

Evidence profile of included studies

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

Observational studies

Male sexual function (n=1)

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
Brown 2009 ⁴	Retrospective cohort Postal questionnaire and clinical assessments	Australia	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: self-reported questionnaire - International Index of Erectile Function (IIEF)⁵⁰ 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. 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.⁸¹</p> <p>Findings: 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>								

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
<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> <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>								

Endocrine profile (n=5)

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
Chia 1997 ¹	Cross-sectional Information collected through a medical examination & an interview questionnaire	Singapore	Male workers in an electronics factory who used trichloroethylene (TCE) as a degreaser N=450	Workers who volunteered for a free medical check and agreed for blood to be taken for hormonal assessment n=85	No comparison group	Hormonal assays of testosterone, Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH), dehydroepiandrosterone sulphate (DHEAS) and Sex-Hormone Binding Globulin (SHBG) were assessed via a single morning venous blood sample Covariates: Age, smoking history, and size of testes	Air: Measured using organic vapour monitors in 12 workers Urine: Spot sample analysed for trichloroacetic acid (a metabolite of TCE)	All male Age mean (SD) 27.8 (3.0) years Range 22-39 years
<p>Note: The analysis is based on years of exposure.</p> <p>Findings:</p>								

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
<p>Workers were generally exposed to below the threshold limit value (TLV) of 50 ppm in the air for toluene. However, the current ACGIH TLVs[®] for TCE is 10 ppm.⁵¹</p> <p>Mean hormonal levels of serum FSH, testosterone, LH and SHBG showed a decrease by years of exposure until 5-7 years of exposure and mean serum testosterone, LH and SHBG were at similar levels at ≥7 years. Mean FSH was lower at ≥7 years and significantly lower when compared with levels <3years (p<0.05).</p> <p>FSH: <3 years: 2.6, 3-5 years: 1.69, 5-7 years: 1.66, ≥7 years: 1.51 (IU/l)</p> <p>Testosterone: <3 years: 5.27, 3-5 years: 5.14, 5-7 years: 4.40, ≥7 years: 4.75 (ng/ml)</p> <p>LH: <3 years: 5.03, 3-5 years: 5.0, 5-7 years: 4.62, ≥7 years: 4.95 (IU/l)</p> <p>SHBG: <3 years: 33.00, 3-5 years: 28.90, 5-7 years: 23.20, ≥7 years:24.30 (nmol/ml)</p> <p>Authors considered that the findings indicated that reductions in FSH and testosterone in men exposed to TCE could be due to disruption of peripheral endocrine function via TCE induced reduction in liver production of SHBG, but that the longer terms implications of such findings remain ill-defined.</p>								
Gericke 2001 ¹⁰	Cross-sectional Data from a multi-centre controlled field trial conducted between 1993-1995 in 12 participating factories ⁵²	Germany	N=1077 (recruited) Current rotogravure printing workers who volunteered to participate and randomly selected by an industry association	n=768 (analysed) Male printers or helpers exposed to toluene	Non-printers n=309 External reference group from paper industry (n=109)	Serum FSH, LH and testosterone Covariates: age	Air: Ambient air at the work area through personal monitors ⁵² Blood: Before and after work-shift ⁵²	All males Not reported
<p>Note: Only male reproductive system-related outcomes are reported here. Median (range) exposure for toluene: [mg toluene / m³ air] Printers and helpers: 91 (1.6 – 800), Non-printers 17 (0.3-200); [µg toluene/litre blood] Printers and helpers 39 (1.7 – 911), Non-printers 14 (0.7 – 876). (10 mg toluene/m³=2.7 ppm)</p> <p>Findings:</p> <p>The study found no significant effect on serum FSH, LH, or serum testosterone when printers and helpers were evaluated against non-printers. Of exposed printers and helpers, 9% had FSH levels outside reference ranges (i.e. increased or decreased) compared to 10% non-printers (p=0.42). For LH, 8% of printers and 8% of non-printers were outside reference range (p=0.47) as well as 9% of printers and helpers compared to 13% of non-printers (p=0.07) for testosterone.</p> <p>The authors concluded that no clear-cut alteration in levels of male sex hormones was found in workers with long terms occupational exposure to toluene.</p>								
Goh 1998 ³	Cross-sectional Information collected through a medical	Singapore	Male workers in an electronics factory who used trichloroethylen	Workers who volunteered for a free medical check-up and agreed for blood to be	No comparison group	Serum testosterone and sex hormone binding globulin (SHBG) were measured in a single morning venous blood sample Covariates:	Air: Measured using organic vapour monitors in 12 workers Urine:	All males Mean age (SD) 27.8 (3.0) years

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
	examination & an interview questionnaire		e (TCE) as a degreaser N=450	taken for hormonal assessment n=85		Age, smoking, size of testis	Spot samples analysed for trichloroacetic acid	
<p>Note: The analysis is based on years of exposure</p> <p>Findings: A reduction in mean (SE) testosterone levels (ng/ml) was observed with years of exposure (<2 yrs: 5.71 (0.6), 2-4 yrs: 5.69 (0.6), 4-6 yrs: 5.28 (0.4) and ≥6 yrs: 4.60 (0.3). Mean (SE) SHBG levels (nmol/l) decreased with years of exposure (<2 yrs: 37.8 (3.8), 2-4 yrs: 33.0 (3.9), 4-6 yrs: 27.4 (2.4) and ≥6 yrs: 24.8.60 (1.8)), and mean levels in 4-6 year and ≥6 years of exposure groups were significantly less than the group with <2years of exposure</p>								
Svensson 1992a ¹⁶ (Title: Hormone status...)	Cross-sectional	Sweden	Toluene-exposed rotogravure printers, without signs of solvent-induced toxic encephalopathy N=20	Exposed n=20	Referents: male industrial workers from a margarine factory and a gelatin-extracting company, without exposure to organic solvents n=44	Serum levels of LH, FSH, prolactin (PRL), sex hormone binding globulin (SHBG), total and free testosterone (t-Test & f-Test) from two blood samples taken within 60 minutes interval at mid-day, mid-week, while in supine condition	Air: Personal sampling, drawn from the subject's respiratory zone at work was used to calculate daily time-weighted average (TWA) Blood: Two midday blood samples within 1hour interval to assess blood toluene, in the middle of a working week Adipose tissue: Biopsies of subcutaneous fat	All males Exposed mean age 48.2 (range 30-63) years Referents mean age 39.0 (range 23-63) years
<p>Note: Participants were assessed for signs of toxic encephalopathy by a screening questionnaire by Hogstedt et al.⁵³</p> <p>Findings: Median weekly TWA air level of toluene for the printers was 36 ppm (range 8-111 ppm). The exposed workers had a blood toluene of 1.7 µmol/l (median, range 1-6.6 µmol/l). Only six of the 21 referents who had their toluene analysed had concentrations above the detection limit with 0.1 µmol/l as the highest value. Median (range) of serum FSH, LH and f-Test were significantly lower in the exposed group compared to the referent group: FSH 3.2 (1.8-7.2) vs. 4.9 (1.8-17.3) IU/l (p=0.008); LH 6.1 (3.8-9.4) vs. 7.2 (4.9-14.4) IU/l (p=0.02) and f-Test 76.8 (48.6-107.2 vs. 86.8 (21.5-141.5) pmol/l (p=0.05) respectively. However, median serum PRL, SHBG and total t-Test were not significantly different: PRL 2.8 (1.3-6.2) vs. 3.4 (1.4-9.2) µg/l, SHBG 1.5 (0.9-3.7) vs. 1.6 (0.6-3.0) mg/ml and t-Test 5.8 (2.7-8.2) ng/ml vs. 6.6 (0.6-3.0) ng/ml, respectively. In eight printers, levels of FSH and LH increased during a 4 week vacation and levels of thyroid hormones decreased during the same period. The study concluded that the observed hormone level changes are likely to have been due to exposure to toluene, and that the results indicated a slight, reversible effect of toluene that could have been on the cortical level or on hypothalamic-pituitary axis.</p>								

