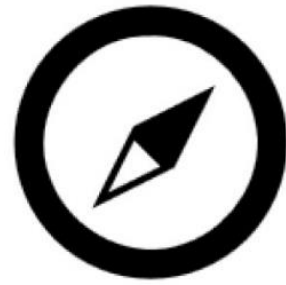


# Evidence Compass



## Summary Report

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

Rapid Evidence Assessment

January 2019

## **Disclaimer**

The material in this report, including selection of articles, summaries, and interpretations is the responsibility of the Monash Centre for Occupational and Environmental Health, School of Public Health and Preventive Medicine, Monash University, and does not necessarily reflect the views of the Australian Government. The Monash Centre for Occupational and Environmental Health does not endorse any particular approach presented here. Evidence was based on, but not limited to, medical scientific literature published since 2000 through June 2018. 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.

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The limitations of an REA mostly arise from the restricted time period, resulting in the omission of literature such as unpublished pilot studies, difficult-to-obtain material and/or non-English language studies.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.

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## Executive Summary

- The aim of this Rapid Evidence Assessment (REA) was to conduct a literature review of adverse sexual and reproductive health outcomes in men from occupational exposure to specified solvents relevant to the Australian military and any of the following health outcomes:
  - Adverse reproductive outcomes: hypogonadism / primary testicular failure, androgen (testosterone) deficiency, impaired semen quality, reduced reproductive success (infertility, involuntary childlessness, not achieving desired family size, increased time-to-pregnancy (TTP), low fecundity, use of assisted reproductive technologies, and adverse pregnancy outcomes or reduced fertility in female partners), altered reproductive hormones levels (testosterone, oestradiol, luteinising hormone (LH) and follicle stimulating hormone (FSH))
  - Adverse sexual outcomes: Erectile dysfunction, libidosexual dysfunction, psychosexual dysfunction
- Solvents relevant to the military included in this review were:
  - ethyl acetate, ethyl benzene, toluene, xylenes, acetone, isopropanol, methyl ethyl ketone (MEK), propylene glycol monomethyl ether (PGME), white spirit and trichloroethylene (TCE).
- This project was conducted using the Rapid Evidence Assessment (REA) methodology<sup>1</sup> as requested by the Departments of Veterans' Affairs and Defence. This was the same methodology as that used for two previous literature reviews: exposure to jet fuel and adverse reproductive outcomes in men<sup>2</sup> and jet fuel and specified solvent exposure and reproductive outcomes in women.<sup>3</sup> The solvent list was used previously for the female reproductive outcome review<sup>3</sup> and the adverse male reproductive outcomes of interest were used in the male reproductive outcomes and jet fuel exposure review<sup>2</sup> and were adopted without modification.
- Using a comprehensive strategy, a search was conducted in 10 electronic databases to identify relevant peer-reviewed studies in humans, published between January 2000 and June 2018 in the English language. Additionally, one military and veteran health journal was electronically searched to identify any published studies. This process 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 one or more of the specified solvents 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.
- A total of 34 records met the inclusion criteria. Of these, 18 records were publications (from 14 primary observational studies) and 16 records were reports. Three publications<sup>4-6</sup> were based on the same population of degreasing workers in Singapore, two were based on the same Australian retrospective cohort study (Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP)),<sup>7, 8</sup> and another two were based on a group of men monitored for exposure to organic solvents by the Finnish Institute of Occupational Health between 1965–1983.<sup>9, 10</sup>
- The designs of the 14 studies were: one prospective cohort (one publication<sup>11</sup>), one retrospective cohort (two publications<sup>7, 8</sup>), one case referent (two publications<sup>9, 10</sup>) and 11 cross-sectional (13 publications<sup>4-6, 12-21</sup>) studies.
- Ten publications reported outcomes related to fertility<sup>i</sup> and/or fecundity<sup>ii</sup>; six<sup>5, 11, 12, 16, 18, 21</sup> conducted semen analysis in exposed men, two reported time to pregnancy (TTP),<sup>14, 17</sup> one investigated fecundity ratios,<sup>9</sup> and the other<sup>8</sup> reported number of pregnancies, problems getting pregnant and visiting a specialist regarding fertility issues in partners of exposed men. The exposures varied across these studies and only three publications reported outcomes assessed in relation to a single specified solvent exposure; two reported on TCE<sup>5, 18</sup> and one on toluene.<sup>17</sup> In all the other publications, exposures to several solvents and associations with reproductive outcomes were reported and the men had been exposed to more than one solvent.
- Of the six publications that investigated semen profile, sperm motility was reported in five<sup>11, 12, 21, 5, 16</sup> a significant decrease in sperm motility was reported in three<sup>11, 12, 21</sup> and two<sup>5, 16</sup> reported no association with sperm motility. Benzene, toluene and xylene were present as co-exposures in all three studies that reported a reduction in sperm motility. The other two

