

Pesticides: Summary of epidemiologic evidence for associations with adverse pregnancy outcomes and child health and development

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1. Overall summary: Epidemiological evidence of associations between pesticides and adverse pregnancy outcome and childhood cancers

a) Adverse pregnancy outcome

Exposure	Window	Spontaneous abortion	Stillbirth	Preterm birth	Fetal growth deficit
TCDD-contaminated phenoxy herbicides or chlorophenate wood preservatives	Paternal	I		I	I
	Maternal	I		I	I
TCDD-free phenoxy herbicides	Paternal	L			
	Maternal	I		I	I
Other herbicides	Paternal	Atrazine – I Glyphosate – I Sulfonylureas – I Imidizolinones – I			
	Maternal	Atrazine – I Glyphosate – I	Paraquat – I		unspecified – I
DDT/DDE	Paternal	I			
	Maternal	L	L	L	L
Other organochlorine pesticides	Paternal	Lindane – I Dieldrin – I			
	Maternal	HCB – I Other – I	Dieldrin – I Heptachlor – I	HCB – I HCH – I	HCB – I HCH – I

Exposure	Window	Spontaneous abortion	Stillbirth	Preterm birth	Fetal growth deficit
			Chlordane – I unspecified – I	Dieldrin – I Heptachlor – I Chlordane – I	Dieldrin – I Heptachlor – I Chlordane – I
Organophosphate insecticides	Paternal	I			
	Maternal	I	I	I	I
Other insecticides, repellents	Paternal	Carbaryl – I unspecified – I			
	Maternal	Carbamates – I DEET – I	Pyrethroid – I Carbamate – I DEET – I	DEET – I Pyrethroid – I	DEET – I Pyrethroid – I Propoxur – I
Other specific pesticides	Paternal	Ethylene oxide – I Fungicides – I			
	Maternal	Ethylene oxide – L Fungicides – I	Fungicides – I		
Unspecified pesticides	Paternal	I	I		
	Maternal	I	L	I	I

Sufficient evidence = based on peer-reviewed reports of expert groups or authoritative reviews that concluded that a causal relationship existed; limited evidence = relationships for which several epidemiologic studies, including at least one case-control or cohort study, showed fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders; inadequate evidence = relationships for which epidemiologic studies were limited in number and quality (e.g., small studies, ecologic studies, limited control of potential confounders), had inconsistent results, or showed little or no evidence of exposure-risk relationships. Levels in parentheses are the author's interpretation of available evidence; other levels are based on expert group reviews.

Adverse pregnancy outcome, continued

Exposure	Window	Neural tube defects	Cardiac defects	Orofacial defects	Musculo-Skeletal defects	Urinary tract defects	Male genital defects
TCDD-contaminated phenoxy herbicides or chlorophenate wood preservatives	Paternal	L	I	I	I	I	I
	Maternal		I		I		
TCDD-free phenoxy herbicides	Maternal	I		I		I	I
Other herbicides	Maternal	Amides – I Glyphosate – I	unspecified – I		unspecified – I		Alachlor – I Atrazine – I Dicamba – I Trifluralin – I Diuron – I
DDT/DDE	Maternal						I
Other organochlorine pesticides	Maternal						Heptachlor – I Other – I
	Maternal			I	I		
Other insecticides, repellents	Maternal			unspecified - I	unspecified – I		Carbaryl – I Permethrin – I
Other specific Pesticides	Maternal	Fungicides – I					

Exposure	Window	Neural tube defects	Cardiac defects	Orofacial defects	Musculo-Skeletal defects	Urinary tract defects	Male genital defects
Unspecified pesticides	Paternal	L	I	I	I	L	I
	Maternal	I	I	I	I		I

b) Childhood cancer

Exposure	Window	Leukemia	Lymphoma	Brain cancer	Neuroblastoma	Wilms' tumour
TCDD-contaminated phenoxy herbicides or chlorophenate wood preservatives	Paternal	I		I		
	Childhood	I				
TCDD-free phenoxy herbicides	Maternal	L				
	Childhood	I				
Other or unspecified herbicides	Paternal			unspecified – I		
	Maternal			unspecified – I Simazine – I Trifluralin – I		unspecified – I
	Childhood		Trifluralin – I Simazine – I	unspecified – I Simazine – I Trifluralin – I	unspecified – I	unspecified – I
Other or unspecified insecticides, repellents	Paternal			unspecified – I	unspecified – I	
	Maternal	unspecified – L	unspecified – I	unspecified – L	unspecified – I	unspecified – I
	Childhood	unspecified – L	unspecified – I	unspecified – L	unspecified – I	unspecified – I
Other specific pesticides	Paternal			Fungicides – I		
	Maternal			Fungicides – I Fumigants – I		
	Childhood	Fungicides – I	Fungicides – I	Fungicides – I		

Exposure	Window	Leukemia	Lymphoma	Brain cancer	Neuroblastoma	Wilms' tumour
		Fumigants – I	Fumigants – I	Fumigants – I		
Unspecified pesticides	Paternal		I	L	unspecified – I	unspecified – I
	Maternal	I	I	I	unspecified – I	unspecified – I
	Childhood	I	I	L		unspecified – I

Childhood cancer, continued

Exposure	Window	Germ cell tumours	Bone cancer	Soft tissue sarcoma	Eye tumours
Other or unspecified herbicides	Paternal	unspecified – I			
	Maternal	unspecified – I		unspecified – I	
	Childhood			unspecified – I	
Other or unspecified insecticides, repellents	Paternal	unspecified – I			
	Maternal	unspecified – I			
	Childhood	unspecified – I	unspecified – I		
Unspecified pesticides	Paternal	I	L	unspecified – I	unspecified – I
	Maternal	I	I	unspecified – I	unspecified – I
	Childhood	I	unspecified – I		

2. Spontaneous abortion

Reviews

Author	Scope of review	Findings	
(Nurminen 1995), Finland	Review of epidemiologic studies of maternal pesticide exposure and adverse pregnancy outcome published during 1979 until early 1995	Positive – 5 studies reported associations between spontaneous abortion and maternal occupational pesticide exposure	Negative – 2 studies found no association; one used maternal residence as exposure index, other assessed employment in agriculture/horticulture but not pesticide use <i>per se</i>
Overall – studies give some support for associations but limitations preclude firm conclusions			
(Longnecker and others 1997), USA	Review of epidemiologic studies of DDT and PCBs; p,p' -DDE and PCBs comprise the bulk of organochlorine residues in human tissues	2 large case-control studies found no association between spontaneous abortion and maternal blood DDT/DDE levels; no other pesticides were assessed	
(Sever and others 1997), USA	Reviewed original epidemiologic studies of occupational pesticide exposure and reproductive/developmental outcomes published during 1970-1996	Found increasing evidence for associations between maternal or paternal occupational pesticide exposure and spontaneous abortion	Specific pesticide exposures linked to spontaneous abortion included occupational use of DDT, lindane, dieldrin, parathion, methyl parathion, dichlorvos or chlordimeform, carbofuan and maternal residential proximity to forestry use of 2,4,5-T
Non-specific pesticide exposure indices linked to spontaneous abortion included self-reported			

Author	Scope of review	Findings	
maternal occupational use of pesticides in indoor gardening including greenhouse work and agricultural employment more generally and paternal employment in farming or gardening			
(Arbuckle and Sever 1998), USA	Review of epidemiologic literature published during 1966 to November 1997 on pesticide exposures and fetal death; noted that many epidemiologic studies had methodologic problems, especially inadequate exposure assessment and limited statistical power	Exposure of U.S. Vietnam veterans to Agent Orange and other herbicides: elevated spontaneous abortion risk related to low paternal TCDD levels measured 15-26 years after the war ended but no dose-response relationship	2,4-D, 2,4,5-T: inadequate evidence for an association between paternal exposure or maternal residential proximity to use and spontaneous abortion
Chlorophenate wood preservatives: limited evidence from a small cohort and case series for association between maternal exposure and spontaneous abortion	Organochlorine pesticides: studies in India suggest that high paternal occupational exposure to DDT and some other organochlorine and organophosphate pesticides was associated with increased risk of spontaneous abortion	Organophosphate insecticides: 2 studies of maternal residence in areas treated with malathion found no association with spontaneous abortion	Carbamates: the only analytical study found an association between spontaneous abortion and carbofuran exposure in China
Agricultural employment: studies to date have shown consistent increased risks of fetal death related to parental (mainly maternal) employment in agriculture	DBCP: the 2 studies of this relationship found that paternal occupational exposure was associated with increased risk of spontaneous abortion	Unspecified pesticides: most studies have focused on maternal exposure and found associations with increased risks of spontaneous abortion	
(Petrelli and Mantovani 2002), Italy	Review of literature on epidemiologic studies published during 1980-2001 on	Limited evidence for association between paternal occupational	

Author	Scope of review	Findings	
	environmental risk factors and male fertility	exposure to DBCP, herbicides or employment as pesticide applicator and spontaneous abortion	
(Weselak and others 2006), Canada	Reviewed epidemiologic and toxicologic studies of adverse pregnancy outcomes and periconceptual exposure to specific pesticides published during 1966-2005	Inadequate evidence for association between spontaneous abortion and maternal exposure to organophosphate insecticides, phenoxy herbicides, triazine herbicides, thiocarbamates; limited evidence for association with maternal DDT/DDE exposure	

Spontaneous abortion: Original studies since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Jarrell and others 1998), Turkey	Retrospective cohort	42 women poisoned by HCB and developed clinically confirmed porphyria cutanea tarda as children, 42 age/region-matched unexposed women, 42 age-matched women from city; self-reported info on	60 spontaneous abortion among 307 pregnancies of exposed women, 57 among 328 pregnancy in comp group 1 and	Serum HCB	Prevalence of serum HCB levels >1 µg/L in exposed women and 2 comparison groups, respectively, were 16.7, 4.8	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		pregnancy outcomes	29 among 185 pregnancy in group 2; only 4 stillbirths in all groups combined		and 0%	
OR, spontaneous abortion, exposed vs all non-exposed women	1.21, 0.82-1.77 [calc from data in paper]	Logistic regression coefficient (SE), spontaneous abortion frequency vs log maternal serum HCB ($\mu\text{g/L}$)	2.88 \pm 0.91, $p < .001$			
(Arbuckle and others 1999), Ontario	Retrospective cohort (see Savitz et al 1997 above)	1,898 farm couples identified from 1988 agricultural census; farms selected to be full-time family-run operations and on basis of crops grown and acreage sprayed with pesticides; self-reported info on outcomes of 3,984 eligible pregs collected during 1990-91	395 spontaneous abortion (GW <20)	Self-reported parental farm activities by calendar month during previous 5 years	Assessed pesticide exposures during 3 months before conception, use of protective equipmt.	Various combinations of maternal education, years of farm residence, alcohol, tea/coffee, per capita income, length of recall, age at menarche, paternal age
OR, spontaneous abortion, 1 st trimester exposure to chlorophenoxy herbicides by GW of spontaneous abortion	Any chlorophenoxy GW <20 1.1, 0.6-2.1 GW <12 1.1, 0.4-3.3 GW 12-19 1.0, 0.4-2.5	2,4-D GW <20 1.0, 0.5-2.0 GW <12 1.1, 0.4-3.1 GW 12-19 1.0, 0.4-2.8	2,4-DB GW <20 0.7, 0.3-1.7 GW <12 1.2, 0.3-3.9 GW 12-19 0.5, 0.1-1.9	MCPA GW <20 0.9, 0.4-2.0 GW <12 0.8, 0.3-2.4 GW 12-19 0.8, 0.3-2.1		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, spontaneous abortion, preconceptual chlorophenoxy herbicide exposure (paternal)	Any chlorophenoxy GW <20 1.1, 0.6-1.9 GW <12 2.5, 1.0-6.4 GW 12-19 0.4, 0.2-1.0	2,4-D GW <20 0.9, 0.5-1.8 GW <12 1.9, 0.7-4.8 GW 12-19 0.4, 0.1-1.0	MCPA GW <20 1.0, 0.5-1.9 GW <12 2.3, 0.8-6.5 GW 12-19 0.4, 0.1-1.2	OR, spontaneous abortion, male partner chlorophenoxy herbicide use without protective equipment	Fetal deaths <12 wk 5.0, 0.7-36.2	
OR, spontaneous abortion, >1 month exposure in preconceptual 3-mth window	Chlorophenoxy herbs GW <20 0.8, 0.4-1.7 GW <12 2.7, 1.0-7.6	MCPA GW <20 1.5, 0.6-3.8 GW <12 5.4, 1.7-17.3				
(Cho and others 1999), China	Retrospective cohort	Survey of residents of cotton-growing regions, 1993; self-reported pregnancy outcomes	2201 women; pregnancies (n=2953) and spontaneous abortion (GW <28, n=233) during past 5 yr	Self-reported occupational pesticide exposure before conception	Ponds likely contaminated by pesticides used on cotton but no analytic data provided	Season of conception, age at pregnancy, previous adverse pregnancy outcome, parity, occupation, education, general health status, dietary salt intake

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, spontaneous abortion, prenatal maternal occupational pesticide exposure, yes/no	0.60, 0.43-0.84	OR, spontaneous abortion, maternal drinking water source, ponds vs well/river	1.63, 1.11-2.39			
(Petrelli and others 2000), Italy	Retrospective cohort	32 pesticide applicators, 51 food retailers; self-reported pregnancy history	26 spontaneous abortion among 93 total pregnancies among wives of pesticide applicators; 7 spontaneous abortion and 97 total pregnancies among wives of food retailers	Paternal employment as pesticide applicator	Self-reported pesticide use info for 1970-95	Maternal age, parental smoking
OR, spontaneous abortion, paternal pesticide applicators vs food retailers	3.8, 1.2-12.0					
(Arbuckle and others 2001), Ontario	Retrospective cohort (see Savitz et al 1997 and Arbuckle et al 1999 above)	Ontario farm families; self-reported pregnancy history	395 spontaneous abortion (<20 wk) among 3,936 pregnancies of 2,110 women	Self-reported parental (mainly paternal) pesticide use	Assessed use and indirect exposure to agricultural pesticides 4 months before	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					conception and during 1 st trimester	
OR,spontaneous abortion, preconceptual pesticide exposure (mainly paternal)	Herbicides GW <12 1.4, 1.1-1.9 GW 12-19 1.1, 0.8-1.6 GW <20 1.3, 1.0-1.6	chlorophenoxy herbicides GW <12 1.5, 1.1-2.1 GW 12-19 0.8, 0.5-1.9 GW <20 1.2, 0.9-1.5	2,4-D GW <12 1.3, 0.9-2.0 GW 12-19 0.9, 0.5-1.6 GW <20 1.2, 0.8-1.6	MCPA GW <12 1.1, 0.6-1.8 GW 12-19 0.6, 0.3-1.2 GW <20 0.8, 0.5-1.3	Atrazine GW <12 1.3, 0.8-2.0 GW 12-19 1.1, 0.7-1.9 GW <20 1.2, 0.9-1.7	Dicamba GW <12 1.0, 0.5-1.8 GW 12-19 1.1, 0.6-2.2 GW <20 1.0, 0.7-1.7
Glyphosate GW<12 1.4, 1.0-2.1 GW 12-19 1.1, 0.7-1.9 GW <20 1.7, 1.0-2.9	Insecticides GW <12 1.2, 0.9-1.5 GW 12-19 1.1, 0.8-1.5 GW <20 1.1, 0.9-1.4	Organophosphates GW <12 1.0, 0.6-1.6 GW 12-19 1.0, 0.6-1.7 GW <20 1.0, 0.7-1.4	Fungicides GW <12 1.3, 0.9-1.9 GW 12-19 1.4, 0.9-2.1 GW <20 1.4, 1.1-1.8	Thiocarbamates GW <12 1.1, 0.7-1.9 GW 12-19 1.8, 1.1-3.0 GW <20 1.5, 1.0-2.1	Carbaryl GW <12 1.2, 0.9-1.7 GW 12-19 1.2, 0.8-1.9 GW <20 1.2, 0.7-2.0	
OR, spontaneous abortion, postconceptual pesticide use	Herbicide exposure GW <12 0.7, 0.5-1.0 GW 12-19	Fungicides GW <12 0.6, 0.4-1.0 GW 12-19	Any chlorophenoxy GW <12 0.6, 0.4-1.0	2,4-D GW <12 0.6, 0.3-1.2 GW 12-19	MCPA GW <12 0.7, 0.3-1.4 GW 12-19	Dicamba GW <12 0.8, 0.3-1.7 GW 12-19

