

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

Observational Studies

Authors & Year Country	Study design	Study pop ^a and sampling methodology	Study Group (N)	Comparison Group (N)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Brown et al. (2009) ² Australia	Retrospective cohort Postal questionnaire and clinical assessments	Personnel who participated in any F-111 DSRS activities between 1975-1999 N=1479 (males only) Eligible participants identified through maintenance logs, squadron photos, newspaper ads, websites and snowballing techniques	Exposed group at Amberley N=577	Technical personnel posted at RAAF base Richmond (NSW) (n=503)* Other personnel (non-technical) posted at Amberley base (n=399)*	<ul style="list-style-type: none"> Erectile function: 15 item self-reported questionnaire -International Index of Erectile Function (IIEF)³¹ General sexual functioning (two questions on loss of interest in sex and problems with sexual functioning) Prevalence and severity of anxiety and depression (Composite International Diagnostic Interview (CIDI)), a fully structured interview 	<p>“Exposure Questionnaire”, a mailed postal questionnaire, in which respondents indicated the programme(s) they had been involved in, duties, and the length of time.</p> <p>Assessment of possible confounding factors including BMI, blood pressure, medical conditions, psychological health, alcohol use, civilian use of chemicals.</p>	All males Mean age 44 to 45 years
<p>* comparison groups were obtained using stratified random sampling from the computerised Air Force Personnel Executive Management System, with stratification by gender, 5-year age group, posting1 category, and rank category.</p> <p>In analysis, the IIEF scale was dichotomised, with a cut-off score of 25 or less out of 30 providing an indication of clinically significant erectile dysfunction.⁴⁵</p> <p>Findings:</p> <p>No differences between the three groups with respect to the matching variables of rank, posting and age. Exposed at Amberley: mean 44 (±9.3) years BMI mean 28 (±4.1); Richmond mean 45 (±7.9) years, BMI mean 29 (±4.1); Non-technical at Amberley 44 (±7.8) years, BMI mean 30 (±4.9)</p> <p>Those in the exposed group were more likely to be depressed (n=66; 12%), compared to Amberley (n=24; 6.3%) or Richmond (n=26; 5.2%) groups (p=0.0002). Those in the exposed group were more likely to be anxious (n=106; 19%), compared to Amberley (n=49; 13%) or Richmond (n=36; 7.3%) groups (p=0.001).</p>							

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<p>Greater proportion of exposed group reported loss of interest in sex (n=234; 38%) compared to Amberley (n=105; 22%) (OR 1.91; 95% CI 1.37-2.67) and Richmond (n=126; 22%) (OR 1.72; 95% CI 1.26-2.33) groups.</p> <p>Greater proportion of exposed group reported problems with sexual function (n=197; 32%) compared to Amberley (n=93; 19%) (OR 1.91; 95% CI 1.34-2.75) or Richmond (n=91; 16%) groups (OR 2.33; 95% CI 1.64-3.29).</p> <p>Greater proportion of exposed group reported erectile dysfunction (n=169, 33%) compared to Amberley (n=91; 21%) (OR 1.71; 95% CI 1.24-2.36) or Richmond (n=104; 20%) (OR 1.87; 95% CI 1.39-2.52) groups.</p> <p>The findings indicated a significant association between exposure group and reported sexual function outcomes, after adjustment for other potentially confounding factors including depression and anxiety. Sensitivity analyses excluding participants who indicated no sexual partner or activity for the month did not influence the outcome.</p> <p>The study did not find a linear association between dose (duration of exposure) and loss of interest in sex (p=0.06) or loss of sexual function (p=0.2) between groups; no-dose-response relationship was evident.</p> <p>The authors concluded that there was an average two-fold increase in the odds of sexual dysfunction including erectile dysfunction in the DSRS exposed group compared to “different base, similar job” cohort (Richmond) and “same base-different job” cohort (Amberley).</p>							
D’Este et al. 2004 ⁴ Australia	Retrospective cohort Self-reported Female Reproductive Questionnaire administered in the Study of Health Outcomes in Aircraft Maintenance personnel (SHOAMP)	Female F-111 DSRS workers and female partners of male study participants who reported pregnancies during five posting periods over 1975-1999. Female DSRS workers (n=24) and female partners of male DSRS workers (n=767)	Exposed (n=206 reported 484 pregnancies in exposure period of interest)	Technical personnel posted at RAAF base Richmond (NSW) (n=203 reported 492 pregnancies in exposure period). Non-technical posted at Amberley base (n=143 reported 351 pregnancies in exposure period)	Reproductive health outcomes referenced to a posting date: <ul style="list-style-type: none"> • Pregnancy outcomes during the F-111 DSRS period • For any pregnancies recorded, asked if there were reported difficulties getting pregnant and if reported seeing a specialist Analysed female DSRS workers and female partners combined as: Pregnancy result- live birth vs other incl. still birth or miscarriage	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
<p>*SHOAMP had 4 programs: Program 1 (1977-1982), Wing program (1985-1992), Program 2 (1990-1993) and Spray seal (1996-1999)</p> <p>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 few participants.</p>							