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<sup>i</sup> the ability to deliver a live-born infant.<sup>22.</sup>

<sup>ii</sup> biological capacity for conception and may encompass hormonal profiles, gynecological health, sexual function, time to pregnancy (TTP), conception delays, pregnancy loss and (premature) reproductive senescence or menopause.<sup>22.</sup>

publications reported no association of TCE<sup>5</sup> or PGME (assessed through a urinary metabolite, 2-methoxypropionic acid (2-MPA))<sup>5, 16</sup> with sperm motility.

- Five publications<sup>4, 6, 13, 19, 20</sup> from four cross-sectional studies reported on endocrine profiles. Four publications<sup>4, 13, 19, 20</sup> reported serum levels of FSH, LH and testosterone. Toluene was investigated in three publications<sup>13, 19, 20</sup> and TCE in two.<sup>4, 6</sup> For TCE, exposure dose was quantified based on the number of years of occupational exposure to TCE. In TCE exposed workers, the studies found that the mean serum FSH, LH, and testosterone levels decreased with the number of years' exposure up to seven years of exposure, FSH levels were lower in those with greater than seven years of exposure. The association between exposure to toluene and reproductive hormone outcomes were equivocal; two publications<sup>13, 20</sup> reported no significant associations with FSH, LH and testosterone levels in the exposed group compared to the comparison group. However, one of these studies<sup>20</sup> reported significantly lower levels of FSH and LH in a subgroup of workers less than 40 years old. The third study<sup>19</sup> reported that exposure to toluene was associated with significantly lower levels of FSH, LH and free testosterone.
- Four studies (four publications) reported pregnancy outcomes in partners of exposed men; three<sup>10, 14, 15</sup> reported on spontaneous abortion and one on miscarriage.<sup>8</sup> Three publications<sup>8, 10, 14</sup> reported co-exposure to a number of solvents including solvents in general.<sup>8, 10</sup> None of the publications reported significant associations with pregnancy outcomes in partners of exposed men when the exposed group was compared with the comparison group without subgroup analysis. However, one publication<sup>10</sup> conducted a subgroup analysis and found a significant increase in risk of spontaneous abortion in the high toluene exposure subgroup and solvents in general.
- Two publications<sup>10, 14</sup> reported on the incidence of birth defects. One publication<sup>14</sup> found a significantly higher risk of congenital defects in the solvent-exposed group based on quantitative model predicted exposure estimates using toluene as a marker, but the numbers were low; based on 37 birth defects (398 pregnancies) in the exposed group and 11 birth defects (302 pregnancies) in the unexposed group. However, it was difficult to establish any clear association between exposure and outcome due to uncertainty in the specific solvent exposures. The other publication<sup>10</sup> did not find any association between toluene or xylene exposure and birth defects.
- One publication<sup>7</sup> reported adverse sexual health effects (i.e. erectile dysfunction and poor sexual function) in solvent exposed male Deseal/Reseal (DSRS) personnel compared to

non-exposed personnel. However, the participants had been exposed to a wide range of solvents.