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	1.1, 0.7-1.5 GW <20 0.8, 0.7-1.1	1.0, 0.6-1.6 GW <20 0.8, 0.5-1.1	GW 12-19 1.3, 0.8-2.0 GW <20 0.9, 0.6-1.2	1.6, 0.9-2.7 GW <20 1.0, 0.7-1.6	0.9, 0.4-1.8 GW <20 0.8, 0.5-1.3	1.6, 0.8-3.2 GW <20 1.1, 0.7-1.9
Atrazine GW <12 0.7, 0.3-1.5 GW 12-19 0.8, 0.4-1.6 GW <20 0.8, 0.5-1.2	Glyphosate GW <12 0.8, 0.4-1.6 GW 12-19 1.4, 0.8-2.5 GW <20 1.1, 0.7-1.7	Any insecticide GW <12 0.7, 0.5-1.1 GW 12-19 1.0, 0.8-1.4 GW <20 0.8, 0.6-1.1	Organophosphates GW <12 0.5, 0.3-1.0 GW 12-19 0.9, 0.5-1.5 GW <20 0.6, 0.4-1.0	Thiocarbamates GW <12 0.6, 0.3-1.3 GW 12-19 1.1, 0.5-2.2 GW <20 0.8, 0.5-1.3		
OR, spontaneous abortion, preconceptual vs postconceptual farm pesticide use	Herbicides GW <12 2.3, 1.3-3.9 GW 12-19 1.1, 0.7-1.8 GW <20 1.6, 1.1-2.4	Chlorophenoxy herbicides GW <12 3.1, 1.4-6.4 GW 12-19 0.6, 0.3-1.1 GW <20 1.3, 0.8-2.1	2,4-D GW <12 2.9, 1.1-8.0 GW 12-19 0.5, 0.2-1.1 GW <20 1.1, 0.6-2.0	MCPA GW <12 2.0, 0.7-5.7 GW 12-19 0.6, 0.2-1.7 GW <20 1.1, 0.6-2.3	Dicamba GW <12 1.4, 0.4-4.7 GW 12-19 0.6, 0.2-1.6 GW <20 1.0, 0.4-1.9	Atrazine GW <12 1.7, 0.8-3.8 GW 12-19 1.4, 0.6-3.5 GW <20 1.6, 0.9-3.0
Insecticides GW <12	Organophosphates GW <12	Fungicides GW <12	Carbaryl GW <12	Thiocarbamates GW <12		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
2.6, 1.3-5.2 GW 12-19 1.2, 0.6-2.2 GW <20 1.7, 1.1-2.9	3.8, 1.1-13.4 GW 12-19 1.3, 0.4-3.6 GW <20 2.2, 1.0-4.8	3.9, 1.4-10.3 GW 12-19 1.8, 0.7-4.4 GW <20 2.8, 1.4-5.4	1.7, 0.7-4.4 GW 12-19 2.2, 0.8-6.1 GW <20 2.0, 1.0-4.0	2.0, 0.8-5.0 GW 12-19 2.4, 0.8-7.6 GW <20 2.5, 1.1-5.8		
(Korrick and others 2001), China v small study	Nested case-control	Cohort of female Chinese textile workers, recruited in 1996; monthly interviews re pregnancy status	15 spontaneous abortion (GW<13), 15 term live birth controls	Measured maternal serum DDT/DDE, PCBs (67 congeners), other OCs (serum samples collected in 1998)		Maternal age, BMI
OR, spontaneous abortion, per unit increase in serum OC level	ρ,ρ' -DDE (ng/g) 1.13, 1.02-1.26 ρ,ρ' -DDT (ng/100 g) 1.04, 0.99-1.08	HCb (ng/100 g) 1.06, 1.00-1.14				
(McGready and others 2001), Thailand	Randomized controlled trial	Pregnancy women in refugee camps randomly allocated to receive daily application of the insect repellent N, N-diethyl-m-toluamide (DEET) (1.7 g/day) in 2 nd and 3 rd Ts to prevent malaria; weekly interviews re pregnancy status	9 spontaneous abortion and 383 total pregnancies among DEET-treated women, 6 spontaneous abortion and 385 total pregnancies among control	DEET detected in 8% of cord blood samples from a randomly selected subgroup of DEET users		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			women			
OR, spontaneous abortion, treated vs control women	1.52, 0.49-4.85					
(Schnorr and others 2001), USA	Retrospective cohort	Male workers in 2 Agent Orange production plants, comparison group of unexposed neighbourhood males matched for age and race; mother-reported pregnancy history	259 male workers, 200 wives, 632 pregnancies; 243 neighbourhood men, 220 wives, 707 pregnancies	Occupational exposure during prod of trichlorophenol or derivs; measured serum TCDD in 1987-88 and extrapolated to conception; measured serum TCDD in 79 referents and assumed a value of 6 pg/g lipid for other referents	Median, min and max serum TCDD levels: workers – 254, 3 and 16340 pg/g lipid; referent males – 6, 2 and 19 pg/g lipid	Maternal age, Hispanic ethnicity, thyroid disease medication
OR, spontaneous abortion by paternal serum TCDD (pg/g lipid), relative to unexposed workers	1.0 (ref) <20 0.8, 0.5-1.2 20- 0.8, 0.4-1.6	255- 0.7, 0.3-1.6 ≥1120 1.0, 0.4-2.2	OR, spontaneous abortion by paternal serum TCDD (pg/g lipid), relative to exposed workers in lowest serum TCDD category	<20 1.0 20- 1.1, 0.3-3.4	255- 0.9, 0.3-3.1 ≥1120 1.4, 0.4-4.8	OR, spontaneous abortion, per log ₁₀ paternal serum TCDD increment 0.97, 0.88-1.09

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Garry and others 2002), Minnesota	Retrospective cohort	695 families of licensed farm and commercial pesticide applicators (98% were males), 1991-96; reproductive histories reported by father, mother or both parents	1602 pregnancies fathered by 522 applicators, 144 pregnancy losses (spontaneous abortions (GW <28), stillbirths (GW ≥28), neonatal deaths)	Self-reported current and past pesticide use incl product names, d/yr applied, acreage treated, type of crop, use of protective gear		
OR, preg loss, pat pestic use, yes/no	Herbicide only (referent) 1.0 herbicide/insecticide 1.27, 0.68-2.36	herbicide/insecticide/fungicide 1.64, 1.01-2.67 herbicide/insecticide/fumigant 1.17, 0.53-2.59	all 4 pestic classes 1.14, 0.59-2.17	Preg loss vs pat fungicide use No fungicide use (referent) 1.0 organotin 1.55, 1.01-2.37	triazole 1.56, 0.89-2.72 EBDC-containing fungicides (maneb or mancozeb) 1.77, 1.11-2.83	Substituted aromatics 1.01, 0.30-3.39 Benzimidazoles 0.74, 0.26-2.09
Preg loss vs prenatal mat pestic mixing, loading and applications	1.81, 1.04-3.12	OR, 1 st T spont abor, preg.s conceived in spring spray season, pat herbicide use (referent = all other pesticides)	Chlorophenoxy 1.59, 0.77-3.27 Chlorophenoxy + bromophenol 1.66, 0.78-3.56	Chlorophenoxy + sulfonyleurea + benzothiadazole 2.94, 1.40-6.16	Sulfonyleurea 2.11, 1.09-4.09	Imidizolinone 2.56, 1.11-5.87 Oxychlorophenoxy 1.40, 0.69-2.82
(Petrelli and others 2003), Italy	Retrospective cohort	184 male greenhouse workers, enrolled 2000; father-reported reproductive history	7 spontaneous abortion among 48 exposed pregnancies and 6 among 136	Father-reported exposure info incl specific pesticides (benomyl),	Greenhouse workers who did not report pesticide use were considered	Paternal age, smoking, education, maternal age, smoking,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			unexposed pregnancies	carbendazim, carbaryl, DDT, atrazine)	unexposed	education, work (housekeeper, agricultural, other), time between interview and pregnancy
Crude OR, spontaneous abortion, paternal pesticide use in greenhouses	3.70, 1.04-13.3 [calc from data in paper]					
(Sugiura-Ogasawara and others 2003), Japan	Case-control	Women with history of 3 or more consecutive 1 st trimester spontaneous abortion, recruited 2001-2002	45 cases with history of 3+ 1 st trimester spontaneous abortion, 2001-02; 30 healthy non-pregnancy women with no history of live birth or infertility	Measured serum levels of 18 PCBs, HCB, DDE		
Mean organochlorine concentration (\pm SD) ng/g lipid, cases vs controls	HCB 17.6 \pm 10.2 vs 21.2 \pm 10.0 ng/g lipid, p>.05	DDE 346.9 \pm 200.5 vs 487.4 \pm 369.8 ng/g lipid, p>.05				
(Eskenazi and others 2003), Seveso, Italy	Cohort	981 women age \leq 40 at trichlorophenol plant explosion in 1976, lived in	97 spontaneous abortion among 769 pregnancies	Serum TCDD measured	Median serum TCDD level soon after explosion	Maternal age, education, history of early fetal

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		TCDD-contaminated region; followed to 1996-98; self-reported pregnancy history, medical records available for 70/97 spontaneous abortion	of 476 women		was 47 (range 24-104 pg/g lipid)	death
OR, spontaneous abortion during first 8 years of followup, per log ₁₀ increase in maternal serum TCDD	1.0, 0.6-1.6					
(Salazar-Garcia and others 2004), Mexico	Retrospective cohort	2033 male antimalaria workers, age 28-82 yr, enrolled during 2000, self-reported reproductive outcomes for 9187 pregnancies during 1956-1990; father-reported pregnancy history	55 birth defects, 399 spontaneous abortion, 114 stillbirths, 8547 total live births; included pregnancy outcomes before and after paternal pesticide exposure began	Father-reported info on exposure to DDT and other pesticides during 1956-1990	Estimated body burden of DDE at time of pregnancies from timing, intensity and duration of exposure to DDT	Maternal age, paternal malathion exposure
Adj OR, spontaneous abortion, est'd paternal serum DDE level	Est'd paternal serum DDE quartiles (2 nd to 4 th vs 1 st) 1.05, 0.76-1.46 1.13, 0.83-1.53	Adj OR, spontaneous abortion, malathion use (yes vs no) 0.88, 0.56-1.39	OR, bivariate analyses, exposed vs unexposed	Lindane 1.22, 0.68-2.20 Dieldrin 1.22, 0.68-2.20	Temephos 1.13, 0.76-1.68 Fenitrothion 0.50, 0.17-1.50	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	1.24, 0.91-1.70					
(Longnecker and others 2005), US Collaborative Perinatal Project	Retrospective cohort	About 42000 women recruited during early pregnancy, 1959-1965, 12 US study centres, 55000 infants born during study; cohort ltd to women with prenatal serum DDE measured; cases identified from mother-reported pregnancy history and hospital/clinic records	5215 pregnancies, 604 spontaneous abortion (GW <20), 165 stillbirths (GW ≥20)	Measured DDT/DDE and other OC pesticide and PCB levels in a subset of women using stored maternal 3 rd trimester serum samples	Median DDE level was 25 µg/L (range 3-178)	Study centre, serum triglycerides and cholesterol, maternal age at conception, race, smoking, dieldrin, β-HCH
OR, fetal death (any gestation length) vs prenatal maternal serum DDE quintile (relative to 1 st quintile)	1.1, 0.9-1.5 1.4, 1.0-1.9 1.6, 1.1-2.4 1.2, 0.7-1.9	OR, fetal death at any gestation length, per prenatal maternal serum DDE increment of 60 µg/L (continuous variable)	1.4, 1.1-1.6	Association between fetal death and maternal serum DDE similar for early and late fetal deaths; result stated without showing data	No association between fetal death and prenatal maternal serum DDT levels	
(Venners and others 2005), China	Cohort (see also pilot study by Korrick et al 2001 above)	388 newly married Chinese female textile workers, non-smokers, non-drinkers ; pregnancy detected using daily urinary HCG measuredurements	128 early pregnancy losses in 500 conceptions; 36 clinically apparent spontaneous	Serum DDT/DDE	Median preconceptualtio n serum DDT/DDE 1.58/26.54 ng/g serum, ranges	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			abortion (GW 6-19) in 372 clinical pregnancies		0.41-14.61 and 4.84-99.57	
OR, early pregnancy loss plus spontaneous abortion, 2 nd and 3 rd vs 1 st tertile serum DDT	1.17, 0.67-2.06 1.90, 1.09-3.33 p-trend=.018	OR, early pregnancy loss, 2 nd and 3 rd vs 1 st tertile serum DDT	1.07, 0.58-1.99 1.71, 0.93-3.12 p-trend=.06	OR, clinical spontaneous abortion, 2 nd and 3 rd vs 1 st tertile serum DDT	1.22, 0.51-2.92 1.28, 0.53-3.10 p-trend=.61	
(Khanjani and Sim 2006a), Australia	Retrospective cohort	Primiparous women, 6-12 wk postpartum, recruited in centres throughout Victoria state during early 1990's; pregnancy outcomes based on clinic records	814 mothers, 93 previous spontaneous abortion or stillbirths	Breast milk DDT/DDE measured	Breast milk tertiles ($\mu\text{g}/\text{kg}$ lipid) DDT: ≤ 39 , 39-66, >66 DDE: ≤ 400 , 401-730, >730	Maternal age, wt, education, smok, alcohol
OR, spontaneous abortion or stillbirth by breast milk DDT/DDE tertile	1 st tertile DDT 1.0 (ref) 0.84, 0.49-1.43 0.63, 0.36-1.13	1 st tertile DDE 1.0 (ref) 0.81, 0.47-1.42 0.76, 0.41-1.39				
(Khanjani and Sim 2006b), Australia	Retrospective cohort	Primiparous women, 6-12 wk postpartum, recruited in centres throughout Victoria state during early 1990's;	814 mothers, 93 previous spontaneous abortion or	Breast milk organochlorines measured	Breast milk tertiles ($\mu\text{g}/\text{kg}$ lipid):	Maternal age, wt, education, smok, alcohol

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		pregnancy outcome based on clinic records	stillbirths		dieldrin: ≤33, 34-48, >48 heptachlor epoxide or oxychlorane: ≤5, 5-9, >9 HCB: ≤27, 28-48, >48	
OR, spontaneous abortion or stillbirth, 2 nd and 3 rd vs 1 st tertile of breast milk organochlorine pesticide level	Dieldrin 1 st tertile 1.0 0.96, 0.57-1.64 0.73, 0.42-1.27	Heptachlor epoxide 1.0 1.10, 0.64-1.91 0.82, 0.48-1.39	Oxychlorane 1.0 1.47, 0.88-2.43 0.54, 0.29-1.00	HCB 1.0 1.03, 0.61-1.75 0.49, 0.26-0.90		

Summary: Spontaneous abortion, reviews

Reviews

Maternal exposure

A reviewer found limited evidence for an association between spontaneous abortion and maternal occupational pesticide exposure (Nurminen 1995). A review of DDT/DDE and reproductive outcomes noted that 2 large case-control studies found associations between spontaneous abortion and maternal serum DDT/DDE levels (Longnecker and others 1997). A review of studies published during 1970-96 noted that spontaneous abortions had been linked to maternal or paternal occupational use of specific pesticides including DDT, lindane, dieldrin, parathion, methyl parathion, dichlorvos, chlordimeform and carbofuan, maternal residential proximity to use of 2,4,5-T in forestry, self-reported maternal occupational use of pesticides in indoor gardening including greenhouse work and, more generally, to maternal or paternal employment in farming or gardening (Sever and others 1997). In a subsequent review, Arbuckle and Sever concluded that there was inadequate evidence for an association between spontaneous abortion and maternal residential proximity to 2,4,5-T use in forestry (based on an ecologic study in Oregon) (Arbuckle and Sever 1998). This review noted limited evidence from a small cohort study and case series for an association between maternal exposure to chlorophenate wood preservatives and spontaneous abortion. It also cited 2 studies of maternal residence in areas treated with malathion that found no association with spontaneous abortion and a study that found an association between spontaneous abortion and

carbofuran exposure in China. The authors also noted that most studies of spontaneous abortion and maternal exposure to unspecified pesticides or maternal employment in agriculture have reported elevated risks. A recent review examined evidence from epidemiologic studies of pregnancy outcome that assessed pesticide class, family and/or active ingredient (Weselak and others 2006). These reviewers found limited epidemiologic evidence for associations between spontaneous abortion and DDT and inadequate evidence for associations with other pesticide categories including phenoxy herbicides, triazine herbicides or thiocarbamate fungicides.