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
Svensson 1992b ¹⁷ (Title: Neuroendocrine effects...)	Cross-sectional Clinical examination, information from medical records and personal interviews	Sweden	Rotogravure printers from two companies N=47	Printers exposed to toluene n=47	Unexposed referents from metal industry or hospital workshops n=46	Plasma concentrations of Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH), prolactin (PRL) and total testosterone (Test) were measured in a midweek venous blood sample Outcomes were categorised as: influence of present exposure and influence of cumulative exposure Covariates: age	Current exposure to toluene: Air: Personal sampling (workers wearing motor-powered syringes) and spot and area sampling Blood: Via pre and post shift venous blood	All males Exposed: Mean (range) 44.4 (23-62) years Referent group: Mean (range) 43.5 (20-61) years
<p>Note: The normal reference ranges for FSH, LH, PRL, and Test were considered as 0.3-2.7 µg/l, 0.3-1.4 µg/l, 2-12 µg/l, and 6-30 nmol/l respectively. Swedish threshold limit value (TLV) for toluene is 80 ppm at the time of the sampling.</p> <p>Findings:</p> <p>Toluene concentrations in blood ranged from 0.05-0.83 µmo/l pre-shift to 0.09-8.0 µmo/l post shift.</p> <p>There was no statistically significant difference in serum LH, FSH, PRL and total Test between total exposed workers compared with referents (0.9 vs. 1.0 µg/ml, 0.9 vs. 1.1 µg/ml, 3.0 vs 3.2 µg/ml and 15.8 vs. 16.0 nmol/l respectively). However, when stratified for age, significantly lower median serum hormone concentration levels of LH (0.8 vs. 1.1 µg/ml, p<0.01) and FSH (0.4 vs. 1.0 µg/ml, p<0.05) were observed in workers <40 years (n=14) in the exposed group compared to the referent group.</p> <p>For subjects exposed to toluene (six classes of average exposure concentrations <5 to >45ppm), increasing toluene exposure concentrations were significantly associated with decreasing concentrations of plasma LH (tau= -0.21, p=0.02) and testosterone (tau = -0.25, p = 0.02). No effects were seen with cumulative exposure.</p> <p>The study showed effects of toluene exposure on some hormone concentrations, although no statistically significant differences were found in any hormone concentrations between the total exposed compared with referent group. The authors concluded the study could indicate an effect of low toluene exposure on the hypothalamic pituitary axis, with a secondary decrease in testosterone secretion.</p>								

Pregnancy outcomes in partners (n=4)

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
D'Este 2004 ⁵	Retrospective cohort Self-reported Female	Australia	Female DSRS workers (n=24) and female partners of male DSRS	Exposed (n=206 reported 484 pregnancies in exposure	Technical personnel posted at RAAF base Richmond	Reproductive health outcomes referenced to a posting date: <ul style="list-style-type: none"> Pregnancy outcomes during the F-111 DSRS period 	Exposure was difficult to define. Advisors and key decision makers defined exposure at the program level.*	Age: 16-46 y Female (of male study

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
	Reproductive Questionnaire administered in the Study of Health Outcomes in Aircraft Maintenance personnel (SHOAMP)		workers (n=767) who reported pregnancies during five posting periods over 1975-1999	period of interest)	(NSW) (n=203 reported 492 pregnancies in exposure period). Non-technical posted at Amberley base (n=143 reported 351 pregnancies in exposure period)	<ul style="list-style-type: none"> 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. stillbirth or miscarriage	Exposure sub grouped for analysis by DSRS Program as: Program 1 1977-1982 Program 2 1991-1993	participants)
<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: Programme 1 and 2 as they had the greatest number of participants. Spray seal had very few participants.</p> <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 evidence of an association in female DSRS personnel or female partners of male DSRS personnel and miscarriage or stillbirth.</p>								
Hooiveld 2006 ¹¹	Cross-sectional Self-administered mailed questionnaire focused on most recent pregnancy. Two reminders at 2 & 4 weeks for non-responders	Netherlands	A random sample of male painters and carpenters born between 1950 and 1975, in the membership register of the Trade Union for Construction	Male painters who ever fathered a pregnancy and were exposed to solvents at 3 months before pregnancy n=398	Carpenters with nil or negligible exposure to solvents n=302	Information collected through the self-administered questionnaire: <ul style="list-style-type: none"> Preterm delivery (delivery <37 weeks of gestation) Low birth weight (<2.5kg) Birth defects in offspring Spontaneous abortion (a pregnancy that ended <20 weeks of gestation) Time to pregnancy (TTP) (cut off point 12 months) 	Exposure was assessed based on responses to questionnaire; job title at 3 months before pregnancy were combined with self-reported exposure to paints, thinners or cleaning agents. For quantitative exposure assessment the model described by Burstyn and Kromhout. ⁵⁴ was used as developed in a similar population in the Netherlands. Toluene was selected as a marker for solvent exposure, since	Not reported

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
			Workers in 2001 N=700			Covariates: year of pregnancy, maternal age at conception, paternal smoking and alcohol use before pregnancy, maternal smoking, alcohol use, chemical occupational exposure, physical occupational exposure, medication use during pregnancy	measured hydrocarbon exposures appeared strongly correlated ¹¹	
<p>Findings: There was no increased risk of prolonged TTP, low fecundity, spontaneous abortion (OR 1.1; 95% CI 0.4-2.7) or preterm births (OR 1.2; 95% CI 0.7-2.2) in partners of painters compared to carpenters. Birth defects in offspring of painters were significantly higher compared to unexposed carpenters (OR 2.4; 95% CI 1.2-4.9), mainly due to a higher risk of congenital malformations (OR 6.2; 95% CI 1.4-27.9). Malformations reported by painters were: cardiovascular (n=4), gastrointestinal (n=2), central nervous system (n=1), eye (n=1), urogenital malformations (n=1), oro-facial clefts (n=3), Down's syndrome (n=1), and other syndromes (n=3). Non-exposed workers reported 1 urogenital defect and 1 hip dysplasia</p>								
Taskinen 1989 ⁷ [See Sallmén et al. 1998 ⁶ for follow-up]	Case referent Mailed questionnaire Information on occupational exposures related to the study pregnancy was collected from men and, lifestyle factors and medical issues from the wives using a mailed questionnaire	Finland	Male workers who were monitored for organic solvent exposure* by the Finnish Institute of Occupational Health during 1965-1983 and in their first marriage during 1985 and with wives 18-40 years at first trimester n=371	Cases: Wives who had a spontaneous abortion or a congenitally malformed child n=120	Referents: Women who did not have a registered spontaneous abortion or a registered malformed child between 1973-1983 matched for age at conception (within 30 m) n=251	Pregnancies were identified from hospital discharge registers Spontaneous abortion were obtained from hospital polyclinics Congenital malformations were obtained from the Finnish Register of Congenital Malformations Covariates: paternal exposure to dusts, maternal exposure to organic solvents, heavy lifting, and previous spontaneous abortion	Exposure to various solvents were determined and quantified based on the responses to the questionnaire and biological monitoring data (blood and urine concentrations of some parameters) available at Finnish Institute of Occupational Health Quantification of exposure: High/frequent: daily exposure or biological measurements above reference values Intermediate: usage 1-4 days a week and biological measurements indicated intermediate/low exposure Low/rare: solvent handling occurred more rarely	Age not reported
<p>*trichloroethylene (TCE), tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, and toluene Note: Only outcomes related specifically to paternal exposure to toluene, xylene, acetone and/TCE are reported here.</p> <p>Findings:</p>								

