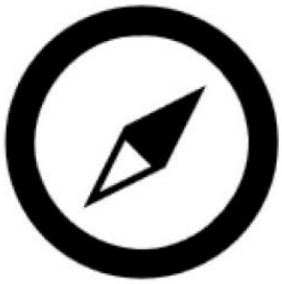
Evidence Compass



Summary Report

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

Summary of the Rapid Evidence Assessment

September 2018

Disclaimer

The material in this report, including selection of articles, summaries, and interpretations is the responsibility of the Monash University, and does not necessarily reflect the views of the Australian Government. The Monash University does not endorse any particular approach presented here. Evidence predating the year 2000 was not considered in this review. Readers are advised to consider new evidence arising post publication of this review. It is recommended the reader source not only the papers and reports described here, but other sources of information if they are interested in this area. The review has not been peer reviewed.

This project utilised a rapid evidence assessment (REA) methodology. An REA streamlines traditional systematic review methods in order to synthesise evidence within a shortened timeframe. The advantage of an REA is that it uses rigorous methods for locating, appraising and synthesising evidence from previous studies. Also, the studies can be reported with the same level of detail as in a systematic review, but results can be produced in substantially less time than is required for a full systematic review. The limitations of an REA mostly arise from the restricted time period, resulting in the omission of literature such as unpublished pilot studies, difficult-to-obtain material and/or non-English language studies. A strength, however, is that an REA can inform policy and decision makers efficiently by synthesising the evidence in a particular area within a relatively short space of time and at less cost.

Please address any comments or queries about this report to

EvidenceCompass@dva.gov.au

Executive Summary

- Following concerns expressed by some women in the Royal Australian Air Force (RAAF), in 2017 the Department of Veterans' Affairs (DVA) requested Monash Centre for Occupational and Environmental Health (MonCOEH) to conduct a Rapid Evidence Assessment (REA) on associations between occupational exposure to Military Aviation Turbine Fuels (MATFs) (herein referred to as jet fuels) and adverse reproductive health outcomes in women.

- The 2017 MonCOEH report[1] found that there were a limited number of studies that investigated the effects of jet fuel exposure and adverse reproductive health outcomes in women. The available data showed limited evidence of associations between jet fuel exposure and adverse fertility and pregnancy outcomes. The data showed some evidence of effects of jet fuel on hormones relevant to menstrual cycle function that could potentially have an impact on fertility.

- The aim for this project was to conduct a literature review of adverse sexual and reproductive health outcomes in men from occupational exposure to jet fuels of the types used in the Australian military. The REA was restricted to evidence from human studies.

- Specifically, the review aimed to determine whether there are any associations between occupational exposure to military jet fuels and any of the following adverse sexual and reproductive health outcomes in men:

    - Adverse reproductive outcomes: hypogonadism / primary testicular failure, androgen (testosterone) deficiency, impaired semen quality, reduced reproductive success (infertility, involuntary childlessness, not achieving desired family size, increased time-to-pregnancy, low fecundity, use of assisted reproductive technologies, and adverse pregnancy and fertility outcomes in female partners), altered reproductive hormones (testosterone, oestradiol, luteinising hormone (LH) and follicle stimulating hormone (FSH))

    - Adverse sexual outcomes: Erectile dysfunction, libidosexual dysfunction, psychosexual dysfunction

- Fuels most relevant to the military to include in the review were:

    - Military jet fuels: JP-4, JP-5, JP-7 JP-8, F 33, F 34

    - Civilian jet fuels: Jet A, Jet A-1, Jet B

- Using a comprehensive strategy, a search was conducted in 10 electronic scientific data bases and an online military health journal to identify peer-reviewed studies in humans, published between January 2000 and April 2018 in the English language. This was supplemented by a website search to identify any publicly available relevant government agency or independent medical scientific advisory committee reports, toxicological profiles, or risk assessment reports (herein referred to as reports).

- The studies were screened against strict inclusion and exclusion criteria. Only studies with male populations exposed to jet fuels and which reported sexual function or sexual or reproductive health outcomes were included.

- The studies that were included were assessed for quality and were evaluated for risk of bias, the data source, quantity of evidence and the generalisability of the body of evidence. The study quality implications were discussed conforming to the REA methodology protocol for the project.