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<p>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).</p> <p>Findings:</p> <p>N=552 total females included in analysis who reported pregnancies within exposure period of interest. N=1327 reported pregnancies eligible to be used in the analyses.</p> <p>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%) and exposed group (20%).</p> <p>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, CL 0.65-1.3)</p> <p>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)</p> <p>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)</p> <p>There was no dose response relationship for mild, moderate or prolonged exposure (p=0.99).</p> <p>Formal analysis for pregnancy outcomes regarding difficulties getting pregnant and visits to a specialist for fertility problems was not possible as key confounders such as maternal age 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.</p> <p>Conclusions: There was no evidence of an association in female DSRS personnel or female partners of male DSRS personnel and miscarriage or stillbirth, or in reported difficulties getting pregnant or seeing a fertility specialist.</p>							
Desrosiers et al. 2012 ³ USA	Case control study	National Birth Defects Prevention Study (NBDPS) eligible live births with 60 major birth defect categories and controls randomly selected from hospital records or birth certificates without major defects. 1997 to 2005 Study popn: 1492 cases, 5771 controls*	Fathers of 9998 cases N=71* fathers of cases who worked in gas and petroleum industry	Fathers of 4066 controls N=20* fathers of babies without major defects who worked in gas and petroleum industry	Babies with non-syndromic isolated and multiple birth defects reported in the NBDPS database Defect categories were considered to be associated with an occupation if 95% credible interval (CI) around the odds ratio (OR) for occupation-defect combinations with any exposed cases excluded the null, or if OR was ≥ 2.0 or ≤ 0.5 for either isolated defects or for all cases combined.	Paternal occupation histories reported by mothers in telephone interview re fathers' jobs 3 months preceding expended date of conception through the first month of pregnancy. <i>A priori</i> set of maternal confounding factors incl. residence at delivery, age, race/ethnicity, education, use of supplemental folic acid or prenatal vitamins, smoking and alcohol use.	No information on fathers across occupational groups incl. gas and petroleum workers were available
* only outcomes related to gas and petroleum workers are reported here							

