Evidence Profile

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

Observational studies – jet fuels

Authors & 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
Reutman et al. (2002)	Cross-sectional study. Data collected by: telephone and in person interview, self-report via diary entry, exhaled breath, and urine sample analysis	USA	Female United States Air Force (USAF) employees: civilian and active military female personnel at 10 USAF bases were screened for age, medication use, medical diagnoses, and surgical procedures. Non-smokers were targeted. (N=335)	Completed questionnaire and daily diaries N=170 (51%) Subgroup: Endocrine data and provided urine samples (n=100) Subgroup: Endocrine and breath analysis data (n=63 breath samples)		Reproductive endocrine endpoints predictive of non-conceptive menstrual cycles measured using urinary endocrine markers: • Preovulatory luteinizing hormone (LH) • mid-luteal phase pregnanediol 3-glucuronide (Pd3G) • mid-luteal estrone 3-glucuronide($E_1$3G) • follicle phase Pd3G. Menstrual cycles were calculated from diary records. Morning urine samples were collected daily. Urinary endocrine measurements and menses dates were used to derive the endocrine endpoints.	Internal doses of aliphatic and aromatic hydrocarbons (HCs) from fuels and solvents (reported in Tables 2 & 3) measured by post-shift exhaled breath analysis for exposure to aliphatic (C_6-C_{16}) and aromatic (BTEX) HC levels. Exposure characterised as low versus high exposure groups for C_6-C_{16} and BTEX based on the median. Reported exposure to fuels (not clearly stated but indirectly reference made to JP-8 predominance in introduction) (and solvents) and job titles/codes collected and compared.	Age: 18-42 y Female
Findings: There was no significant (p≤0.05) difference in endocrine levels between self-reported exposed versus non-exposed participants when examined bivariately or in multivariable regression models including potential confounders and covariates. Urinary preovulatory LH mean levels (unadjusted) were significantly lower (p=0.01) in the high versus low aliphatic HC exposure group (mean ± SD 15.4±8 versus 22.6± 12.0 mIU/mgCr) respectively. For mid Pd3G, mid $E_1$3G and follicle phase Pd3G there were no significant differences in the mean endocrine levels (unadjusted) in the high versus low aliphatic HC exposure group (high 10.5± 7.4 versus low 10.0± 6.3), (24.9± 13.1 versus 27.2± 13.6) and (1.2± 0.8 versus 1.2 ± 0.7) respectively.								

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For BTEX, the urinary preovulatory mean LH levels (unadjusted) were also significantly lower in the high exposure group (15.8± 8.2 versus 22.0± 12.2 mIU/mgCr). For BTEX there were no significant differences between the high and low exposure groups for the other three endocrine markers. Adjusted regression analysis of the four endocrine outcomes separately showed that preovulatory LH levels were significantly lower β= -7.34 (p=0.007) in women whose total aliphatic HC levels were above the median (high dose). Reported hours of exposure were consistent with job categories (women in fuel handling, flight line and maintenance jobs reported more exposure than 'non-exposed' jobs) but were similar for women with high and low levels of aliphatic and BTEX HCs in exhaled breath and some possible explanations were considered.								
Hourani & Hilton (2000)	Case–control study. Mailed questionnaire sent as a reproductive health survey	USA	All pregnant Navy active duty women, who, based on hospital records, visited an inpatient/ outpatient obstetric clinic at any of three Navy hospitals (San Diego, Portsmouth, Jacksonville, to enable large numbers and aviation occupations) Jan to Oct 1993 (N=3099)	Response rate 56% among reached, 38% among target subjects. Women >30 y with a hospitalised foetal death outcome under-represented. So analyses restricted to women whose pregnancy in 1993 resulted in a live birth and who had none or any of five outcomes (n=1032)	Civilian beneficiaries identified from San Diego clinic N=109 (Response rate 66% among reached, 49% among targeted) included in initial analyses	Mother reported adverse live–birth outcomes: • low birth weight (<2500g at birth) • preterm birth (<37 weeks gestation) • small for gestational age (yes/no) • birth defect (yes/no) • foetal distress prior to or during delivery (yes/no) Cases: defined as women with ≥1 of five adverse outcomes. Controls: women with none of the adverse outcomes	Exposures included: • Duty station at pregnancy inception (ship vs shore) • Mother or father had spent time in Persian Gulf since 1990 • Mother-reported maternal and paternal occupational and environment exposures (yes/no) in 3 months preceding conception including: petroleum products (eg jet fuel and diesel fuel). Level of exposure and route of exposure was not documented. • Other variables including demographics, maternal medical history, and lifestyle factors	Age: 17-44 y Female
Findings: Active duty women were significantly more likely than civilian beneficiaries to report exposure to petroleum products (χ^2=10.7, p < 0.002), solvents (χ^2=30.8, p < 0.001), heavy metals and some lifestyle factors, more likely to experience preterm labour during pregnancy (χ^2=4.2, p <0.05), but did not differ on live-birth outcomes; and were excluded from further analyses. Solvents and petroleum products were the second most frequently reported exposures in the workplace for both mothers and fathers. Pesticides and solvents were second most frequently reported exposures at home. No outcome variables were associated with solvent, shipboard duty or Persian Gulf duty in unadjusted OR. Maternal exposure to petroleum products at home was the only exposure variable related to low birth weight (unadjusted OR 2.4; 95% CI 1.03-5.56). No association between reported exposure to petroleum products (and solvents) in multivariate regression models controlling for maternal demographic, lifestyle and health variables. Only a single exposure variable, paternal but not maternal occupational exposure to pesticides, was associated with OR > 2 of preterm delivery. No evidence of association of adverse live-birth outcomes considered with reported exposure to petroleum products or solvents in this group of Navy military women.								

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DVA (2004)	Self-reported Reproductive questionnaire administered in the Study of Health Outcomes in Aircraft Maintenance personnel (SHOAMP)	Australia	Female F-111 Deseal/Reseal (DSRS) workers and female partners of male study participants who reported pregnancies during the five posting periods over 1975-1999. Reproductive Questionnaire included in invitation package and males instructed to forward to current or past female partner for completion. Female DSRS personnel (n=24) and female partners of male DSRS personnel (n=767) for analysis	DSRS Exposed (n=293 respondents)	Technical personnel posted at RAAF base Richmond (NSW) (n=294 respondents). Other personnel (non-technical) posted at Amberley base (n=204 respondents)	Reproductive health outcomes referenced to a posting date: • Outcome of pregnancies during the period of F-111 DSRS • For any pregnancies recorded, if there were reported difficulties getting pregnant and if reported seeing a specialist Analysed in female participants or partners only as: • Pregnancy result (live birth vs other incl. still birth or miscarriage) Also asked about age at conception, lifestyle factors during pregnancy, male partner rank and posting	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
SHOAMP personnel were exposed to a number of materials, some at low levels and others at higher levels. The exposures varied in the different programs over the years. There was exposure to a number of solid and liquid materials. These included: jet fuels JP A1, JP 4 and JP 8, from mopping out the tanks prior to desealing; desealants which contained dimethyl acetamide, thiophenol and an aromatic solvent; Sealants; Alkaline detergent washes which contains glycol ethers and thiophenol residues; a range of solvents eg MEK, naphtha, ethyl acetate, isopropanol eg for cleaning the surfaces; metal surface protector including toluene, xylene, isopropanol; epoxys and primers. *SHOAMP had 4 programs: Program 1 (1975-1982), Wing program (1985-1992), Program 2 (1990-1993) and Spray seal (1996-1999)								

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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. 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).								
Findings: N=552 total females included in analysis who reported pregnancies within exposure period of interest. N=1327 total reported pregnancies eligible to be used in the analyses. 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% of births) and exposed group (20% of births). 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, CL0.65-1.3) 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) 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) There was no dose repose relationship for mild, moderate or prolonged exposure (p=0.99). Formal analysis was not possible for pregnancy outcomes regarding difficulties getting pregnant and visits to a specialist for fertility problems as key confounders such as maternal age at the time 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. **Conclusions:** There was no evidence of an association in female DSRS personnel or partners of male DSRS personnel and miscarriage or stillbirth, or in reported difficulties getting pregnant or seeing a fertility specialist.								
Shaw et al (2003)	Case- control study Data collected by: telephone interview	USA	All women residing in the California counties (1987-1989) that had infant and foetal deaths ≥20 weeks and listed anomalies diagnosed within the first birthday (N=552,601)	Cases: mothers of 662 CLP and CP cases, 207 conotruncal defect cases, 165 limb deficiency cases (n=) mothers with periconceptional occupational exposure	Controls: mothers of 972 control infants with no major congenital anomalies randomly selected from all infants born in same area and time	Risk of congenital anomalies: • Cleft palate (CP) • Cleft lip with or without CP (CLP) • Conotruncal heart defects • Limb deficiencies Case eligibility determined by a clinical geneticist reviewing medical records information. CP or CLP with no other major anomaly were categorised as isolated CP or CLP cases; with one accompanying major anomaly as multiple CP or CLP cases	Exposure assigned based on an industrial hygienist assessment of periconceptual (1 m before to 3 m after conception) occupational tasks and assigned to *a priori* defined exposure categories as likely, maybe or not exposed to 74 chemical agent groups and nine 'end-use' groups, including aliphatic hydrocarbons(C_1-C_4) and (C_5-C_{12}) as groups (i.e. kerosene)	Age: Foetus ≥ 20 weeks and up to 1 yr Mother's age range not stated but reference range <20->39y [54]