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
<p>Spontaneous abortion:</p> <p>Toluene: Risk of spontaneous abortion was significantly increased in the wives of high/frequent exposure group (OR 2.3; 95% CI 1.1-4.7, p<0.05) but not in low/rare (OR 0.9; 95% CI 0.4-2.2) or intermediate (OR 0.7; 95% CI 0.3-1.7) exposure groups.</p> <p>Xylene: risk of spontaneous abortion was not increased in the wives of low/rare, intermediate or high exposed workers (OR 1.2; 95% CI 0.4-3.3, OR 1.7; 95% CI 0.7-4.2, OR 1.6; 95% CI 0.8-3.2 respectively).</p> <p>Paternal exposure to TCE and to acetone were not associated with spontaneous abortion (OR 1.0; 95% CI 0.6-2.0, OR 1.0; 95% CI 0.6-1.7 respectively) when not controlled for confounders. Adjusted values were not reported.</p> <p>Congenital malformations:</p> <p>The results available for congenital malformation were limited. In multivariate analysis when hip luxation was excluded, paternal exposure to toluene (OR 1.5; 95% CI 0.4-5.4) and xylene (OR 1.6, 95% CI 0.4-5.7) was not associated with risk of congenital malformations when adjusted for paternal dust exposure and maternal febrile diseases in the first trimester of pregnancy.</p>								
Lindbohm 1991 ¹²	Nationwide Hospital Discharge Register and hospital records (1973-1982) data on spontaneous abortion linked with census data (1975 & 1980)	Finland	All pregnancies with a diagnosis of spontaneous abortion (ICD-8 codes 643 and 645), induced abortion (ICD-8 codes 640-642) and birth (ICD-8 codes 650-662) between 1973 and 1982 N=99186	Incidence of spontaneous abortion from medically recognised pregnancies of the wives of men exposed to mutagenic agents n=959 (n=11570, all pregnancies)	Incidence of spontaneous abortion of medically recognised pregnancies of the wives of men not exposed to mutagenic agents n=7772 (n=87616, all pregnancies)	Data on spontaneous abortion between 1973 and 1982 were collected from nationwide hospital register and hospital clinics	Census data was used to identify the job category in husbands. Occupational exposure was determined by assessing job categories against Institute of Occupational Health measurements and Finnish register of Employees Occupationally Exposed to Carcinogens Three levels of exposures were determined: moderate/high, potential/low and no exposure	Not reported
<p>Note: Only results for trichloroethylene (TCE) (low and moderate or high exposure) are reported here.</p> <p>Findings:</p> <p>TCE was not associated with spontaneous abortion in the wives of exposed workers; 5 spontaneous abortions were reported in 66 pregnancies (OR 0.9; 95% CI 0.3-2.1, adj for age).</p>								

Fertility / fecundity (n=10)

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
Chia	Cross-sectional	Singapore	Male workers in an	Workers who volunteered for	No comparison	Semen was analysed for volume, sperm density,	Air:	All male

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
1996 ²	Information collected through a medical examination and an interview questionnaire		electronics factory who used trichloroethylene (TCE) as a degreaser N=450	a free medical check-up and agreed to have their semen analysed n=85	group. Results compared to WHO criteria	percent motile sperm, percent normal sperm morphology-measured in a morning semen sample after 3 days of sexual abstinence Covariate: marital status	Measured using organic vapour monitors in 12 workers Urine: Spot samples analysed for trichloroacetic acid (TCA)	Age Mean (SD) 27.8 (3.0) years
<p>Findings: The workers were generally exposed to below the threshold limit value (TLV) of 50 ppm in the air for TCE. The current ACGIH TLVs[®] for TCE is 10 ppm.⁵¹ For all workers, mean semen volume, sperm density and mean sperm motility were within WHO reference ranges, except for mean percent normal sperm morphology which was below the WHO reference value. Mean (SD) [WHO reference values]: Volume: 2.6 (1.2) ml [≥2], sperm density: 59.8 (2.7) million/ml [≥20.0], sperm motility: 50.8 (14.0) % [≥50], normal morphology: 25 (9.4) % [≥30]. Comparison between high exposure (urinary TCA ≥25 mg/g creatinine) and low exposure (urinary TCA <25 mg/g creatinine): There was no statistically significant difference between high and low exposure groups in volume, sperm motility and normal morphology. However mean sperm density was significantly lower in the high exposure group compared to the low exposure group (mean (SD) 56.9 (3.0) vs. 63.6 (2.2), p=0.0442), although both groups were above the WHO standard normal sperms density of 20million/ml of ejaculate.</p>								
De Celis 2000 ⁹	Cross-sectional Medical history (including reproductive history) & physical examination	Mexico	Workers employed in a rubber factory in Mexico City N=90	Workers from the production area exposed to a mixture of hydrocarbons for ≥2 years n=48	Workers from the administrative office not exposed to this mixture of hydrocarbons n=42	Semen was analysed for liquefaction, volume, pH, viscosity, sperm agglutination, nonspecific aggregation, sperm count, % spermatozoa with motility of grades 1–3 and immotile sperm, and concentration of white blood cells from three weekly semen samples obtained following sexual abstinence for 3 days	Air: Continuous monitoring of environmental concentrations by passive organic vapour monitor during a workday	Exposed Mean (SD) age 32 (5) years Unexposed 31.5 (5) years All males
<p>Findings: Workers were exposed to the following hydrocarbon concentrations: ethylbenzene; 220.7–234 mg/m³ (50–53 ppm), benzene; 31.9–47.8 mg/m³ (10–15 ppm), toluene: 189.7–212.5 mg/m³ (50–56 ppm), and xylene, 47–56.4 mg/m³ (10–12 ppm). The current ACGIH TLVs[®] are: ethylbenzene 20 ppm, benzene 0.5 ppm, toluene 20 ppm, xylene 100 ppm.⁵¹ The proportion of subjects with ejaculates with normal characteristics was greater in the unexposed compared with exposed group (76% vs 17%). The exposed group had significantly increased abnormal semen viscosity (OR 4.00, 95% CI 1.53-10.58; p<.001), liquefaction (OR 3.99, 95% CI 1.45-11.44; p<.002), sperm aggregation (p<0.001), sperm count (OR 14.13, 95% CI 3.60-78.72; p<.001) and mean motile sperm (p<0.001). Asthenozoospermia (reduced sperm motility) and abnormal spermatozoa were more common in the exposed workers compared to the unexposed workers (OR 9.67, 95% CI 3.11-32.91; p<.001 and OR 27.82, no CI provided, p<.001 respectively).</p>								