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<p>Findings:</p> <p>71 (0.7%) fathers worked in the gas and petroleum industry in the study group and 20 (0.5%) in control group. There were 11 cases of atrial septal defects in the study group (OR 1.6; 95% CI 1.0-2.4), 2 cases of limb deficiency (OR 2.6; 95% CI 1.1-6.5), 1 case of colonic atresia/stenosis (OR 2.8; 95% CI 0.9-9.1) and 1 case of glaucoma/anterior chamber defects (OR 2.0; 95% CI 0.8-5.1).</p> <p>The authors concluded that paternal petroleum and gas worker occupation was associated with increased prevalence of birth defects in offspring.</p> <p>Several occupations were also associated with an increased prevalence of 3 or more birth defect categories, including: mathematical, physical and computer scientists; artists; photographers and photo processors; food service workers; landscapers and groundskeepers; hairdressers and cosmetologists; office and administrative support workers; sawmill workers; petroleum and gas workers; chemical workers; printers; material moving equipment operators; and motor vehicle operators, compared with manager/administrators and sales workers groups combined (primary referent group).</p>							
Kesner et al. 2001 ⁵ USA	Cross-sectional study (situated in a larger risk assessment) Questionnaire and venous blood samples	Personnel from United States Air Force (USAF) bases Sampling method not reported	Male tank-entry personnel with ≥9 months of persistent exposure to jet fuel, (i.e., one hour entry, twice a week) N=134	N=not reported USAF from 3 bases who did not routinely work with or have significant exposure to fuels or solvents	Venous blood analysed for endocrine concentrations: <ul style="list-style-type: none"> • Follicle stimulating hormone (FSH) • Luteinising hormone (LH) • Prolactin • Cortisol • Oestradiol • Inhibin-B • Total and free testosterone 	A self-reported questionnaire including job, months on the job, exposure, medical and demographic information. Correlation coefficients derived for each of the 8 hormonal endpoints against variables. Linear models assessed effect of months on the job and exposure and their interaction, controlling for confounders.	Males. Age not reported
<p>Findings:</p> <p>Study group characteristics were not reported.</p> <p>For FSH, the main effect of exposure was significant ($p = 0.03$), though none of the adjusted means were significantly different from each other. The slope for the high exposure group tended to greater than zero ($B=0.015$, $p=0.055$) FSH level was also directly related to age ($b = 0.10$, $p = 0.005$).</p> <p>The main effect of exposure was significantly related to inhibin B levels ($p=0.035$) Adjusted serum levels of the high exposure group were significantly greater than for the low exposure group.</p> <p>The association between months on the job and total testosterone was significant ($r=0.263$; $p=0.002$) Months on the job was inversely correlated with testosterone level but this association disappeared when adjusted against age in the multivariate analysis.</p> <p>The authors concluded that FSH levels may be higher in personnel who have worked longer in jobs with higher naphthalene exposure and that the results also suggest that men with higher naphthalene exposure have elevated inhibin B levels. The authors suggested this finding could be consistent with an exposure effect stimulating FSH secretion leading to elevated inhibin B levels, and/or a relative desensitisation of the feedback setting.</p>							

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LeMasters et al. 1999 ⁶	Prospective cohort (repeated measure design) Questionnaires administered face to face; exposure assessment and semen analysis	Volunteer civilian or active-duty military personnel at one USAF base who performed aircraft maintenance duties (N=58)	Jet fuel workers (N=15) Flight line workers (N=23) Sheet metal workers (N=6) Paint shop workers (N=6)	Not exposed (N=8)	Sperm production, structure and function: <ul style="list-style-type: none"> Sperm concentration (million per ml) Percent motile sperm Percent normal morphology Morphometry: <ul style="list-style-type: none"> Length (µm) Width (µm) Width to length ratio Standard chromatic structure assay (SCSA) <ul style="list-style-type: none"> % cells DNA denatured Time points of outcome assessment: <ul style="list-style-type: none"> Baseline At 15 weeks At 30 weeks 	Questionnaires: included medical and occupational history, lifestyle characteristics Standard personal industrial hygiene (IH) sampling and expired breath samples according to National Institute for Occupational Safety and Health (NIOSH) guidelines to measure following exposures: <ol style="list-style-type: none"> Jet fuel (primarily JP-4) as naphtha Total solvents [methyl ethyl ketone (MEK), methylene chloride, xylenes, toluene, and 1,1,1-trichloroethane (TCA)] Benzene 	Males ≤51 years Mean age, years (SD) Jet fuel workers: 24.1 (± 7.2) Flight line: 24.8 (± 8.3) Sheet metal: 34.5 (± 3.6) Paint shop: 31.7 (± 13.0) Comparison: 26.0 (± 6.0)
<ul style="list-style-type: none"> Jet fuel workers: mainly exposed to jet fuel (JP-4) and purging fluid; duties consisted of fuel delivery, fuelling/defueling aircraft, repairing fuel systems of F-16 aircraft Flight line workers: exposed to jet fuel and exhaust, solvents, and occasionally paint Sheet metal workers: performed assembly and maintenance activities, were exposed mainly to solvents, adhesives, and sealants, some purging fluid and jet fuel Paint shop workers: exposed to mainly solvents and paints <p>Findings:</p> <p>Exposure: The exposure assessment revealed that all the workers had low exposures for solvents (mean of <6 ppm, which was <10% of the Occupational Safety and Health Administration [OSHA] standard for all chemicals except benzene). For all exposed subjects, mean breath level of jet fuels measured as naphtha was 19.1 ppb (OSHA permissible exposure limit was 100 ppm).</p> <p>Reproductive assays:</p> <p>Sperm concentration (million/ml): The flight line group demonstrated a significant increase of 34.0% (p=0.01) at 15 weeks and 32.9% (p= 0.02) at 30 weeks. Paint shop group demonstrated a statistically non-significant increase of 33.4% (15 weeks) and 43.8% (30 weeks). Jet fuel group demonstrated 9.7% and 9.0% increase at the same time points, and unexposed group also demonstrated an increase (1.4% and 23.7%) for the same time points. Only sheet metal group demonstrated a decrease (18.3% and 19.5%) at weeks 15 and 30</p>							