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Findings: Analyses limited to women who reported working during the periconceptual period. OR of 1.5 or greater (based on a minimum 10 exposed cases and controls combined) were observed for a relatively small number of all possible exposure-anomaly comparisons. Isolated CP (n=6) cases OR 2.2 (95% CI 0.9-5.7) and multiple CP (n=2) cases OR 1.5 (CI 0.5-7.0) (n=17 controls) were observed for maternal exposures to aliphatic HC (C_1-C_4). Conotruncal heart (n=14) cases OR 1.6 (95% CI 0.8-3.3) and limb (n=9) cases OR 1.6 (CI 0.7-3.8) (n=35 controls) were observed for maternal exposures to aliphatic HC (C_5-C_{12}). **Conclusions:** OR 1.5 was observed for a small number of exposure-defect comparisons and in association with maternal exposure to aliphatic hydrocarbons these were statistically non-significant, but the number of cases were small. Although potential associations were observed, most results suggested that maternal occupational exposures to a variety of chemicals did not contribute substantially to the risk of conotruncal heart defects, limb deficiencies or oral cleft defects in the study population.								
Gordley et al (2000)	Cross-sectional study. Par Data collected by: in person interview, self-report via diary entry. Urinalysis collection referred to as part of expanded study data collection	USA	Female United States Air Force (USAF) employees: civilian and active military female personnel at 10 USAF bases participating in an expanded study investigating hormonal effects of exposure to jet fuel in women were screened for age, medication use, medical diagnoses, and surgical procedures. (N=170)	Completed questionnaire and daily diaries N=170 (51%)		Menstrual abnormalities: • Abnormal cycle length: intervals <24 or >35 days • Hypermenorrhoea: menses excessive in duration (>7days) or amount of menstrual bleeding reported as 'heavy' • Primary dysmenorrhea: derived from responses to questions "did you miss work..need to lie down..due to [menstrual or premenstrual] symptoms?"	Fuel exposure defined by self-report of having a job either handling or not handling fuel such as aircraft maintenance and refuelling operations Job stress measured by Job Content Questionnaire (JCQ) developed by Karasek et al. Life events measure by Life Events Questionnaire (LEQ) Data on age, marital, education, smoking, passive smoke, race or ethnicity, military vs civilian employment status, occupational jet fuel exposure	18-41 y Female
Findings: Fuel handling reported by n=66, 38.8% participants. No significant differences between fuel and non fuel handlers with respect to the stress factors. Job strain was not significantly associated with any of the menstrual outcomes. 40.9% (n=26) of fuels handlers and 26.0% (n=27) of non fuel handlers had dysmenorrhoea. Fuel handling: non statistically significant association with dysmenorrhoea (n=53) OR 1.83, 95% CI 0.90-3.70, coefficient 0.60; abnormal cycle length (n=20) OR 0.27 (0.08-1.06), coefficient -1.24.								

Guidelines/Reports – jet fuels

Authors & Year	Country	Title and scope	Exposure(s) route	Reproductive and Developmental Effects	References
Agency for Toxic Substances and Disease Registry (ATSDR) (2017)	USA	Toxicological profile for JP-5, JP-8 and Jet A Fuels. The profile was prepared in accordance with guidelines developed by ATSDR and the US Environmental Protection Agency (US EPA). 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 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. The health effects section and human studies findings were considered in relation to this Evidence Profile		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	One study reporting 170 military and civilian women in occupations involving fuel handling found that women did not have significantly higher odds of menstrual disorders in adjusted analyses. Exposure was characterized by measuring aliphatic hydrocarbons (total C_6–C_{16}) and total benzene, toluene, ethylbenzene, and xylene in exhaled breath. The study found a significant (p=0.007) reverse association between preovulatory LH and breath aliphatic hydrocarbons, the mechanism by which this could occur was unknown. Although not clearly stated, the assumption appears to be that the exposure was mainly to JP-8 although other products such as a gasoline, diesel fuels, and the combustion products were not completely ruled out. No studies were located regarding developmental effects in humans after inhalation exposure to JP-5, JP-8, or Jet A fuels.	Army 2001[55]; Reutman et al. 2002[20] as reported above
			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 reproductive effects or developmental effects in humans after dermal exposure to JP-5, JP-8, or Jet A fuels.	
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 have evaluated neurologic, reproductive, genotoxic, or carcinogenic end points following inhalation exposure. Single studies in humans exposed to JP-8 fuel reported an inverse association between aliphatic hydrocarbons in exhaled breath and serum levels of LH. However, exposure to JP-8 was not associated with higher odds of menstrual disorders.					

Authors & Year	Country	Title and scope	Exposure(s) route	Reproductive and Developmental Effects	References
Agency for Toxic Substances and Disease Registry (ATSDR) (1995)	USA	Toxicological profile for Jet Fuels JP-4 and JP-7. The profile was prepared in accordance with guidelines developed by ATSDR and the US EPA and in support of Department of Defense needs. 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 a 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. The health effects section and human studies findings were considered in relation to this Evidence Profile.		Health effects: No long term epidemiological studies were located regarding exposure to JP-4.	
			Inhalation	No studies were located regarding reproductive effects or developmental effects in humans after inhalation exposure to JP-4 and JP-7.	
			Oral	No studies were located regarding reproductive effects or developmental effects in humans after oral exposure to JP-4 and JP-7.	
			Dermal	No studies were located regarding reproductive effects or developmental effects in humans after dermal exposure to JP-4 and JP-7.	
Findings: This profile located no studies reporting reproductive effects or developmental effects in humans after exposure to JP-4 and JP-7.					
Institute of Medicine (IOM) (2005)	USA	Gulf War and Health: Volume 3. Fuels, combustion products and propellants. 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 to the Gulf War.	Fuels. The Committee found that there was a lack of exposure information for individual veterans.	Reproductive and developmental outcomes of interest included infertility, preterm birth and low-birth rate, birth defects and childhood cancers. No studies of infertility in women and exposure to fuels met the committee's inclusion criteria. No studies reported for spontaneous abortion in veterans or that included occupational exposures.	
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 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.					
CONCAWE (2007)	Belgium	Human exposure information for European Union (EU) substance risk assessment of kerosine.	Inhalation	The taskforce discussed the Reutman et al. study [20] of potential reproductive effects of low dose HCs encountered	Reutman et al. 2002[20] as

Authors & Year	Country	Title and scope	Exposure(s) route	Reproductive and Developmental Effects	References
		The activities considered included the manufacture, distribution and use of petroleum production collectively known as kerosines. The assessment was noted to be applicable to products blended with these refinery products, in particular aviation fuel, (jet fuel), automotive fuel etc. CONCAWE is an industry based taskforce that undertook a program of voluntary risk assessments under the framework of the EU chemical substances regulations.		by female US Air Force personnel and changes to urinary hormone levels.	reported above
			Dermal	There is no reported studies or discussion on reproductive effects following dermal exposure.	
Findings: The taskforce concluded that worker exposure levels for kerosines were generally low, there were a wide range of control measures in place and occurrences of elevated exposure appear to be infrequent. Some studies reported in the literature showed higher exposure levels (i.e. maintenance workers).					
National Research Council (NRC) (2001)	USA	Evaluating chemical and other agent exposures for reproductive and developmental toxicity. 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.	Inhalation and Dermal	No human studies have been conducted to assess female reproductive or developmental toxicity caused by exposure to JP-8 or any other ketone-based fuel.	
Findings: There were no human data on the effects of JP-8 on female reproduction.					
National Research Council (NRC) (2003)	USA	Toxicological assessment of jet propulsion fuel 8. The NRC assigned this project to the Committee on Toxicology (COT), which assembled the Subcommittee on Jet-Propulsion Fuel 8 to prepare this report/assessment.	Not applicable	No studies were found that examined the potential for developmental toxicity or adverse reproductive effects of JP-8 or other jet fuels in women.	
Findings: As the data were scarce and the military personnel were occupationally exposed to JP-8, the subcommittee recommended that experimental animal studies be conducted to determine reproductive and developmental toxicity potential of JP-8.					

Observational studies - solvents

Menstrual cycles

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
Cho et al. (2001)	Cross-sectional study. Data collected: Questionnaire on menstrual pattern; and daily urine collection for childbirth permission (CBP) seeking group; and/or those enrolled at marriage health examination (MHE)	China	Petrochemical workers obtaining CBP from local family planning office before having a baby (20 to 40 years, no previous marriage, no previous clinical pregnancy, no diagnosed gynaecological or endocrine disease) N=1,510 (enrolled)	Petrochemical workers n=1,408 including n=338 CBP enrolment group that had urine collection and worked in one of nine selected production facilities		Menstrual pattern: • Oligomenorrhea - average cycle length >35 days during the previous year • Average cycle length, longest and shortest cycle length, average duration of bleeding, perceived irregularity, intermenstrual spotting, and perimenstrual symptoms	Industrial hygienist evaluated exposure at workshop level to organic solvents (benzene, styrene, toluene, or xylene) [presence or absence]. Other variables collected: age, BMI, enrolment group, smoking, exposure to other solvents, parity, presence of indoor coal combustion and cooking oil fumes, alcohol consumption, diet, use of herbal medicines, noise, heavy lifting, exertion, perceived work stress, rotating shift work, and education	20–34.5 y Female
Findings: Prevalence of oligomenorrhea by solvent exposure groups: 12.9% [toluene], 14.1% [xylene], 9.3% [benzene+toluene], 6.9% [benzene+toluene+styrene], 9% [benzene+ toluene+xylene] and 16.3% [benzene+ toluene+xylene+styrene]. Prevalence of oligomenorrhea: 7.7% (MHE group) and 13.1% (CBP group) [unexposed]; 9.3% (MHE group) and 17.1% (CBP group) [exposed]. Exposure to “all aromatic solvents” was associated with oligomenorrhea OR 1.76 (95% CI 1.08-2.82), compared with unexposed group. Exposure to toluene and xylene were associated with oligomenorrhea: OR1.43 (95% CI 0.93-2.17) non-statistically significantly [toluene]; OR 1.63 (95% CI 1.04-2.53) [xylene]; OR 1.76 (95% CI 1.08-2.82) [all aromatic solvents]. A 7% increase in the odds of oligomenorrhea was associated with 1 additional year of exposure, assuming a linear association. Authors concluded exposure to organic solvents was associated with a trend toward increased frequency of oligomenorrhea.								
Lin et al. (2013a)	Cross-sectional study. Data collected:	Taiwan	Premenopausal workers (with 1 year	n=622 completed questionnaire,		Menstrual cycle length • abnormal if <24 or >35 days	Exposure to VOCs including toluene, *m/p* xylene, ethyl acetate, ethylbenzene and acetone assessed	18-44 y Female