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
No differences were found in the volume of semen and mean percentage of live spermatozoa between exposed and unexposed workers. The authors concluded that exposure to the hydrocarbons possibly results in damage to the spermatogenic process.								
D'Este 2004 ⁵	Retrospective cohort Self-reported Female Reproductive Questionnaire administered in the Study of Health Outcomes in Aircraft Maintenance personnel (SHOAMP)	Australia	Female DSRS workers (n=24) and female partners of male DSRS workers (n=767) who reported pregnancies during five posting periods over 1975-1999	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. stillbirth 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 range: 16-46 y (Wives of male study participants)
*SHOAMP had 4 programs: Program 1 (1977-1982), Wing program (1985-1992), Program 2 (1990-1993) and Spray seal (1996-1999)								
Findings: 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. There was no association between all exposed (in all programmes) and unexposed (p=0.54) in number of pregnancies (Amberley vs exposed OR=1.13, CL 0.75-1.72, Richmond vs exposed OR=0.92, CL 0.65-1.3). Similar results were observed when analysis was performed based on the programme (see below). <ul style="list-style-type: none"> Programme 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) Programme 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 response relationship for mild, moderate or prolonged exposure (p=0.99). 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.								
Hoiveld 2006 ¹¹	Cross-sectional Self-administered mailed	The Netherlands	A random sample of male painters and carpenters born between 1950 and	Male painters who ever fathered a pregnancy and exposed to solvents at 3	Carpenters with nil or negligible exposure to solvents	Following information was collected through the self-administered questionnaire: <ul style="list-style-type: none"> Preterm delivery (delivery <37 weeks of gestation) 	Exposure was assessed based on responses to questionnaire; job titles at 3 months before pregnancy were combined with self-reported exposure to paints, thinners or cleaning agents and compared to	Not reported

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
	questionnaire focused on most recent pregnancy. Two reminders at 2 & 4 weeks for non-responders		1975, in the membership register of the Trade Union for Construction Workers in 2001 N=700	months before pregnancy n=398	n=302	<ul style="list-style-type: none"> Low birth weight (<2.5kg) Birth defects in offspring Spontaneous abortion (a pregnancy that ended <20 weeks of gestation) Time to pregnancy (TTP) (cut off point 12 months) Covariates: year of pregnancy, maternal age at conception, paternal smoking and alcohol use before pregnancy, maternal smoking, alcohol use, chemical occupational exposure, physical occupational exposure, and medication use during pregnancy	the model described by Burstyn and Kromhout. ⁵⁴ in a similar population in the Netherlands	
Findings:								
There was no increased risk of prolonged TTP in partners of painters compared to carpenters (OR 1.1; 95% CI 0.7-1.9).								
Lemasters 1999 ⁸	Prospective cohort (repeated measure design) Questionnaires administered face to face; exposure assessment and semen analysis	USA	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 works (n=6) Paint shop workers (n=6)	Not exposed n=6	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 Sperm chromatin 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 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 	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)

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
						Covariates: age, race, smoking, alcohol consumption, presence of sexually transmitted diseases, hot baths and season the sample was taken		Comparis on group: 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>Only outcomes related to flight line workers, sheet metal workers and paint shop workers are reported here because they were most likely to be exposed to solvents</p> <p>Findings:</p> <p>Exposure: Most men were exposed to more than one solvent that was consistently low, therefore a “total solvent” value was derived by summing the concentrations of the analytes MEK, methylene chloride, xylenes, toluene and TCA for the two exposure cycles. The exposure assessment identified that all the workers had low exposures to solvents (mean <6 ppm, which was <10% of the Occupational Safety and Health Administration [OSHA] standard for all chemicals except benzene).</p> <p>Reproductive assays:</p> <p>Mean (SD) values for all exposed workers at baseline, 15 weeks, and 30 weeks of exposure respectively compared to [WHO reference values]:</p> <ul style="list-style-type: none"> ○ Sperm concentration (million per ml): 66.4 (32.6), 72.4 (46.9), and 73.8 (47.7) [≥ 20 (60)] ○ Percent motile sperm (%): 44.5 (12.0), 43.7 (14.9), and 42.0 (12.3) [≥ 50 (60)] ○ Percent normal morphology (%): 18.4 (6.6), 17.8 (8.6), and 18.1 (9.1) [≥ 14 (60)] <p>For most sperm measures, mean values remained in the normal range throughout the 30 weeks of exposure.</p> <p>Analysis by job groups:</p> <p>Sperm concentration (million/ml): Flight line group had 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). 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 respectively.</p> <p>Sperm length (μm): Sheet metal group had a significant 2.1% ($p=0.02$) and 2.9% ($p=0.02$) decline at 15 and 30 weeks, but unexposed group also had a significant 2.5% ($p\leq 0.01$) decline at 15 weeks and non-significant 1.1% decrease at 30 weeks. Paint shop workers had a 1.2% decrease at 15 weeks and no change at 30 weeks. The flight line group had a decrease of 0.3% and 1.6% at 15 and 30 weeks respectively.</p> <p>Sperm width to length ratio: This ratio declined significantly in the paint shop (3.4%, $p=0.02$) and unexposed (3.1%, $p=0.05$) 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%. Flight line group reported a decrease of 0.4% and 1.2% for the same time points.</p> <p>Percentage motility of sperm: Both flight line group (2.9% and 7.2%) and unexposed (15.9% and 8.1%) groups had a statistically non-significant increase at 15 and 30 weeks respectively. For the same time points, sheet metal group (4.6% and 3.2%) had a decline. Paint shop group had 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 had a proportional decline of 3.5% to 43.7% between baseline and 30 weeks.</p>								

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
The authors concluded that when jobs were analysed by exposure subgroups, some adverse changes were observed: men involved in aircraft painting operations, with relatively high exposure to solvents, had a significant decline in sperm motility at 30 weeks. Internal dose measurements were not associated with spermatogenic changes.								
Multigner 2007 ¹³	Cross-sectional Medical interviews to assess medical, surgical, urogenital and reproductive history through a standardised questionnaire and clinical examination	France	Men employed in a permanent position at the Paris Municipality during the period 2000–2001 and aged 20–55 years and volunteered to participate N=98	Workers exposed to ethylene and/or propylene glycol ethers (who declared using a glycol-ether containing product in last 10 years) n=48	Workers not exposed to chemicals between years 1990-2000 n=50	Semen characteristics: volume (ml), sperm density (million/ml), total sperm count (millions) motile sperm (%), sperm morphology (%) were assessed in samples collected after 3-5 days of sexual abstinence 2-3 months after exposure measurement Morning blood samples: assessed for FSH (IU/l), LH (IU/l) and Inhibin B (pg/ml) concentrations collected 2-3 months after exposure measurement Covariates: age, body mass index, alcohol and tobacco consumption, history of genital infections and season of sperm analysis	Exposure to glycol ethers and other agents with reproductive toxicity during last 10 years was assessed by direct interview on professional and/or domestic use Urine: Two urine samples, one month apart collected at the end of two working weeks assessed for metabolites of one propylene glycol ether derivative (2-methoxypropionic acid [2-MPA, derived from the minor β isomer of propylene glycol methyl ether or PGME]) and five ethylene glycol derivatives.	All males Exposed age mean (SD) 41.6 (8.7) years Non-exposed 40.3 (8.1) years
Note: only outcomes of associations with 2-MPA are reported below Findings: Urinary 2-MPA was not significant correlated with seminal volume, sperm density, sperm count, two measures of motile sperm, and morphology (Standardised coefficients of linear regression R (95% CI): 0.05 (-0.15 to 0.025), 0.03 (-0.18 to 0.23), 0.06 (-0.14 to 0.26), -0.03 (-0.23 to 0.18), 0.01 (-0.19 to 0.21) and -0.03 (-0.24 to 0.18 respectively). Urinary 2-MPA was not significant correlated with serum testosterone, FSH, LH and inhibin-B. (Standardised coefficients of linear regression R (95% CI): -0.21 ((-0.40 to 0.01), -0.12 (-0.31 to 0.08), -0.01 (-0.21 to 0.20) and 0.07 (-0.13 to 0.27) respectively).								
Plenge-Bönig 1999 ¹⁴	Cross-sectional Face-to-face interviews by trained interviewers using a modified	Germany	Male workers in printing industry exposed to toluene were selected by stratified	Time to pregnancy (TTP) n=162 Periods of unprotected	Unexposed comparison group (based on exposure assessment	Fecundability ratio (FR) [based on time to pregnancy (TTP) or periods of unprotected intercourse not leading to pregnancy (PUNP) by survival analysis with proportional hazards model	Exposure was assessed and quantified based on the work history: High: ink controllers or operators Medium: galvanisers, Low: book stackers and binders. No exposure (referent)	57% of men were >40 years