Paternal exposure

A review of studies published during 1970-96 noted that spontaneous abortions had been linked to maternal or paternal occupational use of specific pesticides including DDT, lindane, dieldrin, parathion, methyl parathion, dichlorvos, chlordimeform and carbofuran and, more generally, to maternal or paternal employment in farming or gardening (Sever and others 1997). In a subsequent review of studies published during 1966-97, Arbuckle and Sever concluded that there was inadequate evidence for an association between spontaneous abortion and paternal occupational exposure to 2,4,5-T or Agent Orange (a 50:50 mixture of 2,4-D and 2,4,5-T) and other herbicides used by U.S. military personnel during the Vietnam war (Arbuckle and Sever 1998). These authors noted that studies of Vietnam veterans revealed elevated spontaneous abortion risk at low but not at high paternal serum TCDD levels (TCDD levels at conception were estimated from levels measured 15-26 years after the war ended). This review also noted some evidence of associations between spontaneous abortion and high paternal occupational exposure to DDT and some other organochlorine and organophosphate pesticides in India and inadequate evidence for an association with paternal occupational DBCP exposure. Other reviewers found limited evidence for an association between spontaneous abortion and paternal occupational exposure to DBCP or herbicides or employment as pesticide applicators (Petrelli and Mantovani 2002).

Original studies published since 1998

Maternal exposure, TCDD-contaminated chlorophenoxy herbicides, inadequate evidence

Chlorophenoxy herbicides comprise many closely related chemical entities including 2,4-dichlorophenoxyacetic acid (2,4-D^a), 2,4-dichlorophenoxybutyric acid (2,4-DB), 2-methyl-4-chlorophenoxyacetic acid (MCPA) and 2-methyl-4-chlorophenoxypropionic acid (MCP, mecoprop) (Wood 2007). TCDD and/or related dioxins were potential contaminants in the herbicides 2,4-D and 2,4,5-T produced before about 1985. A review of studies published during 1970-96 noted that an ecologic study in Oregon had linked spontaneous abortion to maternal residential proximity to use of 2,4,5-T in forestry (Sever and others 1997). A retrospective cohort study of women exposed to TCDD at Seveso reported no association between spontaneous abortion and serum TCDD levels measured soon after exposure (per log increment of serum TCDD, OR=1.0, 95% CI 0.6-1.6) (Eskenazi and others 2003).

Maternal exposure, "TCDD-free" chlorophenoxy herbicides, inadequate evidence

The Ontario farm family study reported no association between spontaneous abortion at GW <20 and prenatal farm use of any chlorophenoxy herbicide (OR=1.1, 95% CI 0.6-2.1) or subtypes including 2,4-D (OR=1.0, 95% CI 0.5-2.0), 2,4-DB (OR=0.7, 95% CI 0.3-1.7) or MCPA (OR=0.9, 95% CI 0.4-2.0) (Arbuckle and others 1999). The Ontario study also found no association between these herbicides and spontaneous abortions before GW 12 or during GW 12-19. A subsequent report of this study confirmed no association between postconceptual farm use of chlorophenoxy herbicides and spontaneous abortion at GW <12 (OR=0.6, 95% CI 0.4-1.0) or GW 12-19 (OR=1.3, 95% CI 0.8-2.0) (Arbuckle and others 2001). However, there were associations of borderline statistical

^a First used in 1948.

significance between late spontaneous abortion (GW 12-19) and postconceptual farm use of 2,4-D (crude OR=1.6, 95% CI 0.9-2.7) or dicamba (crude OR=1.6, 95% CI 0.8-3.2). In the Ontario study, pesticide exposure reflected both pesticide use by the farm operator spouse (80% males) and indirect exposure of the other spouse since the study was limited to couples on operating farms.

Maternal exposure, other herbicides, inadequate evidence

The Ontario farm family study reported no association between spontaneous abortion before GW 20 and postconceptual farm use of atrazine (OR=0.8, 95% CI 0.5-1.2) or glyphosate (OR=1.1, 95% CI 0.7-1.7) (Arbuckle and others 2001). There was also no association between these pesticides and spontaneous abortions before GW 12 or during GW 12-19.

Maternal exposure, DDT/DDE, limited evidence

A recent review found limited evidence for an association between spontaneous abortion and maternal DDT/DDE exposure based on 5 studies that used biomarkers of prenatal DDT/DDE exposure (Weselak and others 2006). In a very small case-control study nested within a cohort of female Chinese textile workers, spontaneous abortion risk was related to serum DDE (per unit increase in serum p,p' -DDE (ng/g serum), OR=1.13, 95% CI 1.02-1.26; serum p,p' -DDT (ng/100 g serum, OR=1.04, 0.99-1.08) (Korrick and others 2001). A Japanese case-control study reported no association between a history of 3 or more consecutive spontaneous abortions and maternal serum DDE levels (mean levels, cases vs controls, 346.9±200.5(SD) vs 487.4±369.8 ng/g lipid, $p>.05$) (Sugiura-Ogasawara and others 2003). A large U.S. nation-wide retrospective cohort study revealed a non-monotonic dose-response relationship between fetal death at any gestation length and prenatal serum DDE concentration (per increment of 60 µg/L, OR=1.4, 95% CI 1.1-1.6) but not DDT levels (Longnecker and others 2005). Among newly married Chinese female textile workers monitored for conception using daily urinary hCG measurements, there was no association between clinical spontaneous abortion (GW 6-19) and maternal preconceptual serum DDT levels (2nd vs 1st tertile, OR=1.22, 95% CI 0.51-2.92; 3rd vs 1st tertile, OR=1.28, 95% CI 0.53-3.10, p -trend=.61); there were similar results when serum DDE was modeled (Venners and others 2005). This study did, however, find an association between clinically non-apparent pregnancy loss before GW 6 and maternal serum DDT levels (2nd vs 1st tertile, OR=1.17, 95% CI 0.67-2.06; 3rd vs 1st tertile, OR=1.90, 95% CI 1.09-3.33, p -trend=.02). In an Australian retrospective cohort study, fetal death (any gestation length) was not associated with breast milk DDT or DDE levels (2nd vs 1st tertile DDE, OR=0.81, 95% CI 0.0.47-1.42; 3rd vs 1st tertile, OR=0.76, 95% CI 0.41-1.39) (Khanjani and Sim 2006b).

Maternal exposure, hexachlorobenzene, inadequate evidence

Hexachlorobenzene (HCB) is an organochlorine fungicide used as a seed treatment, especially on wheat. A retrospective cohort study of women poisoned as children (at average age 6 years) by hexachlorobenzene (HCB) revealed a dose-response relationship between spontaneous abortion and log maternal serum HCB levels (per log HCB (µg/L), β =2.88±0.91(SE), $p<.001$) but did not assess or adjust for potential confounders (Jarrell and others 1998). A Japanese case-control study reported no association between a history of 3 or more consecutive spontaneous abortions and maternal serum HCB levels (mean levels, cases vs controls, 17.6±10.2(SD) vs 21.2±10.0 ng/g lipid, $p>.05$) (Sugiura-Ogasawara and others 2003). A small case-control pilot study nested within a cohort of Chinese textile workers revealed an association of borderline statistical significance between spontaneous abortion and prenatal serum HCB (per 1 ng/100 g serum increment, OR=1.06, 95% CI 1.00-1.14) (Korrick and others 2001). In an Australian retrospective cohort study, fetal death (any gestation length) was not associated with breast milk HCB levels (2nd vs 1st tertile, OR=1.03, 95% CI 0.61-1.75; 3rd vs 1st tertile, OR=0.49, 95% CI 0.26-0.90) (Khanjani and Sim 2006b).

Maternal exposure, other organochlorine insecticides, inadequate evidence

In an Australian retrospective cohort study, fetal death (any gestation length) was not associated with breast milk dieldrin (3rd vs 1st tertile, OR=0.73, 95% CI 0.42-1.27), heptachlor epoxide (OR=0.82, 95% CI 0.48-1.39) or oxychlorane levels (OR=0.54, 95% CI 0.29-1.00) (Khanjani and Sim 2006b).

Maternal exposure, organophosphate insecticides, inadequate evidence

A retrospective cohort study of Ontario farm families reported no association between spontaneous abortion (GW <20) and postconceptual farm use of organophosphate insecticides (OR=0.6, 95% CI 0.4-1.0); there was also no relationship between such exposure and spontaneous abortion at GW <12 or 12-19 (Arbuckle and others 2001).

Maternal exposure, other specified insecticides or insect repellents, inadequate evidence

The Ontario farm family study reported no association between spontaneous abortion (GW <20) and postconceptual farm use of carbamate insecticides (OR=0.8, 95% CI 0.5-1.3); there was also no relationship between such exposure and spontaneous abortion at GW <12 or 12-19 (Arbuckle and others 2001). In a randomized controlled trial of N, N-diethyl-m-toluamide (DEET) to prevent malaria during pregnancy in Thailand, spontaneous abortion risk was not increased among exposed women (OR=1.52, 95% CI 0.49-4.85) (McGready and others 2001).

Maternal exposure, ethylene oxide, limited evidence

Among Finnish nurses, spontaneous abortion was not associated with exposure to anaesthetic gases (Hemminki and others 1985). In a retrospective cohort study of most recent pregnancies among female dental assistants in California who conceived while working full-time, spontaneous abortion was associated with self-reported occupational ethylene oxide exposure (OR=2.5, 95% CI 1.0-6.3) and was independent of age and exposure to nitrous oxide or preparation of mercury amalgams (Rowland and others 1996). A South African retrospective cohort study revealed a strong association between spontaneous abortion and occupational exposure to ethylene oxide in hospital sterilizing units while working full-time during the relevant pregnancy (high vs low exposure, OR=20.8, 95% CI 2.1-199); this estimate was based on only 4 spontaneous abortions among 19 highly exposed pregnancies and 1 among 78 pregnancies of women with relatively low exposure (Gresie-Brusin and others 2006).

Maternal exposure, other specified pesticides, inadequate evidence

The Ontario farm family study reported no association between spontaneous abortion (GW <20) and postconceptual farm use of the broad class of fungicides (OR=0.8, 95% CI 0.5-1.1); there was also no relationship between such exposure and spontaneous abortion at GW <12 or 12-19 (Arbuckle and others 2001).

Maternal exposure, unspecified pesticides, inadequate evidence

In a Chinese retrospective cohort, spontaneous abortion was not associated with self-reported maternal occupational pesticide exposure before conception (OR=0.60, 95% CI 0.43-0.84) but risk was elevated among women who obtained drinking water from a surface water subject to runoff from pesticide-treated cotton fields (OR=1.63, 95% CI 1.11-2.39) (Cho and others 1999). A retrospective cohort study in Minnesota revealed an association between spontaneous abortion before GW 13 and prenatal maternal mixing, loading or application of agricultural pesticides (OR=1.81, 95% CI 1.04-3.12) (Garry and others 2002).

Paternal occupational exposure, TCDD-contaminated chlorophenoxy herbicides, inadequate evidence

Reviewers found inadequate evidence for an association between spontaneous abortion and paternal occupational exposure to phenoxy herbicides potentially contaminated with TCDD (Arbuckle and Sever 1998; National Academy of Sciences 2003). These reviews focused mainly on health risks for Vietnam veterans potentially exposed to Agent Orange (a 50:50 mixture of 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) known to be contaminated with TCDD). In this group, there was an elevated spontaneous abortion risk among men with low serum TCDD levels but not those with high serum TCDD levels (note that serum TCDD was measured 15-26 years after the war ended). A subsequent study of wives of men highly exposed to TCDD during production of Agent Orange revealed no association between spontaneous abortion and paternal serum TCDD (per 10-fold increment of paternal serum TCDD at conception, OR=0.97, 95% CI 0.88-1.09) (Schnorr and others 2001).

Paternal occupational exposure, "TCDD-free" chlorophenoxy herbicides, limited evidence

Several studies have assessed paternal exposure to chlorophenoxy herbicides during recent decades when they were unlikely to be TCDD-contaminated. Registration of 2,4,5-T for use in the USA and Canada was removed in 1985. Also, 2,4-D production methods since the early 1980's are less likely to yield dioxin by-products (Pest Management Review Agency 2006). The Ontario farm family study reported no association between spontaneous abortion at GW <20 and preconceptual farm use of any chlorophenoxy herbicide (OR=1.1, 95% CI 0.6-1.9) or subtypes including 2,4-D (OR=0.9, 95% CI 0.5-1.8) or MCPA (OR=1.0, 95% CI 0.5-1.9) (Arbuckle and others 1999). There were, however, elevated risks of spontaneous abortion before GW 12 and preconceptual farm use of any chlorophenoxy herbicide (OR=2.5, 95% CI 1.0-6.4) or subtypes including 2,4-D (OR=1.9, 95% CI 0.7-4.8) or MCPA (OR=2.3, 95% CI 0.8-6.5). Risks were somewhat higher among those exposed for at least 1 month during the 3-month preconception period to any chlorophenoxy herbicide (OR=2.7, 95% CI 1.0-7.6) or MCPA (OR=5.4, 95% CI 1.7-17.3). A subsequent report of the Ontario study indicated that spontaneous abortion at GW <12 was associated with preconceptual chlorophenoxy herbicide use (crude OR=1.5, 95% CI 1.1-2.1) and weakly with 2,4-D use (crude OR=1.3, 95% CI 0.9-2.0); spontaneous abortion at GW 12-19 was not associated with either exposure (Arbuckle and others 2001). There was no association between preconceptual farm use of dicamba and spontaneous abortion at GW <12 (OR=1.0, 95% CI 0.5-1.8) or 12-19 (OR=1.1, 95% CI 0.6-2.2) (Arbuckle and others 2001). In a case-only analysis, early spontaneous abortions (GW <12) were more likely after preconceptual compared to postconceptual exposure to any chlorophenoxy herbicide (OR=3.1, 95% CI 1.4-6.4) or specifically to 2,4-D (OR=2.9, 95% CI 1.1-8.0) (Arbuckle and others 2001). A retrospective cohort study in Minnesota revealed a statistically non-significant association between spontaneous abortion before GW 13 among the subset of pregnancies conceived during the spring spray season and use of any chlorophenoxy herbicide (relative to use of any other pesticides, OR=1.59, 95% CI 0.77-3.27) (Garry and others 2002). This study reported an association between spontaneous abortions conceived during spring and paternal combined use of chlorophenoxy, sulfonylurea and benzothiodazole herbicides (relative to use of any other pesticides, OR=2.94, 95% CI 1.40-6.16). In Minnesota, herbicides are generally applied to crops in spring, insecticides in summer and fungicides as needed in summer and fall (Garry and others 2002).

Paternal occupational exposure, other herbicides, inadequate evidence

The Ontario study revealed no association between spontaneous abortion at GW <20 and preconceptual farm use of atrazine (OR=1.2, 95% CI 0.9-1.7); there was no also association between atrazine and spontaneous abortion at GW <12 or 12-19 (Arbuckle and others 2001). This study reported an association between preconceptual glyphosate use and spontaneous abortion at GW <20 (OR=1.7, 95% CI 1.0-2.9); there was also an association at GW <12 (OR=1.4, 95% CI 1.0-2.1) but not GW 12-19. The Minnesota retrospective cohort study revealed associations between spontaneous abortion before GW 13 among the subset of pregnancies conceived during the spring spray season and use of sulfonylurea (relative to use of any other pesticides, OR=2.11, 95% CI 1.09-4.09) and

imidazolinone herbicides (OR=2.56, 95% CI 1.11-5.87) (Garry and others 2002). Further studies are needed to assess specific herbicides, critical exposure windows and dose-response relationships.

Paternal occupational exposure, organochlorine insecticides, inadequate evidence

A retrospective cohort study of male malaria control workers in Mexico reported a weak and statistically non-significant association between spontaneous abortion and paternal DDE body burden estimated from self-reported information on timing, intensity and duration of DDT exposure (4th vs 1st quartile estimated paternal DDE, OR=1.24, 95% CI 0.91-1.70); note that serum DDE was not actually measured (Salazar-Garcia and others 2004). A retrospective cohort study of male malaria control workers in Mexico reported no associations between self-reported spousal spontaneous abortion history and self-reported use of the organochlorine insecticides lindane (yes/no, OR=1.22, 95% CI 0.68-2.20) or dieldrin (OR=1.22, 95% CI 0.68-2.20) (Salazar-Garcia and others 2004).

Paternal occupational exposure, organophosphate insecticides, inadequate evidence

The Ontario farm family study revealed no association between preconceptual organophosphate insecticide use and early (GW <12) (OR=1.0, 95% CI 0.6-1.6) or late (GW 12-19) spontaneous abortion (OR=1.0, 95% CI 0.6-1.7) (Arbuckle and others 2001). In a case-only analysis, the Ontario study showed that early spontaneous abortion was associated with preconceptual organophosphate insecticide use (compared to postconceptual use, OR=3.8, 95% CI 1.1-13.4); there was no association at GW 12-19. The significance of the latter finding is not clear but supports the need for research to clarify the role of preconceptual organophosphate insecticide exposure. A retrospective cohort study of male malaria control workers in Mexico reported no associations between self-reported spousal spontaneous abortion history and self-reported use of the organophosphate insecticides temephos (OR=1.13, 95% CI 0.76-1.68) or fenitrothion (OR=0.50, 95% CI 0.17-1.50) (Salazar-Garcia and others 2004).