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
	Questionnaires on menstrual cycle characteristics, risk factors; Hand held volatile organic compound (VOC) monitors for chemical exposures		employment) undergoing annual health examinations at a liquid crystal display (LCD) manufacturing plant in 2002 N=666	response rate =93%; n=288 for analysis sample after exclusions		• short <24 days • long >35 days Abnormally heavy flow: • use of >8 sanitary towels daily	with hand-held VOC monitors with 24h canister sampling in office (reference group) and each fabrication area (array, panel, module) which result in different levels of VOC exposure. Other variables collected: demographics, BMI, working history/pattern, medical and reproductive history, alcohol, tobacco, exercise	
Findings: Measured levels of VOCs (in ppb) [canister sampling] were: i) toluene 20.6 [office], 7.5 [panel], 11.1 [module], 20.8 [array]; ii) *m/p* xylene 3.2 [office], 1.7 [panel], 1.1 [module], 6.9 [array]; iii) ethylbenzene 0.9 [office], 0.6 [panel], 0.7 [module], 4.6 [array]; ethyl acetate 1.5 [office], 1.8 [panel], 2.0 [module], 2.6 [array]; and acetone 15.4 [office], 592 [panel], 2283 [module], 58.9 [array]. Concentrations were well below the occupational exposure limits. Short cycle length was more common amongst the panel (17%) and module (22%) groups, ii) these groups also showed increased odds of a shorter menstrual cycle (OR 7.68; 95% CI 1.51–39.15) [panel] (OR 8.38; 95% CI 1.72–40.95) [module] but not array group (OR 0.73 95% CI 0.07-7.76) compared with office group. No significant difference in risk were observed for long menstrual cycles. Authors conclusions– possible link between repeated exposure to multiple organic solvents such as ethanol and acetone and increased prevalence of short menstrual cycles in premenopausal women.								
Lin et al. (2013b)	Cross-sectional study. Data collected: self-administered questionnaire; Morning urine sample collected for at least one menstrual cycle	Taiwan	Female employees (at least one year of employment) at an LCD manufacturing plant; pre-menopausal women. 2002	N=178 recruited; n=94 (excluding drop-outs) analysed from 3 subgroups (work areas): array n=23, panel n=53 and module n=18		Daily urinary metabolites of sex steroid hormones: estrone sulphate and estrone glucuronide (estrone conjugates) (E1C); progesterone metabolite pregnanediol-3-glucuronide (PdG); and total urinary follicle-stimulating hormone (FSH). Menstrual diary records, urinary endocrine measurements and menses phases (early follicular, periovulatory and luteal) were used to derive the endocrine endpoints.	Exposure measured with VOC, e.g. toluene, xylene, ethyl benzene, ethyl acetate, acetone, isopropyl alcohol, etc. monitors in working areas, and 24 hour canister collection.	<30 years to >45 y Female

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Findings: Mean FSH, E1C and PdG urinary concentrations were significantly higher in the module group than any other work area groups [early follicular phase]. E1C and PdG urinary concentrations in the module group were significantly higher than any other groups [periovulatory phase]. E1C concentrations in the panel group were lower but FSH concentrations in the module group were higher than other groups [luteal phase]. Compared to the work array area group, the module area group was significantly associated with i) higher levels of E1C and PdG levels (β (95% CI)): 12.55 (8.49, 16.61); 0.53 (0.29, 0.77), respectively [early follicular phase], and ii) β (95% CI): 11.93 (6.21, 17.65); 0.53 (0.29, 0.77) respectively [periovulatory phase], and ii) higher levels of E1C, PdG and FSH levels (β 95% CI): 9.29 (4.92, 13.66); 1.01 (0.42, 1.60); and 1.48 (0.81, 2.15) respectively [luteal phase]. Compared to the work in array area, the panel area work was significantly associated with higher levels of FSH; β (95% CI): 0.89 (0.07, 1.71) and lower levels of E1C -4.49 (-7.90, -1.08) [early follicular phase] and significantly lower levels of E1C -5.16 (-9.16, 0.71) [periovulatory phase]. Analyses were adjusted for age, BMI, education, smoking, alcohol, working patterns.							
Reutman et al. (2002)	Cross-sectional, Cross-sectional study. Data collected by: telephone and in person interview, self-report via diary entry, exhaled breath, and morning urine sample analysis	USA	Female United States Air Force (USAF) employees: civilian and active military female personnel at 10 USAF bases were screened for age, medication use, medical diagnoses, and surgical procedures. Non-smokers were targeted. (N=335)	Completed questionnaire and daily diaries N=170 (51%) Subgroup: Endocrine data and provided urine samples (n=100) Subgroup: Endocrine and breath analysis data (n=63 breath samples)		Reproductive endocrine endpoints predictive of non-conceptive menstrual cycles measured using urinary endocrine markers: • Preovulatory luteinizing hormone (LH) • mid-luteal phase pregnanediol 3-glucuronide (Pd3G) • mid-luteal estrone 3-glucuronide($E_1$3G) • follicle phase Pd3G. Menstrual cycles calculated from diary records. Morning urine samples were collected daily. Urinary endocrine measurements and menses dates were used to derive the endocrine endpoints.	Exhaled breath samples (N=63) analysed for internal doses of aromatic (benzene, toluene, ethyl benzene and *m, p, o*-xylene, BTEX) and aliphatic (C_6-C_{16}) hydrocarbons. Exposure characterised as low versus high exposure groups for C_6-C_{16} and BTEX based on the median. Other variables collected: included socio-demographics, BMI, alcohol, coffee, caffeine, smoking, history of illness, second-hand smoke, job strain, hours/shifts worked, reproductive and menstrual histories.	18-42 years Females
Findings: Breath levels (ppb) in exposed groups (mean±SD): toluene=1.3±2.2 [low], 9.0±12.3 [high]; ethylbenzene=1.0±0.5 [low], 3.0±6.9 [high]; *m, p*-xylene=0.8±1.2 [low], 37.3±85.6 [high]; *o*-xylene=1.0±2.0 [low], 11.3±15.0 [high]. No significant difference in endocrine levels between self-reported exposed vs non exposed participants in adjusted regression models. Multiple regression of BTEX and endocrine outcomes: β = -4.61 (p=0.10) [pre-ovulatory LH]; β = -0.10 (p=0.34) [follicular Pd3G]; β = -3.59 (p=0.08) [mid-luteal Pd3G]; β = -2.73 (p=0.32) [midluteal E13G].								

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
Total BTEX nor toluene analysed as continuous variables were not significantly associated with any of the hormone levels. Toluene exposure approached statistical significance, β = -0.19, p=0.058 with pre-ovulatory LH exposure when analysed in a model together with the aliphatic hydrocarbons (C_6-C_{16}) and age.								
Thurston et al. 2000	Retrospective cross-sectional study 1993 Data collected: Questionnaire administered to worker asked about menstrual outcomes, petrochemical exposure, working conditions.	China	Women who worked for a petrochemical company with 17 production plants and institutes	Completed questionnaire (after exclusions) N=3,343		Abnormal menstrual cycle length (AMCL): • an average menstrual cycle length >35 days or <21 days	Self-reported exposure to benzene, gasoline, toluene including number of years exposed and coded as exposed or not exposed Additional data collected on: ergonomic factors, noise levels, age, BMI, green tea consumption, contraception use, exposure to passive smoke, history of pregnancy or menstrual problems, or diseases associated with menstrual disorders	20-44 years Female
Findings: Key exposure of interest as reported was benzene. Benzene exposure for ≤ 7 years exposure OR 0.79 (95% CI 0.55-1.13); for >7 years exposure OR 1.71 (95% CI 1.27-2.31) Toluene: no exposure 325/3285 (9.9%) AMCL; 1-9 years 2/28 (7.1%) AMCL; 10+ years exposure 6/30 (20%) In separate logistic regression models in which years of exposure to a particular chemical (hydrogen sulfide, lime dust, acid, manganese, ammonia, gasoline) was substituted for years of exposure to benzene, only the odds ratio for toluene was larger than for benzene when each was put in linearly (data not included in the paper).								

Fertility

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
Garlantézec et al. (2013)	Cohort study. Data collected by: self-administered questionnaire by mail and	France	Pregnant women between 2002 and 2006 in 3 districts of Brittany; recruited by	3,421 pregnant women in PELAGIE Study		Time to pregnancy (TTP) as a measure of fertility: • TTP = time length (months) that the women required to become pregnant	Urinary measurements of exposure to glycol ethers (GEs) and their main urinary metabolites: eight alkoxycarboxylic acids [methoxyacetic acid (MAA), methoxyethoxyacetic acid (MEAA), ethoxyacetic acid (EAA),	<25 to ≥35 y Female

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
	urine sample (1st morning void)		gynaecologists, obstetrics, or ultrasonographers at visits for prenatal care before 19 weeks of gestation and followed through the end of pregnancy	Random subset of women with urine analysis, n=609; TTP was available for 519 of these subjects (85%)			ethoxyethoxyacetic acid (EEAA), 2-butoxyacetic acid (BAA), *n*-propoxyacetic acid (PAA), phenoxyacetic acid (PhAA), and 2-methoxypropionic acid (2-MPA)* were measured. Potential covariates included paternal occupational exposure to solvents evaluated according to job-exposure matrix. Other variables included demographics, diet, and life style, contraceptive use, reproductive history, and fertility medication *2-MPA noted to be a metabolite of minor β isomer of PGME or methoxypropanol	
Findings: Median TTP = 3 months (Quartile 1-Quartile 3, 2-7 months). Glycol ether metabolites detected in 6% (for ethoxyacetic acid) to 93% (for BAA and PhAA) and MEAA in more than 50% of women's urine. Highest median level of PhAA: 0.48 mg/L. Fecundability non significantly increased with PAA detection fecundability OR (fOR) 1.30; 95% CI 0.94-1.80. PhAA was only metabolite significantly associated with longer TTP: fOR 0.82; 95% CI 0.63-1.06 for Q2 and Q3 combined and fOR OR 0.70; 95% CI 0.52-0.95 for Q4 level concentration of PhAA (≥1.38 mg/L) vs Q1 concentration (<0.14 mg/L). A statistically significant dose response trend: Fecundability decreased with increase in PhAA level (p-trend 0.02) – for a 1 mg/L increase in PhAA = 0.95, 95% CI 0.90-1.00. EEAA detection was significantly associated with a longer TTP among primiparous women. *2-MPA was not associated with a longer TTP OR 1.10; 95% CI 0.69-1.75.								