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
	version of European study on infertility and subfecundity questionnaire ⁶¹		random sampling N=300	intercourse not leading to pregnancy (PUNP) n=7	in previous years	Covariates: age at time of starting unprotected intercourse, smoking, parity, ethnicity, pelvic inflammatory diseases, planning of the pregnancy and frequency of intercourse		
<p>Note: only data related to partners of male workers are reported here. The two periods, TTP or PUNP, are called time of unprotected intercourse (TUI), independent of their outcome.</p> <p>Findings:</p> <p>There was no association between exposure of men to toluene and duration of TUIs, after adjustment for age and smoking of the partner (FR 1.05; 95% CI 0.93-1.19, p=0.43). Use of the four exposure categories did not affect the result (no exposure reference group n=65 periods; low exposure: n=27 periods (FR 0.78; 95% CI 0.47-1.29), medium exposure: n=17 periods (FR 0.81; 95% CI 0.45-1.46), high exposure: n=60 periods (FR 1.11; 95% CI 0.75-1.62)</p>								
Rasmussen 1988 ¹⁵	Cross-sectional Data collected through occupational medical interview	Denmark	All known working metal degreasers in a well-defined geographical area exposed to high doses of trichloroethylene (TCE) N=99	Workers degreasing for >20h per week and who delivered a semen sample n=12	Non-exposed physicians working at university institutions n=14	Semen characteristics: sperm count (million/ml), sperm morphology, the presence of two fluorescent bodies (YFF%) in spermatozoa (which may indicate the presence of non-disjunction of the Y chromosome during spermiogenesis) Covariates: Evidence for X-ray examination, febrilia (not defined but may mean fever or fever of unknown origin), viral disease during the last three months prior to sampling, and alcohol consumption	Not reported (may have been based on the information collected at occupational medical interview)	All males Age mean (range) Exposed 35.5 (20-62) years Unexposed 36.3 (29-42) years
<p>Findings:</p> <p>Note: Briefly, spermatogonia are immature germ cells that undergo a process of mitotic division, differentiation and meiotic divisions and development into mature sperm</p> <p>There were no significant differences in sperm count and morphology in semen of exposed and unexposed groups.</p> <p>The YFF% was increased in the exposed group but this was not statistically significant (mean 1.7; 95 CI 1.4-2.0 vs. 1.4; 95% CI 1.1-1.7, p>0.10).</p> <p>The authors concluded that no effect on male germ cells was demonstrated.</p>								
Sallmén 1998 ⁶	Cross-sectional	Finland	Men monitored for exposure to organic	Wives with a clinically recognised	Wives of workers who were not-	Fecundability density ratio (FDR)	Paternal work history, detailed work tasks, and details of handling the monitored or other solvents during	Wives of males

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
[Extension of Taskinen et al. 1989] ⁷	A mailed questionnaire to collect information on fertility. New data was collected including on medical and surgical history, treatment for infertility, and menstrual history and cycle.		solvents* by the Finnish Institute of Occupational Health between 1965–1983 N=282	pregnancy of workers who were exposed to solvents n=221	exposed and had given birth without having a spontaneous abortion or a malformed child n=61	Covariates: short menstrual cycle, long or irregular menstrual cycle, older age at menarche, frequency of intercourse, maternal age, maternal exposure to organic solvents, and a variable controlling for missing information	the calendar year in which his wife's pregnancy started had been collected previously ⁷ Three exposure levels were determined: <ul style="list-style-type: none"> high/frequent (the worker handled solvents daily or biological measurements indicated clear occupational exposure) intermediate (the solvent was used 1-4 days a week, and level of exposure was low), low/rare (solvent handling occurred more rarely). 	18-21 years: 7.4% 21-31 years: 75.5% 31-35 years: 11.7% 36-40 years: 5.0%
<p>Note: *trichloroethylene (TCE), tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, and toluene</p> <p>Findings: Paternal exposure to TCE, toluene or xylene were not associated with a significant effect on fecundity when compared to unexposed fathers:</p> <ul style="list-style-type: none"> o TCE: FDR (95% CI) low 0.99 (95% CI 0.63-1.56) and intermediate/high 1.03 (95% CI 0.60-1.76) o toluene: FDR (95% CI) low/intermediate 0.76 (95% CI 0.52-1.09) and high 0.93 (95% CI 0.62-1.40) o xylene: FDR (95% CI) low/intermediate 0.75 (95% CI 0.52-1.09) and high 0.91 (95% CI 0.61-1.36) <p>High/frequent and low/intermediate exposure to organic solvents were related to decreased fecundability among primagravidas (FDR 0.36; 95% CI 0.19-0.66, and (non significantly) FDR 0.53; 95% CI 0.27-1.04 respectively) but not among couples with at least one previous pregnancy.</p>								
Xiao 2001 ¹⁸	Cross-sectional 1994-1996) Information collected via interviews	China	Married workers with ≥1 year working history at shoemaking, spray painting, or paint manufacturing exposed to high airborne levels of benzene, toluene and xylene N=56	Workers who volunteered to donate blood and semen samples n=24	Non-exposed managers matched for age, occupation and physical activity n=37	Semen characteristics including liquefaction time, pH, sperm concentration, total sperm count, percentage vitality, sperm activity, acrosin activity, seminal fructose and γ-Glutamyltransferase (γ-GT) activity were measured in semen samples collected after 48 hours of sexual abstinence Covariates: Not reported	Blood: Analysed for benzene, toluene, and xylene	Exposed Age mean (SD) 33.18 (6.88) years Unexposed 31.78 (6.36) years All males

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 concentrations of airborne benzene, toluene, xylene in workplaces were 103.34 (0~7070.3), 42.73 (0~435.8), 8.21 (0~133.1) mg/m ³ respectively (method of measurement not reported). The current ACGIH TLVs [®] are: benzene 0.5 ppm, toluene 20 ppm, xylene 100 ppm. ⁵¹								
Exposed and non-exposed groups were similar for age (years), work standing (years), duration of marriage (years), duration of smoking (years), smoking quantity (pieces per day), duration of drinking (years) and drinking volume (ml/d).								
In exposed group, benzene, toluene and xylene was present in 13, 11 and 11 out of 24 worker's blood respectively. Semen samples were provided by 17 exposed workers and benzene, toluene and xylene was present in 12, 6 and 10 worker's semen respectively. These solvents were not detected in blood and semen in the control group.								
There was no significant difference between mean volume of semen, pH value, liquefaction time, sperm density and total sperm count in exposed and unexposed groups.								
In exposed group the following parameters were reduced: sperm activity (grade) (mean (SD)): 2.52 (0.96) vs. 3.17 (0.75), p<0.01; acrosin activity (mean (SD)): 18.02 (7.24) vs. 30.74 (10.05) U/L, p<0.001. γ -GT activity 1714.43 (873.88) vs 2418.97 (411.92) U/L, p<0.05. LDH-C4 (%) 13.48 (3.64) vs 19.14 (2.10), p<0.001.								
There were negative correlations between sperm vitality, sperm activity, acrosin activity or LDH-C4 relative activity and working duration.								
The authors concluded that the results suggested that the mixture of these solvents could affect the quality of semen and sperm by influencing the function of the testicle and / or the function of the accessory gonad.								

