

Evidence Compass



Summary Report

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

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EvidenceCompass@dva.gov.au

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. SHOAMP personnel may have been exposed to a number of materials including jet fuels, desealants, sealants and specified solvents, and exposures varied over time.
- 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.
- 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 body of literature on fuels and solvents and health effects *per se* is quite extensive. However, the evidence relating exposure to jet fuels and/or to specified solvents and the adverse reproductive health outcomes under consideration was relatively limited. 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.

Evaluating 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, 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.

The studies and their evaluation are described in the Evidence Profile and in the Summary of Evidence within the Technical Report.

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

Implications for policy makers and service delivery

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 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.

The individual epidemiological studies relevant to fuels and to specified solvents in relation to each of the adverse reproductive health outcomes under consideration provided some evidence of association or no association, however the body of evidence on which to report findings was not substantial. 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 exposures and preventive measures in relation to the relevant occupational exposures in women in the military.

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.