducted through Lyon Poison	No	General occupational solvent exposure assessment and/or reporting

Authors & Year	Title	Comments	Include	Reason for exclusion
		Centre		
Thurston et al 2000	Petrochemical exposure and menstrual disturbances	Survey administered to over 3000 women who worked in a petrochemical plant in China. Assessed occupational exposures and abnormal menstrual length cycle. Results mainly reported in relation to benzene but toluene also assessed. Effect estimate not reported other than in relation to benzene	Yes	
Till et al 2001	Effects of maternal occupational exposure to organic solvents on offspring visual functioning: A prospective controlled study	Study of organic solvent exposure and colour vision deficits in children age 3-7 years	No	General occupational solvent exposure assessment and/or reporting
Valcke & Haddad 2015	Assessing human variability in kinetics for exposures to multiple environmental chemicals: a physiologically based pharmacokinetic modeling case study with dichloromethane, benzene, toluene, ethylbenzene and m-xylene.	Modelling exposure and dose metrics, no adverse reproductive endpoints	No	No reproductive endpoints
Veenstra 2009	Human health risk assessment of long chain alcohols.	Summary of testing of representative chemicals from the long chain alcohols category (chemicals broadly used across consumer products industry with highest per person consumer exposures resulting from use in personal care products) including animal reproductive and developmental toxicity studies	No	Not relevant
Vulimiri et al 2011	Reproductive and developmental toxicology: toxic solvents and gases	Book chapter generally reviewing reproductive and developmental toxicology included toluene but limited human study refs were pre 2000 or related to toluene abuse. Referred to kerosene and jet fuels and discussed under that summary of studies as well	No	Review chapter
Watson et al 2005	Gestational exposure to trichloroethylene and risk of congenital heart defects: An assessment	Teratology Society Abstract on trichloroethylene	No	Review Article
Watson et al 2006	Trichlorethylene-contaminated drinking water and congenital heart defects: A critical analysis of the literature	Critical review of studies related to trichloroethylene contaminated drinking water and association with congenital heart defects. Methodology not fully described. Authors concluded that gestational TCE exposure did not increase prevalence of CHDs, application of Hill's causality guidelines to body of data did not indicate a causal link of environmentally relevant concentrations of TCE and CHD.	No	Non-occupational exposure

Authors & Year	Title	Comments	Include	Reason for exclusion
		Three of Hill's criteria met.		
Webb et al 2014	Developmental and reproductive effects of chemicals associated with unconventional oil and natural gas operations	Commentary/non-systematic review paper on air and water pollutants including volatile organic compounds and heavy metals which may occur as a result of unconventional oil and gas operations and the potential for adverse reproductive and developmental effects	No	Review article and non-occupational exposures
Wennborg et al 2001	Solvent use and time to pregnancy among female personnel in biomedical laboratories in Sweden	Retrospective study of female personnel who worked at a Swedish biomedical research laboratory. Exposure to solvents and fecundability ratios	No	General occupational solvent exposure assessment and/or reporting
Wennborg et al 2005	Congenital malformations related to maternal exposure to specific agents in biomedical research laboratories	Retrospective study of female personnel who worked at a Swedish biomedical research laboratories and other departments. Exposure to laboratory work in general, benzene and solvent exposure other than benzene and associations with major congenital malformations and neural crest malformations	No	General occupational solvent exposure assessment and/or reporting
White et al 2016	Toluene disruption of the functions of L1 cell adhesion molecule at concentrations associated with occupational exposures	Cell cultures from Rats- harvesting cerebellar granule neurons	No	Animal study
Williams-Johnson et al 2001	Trichloroethylene in the environment: Public health concerns	Summarised/evaluated studies reporting developmental and carcinogenic effects from trichloroethylene (TCE) exposures in human and animal studies, as relevant to environmental exposures particularly in drinking water. Based on Agency for Toxic Substances and Disease Registry (ATSDR) 1997 update on toxicological profile for TCE. ATSDR 2014 Tox profile update for TCE is reported	No	Review article.
Wilson et al 2009	Preliminary Data on Exposure to Trichloroethylene During Pregnancy	Conference abstract	No	Abstract
Wilson et al 2007	Principles of human teratology: Drug, chemical, and infectious exposure	Information on teratology risks for drugs, chemicals and infections during pregnancy. Drugs referred to toluene as a street drug. Chemicals reviewed were lead, organic mercury and PCB. Not relevant to our search	No	Not relevant
Woodruff et al 2011	Environmental chemicals in pregnant women in the United States: NHANES 2003-2004	Analyzed biomonitoring data to determine chemical exposures in US pregnant women - No reproductive outcomes	No	No reproductive endpoints
Zaleski 2007	Methyl Ethyl Ketone Safety Characterization for Infants and Children:	Report on a safety characterization specific to children performed for methyl ethyl ketone (MEK) according	No	Not relevant