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					respectively. The mean sperm concentration was 66.4 (±32.6) at baseline, 72.4 (±46.9) at 15 weeks and 73.8 (±47.7) at 30 weeks of exposure for the combined exposed groups (n=50). The reference values* were ≥20 (±60).		
					Mean sperm concentration (million/ml): was 66.4 (± 32.6) at baseline, 72.4 (± 46.9) at 15 weeks and 73.8 (± 47.7) at 30 weeks of exposure for the combined exposed group (n=50). Mean reference vale* was ≥20 (±60).		
					Sperm length (µm): Sperm length demonstrated a significant 2.1% (p= 0.02) and 2.9% (p= 0.02) decline at 15 and 30 weeks in the sheet metal group, but a significant (p≤ 0.01) 2.5% decline at 15 weeks and non-significant 1.1% decrease at 30 weeks also was found in the unexposed group. Paint shop workers reported 1.2% decrease at 15 weeks and no change at 30 weeks. Jet fuel group demonstrated 1.5% and 0.8% increase at 15 and 30 weeks respectively. The flight line group demonstrated a decrease of 0.3% and 1.6% at 15 and 30 weeks respectively.		
					Mean sperm length (µm): was 4.26 (± 0.28) at baseline, 4.25 (± 0.27) at 15 weeks and 4.21 (± 0.25) at 30 weeks of exposure for the combined exposed group (n=50). Mean reference value* was 4.5 (± 63).		
					Sperm width to length ratio: This ratio significantly declined in the unexposed (3.1%, p= 0.05) and the paint shop (3.4%, p= 0.02) groups at 30 weeks. The unexposed group also reported a non-significant decrease at 15 weeks (1.5%) but the paint shop group reported an increase of 1.0% at the same time point. Sheet metal group reported an increase of 0.6% and 2.0% as well as the jet fuel group (1.1% and 0.1%). Flight line group reported a decrease of 0.4% and 1.2% for the same time points.		
					Mean sperm width/length ratio was 0.67 (± 0.05) at baseline, 0.67 (± 0.04) at 15 weeks and 0.67 (± 0.04) at 30 weeks of exposure for the combined exposed group (n=50). Mean reference value* was 0.6 (± 63).		
					Percentage motility of sperm: Both unexposed group (15.9% and 8.1%) and flight line group (2.9% and 7.2%) reported an increase, but statistically non-significant, at 15 and 30 weeks respectively. For the same time points, sheet metal group (4.6% and 3.2%) and jet fuel group (2.1% and 6.2%) reported a decline. Paint shop group reported a decline of 6.4% at 15 weeks and a significant 19.5 decline (p=0.04) at 30 weeks. Five out of six painters reported a proportional decline of 3.5% to 43.7% between baseline and 30 weeks.		
					The mean percent (%) motile sperm was 44.5 (12 ±) at baseline, 43.7 (± 14.9) at 15 weeks and 42 (± 12.3) at 30 weeks of exposure for the combined exposed group (n=50). The reference values* were ≥50 (60).		
					Percent normal morphology: The mean percent normal morphology was 18.4% (± 6.6) at baseline, 17.8% (± 8.6) at 15 weeks and 18.1% (± 9.1) at 30 weeks of exposure for the combined exposed group (n=50). The mean reference value* was ≥14% (± 60)		
					Sperm directional movement: as measured by linearity (VSL/VCL) was significantly depressed at 30 weeks in the sheet metal (8.8%, p= 0.03) and the jet fuels (7.7%, p= 0.02) groups. The unexposed group also reported a decline (5.1% and 3.9%) for the same time points.		
					The mean percent DNA denatured cells was 18.3% (± 11.9) at baseline, 19.0% (± 11.4) at 15 weeks and 17.1% (± 9.3) at 30 weeks of exposure for the combined exposed group (n=50). The reference value* was 16.8% (± 7.2).		
					The authors reported that the findings indicated that for most sperm measures the mean values remained in normal range during the 30 weeks of exposure. When jobs were analysed by exposure groups some adverse changes were observed. The paint shop group had a significant decline in sperm motility at 30 weeks. Internal dose measures did not show a significant association with spermatogenic changes. Exposure to jet fuels did not indicate any obvious effect on semen quality. However, the authors cautioned ab the low statistical power when interpreting results and suggested further research to determine whether there could be effects from exposure to solvents (i.e. in paint shop group).		