- A total of eight records met the inclusion criteria; five primary studies and three reports. Of the primary studies, two were based on the same Australian retrospective cohort study (Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP)).[2, 3] The remaining three studies were from the USA; one was a prospective cohort,[4] one was a cross sectional study,[5] and one was a case control study.[6] Each of the five primary studies reported on different outcomes: male sexual function,[3] semen profile,[4] pregnancy outcomes in partners,[2] reproductive hormone assays[5] and incidence of birth defects.[6]

- The three reports, which were publicly available and included reviews of literature, were a US Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for jet fuels,[7] a US Institute of Medicine Committee on Gulf War and Health report,[8] and a US National Research Council Subcommittee on Reproductive and Developmental Toxicology report.[9].

- One study reported adverse sexual health effects[3] (i.e. erectile dysfunction and poor sexual function) in exposed male personnel compared to non-exposed. However, the participants were potentially exposed to a range of solvents in addition to jet fuel.

- The available evidence[2] reported no evidence of an association between male exposure to jet fuels and miscarriage or stillbirths[2] or difficulties in getting pregnant[2] for partners of exposed men. There was also no evidence that exposure to jet fuels is associated with changes in semen profile in men or serum levels of testosterone, oestradiol, luteinising hormone, prolactin or cortisol.[5] Very limited evidence was available suggesting an

association between congenital abnormalities of children born to fathers working in the petroleum and gas industry.[6]

- The range of the available studies was limited and did not enable all the adverse reproductive outcome endpoints identified in the aims to be assessed, , including very limited assessment of hypogonadism[5] and infertility.[4] No studies were identified that investigated the relationship between jet fuel exposure and the following male reproductive outcomes: primary testicular failure, androgen (testosterone) deficiency, and reduced reproductive success measures more specifically of involuntary childlessness, not achieving desired family size, and low fecundity. For reported pregnancies, the SHOAMP asked about difficulties getting pregnant and if reported seeing a specialist but not specifically about increased time-to-pregnancy or use of assisted reproductive technologies.

- This REA summarised the limited literature in relation to adverse reproductive health outcomes in men following occupational exposure to jet fuels. There was limited evidence of adverse sexual health outcomes. A limited number of studies and methodological limitations resulted in a relatively weak body of evidence. More substantial high quality evidence is needed to draw firm conclusions.. The data limitations included the small number of studies, studies with a small number of participants or cases and limited power to detect statistical significant differences in adverse reproductive outcomes, limitations in exposure assessment or in health outcome assessment, such as self-reported exposure and health outcomes, possible recall bias, and co-exposure with other solvent(s) or other chemical(s), which made it difficult to attribute any health effect to fuel exposure.

  Limitations of the REA include the omission of possibly relevant papers that were published prior to 2000 or after April 2018 and of non-English language papers. However, an ATSDR toxicological profile for JP-5, JP-8 and Jet A Fuels published as recently as 2017[7] did not identify articles not included in this review.

- Although the effects of occupational exposure of male servicemen to jet fuels used in the Australian military was of prime interest, the search was not restricted to articles on military populations. This resulted in few additional articles. This could be the result of scarcity of evidence on this topic and/or the restricted search period.

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

Background and methods

This report summarises the results of a REA undertaken to examine the effects of exposure to Military Aviation Turbine Fuels (MATFs), herein referred to as “jet fuels”, on sexual function and reproductive health in men and their (unexposed) female partners.

This review examined the empirical evidence for adverse reproductive outcomes (i.e. hypogonadism / primary testicular failure, androgen (testosterone) deficiency impaired semen quality, reproductive success (measured by infertility, involuntary childlessness, not achieving desired family size, time-to-pregnancy, fecundity, use of assisted reproductive technologies, and adverse pregnancy and fertility outcomes in female partners), altered reproductive hormones (testosterone, oestradiol, luteinising hormone (LH) and follicle stimulating hormone (FSH)) and sexual outcomes (i.e. erectile dysfunction, libidosexual dysfunction, psychosexual dysfunction) in men exposed to jet fuels.

Aviation fuel consists of a mixture of hydrocarbons[10, 11] and the fractions are blended with additives to ensure the required fuel performance specifications are met.[12] A list of military and civilian jet fuels used by Australian military aircraft was developed previously.[1] For consistency and comparability, the same list was used in the search strategy for this review. A comprehensive search from January 2000 to April 2018 in 10 electronic scientific databases and an online military health journal was conducted and was supplemented by a web search to identify published studies and any relevant publicly available reports. This review focused on potential exposure to jet fuel as a whole, so studies that only reported outcomes in relation to exposure to individual constituents (e.g. benzene) were not included.