Authors & Year	Title	Comments	Include	Reason for exclusion
	Assessment in the USEPA Voluntary Children's Chemical Evaluation Program.	to guidelines of the Voluntary Children's Chemical Evaluation Program (VCCEP). Reported that the characterization indicated that MEK exposures are not expected to pose an acute or chronic risk to children. Indicated no need for additional studies.		
Zhu et al 2006	Laboratory work and pregnancy outcomes: a study within the National Birth Cohort in Denmark	Prospective cohort study of female laboratory technicians and female teachers link to national birth registers investigating adverse reproductive outcomes and occupational exposures including job exposure matrix for organic solvents	No	General occupational solvent exposure assessment and/or reporting
Grey literature or additional records				
U.S. Environmental Protection Agency (EPA) National Center for Environmental Assessment (2011)	Toxicological Review of Trichloroethylene		Yes	
Chiu et al 2013	Human health effects of trichloroethylene: key findings and scientific issues	Review Paper which summarises key findings of a toxicological review for TCE conducted by the US EPA. EPA reports & NRC reports are also referred to directly	Yes	
Makris et al 2016	A systematic evaluation of the potential effects of trichloroethylene exposure and cardiac development	Systematic review of epidemiological, toxicological studies relevant to cardiac defects and exposure to TCE	Yes	
Agency for Toxic Substances and Disease Registry (ATSDR) (1992)	Toxicological Profile for 2-Butanone [methyl ethyl ketone (MEK)]		Yes	
ATSDR 2015	Draft Toxicological Profile for Toluene	Profile prepared in accordance with guidelines developed by ATSDR and the US Environmental Protection Agency (EPA)	Yes	
ATSDR 2014	Draft Toxicological Profile Trichloroethylene	ASTDR toxicological profile	Yes	
ATSDR 2007	Toxicological Profile for Xylene	ASTDR toxicological profile	Yes	
Agency for Toxic Substances and Disease Registry (ATSDR) (1994)	Toxicological Profile for Acetone		Yes	
Institute of Medicine of the National Academies (2003)	Gulf War and Health: Vol 2 Insecticides and solvents	Focus on long term adverse health outcomes of exposures during Gulf War. Published 2003 so over 10 years after Gulf War. Reproductive and developmental effects of exposure to solvents and mixture of solvents	Yes	

Authors & Year	Title	Comments	Include	Reason for exclusion
		considered.		
National Research Council; Division on Earth and Life Studies; Board on Environmental Studies and Toxicology; Committee on Human Health Risks of Trichloroethylene (2006)	Assessing the human health risks of trichloroethylene: Key scientific issues	Reproductive and Developmental Toxicity chapter	Yes	
Health Council of the Netherlands Committee for Compounds Toxic to Reproduction 2008	Occupational exposure to organic solvents: effects on human reproduction	Section on toluene, xylene and acetone	Yes	
Health Council of the Netherlands Committee for Compounds Toxic to Reproduction 2001	Toluene. Xylene: Evaluation of the effects on reproduction recommendation for classification	Section on toluene, xylene	Yes	
Health Council of the Netherlands The Committee for Compounds Toxic to Reproduction 2003	Trichloroethylene: Evaluation of the effects on reproduction recommendation for classification		Yes	
World Health Organisation - International Agency for Research on Cancer (IARC) (2000)	Ethylbenzene - IARC Monograph	Section on Reproductive and developmental toxicity. Monograph predominantly relates to evaluation of carcinogenic risks of chemicals reviewed in the monograph but also reviewed other data relevant to an evaluation of carcinogenicity and its mechanisms in humans including reproductive and developmental effects	Yes	
World Health Organization 1996	Environmental Health Criteria 187 - White Spirit (Stoddard Solvent)	Reproductive toxicity section, but appraisal notes that no distinction generally made between the types of solvent, as to whether they are chlorinated hydrocarbons or oxygenated solvents, and not always clear which solvents have been used or extent of exposure	No	General occupational solvent exposure assessment and/or reporting

Appendix 5

Table 10: Checklist for considering the quality of descriptive, observational prevalence studies

Modified from Giannakopolous, Rammelsberg, Eberhard, Schmitter (2012)

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

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

- **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.