Paternal occupational exposure, other or unspecified insecticides, inadequate evidence

The Ontario farm family study reported that spontaneous abortion before GW 20 was not associated with preconceptual carbaryl use (OR=1.2, 95% CI 0.7-2.0); there was also no association for spontaneous abortion at GW <12 or 12-19 (Arbuckle and others 2001). In case-only analyses, spontaneous abortion at GW <20 was associated with preconceptual compared to postconceptual carbaryl use (OR=2.0, 95% CI 1.0-4.0). In a large retrospective cohort of licensed pesticide applicators in Minnesota, spontaneous abortion was not associated with insecticide use (insecticide and herbicide vs herbicide only use, OR=1.27, 95% CI 0.68-2.36) (Garry and others 2002).

Paternal occupational exposure, fungicides, inadequate evidence

The Ontario farm family study reported an association between preconceptual fungicide use and spontaneous abortion before GW 20 (OR=1.4, 95% CI 1.1-1.8) (Arbuckle and others 2001). There were elevated spontaneous abortion risk related to such exposure during both GW 12 (OR=1.3, 95% CI 0.9-1.9) and GW 12-19 (OR=1.4, 95% CI 0.9-2.1). In a case-only analysis, spontaneous abortion before GW 12 (but not those at GW 12-19) was associated with preconceptual farm fungicide use (compared to postconceptual use, OR=3.9, 95% CI 1.4-10.3). The Minnesota study revealed associations between spontaneous abortion and application of the fungicides mancozeb and/or maneb (compared to unexposed men, OR=1.77, 95% CI 1.11-2.83) and organotin fungicides (OR=1.55, 95% CI 1.01-2.37) (Garry and others 2002).

Paternal exposure, ethylene oxide, inadequate evidence

In a Finnish retrospective cohort study based on linkage of national databases on pregnancy outcome and census information, spontaneous abortion was associated with paternal occupations likely exposed to ethylene oxide (based on job-exposure matrix) (OR=4.7, 95% CI 1.2-18.4) (Lindbohm and others 1991).

Paternal occupational exposure, unspecified pesticides, inadequate evidence

A small retrospective cohort study in Italy reported an association between spontaneous abortion and paternal occupation as a pesticide applicator (OR=3.8, 95% CI 1.2-12.0) (Petrelli and others 2000). In a retrospective cohort of Italian male greenhouse workers, there was a strong association between self-reported spousal history of spontaneous abortion and self-reported pesticide use (compared to unexposed greenhouse workers, crude OR=3.70, 95% CI 1.04-13.3, calculated from data in paper) (Petrelli and others 2003). Although the collective evidence from these studies is suggestive, the heterogeneity of exposure indices precludes firm conclusions.

3. Stillbirth

Reviews

Author	Scope of review	Findings	
(Nurminen 1995), Finland	Review of epidemiologic studies of maternal pesticide exposure and adverse pregnancy outcome published during 1979 until early 1995	6 studies assessed stillbirths – 2 studies found associations with maternal environmental pesticide exposure and 2 found associations with maternal occupational exposure; an ecologic study and a study of employment in floriculture found no association	Overall – studies give some support for associations but limitations preclude firm conclusions
(Sever and others 1997), USA	Reviewed original epidemiologic studies of occupational pesticide exposure and reproductive/developmental outcomes published during 1970-1996	Specific occupational pesticide exposures linked to stillbirth include malathion	Non-specific pesticide exposure indices linked to stillbirth included self-reported occupational use of pesticides and/or germicides, maternal or paternal use of agricultural pesticides, maternal residential pesticide use
(Arbuckle and Sever 1998), USA	Review of epidemiologic literature published during 1966 to November 1997 on pesticide exposures and fetal death; noted that many epidemiologic studies had methodologic problems, especially inadequate exposure assessment and limited statistical power	Exposure of U.S. Vietnam veterans to Agent Orange and other herbicides: elevated stillbirth risk related to background and low paternal serum TCDD levels measured 15-26 years after the war but no dose-response relationship	2,4-D, 2,4,5-T: inadequate evidence for an association between paternal exposure or maternal residential proximity to use and stillbirth

Author	Scope of review	Findings	
Organochlorine pesticides: studies in India suggest that high paternal occupational exposure to DDT and some other organochlorine and organophosphate pesticides was associated with increased risk of stillbirth; a larger US study found no association between stillbirth and maternal or paternal occupations likely exposed to classes of organic chemicals that include pesticides and other toxicants	Organophosphate insecticides: the one study that assessed stillbirth found an association with such exposure	Agricultural employment: studies to date have shown consistent increased risks of fetal death related to parental (mainly maternal) employment in agriculture	Unspecified pesticides: most studies have focused on maternal exposure and found associations with increased risks of stillbirth

Stillbirth: Original studies published since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(McGready and others 2001), Thailand	Randomized controlled trial	Pregnancy women in refugee camps randomly allocated to receive daily application of the insect repellent N, N-diethyl-m-toluamide (DEET) (1.7 g/day) in 2 nd and 3 rd Ts to prevent malaria; pregnancy status assessed during	6 stillbirths and 368 livebirths among DEET-treated women, 6 stillbirths and 373 livebirths among control women	DEET detected in 8% of cord blood samples from a randomly selected subgroup of DEET users		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		weekly interviews				
OR, stillbirth, treated vs control women	1.01, 0.29-3.58					
(Bell and others 2001c), California	Case-cohort	10 agricultural counties, all stillbirths (GW \geq 20) and infant deaths within 24 hr of birth, 1984; pregnancy outcome based on birth and death records	233 stillbirths (GW \geq 20) and 86 infant deaths age <24 hr, excl deaths from birth defects, mult births and umb cord compression, 611 healthy live birth controls	Parent-reported exposure info; Calif Pesticide Use Report database for 1983-84	Agricultural use of restricted pesticides within 1.6 km of maternal residence by chemical used, amount, date (each day of gestation) and location in relation to each day of pregnancy	Maternal age, county
OR, stillbirth or neonatal death from causes other than birth defects, agricultural use of pesticides in same 1 sq mile section as prenatal maternal residence	Organophosphates (mainly insecticides) 1 st trimester exposure 1.0, 0.7-1.3 2 nd trimester 0.9, 0.7-1.3 3 rd trimester 0.8, 0.5-1.2	Pyrethroid insecticides 1 st trimester exposure 1.0, 0.6-1.6 2 nd trimester 0.9, 0.6-1.5 3 rd trimester 1.4, 0.7-2.8	Halogenated hydrocarbons (fumigants, insecticides) 1 st trimester exposure 1.1, 0.8-1.0 [?] 2 nd trimester 1.3, 1.0-1.8 3 rd trimester 0.8, 0.5-1.2	Carbamates/thiocarbamates (insecticides, fungicides) 1 st trimester exposure 1.2, 0.9-1.6 2 nd trimester 1.3, 1.0-1.8 3 rd trimester 1.1, 0.7-1.6		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Bell and others 2001a), California	Case-control See also Bell et al 2001 below for correction of errata	10 agricultural counties, all stillbirths (GW \geq 20) and infant deaths within 24 hr of birth, 1984; pregnancy outcome based on birth and death records	73 stillbirths and early neonatal deaths from birth defects, 611 controls	Calif Pesticide Use Report database for 1983-84	Assessed agricultural use of restricted pesticides within 1.6 km of maternal residence by chemical used, amount, date and location in relation to each day of pregnancy	Maternal age, county
OR, stillbirth or neonatal death from birth defect vs mat residence in the same sq mi section where specified agric pestic class but not other classes applied during GW 3-8	Organophosphates 2.9, 1.3-6.4 Carbamates 2.3, 0.9-6.4	OR, stillbirth, ground vs aerial applic of agric pesticides during GW 3-8 within 9 sq mile centred on mat residence	Organophosphates Ground vs no pestic use 1.5, 0.8-2.8 Aerial vs no pestic use 1.4, 0.7-2.8	Pyrethroids Ground vs no pestic use 2.1, 0.9-4.7 Aerial vs no pestic use 2.4, 0.7-8.5	Organochlorines Ground vs no pestic use 2.1, 0.9-4.1 Aerial vs no pestic use na	Carbamates Ground vs no pestic use 1.6, 0.8-3.0 Aerial vs no pestic use 1.6, 0.8-3.4
(Bell and others 2001b), California	Correction of errors in above report (Bell et al 2001)		Stillbirths and infant deaths age <24 hr from birth defects			
OR, stillbirth or	Pyrethroids	Paraquat				

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
neonatal death from birth defect vs maternal residence in the same sq mi section where specified agricultural pesticide class but not other classes applied during GW 3-8	4.9, 1.9-12.9	1.8, 0.9-3.9				
(Regidor and others 2004), Spain	Retrospective cohort	80% of all births and stillbirths in Spain during 1995-99; total n=1,473,146; pregnancy outcome based on nNational birth and death records	Stillbirths (GW \geq 26) plus neonatal deaths <24 hr after delivery	Paternal occupation in agricultural, forestry or fishing based on late fetal death and birth records; also assessed residence in south-eastern Spain (uses over 6 million tons of pesticides per yr)		
RR, stillbirths and neonatal deaths vs paternal occupation in agricultural (ref = non-manual workers), SE Spain	Conceived during April-Sept pesticide use season Stillbirths caused by birth defects 1.62, 1.01-2.60 Other stillbirths 1.35, 1.11-1.65	Conceived during rest of year Stillbirths caused by birth defects 0.85, 0.47-1.52 Other stillbirths 1.22, 0.99-1.49				

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Longnecker and others 2005), US Collaborative Perinatal Project	Case-control	Nested within cohort; about 42000 women recruited during early pregnancy, 1959-1965, 12 US study centres; cohort ltd to women with prenatal serum DDE measured; ; cases identified from mother-reported pregnancy history and hospital/clinic records	5215 pregnancies, 604 spontaneous abortion (GW <20), 165 stillbirths (GW ≥20)	Measured DDT/DDE and other OC pesticide and PCB levels in a subset of women using stored maternal 3 rd trimester serum samples	Median DDE level was 25 µg/L (range 3-178)	Study centre, serum triglycerides and cholesterol, maternal age at conception, race, smoking, dieldrin, β-HCH
OR, fetal death (any gestation length) vs prenatal maternal serum DDE quintile (relative to 1 st quintile)	1.1, 0.9-1.5 1.4, 1.0-1.9 1.6, 1.1-2.4 1.2, 0.7-1.9	OR, fetal death at any gestation length, per prenatal maternal serum DDE increment of 60 µg/L (continuous variable)	1.4, 1.1-1.6	Association between fetal death and maternal serum DDE similar for early and late fetal deaths; result stated without showing data	No association between fetal death and prenatal maternal serum DDT levels	
(Zhu and others 2006), Denmark	Pregnancy cohort	Danish National Birth Cohort; recruited during 1997-2003; pregnancy	Identified 5 late spontaneous abortion and stillbirths among 226 pregnancies of	Self-reported work activities and exposure to pesticides during pregnancy and 3 months before conception solicited at about gestation		Maternal age, gravidity, history of spontaneous abortion, BMI,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		outcome based on national registries	female gardeners and 2 among 214 pregnancies of female farmers; comparison group was 62,164 pregnancies of women in other occupa	wk 16		smoking, alcohol, paternal occupation
OR, late spontaneous abortion and stillbirths vs maternal occupation	Gardeners 1.7, 0.7-4.0 Farmers 0.7, 0.2-2.7					
(Khanjani and Sim 2006a), Australia	Retrospective cohort	Primiparous women, 6-12 wk postpartum, recruited in centres throughout Victoria state during early 1990's; pregnancy outcomes based on clinic records	814 mothers, 93 previous spontaneous abortion or stillbirths	Measured breast milk DDT/DDE	Breast milk tertiles ($\mu\text{g}/\text{kg}$ lipid) DDT: ≤ 39 , 39-66, >66 DDE: ≤ 400 , 401-730, >730	Maternal age, wt, education, smok, alcohol
OR, spontaneous abortion or stillbirth, 2 nd and 3 rd vs 1 st tertile of breast milk DDT/DDE level (mg/kg lipid)	DDT 1.0 (ref) 0.84, 0.49-1.43	DDE 1.0 (ref) 0.81, 0.47-1.42				

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	0.63, 0.36-1.13	0.76, 0.41-1.39				
(Khanjani and Sim 2006b), Australia	Retrospective cohort	Primiparous women, 6-12 wk postpartum, recruited in centres throughout Victoria state during early 1990's; pregnancy outcomes based on clinic records	814 mothers, 93 previous spontaneous abortion or stillbirths	Measured breast milk organochlorines	Breast milk tertiles ($\mu\text{g}/\text{kg}$ lipid): dieldrin: ≤ 33 , 34-48, >48 heptachlor epoxide or oxychlorane: ≤ 5 , 5-9, >9 HCB: ≤ 27 , 28-48, >48	Maternal age, wt, education, smok, alcohol
OR, spontaneous abortion or stillbirth, 2 nd and 3 rd vs 1 st tertile of breast milk organochlorine pesticide level	Dieldrin 1.0 0.96, 0.57-1.64 0.73, 0.42-1.27	Heptachlor epoxide 1.0 1.10, 0.64-1.91 0.82, 0.48-1.39	Oxychlorane 1.0 1.47, 0.88-2.43 0.54, 0.29-1.00	HCB 1.0 1.03, 0.61-1.75 0.49, 0.26-0.90		
(Mueller and others 2007), Washington State	Case-control	Population-based, state-wide birth and fetal death records for 1987-2001	7054 stillbirths at GW ≥ 20 , 10 live birth controls per case	Maternal residential proximity at time of delivery to 939 hazardous waste disposal sites in State registry		Screened var.s included mat/pat age, mat race/ethnicity, parity, gravidity, prenatal

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
						smoking, alcohol, urban/rural residence, preg complications, mat education, Medicaid use; adj for mat age, prenatal smoking, # previous preg.s
OR, stillbirth, distance of mat residence to hazardous waste site containing pesticides	>5 mi 1.0 (ref) 2-4.99 mi 1.13, 1.05-1.22	1-1.99 mi 1.17, 1.06-1.29 ≤1 mi 1.28, 1.13-1.46	OR, stillbirth, distance of mat residence to hazardous waste site containing pesticides	Distance as continuous variable: OR decreased by 1% per 1 mile increment, $p < .05$		

Summary: Stillbirth, reviews

Maternal exposure

A review of studies published during 1979 to early 1995 found limited evidence for an association between stillbirth and maternal environmental or occupational pesticide exposure (Nurminen 1995). A review of studies published during 1970-96 noted that stillbirths had been linked to maternal residence in corridors subjected to aerial spraying of malathion, self-reported maternal occupational use of pesticides and/or germicides, pesticide use in or around the maternal residence and maternal or paternal occupational use of agricultural pesticides (Sever and others 1997). In a subsequent review, Arbuckle and Sever concluded that there was inadequate evidence for an association between stillbirth and maternal residential proximity to 2,4,5-T use in forestry (based on an ecologic study in Oregon) (Arbuckle and Sever 1998). This review also noted a large US study that found no association between stillbirth and maternal occupations likely exposed to classes of organic chemicals that include pesticides and other toxicants. The authors also noted that most studies of stillbirth and maternal exposure to unspecified pesticides or maternal employment in agriculture have reported elevated risks. A recent review examined evidence from epidemiologic studies of pregnancy outcome that assessed pesticide class, family and/or active ingredient (Weselak and others 2006). These reviewers found inadequate evidence for associations between stillbirth and specific pesticide categories including DDT/DDE, phenoxy herbicides, triazine herbicides or thiocarbamate fungicides.

Paternal exposure

A review of studies published during 1970-96 noted that stillbirths had been linked to maternal or paternal occupational use of agricultural pesticides (Sever and others 1997). In a subsequent review of studies published during 1966-97, Arbuckle and Sever concluded that there was inadequate evidence for an association between spontaneous abortion and paternal occupational exposure to 2,4,5-T (Arbuckle and Sever 1998). These authors noted that studies of Vietnam veterans revealed elevated stillbirth risk at low but not at high paternal serum TCDD levels (TCDD levels at conception were estimated from levels measured 15-26 years after the war ended). This review also noted that high paternal occupational exposure to DDT and some other organochlorine and organophosphate pesticides in India was associated with increased risk of stillbirth but a larger US study found no association between stillbirth and paternal occupations likely exposed to classes of organic chemicals that include pesticides and other toxicants.