Pregnancy outcomes

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Cordier et al. (2012)	Cohort, and nested case–control study.	France	Cohort of pregnant women recruited at	N=3,421 [cohort]	N=580 controls [nested case–control]	Congenital malformations: • in live births diagnosed by paediatricians;	Self-reported occupational exposure during pregnancy assessed [none, occasional, regular] from a JEM.	<20 to >35 y Female

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Data collected: Questionnaire on demographics, occupation and exposures; maternity hospital records on pregnancy outcomes [cohort] Early pregnancy maternal urinary samples for 10 metabolites of glycol ethers and chlorinated solvents		prenatal care visits (2002–2006) in three districts of Brittany (N=3399 pregnancies) 80% participation Chemical analysis of the 79 cases of nonchromosomal nongenetic cases of major malformations (97 total major malformations in cohort)	N=79 cases [nested case–control]		• malformations in foetal deaths and medical pregnancy terminations diagnosed by pathology and karyotype • male genital anomalies later validated by surgery reports within 2 years of follow up	Urine analysis (nested case control) of 79 nonchromosomal, nongenetic major malformations cases for eight alkoxycarboxylic acids as main urinary metabolites of glycol ethers and trichloroethanol (TCOH) and trichloroacetic acid (TCAA) as main urinary metabolites of trichloroethylene and tetrachloroethylene. Other variables collected included socio-demographics, occupation, medical/obstetric history, dietary habits, alcohol, and tobacco use.	

Findings:

Regular occupational exposure to solvents in working population 29%; the JEM classified exposed population=18% [medium-exposed], 3% [high-exposed]. Exposure to solvents during hobbies: 13% of controls

ORs for oral clefts: OR = 4.3, 95% CI 1.0–18.2 [regularly exposed vs. nonregularly exposed by self-report]; OR 12, 95% CI 2.3–60 [exposed vs. nonexposed by the JEM]

OR for urinary tract malformations: OR 2.2, 95% CI 0.6–7.3 [regularly exposed vs. nonregularly exposed, self-report]; and OR 3.0, 95% CI 0.9–9 [exposed vs. nonexposed, the JEM],

OR for male genital malformations: OR 3.6, 95% CI 1.1–12 [regularly exposed vs. nonregularly exposed, self-report]; and OR 2.11 95% CI 0.6–7.3) [exposed vs. nonexposed, the JEM].

No association for solvent exposure during hobby activities and the risk of major malformations.

Detection of TCAA, TCOH and 2-MPA in controls = 7.2 %, 5.9% and 5.2% respectively. Detection of TCAA and TCOH (≥0.01 mg/L) and 2-MPA (≥0.05mg/L) were associated with higher risk of malformations, some statistically significantly – i) TCAA (n=7 cases) OR 2.1, 95% CI 0.9-4.9) [major malformations] and (n=5 cases) OR 8.0 95% CI (2.5-25.9) [limb malformations]; ii) TCOH (n=7 cases) OR 3.3, 95% CI 1.3-8.3 [major malformations] and (n=3 cases) OR 5.8 95% CI 1.4-23.6) [limb malformations]; iii) 2-MPA (n=8 cases) OR 2.9 95% CI (1.2-6.8) (major malformations), (n=2 cases) OR 5.3 95% CI (1.0-27.2) (urinary tract malformations)

Authors' conclusions: Detection of some glycol ether metabolites (of interest in this study 2-MPA) and of trichloroacetic acid and trichloroethanol in urine was associated with oral clefts and of urinary tract and limb defects. Results based on urinary biomarker are limited by small numbers but identify work situations that require further investigation.

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Desrosiers et al. (2012)	Case-control study Data collected: Birth defects surveillance programs identified cases of neural tube defects (NTDs) and orofacial clefts (OFCs)	USA	Participants of population-based National Birth Defects Prevention Study: Mothers of the infants with NTDs OFCs delivered 1997-2002 (N=1,674 and mothers of non-malformed infants (N=5,941, employed for ≥1m from 3 m preceding estimated date of conception through date of delivery	Employed mothers of cases of NTDs and OFCs (live births, and foetal deaths >20 w gestation and prenatally diagnosed elective terminations at most sites) n=1674 [n=511 NTDs cases, n=1,163 OFC cases]	Employed mothers of non-malformed live birth infants [n=2,977 controls] Controls identified and randomly selected through birth certificates or hospital records	NTDs [anencephaly, spina bifida and encephalocele] and OFCs [cleft lip, cleft palate and cleft palate alone] Clinical geneticists reviewed medical records to confirm case eligibility; eligible case further classified by clinicians as having one isolated major congenital anomaly, multiple major anomalies or anomalies representing a complex developmental syndrome Women with family history of NTD/OFCs and pregestational diabetes excluded from analyses	Self-reported job history coded by occupation and industry and assessed for exposure to 10 solvents -organic solvents (including benzene, xylene, toluene), chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, trichloroethylene, 1,1,1-trichlorothane), Stoddard solvent (mineral/white sprits) - estimated by industrial hygienist review Other variables: demographics, mother's job title, job task/duties, chemical/machine handling at work, hours/days worked per week, etc.	<20 to ≥36 y Female
Findings: Probability of exposure for each reported job was estimated as 0 (unexposed), <10%, 10-49%, 50-89% and ≥90%. For Stoddard and aromatic solvents over 90% of exposed mothers worked in at least one job with estimated exposure probability of ≥10%, however for chlorinated solvents, this proportion was only 30%. Data not presented for other exposure probability categories in analyses. Of all women rated as exposed to any solvent during periconceptual period, nearly 85% were exposed to more than one solvent (data not shown). Prevalence of occupational exposure to any organic solvent: 8.2% (control mothers), 13.1% (NTD case mothers), 9.6% (OFC mothers). Prevalence of any solvent exposure was higher in mothers of spina bifida (14.4%) and encephalocele (16.4%) than those of anencephaly 98.4%); exposure prevalence did not differ across OFC mothers. Maternal exposure to chlorinated solvents associated with NTDs (OR 1.96, 95% CI 1.34-2.87) but not with aromatic solvents (OR 0.75, 95% CI 0.36-1.55) or Stoddard solvent (OR 0.63, 95% CI 0.33-1.23). The association was stronger for spina bifida (OR 2.26, 95% CI 1.44-3.53) and encephalocele (OR 2.22, 95% CI 0.84-5.82) than for of anencephaly (OR 1.25, 95% CI 0.58-2.71). No significant difference in effects for NTD phenotypes (p=0.36). No significant associations of any solvent class and OFC.								
Desrosiers et al. (2015)	Controls from a case-control study (multisite, population-based) used to	USA	Participating mothers of National Birth Defects Prevention	NPDPS controls – unmatched (non-malformed, live		SGA as a surrogate for foetal growth restriction (FGR) • SGA = birth weight < 10th centile for a given	Self-reported job history coded by occupation and industry and assessed for exposure to 10 solvents -organic solvents (including benzene, xylene, toluene),	<20 to ≥36 y Females

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	investigate risk factors for major congenital malformations and other adverse pregnancy outcomes Data collected: telephone interview		Study (NPDPS), during 1997-2002. NPDPS control mothers were the subjects in this study. N=2,886 eligible mother-infant pairs	born infants from same geographical/ temporal base population as cases in NPDPS). N=2,861 mother-infant pairs - of these n=230 infants were classified as SGA		gestational age at delivery in weeks; Data on infants sex and gestational age obtained from birth certificate/medical record Restricted analysis of birthweight to term births	chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, trichloroethylene, 1,1,1-trichlorothane), Stoddard solvent (mineral/white sprits) - estimated by industrial hygienist review Probability of exposure estimated mothers to be exposed to a particular solvent if any of her jobs during pregnancy or month before conception classified as exposed (exposure probability >0) and unexposed (exposure probability=0). Other variables collected: demographics, mother's employment at time of, during pregnancy and before conception, job title, job task/duties, chemical/ machine handling at work, hours/days worked, etc.	
Findings: Prevalence of occupational exposure to organic solvents: 8.4% (mothers of non-SGA infants) and 10.1% (mothers of SGA infants). Exposure prevalence (regardless of SGA categorization): chlorinated solvent(s) (7.9% of SGA infants; 7.2% of non-SGA infants), 3% or fewer women were exposed to Stoddard/aromatic solvents. The number of women with ≥50% probability of exposure were none (Stoddard solvents), six (chlorinated solvent(s), six (aromatic solvent(s). Among women with any probability of exposure during the month before conception or pregnancy, maternal exposure to any solvent(s) was not associated with SGA (OR 1.16, 95% CI 0.73-1.83). Exposure to chlorinated solvents and Stoddard solvents were not associated with SGA (OR 1.03, 95% CI 0.62-1.71; OR 0.98, 95% CI 0.44-2.18, respectively). Exposure to aromatic solvents associated with a non-significant increase in odds of SGA (OR 1.60, 95% CI 0.71-3.58), likely driven by assessed exposure to toluene and xylene. In analysis restricted to the sample of women with ≥ 50% probability of exposure, ORs = 1.71, 95% CI 0.86-3.40 [any solvents]; 1.70, 95% CI 0.69-4.01 [chlorinated solvent(s)]; 1.87, 95% CI 0.78-4.50 [aromatic solvent(s)]. This was not estimated in relation to Stoddard solvent as the number of cases was n=0. Maternal exposure to any solvent/solvent class was not associated with a meaningful effect on distribution of term birthweight. Authors' conclusions: women in the study population assessed to have a higher probability of workplace exposure to chlorinated and aromatic solvents had a small increase risk for delivery a growth restricted infant, although effect estimates were based on small numbers and imprecise (and were not statistically significant).								
Gilboa et al. (2012)	Case-control study. (The National Birth Defects	USA	Mothers of infants with simple and isolated CHD cases and	Mothers of infants with simple and isolated CHD; response rate	Randomly selected mothers of infants without major	CHD status –confirmed by echocardiography, cardiac catheterization, surgery, or autopsy, and diagnostic information was assessed by	Exposure assessment: • Reported job history (full/part-time) for ≥1 month from 3 months before conception through the end of pregnancy	<20 years to ≥35 y Female