Reports

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Toluene					
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2000) ⁴⁰	The Netherlands	Toluene – Evaluation of the effects on reproduction, recommendation for classification. The peer-reviewed report for toluene 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.	Toluene	Five publications that investigated occupational exposure of men to toluene (or mixture of organic solvents including toluene) and reproductive health effects were identified. <ul style="list-style-type: none"> One study found spontaneous abortion was slightly, not statistically significantly, higher among the wives of men occupationally exposed to toluene (crude OR 1.5; CI 0.9-2.5). However, high or frequent exposure to toluene was associated with spontaneous abortion OR 2.3; CI 1.1-4.7). Another study found median serum concentration of FSH, LG and free testosterone were lower in the toluene exposed group. 	Taskinen et al. 1989 ⁷ Svensson et al. 1992 ¹⁶

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				<ul style="list-style-type: none"> ○ In another study, increasing concentrations of toluene were significantly associated with decreasing concentrations of LH and testosterone. ○ In a prospective study in which workers were exposed to a number of solvents, mean values of most sperm measures of the exposed group remained within the normal range throughout the 30 weeks exposure period even though some variations in subgroup analysis were observed. ○ Another study reported exposure of male workers did not result in an effect on fecundity (fecundity ratio 1.05; 95% CI 0.93-1.19). 	<p>Svensson et al. 1992¹⁷</p> <p>Lemasters et al. 1999⁸</p> <p>Plenge-Bönig and Karmaus 1999¹⁴</p>
<p>Findings: The committee concluded that it is not clear if the observed effects were due to toluene exposure alone or to other compounds in the working place and concluded that therefore, available data are not sufficient to assess its effects on human fertility and draw any conclusion for toluene.</p>					
Agency for Toxic Substances and Disease Registry (ATSDR) (2017) ⁴⁶	USA	<p>Draft Toxicological Profile for Toluene</p> <p>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.</p> <p>The health effects section and human studies findings were considered in relation to this Evidence Profile.</p>	Toluene	<p>Six publications that investigated occupational exposure of men to toluene (or mixture of organic solvents including toluene) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> ○ The incidence of spontaneous abortion exceeded population norms among the wives of small groups of 28–48 male workers exposed to toluene; however, exposure levels were not reported in these studies and only a small number of cases were included. ○ In another study, fecundity was decreased in female workers, but not in male workers. ○ No statistically significant changes were observed in serum FSH, LH, or testosterone levels in male rotogravure workers compared with unexposed referents ○ Significantly decreased serum levels of LH, FSH, and testosterone were found in male toluene-exposed rotogravure printers, compared with unexposed referents. ○ Increasing workplace air concentrations were not significantly ($p>0.05$) associated with plasma concentrations of LH, FSH, testosterone, or prolactin, after adjustments for age, in a study of male toluene-exposed printers 	<p>Lindbohm et al. 1992⁷⁷</p> <p>Taskinen et al. 1989⁷</p> <p>Plenge-Bönig and Karmaus 1999¹⁴</p> <p>Gericke et al. 2001¹⁰</p> <p>Svensson et al. 1992¹⁶</p> <p>Svensson et al. 1992¹⁷</p>
<p>Findings: Current data do not provide convincing evidence that acute or repeated inhalation exposure to toluene in males may cause reproductive effects.</p>					
National Research Council (NRC) 2014 ⁴⁴	USA	Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 17	Toluene	Three publications that investigated exposure of men to toluene and developmental and reproductive health effects were identified.	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		Committee on Acute Exposure Guideline Levels; Committee on Toxicology; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Research Council		<ul style="list-style-type: none"> An experimental study that reported subtle changes in LH and FSH in men following controlled exposure to 3-h, 50 ppm via a mouthpiece. No effect on blood testosterone was found. Another study found no effect of chronic toluene exposure on FSH, LH, or testosterone of 1,077 male subjects compared with a referent group. Some indications of lower concentrations of LH, FSH and testosterone were identified in another study. 	<p>Luderer et al. 1999⁶⁷</p> <p>Gericke et al. 2001¹⁰</p> <p>Svensson et al. 1992¹⁶</p>
<p>Findings: Data regarding human developmental and reproductive toxicity are restricted to chronic exposures and include only continuous occupational or abuse situations. These studies provide little quantitative information regarding dose response.</p>					
<p>Trichloroethylene</p>					
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2003) ⁴¹	The Netherlands	<p>Trichloroethylene – Evaluation of the effects on reproduction, recommendation for classification.</p> <p>The peer-reviewed report for Trichloroethylene was prepared for the Ministry of Social Affairs and Employment, the Netherlands, to provide advice regarding classifying potentially toxic effects of occupational exposures to toluene.</p>	Trichloroethylene	<p>Three publications that investigated occupational exposure of men to trichloroethylene (or mixture of organic solvents including trichloroethylene) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> One study reported no difference between exposed and non-exposed groups in terms of sperm count or morphology, but in the exposed group a slightly higher (statistically insignificant) prevalence of mature spermatozoa containing two fluorescent Y bodies was observed (may be indicative of Y-chromosomal nondisjunction). Another study that investigated exposure to styrene, xylene, toluene, tetrachloroethylene, trichloroethylene and 1,1,1-trichloroethane reported no association between paternal occupational exposures to trichloroethylene and the incidence of spontaneous abortion (crude OR 1.0; 95% CI 0.6-2.0). Another study that included no non-exposed control group compared results with WHO criteria. There were no differences in volume, motility and morphology among the high-exposure (urine trichloroacetic acid concentration > 25 mg/g creatinine) and low-exposure (urine trichloroacetic acid concentration < 25 mg/g creatinine) groups. In the same group of workers serum concentrations of several hormones were measured. Except for a positive correlation between urine levels of trichloroacetic acid and insulin levels there were no consistent relationships 	<p>Rasmussen et al. 1988¹⁵</p> <p>Taskinen et al. 1989⁷</p> <p>Chia et al. 1996²</p> <p>Chia et al. 1997¹ Goh et al. 1998³</p>