Summary: Stillbirth, original studies published since 1998

Maternal exposure, non-chlorophenoxy herbicides, inadequate evidence

In a California case-cohort study, there was an elevated risk of stillbirths/neonatal deaths from birth defects related to agricultural use of paraquat during GW 3-8 in the same square mile section as the prenatal residence (OR=1.8, 95% CI 0.9-3.9) (Bell and others 2001b).

Maternal exposure, DDT/DDE, limited evidence

A review of available studies found limited evidence of an association between fetal deaths and biomarkers of maternal DDT/DDE exposure (Weselak and others 2006). Among recent studies included in their review, a retrospective cohort study based on the U.S. Collaborative Perinatal Project reported a non-monotonic dose-response relationship between fetal deaths of any gestation length and prenatal serum DDE levels (per 60 µg/L maternal serum DDE increment, OR=1.4, 95% CI 1.1-1.6) (Longnecker and others 2005). The latter authors stated that the association with maternal serum DDE was similar for spontaneous abortions and stillbirths but did not include supporting data. A subsequently reported Australian retrospective cohort study observed no association between fetal death (any gestation length) and breast milk DDT or DDE levels (3rd vs 1st tertile DDT, OR=0.63, 95% CI 0.36-1.13; 3rd vs 1st tertile DDE, OR=0.76, 95% CI 0.41-1.39) (Khanjani and Sim 2006b).

Maternal exposure, organophosphate insecticides, inadequate evidence

A California-wide study revealed that agricultural organophosphate application (mainly insecticides) during GW 3-8 in the same square mile section as the prenatal residence was associated with stillbirths/neonatal deaths from birth defects (OR=2.9, 95% CI 1.3-6.4) (Bell and others 2001b) but not with other stillbirths (1st trimester exposure, OR=1.0, 95% CI 0.7-1.3) (Bell and others 2001c). Although suggestive, these findings require confirmation and exploration of dose-response relationships.

Maternal exposure, pyrethroid insecticides, inadequate evidences

Stillbirths/neonatal deaths from causes other than birth defects in California were not associated with agricultural pyrethroid insecticide application in the same square mile section as the maternal residence (1st trimester use, OR=1.0, 95% CI 0.6-1.6) (Bell and others 2001c). However, there was an association between stillbirths/neonatal deaths from birth defects and agricultural pyrethroid insecticide application during GW 3-8 in the same square mile section as the maternal residence (OR=4.9, 95% CI 1.9-12.9); this analysis excluded subjects for whom other pesticide classes were also used during GW 3-8 (Bell and others

2001a; Bell and others 2001b). The California study used a highly detailed state-wide pesticide use database and did not have to rely on individual pesticide exposure recall; however, it did not assess potential relationships between stillbirths/neonatal deaths and preconceptual paternal exposure.

Maternal exposure, organochlorine insecticides, inadequate evidence

Stillbirths/neonatal deaths from causes other than birth defects in California were not associated with agricultural halogenated hydrocarbon pesticide application in the same square mile section as the maternal residence (1st trimester use, OR=1.1, p>.05) (Bell and others 2001c). An Australian retrospective cohort study found no association between fetal death (any gestation length) and breast milk dieldrin (3rd vs 1st tertile, OR=0.73, 95% CI 0.42-1.27), heptachlor epoxide (OR=0.82, 95% CI 0.48-1.39) or oxychlorane levels (OR=0.54, 95% CI 0.29-1.00) (Khanjani and Sim 2006b).

Maternal exposure, other specified insecticides, inadequate evidence

Stillbirths/neonatal deaths from causes other than birth defects in California were not associated with agricultural use of carbamate/thiocarbamate insecticides or fungicides in the same square mile section as the maternal residence (1st trimester use, OR=1.2, 95% CI 0.9-1.6) (Bell and others 2001c). However, there was an elevated risk of stillbirths/neonatal deaths from birth defects related to agricultural carbamate application during GW 3-8 in the same square mile section as the maternal residence (OR=2.3, 95% CI 0.9-6.4); this analysis excluded subjects for whom other pesticide classes were also used during GW 3-8 (Bell and others 2001a; Bell and others 2001b).

Maternal exposure, insect repellents, inadequate evidence

In a randomized controlled trial of N, N-diethyl-m-toluamide (DEET) to prevent malaria during pregnancy in Thailand, stillbirth risk was not increased among exposed women (OR=1.01, 95% CI 0.29-3.58) (McGready and others 2001).

Maternal exposure, fungicides, inadequate evidence

Stillbirths/neonatal deaths from causes other than birth defects in California were not associated with agricultural use of carbamate/thiocarbamate insecticides or fungicides in the same square mile section as the maternal residence (1st trimester use, OR=1.2, 95% CI 0.9-1.6) (Bell and others 2001c). An Australian retrospective cohort study found no association between fetal death (any gestation length) and breast milk HCB levels (3rd vs 1st tertile, OR=0.49, 95% CI 0.26-0.90) (Khanjani and Sim 2006b).

Maternal exposure, unspecified pesticides, limited evidence

A review noted that most studies of stillbirth and maternal exposure to unspecified pesticides or maternal employment in agriculture have reported elevated risks (Arbuckle and Sever 1998). A recent Danish pregnancy cohort study revealed a statistically non-significant elevated risk of fetal loss at any gestation length related to prenatal occupation as gardeners (OR=1.7, 95% CI 0.7-4.0, 5 exposed case mothers) but not for women employed in farming (OR=0.7, 95% CI 0.2-2.7) (Zhu and others 2006). A case-control study in Washington State revealed an inverse exposure-risk relationship between stillbirth and distance of maternal residence at birth from a hazardous waste site containing pesticides (>5 mi = referent; 2-4.99 mi, OR=1.13, 95% CI 1.05-1.22; 1-1.99 mi, OR=1.17, 95% CI 1.06-1.29; ≤1 mi, OR=1.28, 95% CI 1.13-1.46, p-trend<.05) (Mueller and others 2007).

Paternal occupational exposure, unspecified pesticides, inadequate evidence

In a Spanish retrospective cohort study of pregnancies conceived during the pesticide-use season (April-September), stillbirth (based on official records) was associated with paternal occupation in agriculture (stillbirths caused by birth defects, OR=1.62, 95% CI 1.01-2.60; other stillbirths, OR=1.35, 95% CI 1.11-1.65) (Regidor and others 2004). There was no association with paternal occupation in agriculture for stillbirths conceived during the remainder of the year (stillbirths caused by birth defects, OR=0.85, 95% CI 0.47-1.52; other stillbirths, OR=1.22, 95% CI 0.99-1.49).

4. Preterm birth, gestation length

Reviews

Author	Scope of review	Findings
(Longnecker and others 1997), USA	Review of epidemiologic studies of DDT and PCBs; p,p' -DDE and PCBs comprise the bulk of organochlorine residues in human tissues	3 small studies found higher cord tissue or cord blood DDT/DDE levels in preterm compared to term infants; significance of findings not clear because of potential for confounding by lipid levels or risk factors for preterm birth
(Weselak and others 2006), Canada	Reviewed epidemiologic and toxicologic studies of adverse pregnancy outcomes and periconceptual exposure to specific pesticides published during 1966-2005	Preterm birth: inadequate evidence for association with maternal exposure DDT/DDE or other organochlorine pesticides, phenoxy herbicides, triazine herbicides, thiocarbamates

Preterm birth, gestation length: Original studies since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Michalek and others 1998), USA	Cohort	859 children of U.S. Vietnam war veterans exposed to Agent Orange, 1223 children of unexposed veterans; self-reported and medical record info on pregnancy history plus medical record review	42 preterm infants and 859 total live births among potentially exposed men and 54 preterm infants and 1,223 total live births among comparison group men	Measured paternal serum TCDD and estimated level at time of conception	Median paternal serum TCDD: unexposed 0-10, background 0-10, low 11-78, high 79-1425 pg/g lipid	Paternal race, age, military occupation in SE Asia, prenatal maternal smoking, alcohol, age

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, preterm birth, paternal serum TCDD ≥ 79 vs < 10 pg/g lipid	1.36, 0.75-2.39 [calc from data in paper]					
(McGready and others 2001), Thailand	Randomized controlled trial	Pregnancy women in refugee camps randomly allocated to receive daily application of the insect repellent N, N-diethyl-m-toluamide (DEET) (1.7 g/day) in 2 nd and 3 rd Ts to prevent malaria; pregnancy status based on weekly interviews	25 preterm births among 351 pregnancies to DEET-treated women, 25 preterm births among 352 pregnancies to control women	Measured cord blood DEET	DEET detected in 8% of cord blood samples from a randomly selected subgroup of DEET users	
OR, preterm birth, exposed vs unexposed women	1.00, 0.54-1.85					
(Longnecker and others 2001), Collaborative Perinatal Project, USA	Case-control	Nested within cohort; about 42000 women recruited during early pregnancy, 1959-1965, 12 US study centres; cohort ltd to women with prenatal serum DDE measured; cases identified from mother-reported pregnancy history and hospital/clinic records	361 preterm infants, 2,380 term live births	Measured DDT/DDE and other OC pesticide and PCB levels in a subset of women using stored maternal 3 rd trimester serum samples	Median DDE level was 25 $\mu\text{g/L}$ (range 3-178)	Study centre, serum triglycerides and cholesterol, maternal age at conception, race, smoking, dieldrin, β -HCH

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Logistic regression, OR, increasing quintiles of prenatal maternal serum DDE ($\mu\text{g/L}$)	<p><15 $\mu\text{g/L}$ 1.0</p> <p>15-29 $\mu\text{g/L}$ 1.5, 1.0-2.3</p> <p>30-44 $\mu\text{g/L}$ 1.6, 1.0-2.6</p>	<p>45-59 $\mu\text{g/L}$ 2.5, 1.5-4.2</p> <p>60+ $\mu\text{g/L}$ 3.1, 1.8-5.4</p> <p>$\beta=0.26\pm0.06$ p-trend<0.0001</p>				
(Ribas-Fito and others 2002), Spain	Birth cohort	Village heavily exposed to airborne HCB (HCB) from a chemical factory	98 mother-infant pairs: 4 preterm and 7 SGA infants	Birth records	Measured maternal and cord serum HCB, PCB (sum of 7 congeners), DDE and HCH levels	Infant sex, maternal age, BMI, gestational diabetes, prenatal smoking or alcohol, parental education, gestational age
Mean cord serum OC levels, preterm vs term infants	p,p' -DDE 2.40 vs 0.80 $\mu\text{g/L}$, $p<.05$	HCB 1.94 vs 1.10 $\mu\text{g/L}$, $p<.1$	β -HCH 0.55 vs 0.26 $\mu\text{g/L}$, $p>.05$			
(Schreinemachers 2003), Minnesota, Montana, N Dakota, S Dakota, USA	Retrospective cohort	Counties with at least 50% rural population and at least 20% of land in crops; linked birth and vital stats records 1995-97	3052 preterm infants among total of 43,634 births	1992 US agricultural census info; crop acreage by county and herbicide use by state	Compared 74 high- and 73 low-wheat rural counties (>85% of spring and durum wheat acreage treated with chlorophenoxy herbicides such as	Mothers in high- and low-wheat counties similar re age, education, marital status, parity, prenatal care, previous preterm or IUGR

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					2,4-D and MCPA)	birth, prenatal smoking and alcohol use, infant sex, time of conception (April-June vs other)
OR, preterm birth, maternal prenatal residence in high- vs. low-wheat rural county	1.05, 0.95-1.16					
(Torres-Arreola and others 2003), Mexico City	Case-cohort	Hospital-based; pregnancy outcome based on hospital records	100 cases preterm birth, 133 term controls	Measured maternal serum p,p'-DDE, β -HCH and HCB levels using samples obtained shortly after delivery		Previous preterm birth, pre-pregnancy maternal weight, prenatal care
ORs, 2 nd and 3 rd vs 1 st tertile maternal serum β -HCH levels	1.6, 0.8-3.1 1.9, 0.9-3.7 p-trend=.08	ORs, 2 nd and 3 rd vs 1 st tertile maternal serum p,p'-DDE levels	1.9, 1.0-3.7 1.7, 0.8-3.3 p-trend=.17	ORs, 2 nd and 3 rd vs 1 st tertile maternal serum HCB levels	0.8, 0.4-1.5 0.9, 0.5-1.8 p-trend=.80	
(Eskenazi and others 2003), Seveso, Italy	Cohort	981 women age 40 yr or less at time of ICMESA chemical factory explosion (1976), followed to 1996-1998; mother-reported birth	30 preterm infants among 608 pregs incl 15 among 275 pregs during first 8 yr followup	Trichlorophenol plant explosion in 1976; measured maternal serum TCDD during 1976-80; for post-1977	Median serum TCDD level soon after explosion was 47 (range 24-104 ng/L)	Parity, history of low birth weight, maternal height, body mass index, age, education, smoking, gestation

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		weight and gestation length		samples with TCDD >10 pg/g lipid, used toxicokinetic model to estimate 1976 level		length, infant sex, gestation length squared (covariates varied by outcome modeled)
Change in gestation length per log maternal serum TCDD increment	Adjusted β (days)	-1.2, -2.9 to 0.5		Preterm delivery	Adjusted odds ratio per log maternal serum TCDD increment	1.3, 0.7-2.3
(Berkowitz and others 2004), New York City	Pregnancy cohort	Ethnically diverse cohort recruited in prenatal clinic at Mount Sinai Hospital, 1998-2002; preg outcome based on clinic records	404 births of mothers recruited during early pregnancy, 1998-2002; assessed gestation length of first singleon births	Self-reported maternal pesticide exposure; measured 3 rd trimester maternal urinary PCP and metabolites of chlorpyrifos and pyrethroid insecticides		Race/ethnicity, infant sex
Avg gestation length, pesticide use vs non-use by household member	39.4 vs 39.2 wk, p>0.05	Avg gestation length, detectable vs non-detectable maternal 3 rd trimester urinary pesticide or pesticide metabolite levels	chlorpyrifos metabolite 39.3 vs 39.3 wk	pyrethroid metabolites 39.2 vs 39.4 wk	pentachlorophenol 39.5 vs 39.2 wk p>0.05 for each	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Lawson and others 2004), USA	Retrospective cohort	Male workers exposed to TCDD in trichlorophenol, hexachlorophene and 2,4,5-T production plants in New Jersey and Missouri; neighbourhood occupationally unexposed men matched on age, sex, race; birth weight from birth certificates or mother, self-reported gestation length	513 live, full-term infants of exposed men (221 conceived before exposure) and 604 live, full-term infants of unexposed men	Occupational TCDD exposure, measured current serum TCDD and est'd levels at conception	Median, min, max paternal serum TCDD (pg/g lipid): exposed births – 254, 3, 16340; unexposed births – 6, 2-19	Accident during pregnancy, maternal age, prenatal smoking, drug use
OR, preterm birth vs \log_{10} paternal serum TCDD	0.8, 0.6-1.1					
(Weisskopf and others 2005), Wisconsin, Illinois, Indiana, Ohio, Michigan	Retrospective cohort (Great Lakes Consortium)	Great Lakes sport-fishing charter boat captains and families plus random sample of general population in 5 Great Lakes states; 511 mothers interviewed 1993-1995; preg outcomes based on birth records	143 first-born children, 1970-93	Great Lakes sport-caught fish are contaminated with OCs incl PCBs and DDE; serum collected from 143 women 1994-1995	Median serum DDE was 2.20 $\mu\text{g/L}$ (range 0.25-10.0)	Child sex, maternal age, maternal education, parity, prepreg BMI, prenatal cigarette and alcohol use, weeks of breastfeeding
Multiple regression analysis, β = change in gestation length (wk) per unit increase in ln maternal serum DDE	$\beta = 0.03, -0.50$ to 0.57					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Fenster and others 2006), California	Birth cohort	Low-income pregnancy Latinas living in the Salinas Valley, recruited at prenatal clinics during 1999-2000; mother-reported pregnancy history and medical record abstraction	385 mother-infant pairs	Measured maternal serum levels of p,p'-DDT, p,p-DDE, o,p- DDT, HCB (HCB), HCH (HCH), dieldrin, heptachlor epoxide, oxychlorthane, trans-nonachlor, mirex		Maternal age, parity, country of birth, family income, prenatal care, smoking, total urinary dimethyls at GW 26, maternal prepreg BMI, gestational wt gain, infant sex
Regression analysis, GL vs log ₁₀ maternal serum organochlorine pesticide level	DDE β=-0.10 wk, -0.40 to 0.20, p=.51	HCB β=-0.47 wk, -0.95 to -0.002, p=.05	B-HCH β=0.07, -0.30 to 0.44, p=.71	Dieldrin β=-0.49, -1.14 to 0.16, p=.14	Heptachlor epoxide β=-0.15, -0.71 to 0.42, p=.61	Oxychlorthane β=-0.03, -0.40 to 0.35, p=.89
(Zhu and others 2006), Denmark	Birth cohort	Danish National Birth Cohort; recruited during 1997-2003; assessed sub-cohort of female gardeners and farmers; pregnancy outcome based on national registries	Identified 13 preterm infants among 226 pregnancies of female gardeners and 10 among 214 pregnancies of female farmers; comparison group was 62,164 pregnancies of	Self-reported work activities and exposure to pesticides during pregnancy and 3 months before conception solicited at about gestation wk 16		Maternal age, gravidity, history of spontaneous abortion, BMI, smoking, alcohol, paternal occupation