Results

A comprehensive search in 10 electronic databases and an online military health journal generated 2025 records. An additional 53 records were identified from reference list checks and website searches. The titles and abstracts of these records were then screened to identify potentially relevant studies. Full texts of 113 studies were assessed for eligibility for inclusion. Five primary studies[2-6] and three reports[7-9] that reported exposure to fuels and reproductive and sexual outcomes in men were identified. Two primary studies[2, 3] were based on the Australian SHOAMP study[13] and three were from the USA.[4-6] Each of the five primary studies

reported on different outcomes: male sexual function,[3] semen profile,[4] pregnancy outcomes in partners,[2] reproductive hormone assays[5] and incidence of birth defects.[6]

A greater proportion of workers who took part in the Royal Australian Air Force (RAAF) Deseal/Reseal (DSRS) program self-reported erectile dysfunction, loss of interest in sex and problems with sexual functioning compared to workers who did not participate in DSRS activities[3] However, there was no statistically significant evidence of adverse effects on pregnancy outcomes and reported difficulties getting pregnant or seeing a fertility specialist reported in female partners of male DSRS workers compared to those of workers who did not participate in DSRS activities.[2] The Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP)[13] on which both studies[3,2] were based, was conducted in 2000-2002, potentially years after the exposure period over 1975-1999. Therefore, assessment of erectile dysfunction based on a self-report, but validated, questionnaire, recall bias, and the methodological difficulties in establishing and contacting the cohort of DSRS workers and assessing their exposures could have affected the findings. In addition, there was exposure to jet fuel but also to other agents including solvents such as methyl ethyl ketone (MEK).

A US study did not find any significant adverse effects on semen quality of military personnel who were exposed to fuels compared to aviation industry workers who were not exposed.[4] In this study, the participants were exposed to concentrations well below the American Conference of Government Industrial Hygienists recommended threshold limit values (TLV) and those mandated by the Occupational Safety and Health Administration as personal exposure limits (PEL).[4]

A cross-sectional US study on air force personnel reported an elevation of follicle stimulating hormone (FSH) levels and inhibin B levels in jet-fuel exposed male tank-entry personnel compared to non-exposed workers.[5] However, the study did not investigate whether this increase in FSH and inhibin B levels was due to desensitisation of the negative feedback mechanism or a direct exposure effect of jet fuel stimulating FSH secretion (thus leading to elevated inhibin B levels).

A US case control study reported a statistically significant increased risk of birth defects (atrial septal defects (n=11), limb deficiency (n=2), colonic atresia/stenosis (n=1) and glaucoma/anterior chamber defects (n=1)) in the newborns of female partners of male workers in the gas and petroleum industry compared to those who did not work in this industry.[6] However, the number of cases of birth defects were small and further details on occupational subgroups were not provided.

Three reports,[7-9] an ATSDR toxicological profile for jet fuels, an US Institute of Medicine Committee on Gulf War and Health report, and an US National Research Council Subcommittee on Reproductive and Developmental Toxicology report were included according to the REA protocol. The reports did not identify any additional studies on exposure to aviation fuels in males and reproductive health outcomes other than those described above.

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 prevalence or incidence rate), encompasses four components:

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

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

Implications for policy makers and service delivery

This REA identified peer-reviewed publications and reports available on the effect of jet fuels and adverse human male reproductive health and sexual function. Limited research evidence was available on the effect of exposure to jet fuels and reproductive health outcomes and sexual function in men. The implications of occupational exposure to jet fuels for men should be considered in the light of the findings and the limitations of evidence.

The evidence base was limited and available evidence came from studies with design limitations, co-exposures and methodological biases. Of the identified studies that reported associations between exposure to jet fuel and adverse reproductive health outcomes in men, the associations were in relation to reported adverse sexual health outcomes rather than reproductive health outcomes.

There is very limited evidence in relation to exposure to jet fuel in men and association with adverse pregnancy outcomes in female partners; the one identified study related to paternal occupation in the gas and petroleum industry which had methodological limitations in study design including exposure classification and limited generalisability to the study population of interest in this review.

Available limited evidence suggests that exposure to jet fuels as currently experienced, do not adversely affect sperm morphology and morphometrics and do not significantly affect male reproductive hormones. A cross-sectional study of reproductive health outcomes that identified a rise in FSH, which could result in a negative impact on spermatogenesis, was of a relatively weak study design, and semen analysis was not conducted and therefore it is not known how these changes affected spermatogenesis.[5]

It was difficult from the available evidence to determine whether subjects in the included studies were only exposed to jet fuels. It is possible that co-exposure to solvents or other chemicals could have contributed to the health outcomes.

This review did not identify any studies that had assessed associations between jet fuel exposure and reproductive success (i.e. time-to-pregnancy, fecundity, infertility, use of assisted reproductive technologies and not achieving desired family size).