- The range of the available studies was limited and did not investigate associations between specified solvents and all the specific adverse reproductive outcome endpoints identified in the aims. As an example, studies investigating not achieving desired family size and use of assisted reproductive technologies were not identified.
- The limitations of individual studies investigating associations between specified solvents and adverse male sexual and reproductive health outcomes included the small number of studies, limitations in exposure assessment or in health outcome assessment such as in self-reported outcomes, recall bias, and co-exposure with other solvent(s). For instance, some significant adverse effects were associated with exposure to a mixture of chemicals, some of which were not the aim of this REA. Therefore, establishing clear exposure-outcome associations was difficult. The omission of possibly relevant papers that were published prior to 2000 or after June 2018 and the omission of non-English language papers may have been minor limitations, but this was partly addressed by including relevant studies that were found during a reference check of included publications.
- The effects of occupational exposure of male service members to specified solvents used in the Australian military was of prime interest. However, the search was not restricted to articles on military servicemen and the review considered evidence on reproductive and sexual function outcomes in other occupational groups exposed to these solvents.

## **Evaluating the evidence**

The REA methodology<sup>1</sup> recommends assessing the quality of included studies for prevalence questions on four categories:

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

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

## Implications for policy makers and service delivery

This REA has identified peer reviewed, published studies and high quality report evidence available in relation to the effects of specified solvent exposure and adverse reproductive outcomes in men. The Summary of Evidence and Evidence Profile highlight where associations between occupational exposure to solvents and adverse reproductive outcomes have been reported and the strengths or limitations in relation to these. The number of studies identified for associations with male fertility / fecundity, levels of reproductive hormones, sexual function, and pregnancy outcomes in the partners of exposed men was limited. Very limited epidemiological evidence was available for the research question for men in military settings. The implications for occupational exposures for men in the military needs to be considered in the light of the findings of studies and the limitations of the evidence.

## Conclusion

This REA identified peer reviewed studies of the effects of occupational exposure of specified solvents in men and adverse effects on reproductive health outcomes. The search was comprehensive and 34 records including relevant studies prior to 2000 have been considered in the REA. The existing body of literature for those specified solvents and male reproductive outcomes was limited and establishing specific solvent-outcome association was also complicated by co-exposures of solvents within the scope of this review, as well as solvents that are beyond its scope.

In summary, in relation to the specified solvents considered, this review found:

- The most commonly assessed exposures were toluene, xylene and TCE; the evidence base for other specified solvents of interest was extremely limited.
- There was some limited evidence that occupational exposure to high concentration of a combination of solvents, including solvents of interest in this review such as TCE and BTEX, may be associated with adverse changes in the characteristics of semen.
- There was limited evidence of association with TTP or low fecundity and this did not suggest that specified solvent exposure in men was associated with increased time to pregnancy or reduced fecundity in couples.
- The evidence supporting an association of specified solvent exposure in men with increased risk of spontaneous abortion in their partners is limited and weak.

- The evidence of association of specified solvent exposure with stillbirth or preterm birth was very limited and did not provide evidence that specified solvent exposure in men was associated with increased risk
- There was very limited and conflicting evidence to suggest that specified solvent exposure to toluene in men is associated with higher risk of congenital malformations in babies of partners, and in relevant studies co-exposure of solvents including solvents that were not in the scope of this REA may have occurred.
- There is some weak and limited evidence to suggest that high TCE or toluene exposure in men is associated with reduced serum levels of FSH, LH and testosterone.
- The strength of available evidence was weak because there is a limited number of studies and weak study designs. The majority of evidence came from cross-sectional studies and, in some studies, co-exposure of specified solvents with other solvent(s) or chemical(s) at the workplace made it difficult to ascertain specific exposure-outcome associations. The quality of the studies varied. Overall, limitations of individual studies of the association between specified solvent exposure and adverse male reproductive health outcomes included limitations in study design, 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, and recall bias. The evidence from recent studies was scarce and many studies were conducted before 2000.
- It is difficult to establish strong conclusions on specific solvents without more high-quality evidence.



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