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			women in other occups			
Preterm birth vs maternal occupation	Gardeners: Gardners vs other occups 1.4, 0.8-2.4	Farmers: Farmers vs other occups 1.0, 0.5-1.8	Indoor gardening 2.0, 0.4-10.4 Direct contact with pesticides in workplace 0.7, 0.1-5.7	Sprayed pesticides on farms 1.9, 0.4-9.2		
(Khanjani and Sim 2006a), Australia	Retrospective cohort	Primiparous women, 6-12 wk postpartum, recruited in centres throughout Victoria state during early 1990's; preg outcome based on clinic records	814 mothers, 49 preterm infants	Measured breast milk organochlorines	Breast milk tertiles (µg/kg lipid) DDT: ≤39, 39-66, >66 DDE: ≤400, 401-730, >730	Maternal age, wt, education, smok, alcohol
OR, preterm birth by breast milk DDT/DDE level (mg/kg lipid)	DDT 1.0 (ref)	0.83, 0.40-1.72 0.69, 0.32-1.50	DDE 0-0.4 1.0 (ref)	0.85, 0.39-1.84 1.03, 0.46-2.29		
(Khanjani and Sim 2006b), Australia	Retrospective cohort	Primiparous women, 6-12 wk postpartum, recruited in centres throughout Victoria state during early 1990's; preg outcome based on clinic records	814 mothers, 49 preterm infants	Measured breast milk organochlorines	Breast milk tertiles (µg/kg lipid): dieldrin:≤33, 34-48, >48 heptachlor epoxide	Maternal age, wt, education, smok, alcohol

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					or oxychlordan: ≤5, 5-9, >9 HCB: ≤27, 28-48, >48	
OR, preterm birth, 2 nd and 3 rd vs 1 st tertile of breast milk organochlorine pesticide level	Dieldrin 1.0 0.67, 0.31-1.51 1.22, 0.61-2.45	Heptachlor epoxide 1.0 1.40, 0.66-2.96 1.02, 0.49-2.11	Oxychlordan 1.0 2.34, 1.12-4.87 0.93, 0.39-2.22	HCB 1.0 1.99, 0.92-4.31 1.27, 0.54-3.00		
(Jusko and others 2006), San Francisco	Pregnancy cohort	20,754 pregnancy women, Kaiser Health Plan members, East Bay region of SF Bay, enrolled at prenatal visit, 1963-66; blood samples collected during 2 nd or 3 rd trimester; birth wt and gestation length from medical records, anthropometric measuredures by pediatrician at age 5	399 children examined at age 5; 240 had Raven's Progressive Matrices or Peacock Picture Vocabulary Test scores below 10 th percentile, 159 had higher scores	Measured prenatal maternal serum DDT/DDE		Adj as necessary for maternal BMI, ht, parity, race, alcohol, paternal education and occupation, gestation length, prenatal care, gender
Adj mean diff in gestational age (days), prenatal maternal serum DDT/DDE 75 th vs 25 th percentile	DDE 0.1, -1.5 to 1.8 DDT 1.7, 0.2-3.1					
(Wolff and others	Pregnancy	Pregnancy women	404 mother-	Mother-reported		Maternal age,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
2007), New York City	cohort	enrolled at Mount Sinai Hosp during 1998-2002; measured maternal plasma PON1 activity; conducted standardized measurements of birth wt, length, head circumf	infant pairs	pesticide and other exposure info; 3 rd trimester maternal plasma DDE, PCBs (118, 138, 153, 180), maternal urinary OP metabolites and malathion dicarboxylic acid, maternal or cord bl Pb		race, ethnicity, BMI, pregnancy wt gain, infant sex, gestation length
Regr coeff, gestation length (wk) vs log ₁₀ prenatal mat serum DDE	$\beta = -0.17 \pm 0.26$ (SE) wk, p=.52 $\beta = -0.01 \pm 0.29$ wk, p=.97 (lipid-adjusted)	Regr coeff, gestation length (wk) vs log ₁₀ prenatal mat urinary diethylthiophosphate (nM/L)	$\beta = -0.006 \pm 0.13$ wk, p=.996	Regr coeff, gestation length (wk) vs log ₁₀ prenatal mat urinary malathion dicarboxylic acid (\geq vs <LOD)	$\beta = -0.28 \pm 0.21$ wk, p=.18	

Summary: Preterm birth

Reviews

Maternal exposure

A review of developmental effects of DDT noted that 3 small epidemiologic studies had reported higher cord tissue or cord blood DDT/DDE levels in preterm compared to term infants; the significance of these findings was not clear because of lack of control for potential confounders including lipid levels (Longnecker and others 1997). A recent review examined evidence from epidemiologic studies of pregnancy outcome that assessed pesticide class, family and/or active ingredient (Weselak and others 2006). These reviewers found inadequate evidence for associations between preterm birth and specific pesticide categories including DDT/DDE, phenoxy herbicides, triazine herbicides or thiocarbamate fungicides.

Original studies published since 1998

Maternal exposure, TCDD-contaminated herbicides, inadequate evidence

There were no studies of prenatal exposure to TCDD-contaminated herbicides *per se* but preterm birth during an 8-year follow-up of women exposed at Seveso was not associated with maternal serum TCDD levels (per log serum TCDD increment, OR=1.3, 95% CI 0.7-2.3); there was an inverse association of borderline statistical significance between gestation length analyzed as a continuous variable and maternal serum TCDD (per log increment, β =-1.2 d, 95% CI -2.9 to 0.5) (Eskenazi and others 2003). A pregnancy cohort study in New York found no association between average gestation length and 3rd trimester maternal urinary pentachlorophenol levels (average gestation length, women with detectable vs non-detectable pentachlorophenol, 39.5 vs 39.2 wk, $p>.05$) (Berkowitz and others 2004).

Maternal exposure, "TCDD-free" chlorophenoxy herbicides, inadequate evidence

A large ecologic study in 4 U.S. Midwest states revealed no relationship between preterm birth and maternal residence in high-wheat rural counties (a proxy for chlorophenoxy herbicide exposure) (standardized incidence ratio (SIR)=1.05, 95% CI 0.95-1.16) (Schreinemachers 2003).

Maternal exposure, DDT/DDE, limited evidence

A large U.S. case-control study nested within a retrospective cohort reported a monotonic dose-response relationship between preterm birth and prenatal serum DDE levels (≥ 60 vs < 15 $\mu\text{g/L}$, OR=3.1, 95% CI 1.8-5.4; p -trend $<.0001$); this study exploited preserved prenatal blood samples collected during 1959-1965 when population DDT exposure was much higher than now (Longnecker and others 2001). A small birth cohort study in Spain revealed an association between preterm birth and cord serum DDE levels (mean cord serum DDE, cases vs controls, 2.40 vs 0.80 $\mu\text{g/L}$, $p<.05$) (Ribas-Fito and others 2002). A case-cohort study in Mexico City reported a non-monotonic and statistically non-significant association between preterm birth and 1st trimester maternal serum DDE levels (3rd vs 1st tertile, OR=1.7, 95% CI 0.8-3.3, p -trend=.17) (Torres-Arreola and others 2003). A retrospective cohort study of women who consumed Great Lakes fish showed no relationship between gestation length and maternal serum DDE levels (change in gestation length per natural log serum DDE increment, β =0.03 wk, 95% CI -0.50 to 0.57) (Weisskopf and others 2005). In an Australian retrospective cohort study, preterm birth was not associated with breast milk DDT or DDE levels (2nd vs 1st tertile DDE, OR=0.85, 95% CI 0.39-1.84; 3rd vs 1st tertile, OR=1.03, 95% CI 0.46-2.29); there were similar findings for breast milk DDT levels (Khanjani and Sim 2006b). A birth cohort study in the Salinas Valley of California revealed no association between gestation length and maternal serum DDE (per log₁₀ serum DDE increment, β =-0.10 wk, 95% CI -0.40 to 0.20, $p=.51$) (Fenster and others 2006). In a San Francisco pregnancy cohort, there was no association between gestation length and maternal serum DDE levels (mean difference in gestation length, 75th vs 25th percentiles of maternal serum DDE, 0.1 d, 95% CI -1.5 to 1.8); there was a positive association (i.e., favourable) between gestation length and maternal serum DDT (mean difference in gestation length, 75th vs 25th percentiles of maternal serum DDT, 1.7 d, 95% CI 0.2-3.1) (Jusko and others 2006). In a New York City pregnancy cohort, gestation length was not associated with maternal serum DDE (change in gestation length per log maternal serum DDE increment, β =-0.17 \pm 0.26(SE) wk, $p=.52$) (Wolff and others 2007). Although 5 recent cohort studies found no relationship, the steep decline of population serum or breast milk DDT/DDE levels over the past 40 years may have contributed to negative findings.

Maternal exposure, HCB, inadequate evidence

A small birth cohort study in Spain revealed an association of borderline statistical significance between preterm birth and cord serum HCB levels (mean cord serum HCB, cases vs controls, 1.94 vs 1.10 $\mu\text{g/L}$, $p<.10$) (Ribas-Fito and others 2002). A case-cohort study in Mexico City found no relationship between preterm birth and maternal serum HCB levels (3rd vs 1st tertile, OR=0.9, 95% CI 0.5-1.8, p -trend=.80) (Torres-Arreola and others 2003). A California study reported an inverse dose-response relationship between gestation length and maternal serum lipid-adjusted HCB levels (change in gestation length per natural

log serum HCB increment, $\beta=-0.47$ wk, 95% CI -0.95 to -0.002, $p=.05$) (Fenster and others 2006). In an Australian retrospective cohort study, preterm birth was not associated with breast milk HCB levels (3rd vs 1st tertile, OR=1.27, 95% CI 0.54-3.00) (Khanjani and Sim 2006b).

Maternal exposure, other organochlorine pesticides, inadequate evidence

A small birth cohort study in Spain revealed no relationship between preterm birth and cord serum β -HCH (cord serum β -HCH, cases vs controls, 0.55 vs 0.26 $\mu\text{g/L}$, $p>.05$) (Ribas-Fito and others 2002). A case-cohort study in Mexico City found a dose-response relationship of borderline statistical significance between preterm birth and 1st trimester maternal serum β -HCH levels (3rd vs 1st tertile, OR=1.9, 95% CI 0.9-3.7, $p\text{-trend}=.08$) (Torres-Arreola and others 2003). A California study reported no associations between gestation length and maternal serum organochlorine pesticide levels including β -HCH (change in gestation length per natural log maternal serum β -HCH increment, $\beta=0.07$ wk, 95% CI -0.30 to 0.44, $p=.71$), dieldrin ($\beta=-0.49$ wk, 95% CI -1.14 to 0.16, $p=.14$), heptachlor epoxide ($\beta=-0.15$ wk, 95% CI -0.71 to 0.42, $p=.61$) or oxychlorane ($\beta=-0.03$ wk, 95% CI -0.40 to 0.35, $p=.89$) (Fenster and others 2006). In an Australian retrospective cohort study, preterm birth was not associated with breast milk dieldrin (3rd vs 1st tertile, OR=1.22, 95% CI 0.61-2.45), heptachlor epoxide (OR=1.02, 95% CI 0.49-2.11) or oxychlorane (OR=0.93, 95% CI 0.39-2.22) (Khanjani and Sim 2006b).

Maternal exposure, organophosphate insecticides, inadequate evidence

A pregnancy cohort study in New York found no association between average gestation length and 3rd trimester maternal urinary chlorpyrifos metabolite levels (average gestation length, women with detectable vs non-detectable chlorpyrifos metabolites, 39.3 vs 39.3 wk) (Berkowitz and others 2004). Further investigation revealed no association between gestation length and maternal urinary diethylthiophosphate level (nM/L) or malathion dicarboxylic acid levels (change in gestation length per log maternal urinary diethylphosphate increment, $\beta=-0.006\pm 0.13$ wk, $p=.996$; per log urinary malathion dicarboxylic acid increment, $\beta=-0.28\pm 0.21$ wk, $p=.18$) (Wolff and others 2007).

Maternal exposure, other specified insecticides or repellents, inadequate evidence

Preterm birth was not associated with prenatal DEET exposure in a small Thai randomized trial (exposed vs unexposed, OR=1.00, 95% CI 0.54-1.85) (McGready and others 2001). A pregnancy cohort study in New York found no association between average gestation length and 3rd trimester maternal urinary pyrethroid metabolite levels (average gestation length, women with detectable vs non-detectable pyrethroid metabolites, 39.2 vs 39.4 wk, $p>.05$) (Berkowitz and others 2004).

Maternal exposure, unspecified pesticides, inadequate evidence

A Danish birth cohort study showed no association between preterm birth and prenatal occupation as gardeners (OR=1.4, 95% CI 0.8-2.4) or farmers (OR=1.0, 95% CI 0.5-1.8) or with indoor gardening (OR=2.0, 95% CI 0.4-10.4) or direct contact with pesticides at work (OR=0.7, 95% CI 0.1-5.7) (Zhu and others 2006).

Paternal occupational exposure, TCDD-contaminated chlorophenoxy herbicides, inadequate evidence

Preterm birth was not associated with paternal serum TCDD levels in the study of U.S. veterans exposed to Agent Orange (serum TCDD at conception ≥ 79 vs ≤ 10 pg/g lipid, crude OR=1.36, 95% CI 0.75-2.39, calculated from data in paper) (Michalek and others 1998). Similarly, preterm birth was not related to serum TCDD levels among men exposed during production of trichlorophenol and derivatives such as 2,4,5-T (per log serum TCDD increment, OR=0.8, 95% CI 0.6-1.1) (Lawson and others 2004).

5. Fetal growth deficit

Reviews

(Weselak and others 2006), Canada	Reviewed epidemiologic and toxicologic studies of adverse pregnancy outcomes and periconceptual exposure to specific pesticides published during 1966-2005	Fetal growth deficit: inadequate evidence for association with maternal exposure to DDT/DDE or other organochlorine pesticides, phenoxy herbicides, triazine herbicides, thiocarbamates
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Fetal growth deficit: Original studies since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Michalek and others 1998), USA	Cohort	859 children of U.S. Vietnam war veterans exposed to Agent Orange, 1223 children of unexposed veterans; self-reported and medical record info on pregnancy history	73 IUGR infants and 859 total live births among potentially exposed men and 116 IUGR infants and 1,223 total live births among comparison group men	Paternal serum TCDD	Median paternal serum TCDD at time of conception: unexposed 0-10, background 0-10, low 11-78, high 79-1425 pg/g	Paternal race, age, military occupation in SE Asia, prenatal maternal smoking, alcohol, age
OR, IUGR vs paternal serum TCDD	Low 0.9, 0.6-1.3 High 0.9, 0.6-1.3					
(Seidler and others 1999), Germany	Pregnancy cohort	3216 pregnancy women, enrolled during gestation wk 15-28, 1987-1988; preg outcome based on birth records	Physician-reported pregnancy outcome history, 194 SGA infants	Self-reported maternal occupational history; JEM to assess exposure to PCBs and other toxicants		Maternal age, smoking, alcohol, BMI, parity