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<p>*Reference values for WHO are consensus numbers. OSHA Permissible Exposure Limit (PEL) and ACGIH recommended Threshold Limit Value (TLV) for individual solvents, benzene, and jet fuel as naphthas are listed and identical unless reported otherwise. 1,1,1 trichloroethene=350 ppm; MEK=200 ppm; toluene 200 ppm PEL and 50 ppm TLV; methylene chloride=500 ppm PEL and 50 ppm TLV; benzene=1.0 ppm PEL and 0.5 ppm TLV; jet fuel as naphtha is 100 ppm PEL and unavailable for TLV.</p>							

Reports

Authors & Year	Country	Title and scope	Exposure(s) route	Reproductive and Developmental Effects	References
Agency for Toxic Substances and Disease Registry (ATSDR) (2017) ⁷	USA	<p>Toxicological profile for JP-5, JP-8 and Jet A Fuels.</p> <p>The profile was prepared in accordance with guidelines developed by ATSDR and the US Environmental Protection Agency (US EPA).</p> <p>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 substance's 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.</p>		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	No studies were located regarding developmental effects in humans after inhalation exposure to JP-5, JP-8, or Jet A fuels.	
			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 human reproductive, developmental or endocrine effects after dermal exposure to JP-5, JP-8, or Jet A fuels.	

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		The health effects section and human studies findings were considered in relation to this Evidence Profile			
<p>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 had evaluated neurologic, reproductive, genotoxic, or carcinogenic end points following inhalation exposure. No studies were identified on the effect of jet fuel exposure on reproductive health in men.</p>					
Institute of Medicine (IOM) (2005) ⁸	USA	<p>Gulf War and Health: Volume 3. Fuels, combustion products and propellants.</p> <p>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 during the Gulf War.</p>	Any	<p>Reproductive and developmental outcomes of interest included infertility, preterm birth and low-birth rate, birth defects and childhood cancers.</p> <p>The committee found one study on exposure to jet fuels and semen characteristics.</p> <p>No studies of infertility in women and exposure to fuels met the committee's inclusion criteria.</p> <p>No studies were reported for spontaneous abortion in veterans or that included occupational exposures.</p>	LeMasters 1999 ⁶ [reported above]
<p>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 the 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.</p>					
National Research Council (NRC) (2003) ⁹	USA	<p>Evaluating chemical and other agent exposures for reproductive and developmental toxicity.</p> <p>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.</p>	Inhalation and Dermal	One human study was identified that reported on exposure to jet fuels or solvents and effects on semen characteristics.	LeMasters 1999 ⁶ [reported above]
<p>Findings: One human study was identified that reported on possible reproductive toxicity following exposure to jet fuels or chemicals.</p>					