Conclusion

This REA conducted a comprehensive search across 10 electronic databases, an online military health journal and other open access resources for studies published between 2000 and April 2018. The REA provided a summary of the available evidence in a shorter time frame than a full systematic review.

The review summarised the identified literature in relation to adverse reproductive health outcomes in males following occupational exposure to jet fuels of most relevance to the Australian military.

The existing body of literature on the association between occupational exposure to jet fuel and sexual and reproductive health outcomes in men is very limited. Of the five identified studies that investigated adverse reproductive health outcomes in men, the findings were in relation to reported adverse sexual health outcomes rather than reproductive health outcomes. It was difficult to establish strong conclusions without more substantial high quality evidence.

References

1. Kelsall HL, Glass DG, Priestly BG, Bell RJ, Newman DG, Wallace EM, et al. Literature review of effects of fuel and solvent exposure on human female reproductive outcomes. Report prepared for the Department of Veterans' Affairs. Monash University; 2017. Available at [https://www.dva.gov.au/sites/default/files/Question_14_Fuel_and_Solvent_Exposure_Technical_Report_Sept_2017.pdf], Accessed (22/04/2018)

2. D'Este C, Attia J, Brown A, Byles J, Schofield PW, Gibberd R, et al. Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP). Phase III Report on the General Health and Medical Study. Department of Veterans' Affairs 2004. Available at [https://web.archive.org/web/20080309023912/http://www.defence.gov.au/health/research/shoamp/i-SHOAMP.htm], Accessed (22/04/2018)

3. Brown A, Gibson R, Tavener M, Guest M, D'Este C, Byles J, et al. Sexual function in F-111 maintenance workers: the study of health outcomes in aircraft maintenance personnel. J Sex Med. 2009;6(6):1569-78.

4. Lemasters GK, Olsen DM, Yiin JH, Lockey JE, Shukla R, Selevan SG, et al. Male reproductive effects of solvent and fuel exposure during aircraft maintenance. Reprod Toxicol. 1999;13(3):155-66.

5. Kesner JS, Lemasters GK, Knecht EA, Krieg EF, Jr., Reutman SR. The effects of JP8 jet fuel on serum endocrine concentrations in men: risk assessment of acute exposure to jet fuel. In: Kendall RK, Smith E, editors. JP8: final risk assessment Kendall RK, Smith E, eds Brooks City-Base, TX: Air Force Institute for Operational Health. Air Force Institute for Operational, Health Risk Analysis Directorate, Texas. 2001. p. 91-6.

6. Desrosiers TA, Herring AH, Shapira SK, Hooiveld M, Luben TJ, Herdt-Losavio ML, et al. Paternal occupation and birth defects: findings from the National Birth Defects Prevention Study. Occup Environ Med. 2012;69(8):534-42.

7. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for JP-5, JP-8, and jet A fuels. Altanta, Georgia: Agency for Toxic Substances and Disease Registry (ATSDR) and U.S. Department of Health and Human Services; 2017. Available at [https://www.atsdr.cdc.gov/toxprofiles/tp121.pdf], Accessed (22/04/2018)

8. Institute of Medicine (IOM). Gulf War and Health: Volume 3: Fuels, Combustion Products, and Propellants. Washington, DC: The National Academies Press; 2005. 516 p.

9. National Research Council (NRC). Toxicologic Assessment of Jet-Propulsion Fuel 8. Washington, DC: The National Academies Press; 2003. 229 p.

10. Mehlman MA. Dangerous and cancer-causing properties of products and chemicals in the oil refining and petrochemical industry. VIII. Health effects of motor fuels: carcinogenicity of gasoline--scientific update. Environ Res. 1992;59(1):238-49.

11. Mehlman MA. Dangerous and cancer-causing properties of products and chemicals in the oil-refining and petrochemical industry--Part XXII: Health hazards from exposure to gasoline containing methyl tertiary butyl ether: study of New Jersey residents. Toxicol Ind Health. 1996;12(5):613-27.

12. International Agency for Research on Cancer (IARC). Occupational Exposures in Petroleum Refining: Crude Oil and Major Petroleum Fuels. World Health Organization, editor: International Agency for Research on Cancer - World Health Organization; 1989.

13. Department of Veterans' Affairs (DVA). F-111 fuel tank maintenance > Inquiries and studies > The SHOAMP. Department of Veterans' Affairs; 2014. Available at [https://www.dva.gov.au/benefits-and-payments/f-111-fuel-tank-maintenance/inquiries-and-studies/studies], Accessed (22/04/2018)