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, SGA vs maternal occupational exposure, ref=unexposed	Herbicides low exposure 1.0, 0.2-4.0 moderate exposure 0.9, 0.3-3.0 p-trend=.82	Chlorophenols low exposure 3.7, 0.4-33 moderate exposure 2.5, 0.4-15 p-trend=.17				
(Longnecker and others 2001), Collaborative Perinatal Project, USA	Case-control	Nested within cohort; about 42000 women recruited during early pregnancy, 1959-1965, 12 US study centres; cohort ltd to women with prenatal serum DDE measured; cases identified from mother-reported pregnancy history and hospital/clinic records	221 IUGR infants, 1798 term non-IUGR infants	Measured DDT/DDE and other OC pesticide and PCB levels in a subset of women using stored maternal 3 rd trimester serum samples	Median DDE level was 25 µg/L (range 3-178)	Study centre, serum triglycerides and cholesterol, maternal age at conception, race, smoking, dieldrin, β-HCH
ORs for increasing maternal serum DDE levels	<15 µg/L 1.0 15-29 µg/L 1.9, 1.3-3.5 30-44 µg/L	45-59 µg/L 1.6, 0.8-3.3 60+ µg/L 2.6, 1.3-5.2 p-trend = 0.04	IUGR vs serum DDE as continuous variable β=0.13±0.07	Mean birth weight, serum DDE ≥ 60 vs <15 µg/L	3080 vs 3230 g	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	1.7, 0.9-3.0					
(McGready and others 2001), Thailand	Randomized controlled trial	Pregnancy women in refugee camps randomly allocated to receive daily application of the insect repellent N, N-diethyl-m-toluamide (DEET) (1.7 g/day) in 2 nd and 3 rd Ts to prevent malaria; birth wt from clinic records	368 live births among DEET-treated women, 373 among control women	Cord blood DEET	DEET detected in 8% of cord blood samples from a randomly selected subgroup of DEET users	
Mean birth wt (+SD), exposed vs unexposed women	2868±492 vs 2853±488, p>.05	LBW rate (%), exposed vs unexposed women	14.8 vs 20.2%			
(Ribas-Fito and others 2002), Spain	Birth cohort	Village heavily exposed to airborne HCB (HCB) from a chemical factory; preg outcome from birth records	98 mother-infant pairs	Measured maternal and cord serum HCB, PCB (sum of 7 congeners), DDE and HCH levels	Cord serum DDE 5 th and 95 th percentiles were 0.22 and 3.21 µg/L	Infant sex, maternal age, BMI, gestational diabetes, prenatal smoking or alcohol, parental education, gestational age
Regression coefficient and SE, birth weight adjusted for gestation length vs cord serum organochlorine levels	HCB β=19.8±50.9(SE) g, ns	DDE β=-16.8±37.8 g, ns	HCH β=17.5±17.6 g, ns			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Eskenazi and others 2003), Seveso, Italy	Cohort	981 women age 40 yr or less at time of ICMESA chemical factory explosion (1976), followed to 1996-1998; mother-reported birth weight and gestation length	59 IUGR infants among 608 pregs incl 28 among 275 pregs during the first 8 yr of followup	Trichlorophenol plant explosion in 1976; measured maternal serum TCDD during 1976-80; for post-1977 samples with TCDD >10 pg/g lipid, used toxicokinetic model to estimate 1976 level	Median serum TCDD level soon after explosion was 47 (range 24-104 ng/L)	Var combinations of parity, history of LBW, maternal ht, BMI, age, education, smoking, infant sex, gestation length, gestation length squared
OR, IUGR, per log mat serum TCDD increment	First 8 yr after expos 1.8, 0.7-4.3	all 22 yr after expos 1.5, 0.9-2.6	Regr coeff, birth wt vs log mat serum TCDD; adj for GL + other cov	First 8 yr after expos β =-92, -204 to 19, n=275	all 22 yr after expos β =-4, -68 to 60, n=608	
(Schreinemachers 2003), Minnesota, Montana, N Dakota, S Dakota, USA	Retrospective cohort	Counties with at least 50% rural population and at least 20% of land in crops; linked birth and vital stats records 1995-97	2055 SGA infants among total of 43,634 births	1992 US agricultural census info; crop acreage by county and herbicide use by state	Compared 74 high- and 73 low-wheat rural counties (>85% of spring and durum wheat acreage treated with chlorophenoxy herbicides such as 2,4-D and MCPA)	Mothers in high- and low-wheat counties similar re age, education, marital status, parity, prenatal care, previous preterm or IUGR birth, prenatal smoking and alcohol use, infant sex, time of conception (April-June vs other)

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, SGA, residence in high- vs. low-wheat rural county	1.05, 0.94-1.17					
(Perera and others 2003), New York	Birth cohort	263 nonsmk African-American and Dominican women, delivered at 2 major hospitals or their satellite clinics, 1 st prenatal visit by GW 20; preg outcome from birth records	Birth weight, length, gestational age, head circumf	Measured cotinine and chlorpyrifos levels in maternal and cord plasma; plasma chlorpyrifos highly correlated with other plasma pesticides	Mean maternal or cord plasma chlorpyrifos level was 7.5 pg/g	BMI, parity, cotinine, infant sex, gestation length
Birth weight vs ln maternal or cord plasma chlorpyrifos levels	$\beta=-0.04$, $p=.01$ see Whyatt 2004 below for updated results					
(Gladden and others 2003), Ukraine	Pregnancy cohort	197 mothers recruited during pregnancy, 1993-1994; preg outcome based on medical records	Only 8 infants were preterm	Measured 7 organochlorine pesticides (p,p'-DDT, p,p'-DDE, β -HCH, HCB, trans-nonachlor, oxychlorane, heptachlor epoxide) and 11 PCB congeners in maternal milk 4-5 days after delivery		City, age, parity, maternal age, height, pre-pregnancy BMI, infant sex
Relative birth weight (z-score) vs breast milk	β -HCH 97.8 \pm 1.7(SE)	103.2 \pm 1.5 ($p<.05$, compared to 1 st tertile)	ρ , ρ ;DDE 99.2 \pm 1.6	100.8 \pm 1.7 ($p<.05$, compared to 1 st)		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OC tertiles (low to high)		101.1±1.7	102.4±1.6	tertile)		
(Lawson and others 2004), New Jersey, Missouri, USA	Retrospective cohort	Wives of male workers exposed to TCDD during production of trichlorophenol or its derivatives; comparison group of unexposed neighbourhood wives; assessed birth weight of term infants (≥ 37 wk gestation); birth wt and gestation length based on birth records (82%) or mother's report	1117 live singleton births of 217 referent wives and 176 worker wives	Est' serum TCDD conc at concep based on serum TCDD at exam, dates exposure to TCDD-related processes, BMI; measured TCDD in sample of 79 men in comp group	Exposed men: median TCDD at concep was 254 pg/g lipid (range 3-16340); mean referent serum TCDD was 6 pg/g (value assigned to workers before exposure)	Comparison group men matched on age, race and sex; adjusted for infant sex, maternal education, parity, prenatal cigarette smoking, gestation length
Mean birth wt diff and SE between compar grp and expos men by serum TCDD category (pg/g lipid)	All infants <20 -8±44(SE), n=264 20-254 -42±59, n=98	≥ 255 +83±52, n=144	Term infants <20 -146±91 20-254 156±101	≥ 255 130±76		
(Berkowitz and others 2004), New York City	Pregnancy cohort	Ethnically diverse cohort recruited in prenatal clinic at Mount Sinai Hospital, 1998-2002; preg outcome based on clinic records	404 births of mothers recruited during early pregnancy, 1998-2002; assessed gestation length	Self-reported maternal pesticide exposure; measured 3 rd trimester maternal urinary PCP and metabolites of		Race/ethnicity, infant sex

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			of first singleon births	chlorpyrifos and pyrethroid insecticides		
Average birth weight, pestic use vs non-use by household member	3301±457 vs 3277±419 g, p>.05	Birth weight, detectable vs non-detectable mat 3 rd T urinary pestic or pestic metabolite levels	chlorpyrifos metabolite 3296±434(SD) vs 3284±441 g, p>.05	pyrethroid metabolites 3292±432 vs 3295±438 g, p>.05	PCP 3287±408 vs 3289±468 g, p>.05	
(Whyatt and others 2004), New York City	Birth cohort	Pregnancy cohort; preg outcome based on clinic records	404 births among ethnically diverse cohort of pregnant women recruited in prenatal clinic at Mount Sinai Hospital, 1998-2002	85% of mothers had pesticide exposure during pregnancy; measured chlorpyrifos, diazinon and a propoxur metabolite (2-isopropoxyphenol) in cord and maternal blood and 2-day personal air in 3 rd trimester	Summed chlorpyrifos and diazinon using EPA relative potency factor (chlorpyrifos 6X as potent as diazinon re brain AChE inhibition)	Gestation length, maternal prepreg weight and weight gain during pregnancy, sex, parity, ethnicity, ETS, season of delivery
Regr coeff, change in birth wt (g) by cord plasma chlorpyrifos + diazinon in chlorpyrifos equivalentents	3 rd tertile vs <LOD β =-186.3, -327.2 to -45.4, p=.01	Regr coeff, birth wt per log increase of maternal 3 rd T personal air chlorpyrifos plus diazinon in chlorpyrifos equivalentents	β =-5.1 g (-50.7 to 40.4), p=.82	Regr coeff, change in birth wt per log increase of cord plasma chlorpyrifos plus diazinon in chlorpyrifos equivalentents	β =-49.1, -91.3 to -6.9, p=.02	
Regr coeff, birth wt vs log cord plasma chlorpyrifos plus	Born before Jan 2001 β =-72.5 g (-	Born after Jan 2001 β =0.6 g (-144.7, 145.9)	Birth weight vs log cord plasma propoxur	β =-65.6g (-146.7, 15.4), p=.11	Propoxur is a carbamate insecticide	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
diazinon levels; note that EPA phased out resid use of these pesticides starting Jan 1, 2001	125.0, -20.0), p<.05		metabolite levels			
(Levario-Carrillo and others 2004), Mexico	Case-control	Agricultural region with intense pesticide use, esp. OPs; recruited after delivery in hosp, 2000-2001; maternal info, birth wt measured by study team	79 IUGR infants (no birth defects or infection), 292 controls, 2000-2001	Pesticide exposure during pregnancy based on: living <1 km from crop areas, personal pesticide use, pesticide use by person in same household, spouse working in agricultural	Measured AChE in cord or maternal blood at least 20% below avg background level in community	Maternal fat-free mass, height, age, Hb, smoking, occupation, parity, placental wt, IgM specific for rubella, <i>trimester. gondii</i> and CMV, infant sex
Mean cord blood AChE activity, cases vs controls	3.7 vs 4.0 U/ml, p<0.01	OR, prenatal maternal residence <1 km from crop areas, yes vs no	2.3, 1.0-5.3			
(Weisskopf and others 2005), Wisconsin, Illinois, Indiana, Ohio, Michigan	Retrospective cohort (Great Lakes Consortium)	Great Lakes sport-fishing charter boat captains and families plus random sample of general population in 5 Great Lakes states; 511 mothers interviewed 1993-1995; preg outcome based on birth records	143 first-born children, 1970-93	Great Lakes sport-caught fish are contaminated with OCs incl PCBs and DDE; serum collected from 143 women 1994-1995	Median serum DDE was 2.20 µg/L (range 0.25-10.0)	Child sex, maternal age, maternal education, parity, prepreg BMI, prenatal cigarette and alcohol use, weeks of breastfeeding
Mult regression	$\beta = -146, -35$ to -					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
coefficient, change in birth wt (g) per unit increment in ln maternal serum DDE, ltd to term births	257					
(Tajimi and others 2005), Tokyo	Birth cohort	Tokyo; paper does not state source of birth wt info	240 mother-infant pairs, 1999-2000, maternal age 25-34	Measured 14 PCDDs, 15 PCDFs and 12 coplanar PCB congeners in br milk	Median and range of total PCDD, PCDF and co-PCB TEQ (24.0, 4.2-67.0 pg/g lipid), PCDD and PCDF TEQ (13.8, 2.8-37.2) and co-PCB TEQ (9.9, 1.4-36.4)	Maternal age, parity, weight, smoking
Mult regression coefficient, change in BW (g) per unit change in maternal br milk PHAH conc (pg/g lipid); not adj for GL – 3/240 infants were preterm	Coplanar PCB-TEQ $\beta = -5.09 \pm 4.84$ (SE)	PCDD/PCDF TEQ $\beta = -2.01 \pm 4.16$	PCDD/PCDF/co-PCB TEQ $\beta = -2.30 \pm 2.62$	Octachlorodibenzo-p-dioxin $\beta = -1.23 \pm 0.49$	Note: max. OCDD level was 381 pg/g lipid	
(Fenster and others 2006), California	Birth cohort	Low-income pregnancy Latinas living in the Salinas Valley, recruited at prenatal clinics during 1999-2000; mother-reported pregnancy	385 mother-infant pairs	Measured maternal serum levels of p,p'-DDT, p,p-DDE, o,p-DDT, HCB (HCB), HCH (HCH), dieldrin, heptachlor epoxide,	Median serum DDE was 1004 ng/g lipid (range 49-159,303; 90 th percentile 8417)	Maternal age, parity, country of birth, family income, prenatal care, smoking, total urinary

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		history and medical record abstraction		oxychlorane, trans-nonachlor, mirex		dimethyls at GW 26, maternal prepreg BMI, gestational wt gain, infant sex, GL and GL ²
Regression analysis, birth weight vs log ₁₀ maternal serum organochlorine pesticide level, adj for GL and other cov.s	DDE β=-46 g, -129 to 37, p=.28	HCB β=-23 g. -154 to 108, p=.73	β-HCH β=25, -154 to 108, p=.73	Dieldrin β=18, -164 to 201, p=.84	Heptachlor epoxide β=44, -105 to 194, p=.56	Oxychlorane β=64, -39 to 168, p=.22
(Zhu and others 2006), Denmark	Birth cohort	Danish National Birth Cohort; recruited during 1997-2003; pregnancy outcome based on national registries	Identified 20 SGA infants among 226 pregnancies of female gardeners and 10 among 214 pregnancies of female farmers; comparison group was 62,164 pregnancies of women in other occupa	Self-reported work activities and exposure to pesticides during pregnancy and 3 months before conception solicited at about gestation wk 16		Maternal age, gravidity, history of spontaneous abortion, BMI, smoking, alcohol, paternal occupation
IUGR vs mat occup as gardner vs other occupa	1.0, 0.6-1.6	IUGR among gardeners by exposure status	Indoor work, y/n 0.4, 0.1-1.1	Used pesticides but no direct contact vs no pesticide use 2.7, 0.4-16.1	Used pesticides and had direct contact vs no pesticide use 0.5, 0.1-2.9	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
IUGR among farmers by exposure status	Sprayed pesticides, y/n 0.5, 0.1-4.7					
(Khanjani and Sim 2006a), Australia	Retrospective cohort	Primiparous women, 6-12 wk postpartum, recruited in centres throughout Victoria state during early 1990's; preg outcome based on clinic records	814 mothers, 113 SGA infants	Measured breast milk organochlorines	Breast milk tertiles ($\mu\text{g}/\text{kg}$ lipid) DDT: ≤ 39 , 39-66, >66 DDE: ≤ 400 , 401-730, >730	Maternal age, wt, education, smok, alcohol
OR, SGA by breast milk DDE tertile based on mg/kg lipid	1 st tertile 1.0 (ref) 2 nd tertile 1.21, 0.73-2.00	3 rd tertile 0.79, 0.45-1.39				
(Khanjani and Sim 2006b), Australia	Retrospective cohort	Primiparous women, 6-12 wk postpartum, recruited in centres throughout Victoria state during early 1990's; preg outcome based on clinic records	814 mothers, 113 SGA infants	Measured breast milk organochlorines	Breast milk tertiles ($\mu\text{g}/\text{kg}$ lipid): dieldrin: ≤ 33 , 34-48, >48 heptachlor epoxide or oxychlordane:	Maternal age, wt, education, smok, alcohol

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					≤5, 5-9, >9 HCB: ≤27, 28-48, >48	
OR, SGA, 2 nd and 3 rd vs 1 st tertile of breast milk organochlorine pesticide level	Dieldrin 1.0 0.74, 0.45-1.23 0.92, 0.56-1.51	Heptachlor epoxide 1.0 0.88, 0.52-1.52 1.16, 0.72-1.86	Oxychlorane 1.0 0.53, 0.31-0.90 0.93, 0.58-1.51	HCB 1.0 0.89, 0.54-1.48 0.98, 0.58-1.67		
(Jusko and others 2006), San Francisco	Pregnancy cohort	20,754 pregnancy women, Kaiser Health Plan members, East Bay region of SF Bay, enrolled at prenatal visit, 1963-66; blood samples collected during 2 nd or 3 rd trimester; birth wt and gestation length from medical records, anthropometric measuredures by pediatrician at age 5	399 children examined at age 5; 240 had Raven's Progressive Matrices or Peacock Picture Vocabulary Test scores below 10 th percentile, 159 had higher scores	Prenatal maternal serum DDT/DDE		Adj as necessary for maternal BMI, ht, parity, race, alcohol, paternal education and occupation, gestation length, prenatal care, gender
Adj mean diff in birth wt (z-score), prenatal maternal serum DDT/DDE 75 th vs 25 th percentile	DDE 0.01, -0.11 to 0.14 DDT 0.01, -0.12 to 0.13					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Sagiv and others 2007), Massachusetts, USA	Birth cohort	722 mother-infant pairs recruited at hospital near a Superfund site, New Bedford, Mass, 1993-98; preg outcome based on medical records	Birth weight	Residents of 4 towns near Superfund site (a contam'd harbor); cord serum PCBs (51 congeners), DDE, HCB		Infant sex, gestation length, maternal age, parity, ht, prepreg BMI, prenatal maternal smoking, local fish consumption
Adjusted diff in mean birth wt (g), cord serum HCB quartiles 2-4 vs 1	Q2 172.3, 85.6-259.0 Q3 35.6, -50.4 to 121.7	Q4 -13.1, -104.4 to 78.1 p-trend=.18	Adjusted diff in mean birth wt (g), cord serum DDE quartiles 2-4 vs 1	Q2 -48.9, -137.3 to 39.5 Q3 -19.8, -110.0 to 70.4	Q4 -25.9, -125.5 to 73.7 p-trend=.82	
(Wolff and others 2007), New York City	Pregnancy cohort	Pregnancy women enrolled at Mount Sinai Hosp during 1998-2002; measured maternal plasma PON1 activity; conducted standardized measures of birth wt, length, head circumf	404 mother-infant pairs	Mother-reported pesticide and other exposure info; 3 rd trimester maternal plasma DDE, PCBs (118, 138, 153, 180), maternal urinary OP metabolites and malathion dicarboxylic acid, maternal or cord bl Pb		Maternal age, race, ethnicity, BMI, pregnancy wt gain, infant sex, gestation length
Regression coefficient, birth wt (g) vs log ₁₀ prenatal maternal serum DDE (µg/L)	β=-98±59 g, p=.10 β=-128±67 g,	Regression coefficient, birth wt (g) vs log ₁₀ prenatal maternal urinary diethylthiophosphate	β=-52±32 g, p=.10	Regression coefficient, birth wt (g) vs log ₁₀ prenatal maternal urinary malathion	β=39±52 g, p=.46	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	p=.06 {lipid adjusted}	(nM/L)		dicarboxylic acid (≥ vs <LOD)		

Summary: Intrauterine growth deficit

Reviews

Maternal exposure

A recent review examined evidence from epidemiologic studies of pregnancy outcome that assessed pesticide class, family and/or active ingredient (Weselak and others 2006). These reviewers found inadequate evidence for associations between intrauterine growth deficit and specific pesticide categories including DDT/DDE, phenoxy herbicides, triazine herbicides or thiocarbamate fungicides.