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				between the urine concentration of trichloroacetic acid and serum levels of hormones.	
<p>Findings: The report did not identify studies relevant to paternal occupational exposure and developmental toxicity. The human studies on the potential effects of occupational exposure to trichloroethylene on fertility did not show significant effects or the results of the studies were inconsistent and difficult to interpret. Therefore committee decided not to classify trichloroethylene with respect to effects on fertility because of lack of appropriate data.</p>					
Agency for Toxic Substances and Disease Registry (ATSDR) (2014) ⁴⁷ and US Environmental Protection Agency (EPA) 2011 ³⁵	USA	<p>Draft Toxicological Profile for Trichloroethylene</p> <p>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.</p> <p>The health effects section and human studies findings were considered in relation to this Evidence Profile.</p> <p>The US EPA Toxicological Review is intended to provide scientific support and rationale for the hazard and dose-response assessment in Information on the Integrated Risk Information System (IRIS) pertaining to chronic exposure to trichloroethylene.</p>	Trichloroethylene (TCE)	<p>Eight publications that investigated occupational exposure of men to TCE (or mixture of organic solvents including trichloroethylene) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> ○ Men working in dry cleaning or metal degreasing reported 30% decreased potency ○ Male workers in a money printing shop reported decreased libido (33%), compared to 3 men in the control group (10%) ○ TCE exposed metal degreasers reported non-significant increase in percentage of two YFF in spermatozoa, but no effect on sperm count or morphology ○ Another study on Chinese descent working in an electronics factory reported decreased normal sperm morphology and hyperzoospermia ○ Another study on the same population reported increased DHEAS and decreased FSH, SHBG and testosterone levels; dose-response observed ○ Another study on the same population reported decreased serum levels of testosterone and SHBG were significantly correlated with years of exposure to TCE; increased insulin levels for exposure <2 years ○ A study on men occupationally exposed to solvents, no effect on fecundability (as measured by time to pregnancy) was reported. ○ In another study on male mechanics, infertility could not be assessed for association with TCE as the controls were five men also in treatment for infertility 	<p>Bardodej and Vyskocil 1956⁶⁵ El Ghawabi et al. 1973⁶⁶</p> <p>Rasmussen et al. 1988¹⁵</p> <p>Chia et al. 1996²</p> <p>Chia et al. 1997¹</p> <p>Goh et al. 1998³</p> <p>Sallmen et al. 1998⁶</p> <p>Forkert et al. 2003⁶⁴</p>
<p>Note: The two reports are presented together above as both reports included the same primary epidemiological studies.</p> <p>Findings: The reports did not offer conclusions based only on the above studies. The ATSDR report summarised the effects of TCE exposure in men and reproductive behaviour, sperm quality and fertility and did not offer conclusions specific to exposure of TCE in men. However, it stated that toxicity of TCE to the male reproductive system is demonstrated in animals. The EPA reported that observed adverse reproductive health effects of TCE exposure in men were altered sperm morphology, hyperzoospermia, altered endocrine function, decreased sexual drive and function, and altered fertility.</p>					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
National Research Council (NRC) 2007 ⁴³	USA	Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues by Committee on Human Health Risks of Trichloroethylene; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies of the NRC	Trichloroethylene (TCE)	<p>Eight publications that investigated occupational exposure of men to TCE (or mixture of organic solvents including TCE) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> One study reported decreased libido in male workers exposed to TCE but no control group was present. In another study, sperm counts and morphology as well as Y chromosomal nondisjunction during spermatogenesis did not differ between male factory workers exposed to TCE at least 20 hours/week and physician controls In another study, there were no differences between groups for any of the sperm parameters including volume, motility, and morphology; the values for both groups were within the standards of the World Health Organization (WHO) except density. Further analysis of the same group revealed that the age of workers and years of exposure to TCE were significantly negatively correlated with testosterone concentrations. When the men were stratified by years of exposure, FSH was significantly reduced only in men exposed >7 years. LH and testosterone were statistically equivalent for all durations. The third study on the same population found that Sex-hormone-binding globulin was significantly reduced for 4-6 years and for >6 years of TCE exposure. One study examined eight mechanics with clinical infertility who had occupational exposure to TCE for at least 2 years. Seminal fluid from all eight subjects contained TCE, chloral, and trichloroethanol, whereas dichloroacetic acid and trichloroacetic acid were present in only two and one sample, respectively. Neither TCE nor its metabolites was detected in the five control male seminal fluid samples. Spontaneous abortion was associated with increased paternal exposure to solvents (adjusted OR 2.3; 95% CI 1.1, 5.0). 	<p>Bardodej and Vyskocil 1956⁶⁵ Rasmussen et al. 1988¹⁵</p> <p>Chia et al. 1996²</p> <p>Chia et al. 1997¹</p> <p>Goa et al. 1998³</p> <p>Forkert et al. 2003⁶⁴</p> <p>Taskinen et al. 1989⁷</p>
The committee recommended that more research is needed to better understand the effects of TCE on sperm and possible consequences for reproduction. The committee also added mechanistic studies are needed to determine what metabolites are responsible for the effects.					
Xylene					

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 (2000) ³⁹	The Netherlands	Xylene – Evaluation of the effects on reproduction, recommendation for classification. The peer-reviewed report for Xylene was prepared for the Ministry of Social Affairs and Employment, the Netherlands, to provide advice on classifying potentially toxic effects of occupational exposures to xylene.	Xylene	Three publications that investigated occupational exposure of men to xylene (or mixture of organic solvents including xylene) and reproductive health effects were identified. <ul style="list-style-type: none"> One study reported that the incidence of spontaneous abortion among the wives of men frequently exposed to xylene or exposed to high concentrations of xylene was slightly, but not statistically significantly, increased (adjusted OR 1.6; 95% CI 0.8-3.2). This study also found that there was no significant association between paternal exposure to xylene and the incidence of congenital malformations (OR 1.6; 95% CI 0.4-5.7). In a prospective study, in which workers were exposed to a number of solvents mean values of most sperm measures of the exposed group remained within the normal range throughout the 30 week exposure period even though some variations in subgroup analysis were observed. In another study in which the workers were exposed to number of solvents including xylene (ethylbenzene, benzene and toluene), the incidence of abnormal characteristics found in the semen of exposed men was higher than in the semen of unexposed workers, including alterations in viscosity, liquefaction capacity, sperm count, sperm motility and the proportion of sperm with normal morphology. 	Taskinen et al. 1989 ⁷ Lemasters et al. 1999 ⁸ De Celis et al. 2000 ⁹
<p>Findings: In the studies of Taskinen et al.,⁷ no effects of exposure to xylene (no other exposures) on abortion and fecundity were observed. In the studies of Lemasters et al.⁸ and of De Celis et al.⁹ only the effects of exposure to a mixture of solvents on sperm parameters were studied.</p> <p>The committee concluded that occupational exposure to mixtures of organic solvents, including xylenes, has been shown to increase the incidence of spontaneous abortion among the wives of exposed men and to increase the incidence of abnormal characteristics of sperm of exposed men.</p>					
Agency for Toxic Substances and Disease Registry (ATSDR) (2007) ³⁶	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	Xylene	One publication that investigated occupational exposure of men to xylene (or mixture of organic solvents including xylene) and reproductive health effects were identified. <ul style="list-style-type: none"> No human data were available regarding endocrine effects following inhalation exposure to mixed xylene or xylene isomers. No studies were located regarding reproductive effects in humans following oral exposure to mixed xylene or individual isomers. 	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		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.		<ul style="list-style-type: none"> No studies were located regarding reproductive effects in humans or animals after dermal exposure to mixed xylene or xylene isomers. However, one study suggested that paternal exposure to xylenes in the workplace may increase the likelihood of abortion; however, this study was limited by the size of the sample population. 	Taskinen et al. 1989 ⁷
<p>Findings: Available studies of developmental or reproductive toxicity from occupational exposure to xylene are not definitive because of the small number of subjects and/or concurrent exposure to other chemicals.</p>					
Ethylbenzene					
Agency for Toxic Substances and Disease Registry (ATSDR) (2010) ⁴⁵	USA	Toxicological Profile for Ethylbenzene	Ethylbenzene	<p>No publication that investigated occupational exposure of men to ethylbenzene (or mixture of organic solvents including ethylbenzene) and reproductive health effects were identified.</p> <ul style="list-style-type: none"> No studies were located regarding reproductive effects in humans following inhalation exposure to ethyl-benzene. No studies were located regarding developmental effects in humans following inhalation exposure to ethylbenzene. No studies were located regarding reproductive effects in humans following oral exposure to ethylbenzene. No studies were located regarding developmental effects in humans or animals following oral exposure to ethylbenzene. No studies were located regarding the reproductive health or developmental effects in humans after dermal exposure to ethylbenzene. 	
<p>Findings: No human studies that investigated occupational exposure of ethylbenzene in men and reproductive health outcomes were identified.</p>					
Stoddard Solvent					
Agency for Toxic Substances and Disease Registry (ATSDR) (1995) ³⁸	USA	Toxicological profile for Stoddard Solvent	Stoddard Solvent	<p>Two publications that investigated exposure of men to Stoddard Solvent and reproductive hormones were identified.</p> <ul style="list-style-type: none"> Seven men who were exposed for 6 hours/day for 5 days to 616 mg/m³ of vaporized white spirits had a decrease (p<0.05) in serum FSH levels at 24 and 96 hours after the initiation of exposure as compared to pre-exposure levels. In another study, 11 men in a printing factory were occupationally exposed to a wide variety of solvents, 	Pedersen and Cohr 1984 ⁶⁸