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Prevention Study) Data collected by: telephone interview, self-reported information on maternal occupational exposure to organic solvents		control infants delivered from 1997 to December 2002; worked in paid/volunteer/ military service (part/full time); living in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York and Texas (N=4,998)	69%; cases had at least one of over 30 eligible birth defects and were live born, still born, or electively terminated; cases N=2,047	birth defects from birth certificates or hospital records; response rate 67%; control were live born infants without major birth defects; control N=2,951	the experts in paediatric cardiology and clinical genetics CHD status types: • Simple cardiac defects: hypoplastic left heart syndrome or tetralogy of Fallot • Complex cardiac defects: ventricular septal defects (VSDs) and pulmonary valve stenosis • Extracardiac defects: isolated CHD (no extracardiac defects); multiple CHD (multiple extracardiac defects)	• Job coded for occupation and industry • Two independent exposure assessment strategies: i) Consensus-based and ii) a literature-based approach for exposure assessment of: chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, 1,1,1-trichloroethane/ trichloroethylene) aromatic solvents (benzene, toluene, xylene) and Stoddard solvents Other variables including demographics, exposures (nutritional, behavioural and occupational), medication use before and during pregnancy	
Findings: The two exposure assignment approaches yielded different exposure prevalences. Expert consensus-based approach estimated nearly 4% controls and 5% cases exposed to any solvent during periconceptual period; literature-based approach estimated nearly 8% controls and 10% cases exposed to any solvent. Among controls rated as exposed (consensus-based approach) (N=110), considered exposed to only chlorinated solvents (66%), only Stoddard solvent (8%), both solvents (26%). Among controls rated as exposed (literature-based approach) (N=240), considered exposed to only chlorinated solvents (50%), only aromatic solvents (9%), only Stoddard solvent (6%). The rest, 35% (n=85) estimated exposed to ≥2 classes of solvents. Expert consensus-based approach: Any solvent and chlorinated solvents exposures were both associated with perimembranous ventricular septal defects (VSDs) (any solvents OR 1.6; 95% CI 1.0-2.6; chlorinated solvents; OR 1.7; 95% CI 1.0-2.8). Literature-based approach: Any solvent exposure with aortic stenosis OR 2.1; 95% CI 1.1-4.1; and Stoddard solvent exposure with d-transposition of the great arteries OR 2.0, 95% CI 1.0-4.2, right ventricular outflow tract (RVOT) obstruction defects OR 1.9, 95% CI 1.1-3.3 and pulmonary valve stenosis OR 2.1; 95% CI 1.1-3.8. When analysis was restricted to exposed mothers with at least one job rated as exposed with 50% or greater probability (42% cases; 33% controls), the associations were: any solvent exposure with CHD OR 1.4, 95% CI 1.0-1.9 and septal defects OR 1.5, 95% CI 1.0-2.3; and Stoddard solvent exposure with any CHD OR 2.8, 95% CI 1.3-6.2, septal defects OR 3.1, 95% CI 1.2-8.0, perimembranous VSD OR 3.7, 95% CI 1.1-12.2, and atrial septal defects OR 3.8, 95% CI 1.2-12.6. The ORs for association of Stoddard solvent exposure with RVOT obstruction defects and pulmonary valve stenosis were OR 4.6, 95% CI 1.4-15.3 and OR 4.2, 95% CI 1.1-16.2, respectively.								
Chevrier et al. (2006)	Case-control study	France	Cases and controls, recruited from	Cases = a child diagnosed with cleft lip and/or	Controls: children with no birth	• Cleft lip with/without cleft palate (CL/P) • Cleft palate only	Mothers interviewed and asked to describe occupational tasks for job during first trimester.	<30 to >35 y Female

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	Data collected: mothers of cases and controls were interviewed using a structured questionnaire		seven hospitals 1998-2001. Cases recruited from maxillofacial surgery departments; controls recruited in the same hospital (matched with case for sex, age, mother's geographic origin and residence)	cleft palate) n=240 [164 children with cleft lip with/without cleft palate (CL/P); 76 with cleft palate only (CP)	defect, cancer/genetic disease but hospitalised for treatment of some other disorder, such as respiratory/ urinary) or need for minor surgery, n=236 controls		Expert chemist blinded to case-control status evaluated each mother's exposure to 22 classes of agents, including: organic solvents (e.g. oxygenated solvents, chlorinated solvents and petroleum products, as well as lead compounds and non-ionising and ionising radiation. Other variables collected: sociodemographics, mother's medical and obstetric history, family history of oral clefts and other congenital anomalies, exposure to x rays and surgery during pregnancy, alcohol, tobacco, occupational tasks, etc.	

Findings:

There were more boys in the CL/P (70%) cases, and the sex ratio was balanced in the CP group.

Maternal occupational exposure to oxygenated, chlorinated, and petroleum solvents was associated with an increased risk of CL/P or CP although not all the unadjusted odds were statistically significantly increased:

OR 1.76, 95% CI 1.1-2.9 (CL/P) and OR 1.42, 95% CI 0.7-2.7 (CP) [oxygenated solvents]

OR 1.76, 95% CI 1.0-3.1 (CL/P) and OR 1.56, 95% CI 0.8-3.0 (CP) [aliphatic alcohols]

OR 1.88, 95% CI 1.1-3.5 (CL/P) and OR 1.5, 95% 0.7-3.2 (CP) [glycol ethers]

OR 1.74, 95% CI 1.0-2.9 (CL/P) and OR 1.82, 95% CI 1.0-3.5 [aliphatic aldehydes, esters, and ketones]

OR 9.45, 95% CI 2.5-35.3 (CL/P) and OR 3.78, 95% CI 0.7-20.7 (CP) [chlorinated solvents]

OR 3.64, 95% CI 1.5-8.8 (CL/P) and OR 1.21, 95% CI 0.3-4.9 (CP) [petroleum solvent].

No significant change in these associations after adjusting for maternal smoking status, alcohol consumption, and dietary folate intake during the first trimester. Significant increasing linear trends were observed for the association between CL/P and level of exposure to aliphatic alcohols (p trend=0.02), glycol ethers (p trend=0.009), some types of aliphatic aldehydes, ketones, or esters (p trend=0.02), and petroleum solvents (p trend=0.005). Similar but not significant trends in the CP group were observed when there were enough subjects.

The risks association between the exposure to oxygenated solvents alone (N=33) (when women exposed to chlorinated or petroleum solvents excluded) and CL/P or CP remained elevated but no longer significant: OR 1.44, 95% CI 0.8-2.4 [CL/P] and OR 1.47, 95% CI 0.8-2.8 [CP].

Authors' conclusions: Results of the study suggest that maternal occupational exposure to organic solvents may be associated with the risk of CL/P and CP, however small number of subjects and multiple comparisons require that results be interpreted with caution.

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
Lorente et al. (2000)	Case- referent study Data collected by: interview questionnaire, and European congenital malformation registries used to identify cases between 1989 and 1992 Case: any product of conception with major congenital malformation diagnosed prenatally or during perinatal period (0-6 days)	Europe (France, Scotland, The Netherlands, and Italy)	Mothers who worked during the first trimester of pregnancy, recruited N=851	Mothers of babies with oral clefts, cases recruited from hospitals (France and Italy) and general populations (The Netherlands and Scotland); N=100 (63% eligible cases participated)	Mothers of healthy referent babies [the next child born without malformation (for hospital-based cases), a child born on same date and same town (for population-based cases)] N=751	Cleft lip and cleft palate, as coded locally according to the British Paediatric Association Classification of Diseases	An industrial hygienist, blinded to case-referents, estimated exposure status of women (based on questionnaire data): i) route of exposure (inhalation, cutaneous, both), ii) levels of exposure (low, medium, high), iii) frequency <5%, 5-50%, >50% of worktime) iv) reliability of assessment (possible, probable or certain exposure) Other variables collected: demographics, mother's medical and obstetric history, use of medication, occupation, occupational activities, etc.	≤24 to ≥35 y Female
Findings: Only 14% and 6% women worked in service industries and production, respectively. Service women had highest ORs for each type of cleft. Cleft palate only was associated with maternal occupation as hairdressing (OR 5.1, 95% CI 1.0-26.0) and housekeeping (OR 2.8, 95% CI 1.1-7.2). Occupational exposure to the following chemicals of relevance to this study were non significantly associated with orofacial clefts in a model: aliphatic aldehydes (OR 2.1, 95% CI 0.8-5.9) and glycol ethers (OR 1.7, 95% CI 0.9-3.3) for cleft lip with/without cleft palate; and trichloroethylene (OR 6.7, 95% CI 0.9-49.7) for cleft palate only. Toluene and mineral oil exposures were not significantly associated with oral clefts. The analyses were adjusted for centre, maternal age, mother's socio-economic status, urbanisation, and country of origin.								
Frey et al. (2015)	Prospective cohort Data collected: Questionnaire - at the time of pregnancy report, end of	Germany	Female employees (childbearing age) at a chemical company (2003-2010), N=6,332;	Women with pregnancy documented N=1,402 [live births, N= 1,430]		Pregnancy outcomes: (self – reported) • Pregnancy duration • Preterm birth (<37 weeks) • Miscarriages	Self –reported exposure (i.e. handling of chemical) during the 3 months before conception and during the first trimester. Other variables collected: work type, work load (physical), working hours per week, disease history, medication/supplements during pregnancy, partner's age at	16-45 y Female

Authors and Year	Study design	Country	Study population and sampling methodology	Study Group (n)	Comparison Group (n)	Primary outcome measure (and assessment)	Exposure assessment	Age Gender
	pregnancy, and 1 year later		Eligible: women with announced pregnancy with expected date of delivery 2003-2011 n=1342 (21%) Pregnancy documentation program (86% of those)				conception, smoking and alcohol intake, education, etc.	
Findings: No association between maternal exposure to xylene or acetone and pregnancy duration or miscarriages; β (95% CI): -0.05 (-0.79 to 0.69) [n=20, xylene and pregnancy duration]; 0.02 (-0.29 to 0.33) [n=131, acetone and pregnancy duration], and [n=11, OR 0.97, 95% CI=0.48-1.98 [acetone and preterm birth]. [n=2, OR not applicable because of limited number of cases xylene and preterm birth].								

Guidelines/Reports - solvents

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 (2008)	The Netherlands	Occupational exposure to organic solvents: effects on human reproduction The peer-reviewed report was prepared for the Ministry of Social Affairs and Employment, The Netherlands, providing advice on possible effects on reproduction (i.e. effects on male and female fertility, pregnancy and development effects in offspring) and occupational exposure to organic solvents including, toluene, xylene and acetone. The development effects mainly included spontaneous abortion, birth weight, and congenital malformations. The classification for fertility and development – category 1 [known to impair human fertility (risk	Toluene The Dutch Expert Committee on Occupational Standards (2001) recommended for toluene no classification for effects on fertility. The committee recommended toluene as a	Fertility: four studies were included to assess the effects of exposure to toluene on female fertility.[20, 26, 57, 58] No evidence of association between exposure to toluene: i) and effects on endocrine hormones, luteinizing hormone and follicle stimulating hormone,[20, 58] [experimental study and cross-sectional study] ii) and oligomennorrhoea[26] [cross-sectional study]. Conclusion of the committee: no indication for an association between maternal exposure to toluene and fertility effects. Developmental effects: eight studies were included to assess the effects of exposure to toluene on infant development.	Cho et al.[26]; Sallmén et al.[57]; Luderer et al.[58]; Reutman et al. [20] Taskinen et al. (a)[59]; Ng et al (a).[60] Lindbohm et al.[61] Xu et al.[62]; Taskinen et al. (b)[63]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		phrase (R) R60)/developmental toxicity (R61)], category 2 [should be regarded as if they affect human fertility (R60)/ developmental toxicity (R61)], category 3 [cause concern for human fertility (R62)/ developmental toxicity (R63)], and no classification – were done according to the European Union guidelines.	category 3 - substance causing concerns for humans in relation to possible developmental effects.[56]	Spontaneous abortion: a significant association between maternal exposure to toluene and spontaneous abortion (cross-sectional study and nested case control study).[59, 60] No such significant effect was observed (except for shoe workers) [61-63] Conclusion of the committee: available evidence indicates an association between maternal exposure to toluene and spontaneous abortion. Birth weight: two studies were included to assess the effects of exposure to toluene on birth weight. No evidence for association between of exposure to toluene containing solvent and birth weight (individual compounds not assessed).[64] Significant reduced birth weight was associated with exposure to solvents [individual compounds not assessed].[65] Conclusion of the committee: there was limited human data available to assess the association between toluene and birth weight. Malformations: A single study provided no evidence for association between of exposure to toluene containing solvent and malformations.[59] Conclusion of the committee: there was limited human data available to assess this association.	Chen et al.[64]; Ha et al.[65]
			Xylene The Committee for Compounds Toxic to Reproduction (2001) did not classify xylene in regard to its effects on fertility. The committee recommended for xylene to be classified as a category 3 - substance.	Fertility: seven studies were included to assess the effects of exposure to xylene on female fertility.[20, 26, 57, 61, 66-68] Exposure to xylene, along with other solvents, i) was associated with oligomenorrhoea,[26] yet its relevance to female fertility is unclear; ii) was not associated with endocrine hormones, luteinizing hormone and follicle stimulating hormone [cross-sectional study].[20] No association between exposure to xylene and prolonged time to pregnancy [case-control study].[57] Conclusion of the committee: limited data available limits drawing any conclusions regarding xylene exposure and its effects on female fertility. Developmental effects: nine studies were included to assess the effects of exposure to toluene on infant development.[59, 61, 63-65, 69-72] No significant association was shown between maternal xylene	Cho et al.[26]; Sallmén et al.[57]; Reutman et al.[20]; Lindbohm et al.[61]; Xiao et al.(a)[66]; Xiao et al.(b)[67]; Hanaoka et al.[68]; Taskinen et al. (a)[59]; Lindbohm et al.[61] ; Taskinen et al. (b)[63]; Chen et al.[64]; Ha et al.[65]; Taskinen et al. (c)[69]; Swan et