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				including 294 mg/m ³ of white spirits for 1-17 years. Sperm counts, motility, and morphology were monitored for 2 months, and all values were normal.	Tuohimaa and Wichmann 1981 ⁶⁹
Findings: No human studies for oral or dermal exposure of Stoddard Solvent in men and reproductive health outcomes or developmental abnormalities were identified.					
Multiple solvents					
Institute of Medicine (IOM) of the National Academies (2003) ⁴²	USA	<p>Gulf War and Health: Vol 2 Insecticides and solvents</p> <p>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.</p> <p>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.</p>	Multiple solvents	<p>Eight publications that investigated occupational exposure of men to organic solvents and semen and semen characteristics were identified.</p> <ul style="list-style-type: none"> ○ One study reported that exposure to solvents, defined by work area and personal measurements, was not associated with any decline below normal limits in the measures of semen quality as defined by WHO reference values. There were conflicting results from subgroup analysis based on the job description, and the results were mostly within reference ranges, the study concluded that these conflicting results are even less suggestive of an association between exposure to solvents and semen characteristics. ○ In a case-control study that investigated male painters and their partners for infertility consultation, Changes in semen parameters were not found to be associated with exposure to organic solvents as a general category when evaluated in the total population (OR 0.98; 95% CI 0.60–1.59) or in men with primary infertility (OR 1.15; 95% CI 0.66–1.99).* ○ Reported on two studies in Canada: One study reported increased risk of low active sperm count with high exposure to solvents (OR 3.83; 95% CI 1.37–10.65) and moderate exposure (OR 2.07; 95% CI 1.24–3.44). Another study reported a strong association only in the men with high exposure to solvents (OR 2.90; 95% CI 1.01–8.34).* ○ Another study found associations between solvent exposure and several measures of abnormal semen characteristics (based on WHO guidelines).* ○ A study on metal workers exposed to trichloroethylene found no association between exposure and semen characteristics ○ Two studies found that exposure to toluene was associated with lower blood concentrations of FSH, LH, 	<p>Lemasters et al. 1999⁸</p> <p>Tielemans et al. 1999⁷²</p> <p>Cherry et al. 2001⁷⁰</p> <p>Oliva et al. 2001⁸</p> <p>Rasmussen et al. 1988¹⁵</p> <p>Svensson et al. 1992^{16, 17}</p>

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				<p>prolactin, and testosterone in young male rotogravure printers when compared with factory workers.</p> <ul style="list-style-type: none"> ○ Studies of exposure to trichloroethylene among 85 male workers found moderate decreases in FSH and testosterone with increasing duration of exposure <p>Three publications that investigated occupational exposure of men to organic solvents and infertility were identified.</p> <ul style="list-style-type: none"> ○ One study did not find an effect on TTP in the men who were exposed to toluene on fecundity (FR 1.05; 95% CI 0.93–1.19) and there was no relation to exposure category (none, low, medium, or high). ○ Another study did not find any association between solvent exposure and TTP; an adjusted fecundability measure (fecundability density ratio [FDR]) of 0.80 (95% CI 0.57–1.11) for high or frequent paternal exposure and a similar result for low or intermediate exposure (FDR = 0.74, 95% CI 0.51–1.06). ○ A study of solvent-exposed male workers also found an elevation in the risk of conception delay of more than 6 months (OR 1.69; 95% CI 0.62–4.62).* <p>Two publications that investigated occupational exposure of men to organic solvents and spontaneous abortion were identified.</p> <ul style="list-style-type: none"> ○ One study reported Increased risk associated with exposure to solvents used in petroleum refineries (OR 2.2; 95% CI 1.3–3.8) and solvents used in the manufacture of rubber products (OR 1.9; 95% CI = 1.2–2.8).* ○ Another reported increases in risk in association with high or frequent paternal exposure to toluene (OR 2.3; 95% CI 1.1–4.7), high or frequent use of organic solvents (OR 2.6; 95% CI 1.2–5.9), and high or frequent use of miscellaneous organic solvents (OR 2.1; 95% CI 1.1–3.9). <p>One publication that investigated occupational exposure of men to solvents and congenital malformations were identified.</p> <ul style="list-style-type: none"> ○ One study did not find an increased risk associated with paternal exposure to solvents at any level (OR 0.7; 95% CI 0.4–1.1), low solvent exposure (OR 0.6), or moderate to high solvent exposure (OR 0.9).* 	<p>Chia et al. 1997¹ Goa et al. 1998³</p> <p>Plenge-Bonig and Karmaus 1999¹⁴</p> <p>Sallmén et al. 1998⁶</p> <p>Figa-Talamanca et al. 2000⁷³</p> <p>Lindbohm et al., 1991¹²</p> <p>Taskinen et al., 1989⁷</p> <p>Blatter et al. 1997⁷⁴</p>
<p>Note: *Analysis for general solvent exposure Findings:</p>					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
<p>The committee concluded that there is inadequate/insufficient evidence to determine whether an association exists between exposure to specific organic solvents under review or solvent mixtures and male or female infertility after cessation of exposure.</p> <p>Studies of TTP and other measures of infertility have found inconsistent associations with exposure to solvents regarding paternal exposures.</p> <p>Only a few studies have examined the potential for an association between preconception exposure to solvents among males and spontaneous abortion, and their results have been inconsistent.</p> <p>Few studies of solvent exposure and congenital malformations focused on preconception exposure of either mothers or fathers.</p>					
Methyl ethyl ketone					
Agency for Toxic Substances and Disease Registry (ATSDR) (1992) ³² Addendum 2010 ³³	USA	Toxicological Profile for 2-Butanone The purpose of the addendum is to provide a non-peer reviewed supplement of the scientific data published in the open peer-reviewed literature since the release of the profile in 1992.	Methyl Ethyl ketone		
<p>Findings: No publications that investigated occupational exposure of men to 2-Butanone and reproductive or developmental effects following inhalation, oral or dermal exposure were identified.</p>					
Acetone					
Agency for Toxic Substances and Disease Registry (ATSDR) (1994) ³⁷ Addendum 2011 ³⁴	USA	Toxicological profile for Acetone The purpose of the addendum is to provide a non-peer reviewed supplement of the scientific data published in the open peer-reviewed literature since the release of the profile in 1994.	Acetone		
<p>Findings: No publications that investigated occupational exposure of men to acetone and reproductive or developmental effects following inhalation, oral or dermal exposure were identified.</p>					