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				exposure and spontaneous abortion [population or industry based studies].[61, 63, 71, 72] Weekly handling of xylene for 3-5 times showed increased risk of spontaneous abortion [case-control].[59] Significant association between solvent exposure and spontaneous abortion was observed.[61] Two cohort studies on women in semiconductor industry provided inconsistent findings[70, 71] – one showing higher risk of spontaneous abortion with intermediate and high exposure to xylene, and the other showing no association. Conclusion of the committee: available data suggests an association (but weak) between spontaneous abortion and exposure to xylene. Birth weight: two studies were included to assess the effects of exposure to xylene on birth weight. No evidence for association between exposure to xylene containing solvent and birth weight [individual compounds not assessed].[64] Significant reduced birth weight was associated with exposure to solvents [individual compounds not assessed].[65] Conclusion of the committee: there was limited human data available to assess this association and draw any conclusion. Malformations: the committee concluded that no human data was available to assess this association and draw any conclusion.	al.[70]; Correa et al.[71]; Windham et al.[72] Chen et al.[64]; Ha et al.[65]
			Acetone The Committee for Compounds Toxic to Reproduction (2001) did not evaluate the association between exposure to acetone and effects on female fertility	Fertility: Only one study [cohort] was included to assess the effects of exposure to acetone on female fertility among laboratory workers.[73] A significant association was observed between prolonged time to pregnancy and exposure to acetone. However, this finding is doubtful if the association was specific to exposure to acetone. Conclusion of the committee: available data are not sufficient to assess this association and draw any conclusion. Developmental effects: two studies were included to assess the effects of acetone on development.[59, 74] Both studies showed that spontaneous abortion	Wennborg et al.[73] Axelsson et al.[74]; Taskinen et al. (a)[59]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
			and development.	was not associated with maternal exposure to acetone. Conclusion of the committee: available data do not suggest any association between women's exposure to acetone and developmental effects.	
Findings: Conclusion of the committee: i) available data indicates an association between women's exposure to toluene and spontaneous abortion; insufficient evidence regarding an association between women's exposure to toluene and developmental effects or malformations; ii) available evidence supports for a weak association between women's exposure to xylene and spontaneous abortion; insufficient evidence regarding an association between women's exposure to xylene and developmental effects or malformations; iii) available evidence does not suggest any association between women's exposure to acetone and effects on female fertility and developmental effects.					
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2001)	The Netherlands	Toluene – Evaluation of the effects on reproduction, recommendation for classification. The peer-reviewed reports (for toluene and xylene) were 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 or xylene. The classification for fertility and development) – category 1 [known to impair human fertility (R60)/developmental toxicity (R61)], category 2 [should be regarded as if they affect human fertility (R60)/ developmental toxicity (R61)], category 3 [cause concern for human fertility (R62)/ developmental toxicity (R63)], and no classification – were done according to the European Union guidelines. Xylene – Evaluation of the effects on reproduction, recommendation for classification.	Toluene	Fertility/endocrine effects: Six studies that involved women's occupational exposure to toluene or mixture of organic solvent containing toluene were included.[57, 58, 75-78] No significant effects on luteinizing hormone,[58] or incidence of menstrual disorders[60] and exposure to toluene was found. Reduced fecundity in women with low daily toluene exposure was reported by a study;[78] while no effect on fecundity was demonstrated by another study.[57] Conclusion of the committee: available data are not sufficient to assess fertility and draw any conclusion. Developmental effects: Fifteen studies that involved women's occupational exposure to toluene or mixture of organic solvent containing toluene were included.[61, 63, 75, 79-89] Developmental effects evaluated included were congenital malformations, spontaneous abortions, preterm delivery, growth retardation, perinatal death, birth weight and other growth parameters (e.g. microcephaly, wide nasal bridge, blunt fingertips, etc.). Some of the studies found maternal exposure to toluene affecting infant's developmental outcomes. Conclusion of the committee: Limited human data precludes the classification of toluene for effects on fertility. Toluene was recommended to be classified	Ng et al. (b)[75]; Svensson et al. (a)[76]; Svensson et al. (b)[77]; Sallmén et al.[57]; Luderer et al.[58] ; Plenge-Boenig et al.[78] Holmberg;[79] Holmberg et al.[80]; Kurppa et al.[81] Toutant & Lippman[82] ; Hersch et al.[83]; Hersch[84] ; Taskinen et al. (b)[63]; McDonald et al.[85]; Goodwin et al.[86]; Lindbohm et al.[61]; Wilkins-Haug & Gabow[87]; Ng et al. (b)[75] ; Arnold et al.[88] ; Pearson et al.[89]; Taskinen et al. (a)[59]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				as a category 3 – substance causing concern for developmental toxicity.	
			Xylene	Time to pregnancy: Only one study that involved women's occupational exposure to xylene or mixture of organic solvent containing xylene was included.[57] Conclusion of the committee: lack of relevant data, xylene was recommended not to be classified for effects on fertility. Developmental effects: Eight studies that involved women's occupational exposure to xylene or mixture of organic solvent containing xylene were evaluated.[59, 61, 63, 69, 72, 79-81] Of them, some found positive association while other found no association between maternal exposure to xylene/mixture of solvent containing xylene and developmental effects on infants. Conclusion of the committee: xylene was recommended to be classified as category 3 (substance causing concern for human in relation to possible developmental toxic effects).	Sallmén et al.[57] Holmberg[79]; Holmberg et al.[80] ; Kurppa et al.[81]; Taskinen et al.(b) [63]; Lindbohm et al.[61]; Taskinen et al (a).[59]; Taskinen et al.(c)[69]; Windham et al.[72]
Findings: For toluene, available data are not sufficient to assess its effects on human fertility and draw any conclusion. For developmental toxicity, the committee recommended toluene be classified as category 3 (substance causing concern for human in relation to possible developmental effects). The committee recommended toluene to be classified as a category 3 – substance causing concern for developmental toxicity. For xylene, relevant human data is lacking therefore the committee recommended not to classify it for effects on fertility. For developmental toxicity, the committee recommended xylene be classified as category 3 (substance causing concern for human in relation to possible developmental effects).					
The Committee for Compounds Toxic to Reproduction, Health Council of the Netherlands (2003)	The Netherlands	Trichloroethylene – Evaluation of the effects on reproduction, recommendation for classification. The peer-reviewed report 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 or xylene. The classification for fertility and development) – category 1 [known to impair human fertility (R60)/developmental toxicity (R61)], category 2 [should be regarded as if they affect human fertility (R60)/ developmental toxicity (R61)], category 3 [cause concern for	Trichloroethylene	Time to pregnancy: only one study that involved maternal occupational exposure to ttrichloroethylene in a mixture of organic solvent was included.[57] Incidence density ratios (trichloroethylene exposed) = 1.21 (95% CI 0.73-2, low exposure); 0.61 (95% CI 0.28-1.33, high exposure). Conclusion of the committee: human data are scare, and trichloroethylene was not recommended to be classified in relation to effects on fertility. Developmental effects: Four studies that involved maternal occupational exposure to	Sallmén et al.[57] Kurppa et al.[81]; Lindbohm et al.[61]; Windham et al.[72]; Taskinen et al (a).[59]; Goldberg et al.[90] ; Bove et al.[91]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		human fertility (R62)/ developmental toxicity (R63)], and no classification – were done according to the European Union guidelines.		trichloroethylene or mixture of organic solvent containing trichloroethylene were included.[59, 61, 72, 81] Two studied that included maternal exposure to trichloroethylene via drinking water contamination were also included.[90, 91] Epidemiological studies did not find any significant association between exposure to trichloroethylene and developmental effects.[59, 61, 81] Significantly higher incidence of spontaneous abortion in trichloroethylene was reported by a study.[72] Incidence of congenital heart diseases were found to have association with maternal consumption of trichloroethylene-contaminated drinking water [exposure poorly defined].[90] Incidence of oral cleft, central nervous system and neural tube defects were also found to have association with maternal consumption of trichloroethylene-contaminated drinking water [few cases, exposure misclassification].[91] Conclusion of the committee: based on animal data, the committee recommended that trichloroethylene be classified as category 2 (substance that should be regarded as if they cause developmental toxicity in humans)	
Findings: For effects on fertility, trichloroethylene was not recommended to be classified in relation to effects on fertility on the basis of a lack of sufficient human data, and sufficient animal data which show that no classification is indicated. For developmental toxicity, trichloroethylene should be classified as category 2 (substance that should be regarded as if they cause developmental toxicity in humans)					
Agency for Toxic Substances and Disease Registry (ATSDR) (2015)	USA	Draft Toxicological Profile for Toluene 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. 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	Toluene	Reproductive effects: Current evidence is not adequate to suggest that acute or repeated inhalation exposure to toluene may have reproductive effects in humans. Nevertheless, the profile reported that limited evidence exists to indicate that maternal occupational exposure to toluene may result in an increased incidence of spontaneous abortion or decreased fecundity in females. Numerous studies evaluating blood levels of reproductive hormones in repeatedly exposed populations have not provided consistent and strong evidence for exposure related health effects.	

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.		Developmental effects: several studies reported birth defects in children born following maternal exposure to inhaled toluene during pregnancy. The evidence suggested that high level of toluene exposure can be toxic to the developing foetus. Further, a lower level of occupational exposure to toluene may also increase risk for central nervous system anomalies and neural tube closure defects.	
Findings: This profile reported that there was inadequate data to suggest that acute or repeated exposure to toluene may have reproductive effects in humans; also, limited evidence indicates maternal occupational exposure to toluene is associated with an increased incidence of spontaneous abortion or decreased fecundity in females. It highlighted that that high levels of toluene exposure can be toxic to the developing foetus; one study reported that a lower level of occupational exposure to toluene may also increase risk for central nervous system anomalies and neural tube closure defects. A final report of this draft publication could not be identified.					
Agency for Toxic Substances and Disease Registry (ATSDR) (2007)	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 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.	Xylene	Reproductive effects: a few epidemiological studies reported significant increase in odds of spontaneous abortions or prevalence of oligomennorhea among the females exposed to xylene (together with other organic solvents). No studies were found that examined reproductive effects in humans due to oral exposure to mixed xylene or individual isomers. Developmental effects: limited data suggested a possible association between solvent exposure (unspecified) and developmental toxicity. Available studies involved simultaneous occupational exposure to other solvents, including xylene, and involved a small number of human subjects (N=9-61 subjects). No studies were located that examined developmental effects in humans due to oral exposure to mixed xylene or individual isomers. No studies were located that examined developmental effects in humans due to dermal exposure to mixed xylene or individual isomers. However, occupational dermal exposure to xylene was likely as reported by a few studies.	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Findings: Although human data indicated a possible relationship between maternal exposure to solvent (unspecified) exposure) and adverse developmental effects, the data was considered limited for assessing the relationship between occupational exposure to xylene and developmental effects, as available studies involved concurrent exposure to other solvents in addition to xylene. Available studies of developmental or reproductive toxicity from occupational exposure to xylenes were not definitive because of the small number of subjects and/or concurrent exposure to other chemicals. Very little information was found to be available on the chronic health effects, including reproductive health effects, of xylene exposure in humans.					
Agency for Toxic Substances and Disease Registry (ATSDR) (2014)	USA	Draft Toxicological Profile for Trichloroethylene 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. The health effects section and human studies findings were considered in relation to this Evidence Profile.	Trichloroethylene	Reproductive effects: occupational exposure to unspecified level of trichloroethylene (with concomitant exposure to other chemicals) and increase in miscarriage in nurses has been reported.[92] Inconsistent findings have been reported regarding maternal exposure to trichloroethylene and spontaneous abortions. One study showed a higher rates of spontaneous abortions were observed amongst trichloroethylene and other solvents exposed (occupational and non-occupational) women[72]; while other showed no significant effects.[61] Overall, these studies indicate a potential association between exposure to organic solvent (including trichloroethylene) and reduced fertility, menstrual cycle disturbances or amenorrhoea.[57] No significant association was observed between the exposure and time to pregnancy. Developmental effects: Inconsistent findings have also been reported regarding maternal exposure to trichloroethylene and malformations in babies. No increase in malformations in babies was reported in mothers occupationally exposed to unspecified level of trichloroethylene.[93] No significant risk of congenital heart defects (CHDs) born to mothers aged <38 years exposed to trichloroethylene, compared to unexposed ones. The risk increased with increasing mothers' age (≥ 38 years), OR 6.2, 95% CI 2.6-14.5; suggesting maternal age at delivery may influence risk of CHDs in babies born to trichloroethylene exposed women.[94] Adjusted rate ratios for low birth weight (rate ratio 1.36, 95% CI 1.07-1.73), small for gestational age (rate ratio 1.23, 95% CI 1.03-1.48), term low birth weight (rate ratio 1.68, 95% CI 1.2-2.34), cardiac	Corbett et al. 1974[92]; Windham et al.[72]; Sallmén et al.[57] ; Lindbohm et al.[61] Tola et al.[93]; Yauck et al.[94] ; Forand et al.[52]; Bove et al.[91] ; Goldberg et al.[90] ; Rodenbeck et al[95]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
				defects (rate ratio 2.15, 95% CI 1.27-3.62) and conotruncal defects (rate ratio 4.91, 95% CI 1.58-15.24) were higher amongst babies born to women exposed to trichloroethylene and tetrachloroethylene in indoor air contamination.[52] An association between trichloroethylene levels (contaminated drinking water) and oral clefts, central nervous system defects, neural tube defects, major cardiac defects[91] or chromosomal anomalies. An association was also found between elevated level of trichloroethylene in drinking water and CHD (amongst the child born to exposed mothers) before conception/1st trimester.[90] No significant association was reported between trichloroethylene in drinking water and birth weight.[95] No elevated adverse pregnancy outcomes (including congenital defects) were noted amongst to trichloroethylene and other solvents in drinking water exposed populations.[96] No studies were located in relation to reproductive or developmental effects in humans due to dermal exposure to trichloroethylene.	
Findings: Summary of health effects: the male reproductive system and developing foetus were two of the identified potential targets of trichloroethylene toxicity. Limitations of assessment of the epidemiological evidence in humans of relationship between occupational exposure to trichloroethylene and adverse developmental effects included potential concurrent exposures to other chemicals (unspecified). Case-control studies involved rather small number of cases. Some epidemiological studies related to maternal exposure to trichloroethylene (via environmental sources such as drinking water in which exposure to other potential contaminants was a recognised limitation in exposure assessment. No final report of this draft publication was identified.					
National Research Council; Division on Earth and Life Studies; Board on Environmental Studies and Toxicology; Committee on Human Health	USA	Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues. The National Research Council, the research arm of the National Academy of Sciences, Engineering and Medicine, produces reports that influence policies, inform public opinion, and advance the knowledge of science, engineering and medicine.	Trichloroethylene	A number of human studies, mainly community-based[91, 94, 95, 97-101] were included to discuss reproductive and developmental effects of trichloroethylene. Some of these studies found significant association between exposure to trichloroethylene and adverse reproductive and developmental effects, while others did not.	Lagakos et al.[97]; Yauck et al.[94]; Sonnenfeld et al.[98]; Deane et al.[99]; Wrensch et al.[100]; Swan et al.[101]; Bove et al.[91]; Rodenbeck et al.[95]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Risks of Trichloroethylene (2006)				The report noted that some of these studies had limitations mainly related to ascertainment of exposure and/or outcome and small sample size. The committee suggested that for developmental effects, there is substantial evidence that trichloroethylene in drinking water might cause impaired intrauterine growth at environmentally relevant levels. Furthermore, the committee also identified that impaired intrauterine growth and cardiac teratogenesis have greatest level of plausibility (based on human and animal evidence) to be affected by trichloroethylene exposure.	
Findings: The Committee identified those end points for which animal and human evidence generated the greatest level of plausibility; these end points included impaired intrauterine growth, cardiac teratogenesis, and altered spermatogenesis. The Committee considered that although the evidence suggested that trichloroethylene can generate such effects the lowest-observed-adverse-effect level of human risk assessment remains unclear. The combined human and animal evidence generated to date does not reach levels of reasonable plausibility to indicate that other reproductive or development mental end points do have an association with trichloroethylene.					
U.S. Environmental Protection Agency (EPA), National Center for Environmental Assessment (2011)	USA	Toxicological Review of Trichloroethylene The report provides scientific support and rationale for the hazard and dose-response assessment in relation to chronic exposure to trichloroethylene. In relation to human studies (occupational and community-based), the report reviewed both male and female reproductive effects, and prenatal developmental outcomes.	Trichloroethylene (TCE)	Fertility effects: three studies were included and discussed in the reported in relation to female infertility effects due to occupational/community exposure to TCE.[57, 61, 102] In relation to menstrual cycle disturbance, four studies/reports were included and discussed.[102-105] Developmental effects: three occupational,[59, 61, 72] eleven community-based studies/reports[90, 91, 95, 97, 102, 106-112] were included and discussed in the report. These studies/reports evaluated prenatal/postnatal developmental outcomes in infants such as spontaneous abortion, perinatal death, decreased birth weight, small for gestational age (SGA), postnatal growth, congenital malformations (e.g. cleft lip or cleft palate), and developmental neurotoxicity and immunotoxicity associated with the maternal exposure to TCE.	Sallmén et al.[57]; Lindbohm et al.[61] ; ATSDR[102] ; Zielinski[103] ; Bardodej & Vyskocil[104]; Sagawa et al.[105] Taskinen et al.[59]; Lindbohm et al.[61] ; Windham et al.[72] ; Lagakos et al.[97] ; ATSDR[102]; Goldberg et al.[90] ; Bove et al.[91] ; Bove[106] ; ATSDR (a)[107] ; ATSDR (b)[108] ; Rodenbeck et al.[95]; ATSDR[109] ; ATSDR[110] ; ATSDR[111] ; U.S.GAO[112]

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Findings: Available studies show that maternal exposure to trichloroethylene can result in negative reproductive outcomes such as reduced fertility, as measured by time to pregnancy incidence of fecundability (measured by time to pregnancy), amenorrhea, menstrual cycle disturbances and abnormal cycle length. An evaluation of the human studies, taking the overall weight and strength of the evidence into account, indicate that there is a potential for adverse developmental outcomes associated with pre- and/or postnatal trichloroethylene exposures. Chiu et al.[39] summarized the main findings and scientific issues in relation to the human health effects of trichloroethylene (including developmental cardiac toxicity) in the US EPA's toxicological review. The review reports that cardiac defects have been associated with exposure to trichloroethylene. In addition, other developmental outcomes, including embryonic/foetal mortality, prenatal growth inhibition were also found to be associated with trichloroethylene exposure. The report further states that interpretation of human epidemiological data on ECE exposure has been controversial, as many of them were limited by small number of cases, and methodological limitations. Nevertheless, the data provide a range of trichloroethylene-related cardiac defects, but lack adequate statistical power to identify any particular type of defect that may be more susceptible to trichloroethylene exposure. The report, citing National Research Council (2006) report, noted that elevation of cardiac malformations with similar relative effect size of 2-3-fold (with some significant findings) was associated with the exposure to TCE. Overall, this review (Chiu et al) summarises that that exposure to TCE: i) has strong evidence for male reproductive toxicity, ii) suggestive evidence for female reproductive toxicity, iii) strong evidence (based on - weakly suggestive epidemiological studies) for foetal cardiac malformations. These findings are consistent to those discussed in the EPA report. Makris et al.[38] published a review evaluating potential effects of trichloroethylene and/or its oxidative metabolites (dichloroacetic acid and dichloroacetic acid) on cardiac development. This study also evaluated two additional epidemiological studies (Fornad et al.;[52] Ruckart et al.[53]) that were not included in the EPA's 2011 report, and concluded that epidemiological studies demonstrate some support for the possible relationship between maternal exposure to trichloroethylene and cardiac birth defects. This conclusion is consistent to those discussed in the EPA report.					
World Health Organization - International Agency for Research on Cancer (IARC) (2000)	France	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 77 Some industrial chemicals – Ethylbenzene The IARC evaluates human carcinogenic risks associated with exposures to chemical, biological and physical agents. Whilst the focus is on an evaluation of carcinogenic risks and studies of cancer in humans, other studies relevant to an evaluation of carcinogenicity and its mechanisms are considered. The monograph critically reviewed data on carcinogenicity for ethylbenzene exposure, and represents expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans.	Ethylbenzene	Reproductive and developmental effects: No studies were reported to be available to the working group in relation to reproductive or developmental effects of ethylbenzene	
Findings: The report discussed sources of human (occupational and non-occupational) exposure to ethylbenzene. However, the working group concluded that no studies were found in relation to human reproductive or developmental effects of ethylbenzene.					

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
Agency for Toxic Substances and Disease Registry (ATSDR) (1994)	USA	Toxicological Profile for Acetone 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. The health effects section and human studies findings were considered in relation to this Evidence Profile.	Acetone Inhalation	Reproductive effects: data are limited in relation to inhalation exposure to acetone and reproductive effects -only three studies/reports were included and discussed.[74, 113, 114] Acetone inhalations could possibly have effect on shortening of the menstrual cycle. No statistically significant difference in reproductive effects was observed in women exposure to solvents (including acetone), compared to non-exposed. Developmental effects: data are limited in relation to inhalation exposure to acetone and developmental effects - only two studies/reports were included and discussed.[114, 115] No statistically significant differences in the incidences of miscarriage, prenatal death arte, or malformations were observed in women exposure to solvents (including acetone), compared to non-exposed.	Stewart et al.[113]; Nizyaeva[114]; Axelsson et al.[74]
			Oral exposure	No studies were found regarding reproductive and developmental effects in humans following oral exposure to acetone.	Nizyaeva[114]; Axelsson et al.[74]
			Dermal exposure	No studies were located regarding reproductive and developmental effects in humans following dermal or oral exposure to acetone.	
Findings: The relevance of the reproductive and developmental effects to humans in relation to exposure to acetone is unknown, and there is insufficient data to sufficiently examine these end points in humans.					
Agency for Toxic Substances and Disease Registry (ATSDR) (1992)	USA	Toxicological Profile for 2-Butanone [methyl ethyl ketone (MEK)] 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. The focus of the profiles is on health and toxicological information.	Inhalation Oral exposure Dermal exposure	No studies were located regarding reproductive or developmental effects in humans following inhalation, oral or dermal exposure to 2-Butanone [i.e. methyl ethyl ketone (MEK)].	

Authors & Year	Country	Title and scope	Exposure(s) type/route	Reproductive and Developmental Effects	References
		The health effects section and human studies findings were considered in relation to this Evidence Profile.			
Findings: No concluding remarks in relation to reproductive or developmental effects were located in the report.					
Institute of Medicine of the National Academies (2003)	USA	Gulf War and Health: Vol 2 Insecticides and solvents 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. 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.	Organic solvents. Studies considered specific solvents and mixtures of solvents.	Reproductive and developmental outcomes of interest included those related to preconception (sperm morphology, hormonal changes, infertility), during pregnancy (foetal loss) or as congenital malformations.	
Findings: The committee concluded from its assessment of the epidemiological literature, that there was inadequate/insufficient evidence to determine whether an association exists between exposure to specific solvents under review or solvent mixtures and male or female infertility after cessation of exposure. The committee concluded from its assessment of the epidemiological literature, that there was inadequate/insufficient evidence to determine whether an association exists between maternal or paternal preconception exposure to specific solvents under review or solvent mixtures and spontaneous abortions or other adverse pregnancy outcomes. The committee concluded from its assessment of the epidemiological literature, that there was inadequate/insufficient evidence to determine whether an association exists between maternal or paternal preconception exposure to specific solvents under review or solvent mixtures and congenital malformations.					