Original studies published since 1998

Maternal exposure, TCDD, inadequate evidence

A German pregnancy cohort study revealed a statistically non-significant relationship between FGD and self-reported maternal occupational chlorophenol exposure (low vs no exposure, OR=3.7, 95% CI 0.4-33.0; moderate vs no exposure, OR=2.5, 95% CI 0.4-15.0, p-trend=.17) (Seidler and others 1999). A birth cohort study of women exposed to TCDD at Seveso found a statistically non-significant increased risk of FGD during the first 8 years of follow-up (per log maternal serum TCDD increment, OR=1.8, 95% CI 0.7-4.3); there was an inverse association of borderline statistical significance between birth weight adjusted for gestation length and maternal serum TCDD (per log TCDD increment, β =-92 g, 95% CI -204 to 19) (Eskenazi and others 2003). In a New York City birth cohort study, birth weight adjusted for gestation length was not associated with detectable 3rd trimester maternal urinary pentachlorophenol levels (detectable vs non-detectable, average birth weight 3287±408 vs 3289±468 g, p>.05) (Berkowitz and others 2004). In a Japanese birth cohort, birth weight among mostly term infants was not associated with breast milk total TEQ from polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans and coplanar polychlorinated biphenyls (change in birth weight per unit change in breast milk total TCDD-TEQ (pg/g lipid), β =-2.30±2.62(SE) g, p>.05); however, there was an inverse association between birth weight adjusted for gestation length and breast milk octachlorodibenzo-p-dioxin levels (pg/g lipid) (β =-1.23±0.49 g, p<.05) (Tajimi and others 2005).

Maternal exposure, chlorophenoxy herbicides, inadequate evidence

A large ecologic study in 4 U.S. Midwest states revealed no relationship between FGD and maternal residence in high-wheat rural counties (a proxy for chlorophenoxy herbicide exposure) (high vs low wheat counties, OR=1.05, 95% CI 0.94-1.17) (Schreinemachers 2003).

Maternal exposure, other and unspecified herbicides, inadequate evidence

A German pregnancy cohort study revealed no association between FGD and self-reported maternal occupational herbicide exposure (low vs no exposure, OR=1.0, 95% CI 0.2-4.0; moderate vs no exposure, OR=0.9, 95% CI 0.3-3.0, p-trend=.82) (Seidler and others 1999).

Maternal exposure, DDT/DDE, limited evidence

In the 1959-1966 U.S. Collaborative Perinatal Project cohort, there was a dose-response relationship between FGD and prenatal serum DDE levels (≥ 60 vs < 15 $\mu\text{g/L}$, OR=2.6, 95% CI 1.3-5.2, p-trend=.04); this study used preserved serum samples collected at a time when population-wide DDT exposure was much higher than now (Longnecker and others 2001). Term birth weight was inversely associated with maternal serum DDE levels in a retrospective cohort study of women who consumed Great Lakes fish (change in birth weight per natural log maternal serum DDE increment, $\beta = -146$ g, 95% CI -35 to -257) (Weisskopf and others 2005). Negative findings all came from relatively small studies. A small birth cohort study in Spain revealed no association between birth weight adjusted for gestation length and cord serum DDE levels (change in birth weight per unit change in cord serum DDE, $\beta = -16.8 \pm 37.8$ (SE) g, $p > 0.05$) (Ribas-Fito and others 2002). A Ukrainian pregnancy cohort study revealed increasing average birth weight z-scores (adjusted for gestation length) among infants of women in higher breast milk DDE tertiles (3rd vs 1st tertile, $p < .05$), i.e., an apparently favourable effect (Gladden and others 2003). In an Australian retrospective cohort study, FGD was not associated with breast milk DDE levels (2nd vs 1st tertile DDE, OR=1.21, 95% CI 0.73-2.00; 3rd vs 1st tertile, OR=0.79, 95% CI 0.45-1.39) (Khanjani and Sim 2006b). A birth cohort study in the Salinas Valley of California revealed no association between birth weight (adjusted for gestation length and other potential confounders) and maternal serum DDE (per log increment, $\beta = -46$ g, 95% CI -129 to 37, $p = .28$) (Fenster and others 2006). In a San Francisco pregnancy cohort, birth weight adjusted for gestation length and other factors was not associated with maternal serum DDT or DDE levels (mean difference in birth weight z-score, 75th vs 25th percentile maternal serum DDE, 0.01 g, 95% CI -0.11 to 0.14 (Jusko and others 2006). In a New York City pregnancy cohort, birth weight adjusted for gestation length and other factors was inversely associated with maternal serum DDE (change in birth weight per log lipid-adjusted maternal serum DDE increment, $\beta = -128 \pm 67$ (SD) g, $p = .06$) (Wolff and others 2007).

Maternal exposure, HCB, inadequate evidence

A small birth cohort study in Spain revealed no association between birth weight adjusted for gestation length and cord serum HCB level ($\beta = 19.8 \pm 50.9$ (SE) g, $p > .05$) (Ribas-Fito and others 2002). In an Australian retrospective cohort study, FGD was not associated with breast milk HCB levels (2nd vs 1st tertile, OR=0.89, 95% CI 0.54-1.48; 3rd vs 1st tertile, OR=0.98, 95% CI 0.58-1.67) (Khanjani and Sim 2006b). A birth cohort study in the Salinas Valley of California revealed no association between birth weight (adjusted for gestation length and other potential confounders) and maternal serum HCB (per log increment, $\beta = 23$ g, 95% CI -154 to 108, $p = .73$) (Fenster and others 2006). In a Massachusetts birth cohort, there was a statistically non-significant reduction in average birth weight related to cord serum HCB levels (adjusted mean birth weight difference, 4th vs 1st quartile cord serum HCB, -13.1 g, 95% CI -104.4 to 78.1, p-trend=.18) (Sagiv and others 2007). In a Massachusetts birth cohort, there was no association between birth weight adjusted for gestation length and other factors and cord serum DDE levels (adjusted mean birth weight difference, 4th vs 1st quartile cord serum DDE, -25.9 g, 95% CI -125.5 to 73.7, p-trend=.82) (Sagiv and others 2007).

Maternal exposure, other organochlorine pesticides, inadequate evidence

A small birth cohort study in Spain revealed no association between birth weight adjusted for gestation length and cord serum HCH level ($\beta = 17.5 \pm 17.6$ (SE) g, $p > .05$) (Ribas-Fito and others 2002). A Ukrainian pregnancy cohort study revealed increasing average birth weight z-scores (adjusted for gestation length) among infants of women in higher breast milk HCH tertiles (2nd vs 1st tertile, $p < .05$), i.e., an apparently favourable effect (Gladden and others 2003). In an Australian retrospective cohort study, FGD was not associated with breast milk dieldrin (3rd vs 1st tertile, OR=0.92, 95% CI 0.56-1.51), heptachlor epoxide (3rd vs 1st tertile, OR=1.16, 95% CI 0.72-1.86) or oxychlorodane levels (3rd vs 1st tertile, OR=0.93, 95% CI 0.58-1.51) (Khanjani and Sim 2006b). A birth cohort study in the Salinas Valley of California revealed no association between birth weight (adjusted for gestation length and other potential confounders) and maternal serum

dieldrin (per log increment, $\beta=18$ g, 95% CI -164 to 201, $p=.84$), heptachlor epoxide ($\beta=44$ g, 95% CI -105 to 194, $p=.56$), oxychordane ($\beta=64$ g, 95% CI -39 to 168, $p=.22$) or β -HCH ($\beta=25$ g, 95% CI -154 to 108, $p=.73$) (Fenster and others 2006).

Maternal exposure, organophosphate insecticides, inadequate evidence

In Mexican agricultural communities, FGD was associated with reduced cord blood acetylcholinesterase (AChE) levels (mean AChE activity, cases vs controls, 3.7 vs 4.0 U/ml, $p<.01$) (Levario-Carrillo and others 2004). In a New York City birth cohort study, birth weight adjusted for gestation length was not associated with detectable 3rd trimester maternal urinary chlorpyrifos metabolites (detectable vs non-detectable, average birth weight 3296 \pm 434(SD) vs 3284 \pm 441 g, $p>.05$) (Berkowitz and others 2004). In another report of the New York City birth cohort study, birth weight adjusted for gestation length was inversely associated with cord plasma chlorpyrifos plus diazinon expressed as chlorpyrifos equivalents (mean birth weight difference, 3rd tertile vs non-detectable, -186.3 g, 95% CI -327.2 to -45.4, $p=.01$) (Whyatt and others 2004). This association was stronger for infants born before the January 2001 EPA restriction on residential use of these insecticides (change in birth weight adjusted for gestation length per log increment of cord plasma chlorpyrifos plus diazinon in chlorpyrifos equivalents, born before January 2001, $\beta=-72.5$ g, 95% CI -125.0 to -20.0; born after January 2001, $\beta=0.6$ g, 95% CI -144.7 to 145.9). This study found no association with maternal personal air chlorpyrifos plus diazinon levels over a 2-day period during the 3rd trimester (change in birth weight adjusted for gestation length per log increment of personal air chlorpyrifos plus diazinon levels, $\beta=-5.1$ g, 95% CI -50.7 to 40.4, $p=.82$); the author inferred from this that dietary sources may have determined cord plasma chlorpyrifos and diazinon insecticide levels. In a New York City pregnancy cohort, there was a statistically non-significant inverse association between birth weight adjusted for gestation length and other factors and maternal urinary diethylthiophosphate level (change in birth weight per log maternal urinary diethylthiophosphate increment, $\beta=-52\pm 32$ (SD) g, $p=.10$) (Wolff and others 2007). This study found no association with maternal urinary malathion dicarboxylic acid levels ($\beta=39\pm 52$ g, $p=.46$).

Maternal exposure, other insecticides and repellents, inadequate evidence

In a randomized clinical trial of prenatal DEET treatment in Thai refugee camps, the low birth weight (<2500 g) rate was not increased among exposed (14.8%) compared to unexposed women (20.2%) (McGready and others 2001). In a New York City birth cohort study, birth weight adjusted for gestation length was not associated with detectable 3rd trimester maternal urinary pyrethroid insecticide metabolites (detectable vs non-detectable, average birth weight 3292 \pm 432 vs 3295 \pm 438 g, $p>.05$) (Berkowitz and others 2004). The New York City study reported an inverse association of borderline statistical significance between birth weight adjusted for gestation length and cord plasma propoxur (a carbamate insecticide) levels (mean birth weight difference, 3rd tertile vs non-detectable, -66 g, 95% CI -147 to 15) (Whyatt and others 2004).

Maternal exposure, unspecified pesticides, inadequate evidence

In a New York City birth cohort study, birth weight adjusted for gestation length was not associated with prenatal pesticide use by a household member (yes vs no, average birth weight 3301 \pm 457 vs 3277 \pm 419 g, $p>.05$) (Berkowitz and others 2004). In Mexican agricultural communities, FGD was associated with self-reported prenatal residential proximity to crop areas with intense pesticide use (OR=2.3, 95% CI 1.0-5.3) (Levario-Carrillo and others 2004). A Danish birth cohort study reported no association between FGD and prenatal occupation as gardeners (compared to other occupations, OR=1.0, 95% CI 0.6-1.6) or farmers (OR=0.6, 95% CI 0.3-1.0); this study also found no association with direct pesticide contact among gardeners (compared to gardeners who did not use pesticides, OR=0.5, 95% CI 0.1-2.9) or with pesticide spraying among farmers (compared to farmers who did not spray pesticides, OR=0.5, 95% CI 0.1-4.7) (Zhu and others 2006).

Paternal exposure, TCDD-contaminated chlorophenoxy herbicides, inadequate evidence

Among Vietnam veterans, FGD was not associated with paternal serum TCDD (≥ 79 vs ≤ 10 pg/g lipid, OR=0.9, 95% CI 0.6-1.3) (Michalek and others 1998). Birth weight adjusted for gestation length was not related to serum TCDD levels among men exposed during production of trichlorophenol and derivatives such as 2,4,5-T (mean birth weight difference, TCDD ≥ 255 vs < 20 pg/g lipid, all infants, 83 ± 52 g, $p > .05$; term infants, 130 ± 76 g, $p > .05$), i.e., although not statistically significant, infants of highly exposed men tended to weigh more than those of less exposed men (Lawson and others 2004).

6. Neural tube defects

Original studies published since 1996

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Dimich-Ward and others 1996), British Columbia	Nested case-control	Cohort of 19,675 offspring of 9,512 men exposed for at least one yr in a sawmill using chlorophenate wood preservatives; linked cohort, birth and stillbirth records	22 cases CNS birth defects, 5 controls per case	Father's exposure to chlorophenate wood preservatives known to be contaminated with PCDDs incl TCDD	Exposure levels estimated from job titles and duration of employment in each job	Sex, parental ages
Logistic regression OR, NTD	Per 100-hr exposure <3 months before conception 1.17, ns	Max hr/yr in any job up to 3 months before conception 1.11, p<0.05	Logistic regression OR, NTD, 75 th vs 25 th percentile of exposure index	Per 100-hr exposure <3 months before conception 1.27, 0.8-2.0	Max hr/yr in any job up to 3 months before conception 2.35, 1.1-5.3	
(Garry and others 1996), Minnesota	Cohort and ecologic studies	34,772 licensed agricultural pesticide applicators; linked state birth and birth defect registry records	6 infants with CNS birth defects among offspring of pesticide applicators; also assessed birth defect rates in general population by agricultural region	Occupation as certified applicators of restricted-use pesticides; <10% were females and they were excluded from record linkage		Maternal age
Age-adjusted OR, paternal pesticide applicator vs general	1.10, 0.50-2.40	Non-farm family residence in crop vs non-crop regions;	Corn/soybean region 1.42, 1.09-1.86	wheat/sugar beet/potato region 1.49, 0.92-2.40		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
population (6 exposed case fathers), relative to general pop of Minnesota (Table 1 in paper)		excludes registered agricultural pesticide applicators				
(Blatter and others 1996), The Netherlands	Case-control	Hospital-based cases, 1980-92	349 cases spina bifida, 1604 controls (mainly population-based)	Hospital records	Self-reported prenatal maternal occupational exposures	Population controls matched for municipality size and region; adjusted for paternal fam history of NTDs and maternal use of fertility drugs
OR, spina bifida, maternal occupation in agricultural	3.4, 1.3-9.0	Self-reported agricultural pesticide use:	4/9 case and 5/10 control mothers who worked on farms			
(Blatter and others 1997), The Netherlands	Case-control	Hospital-based cases; diagnosis based on hospital records	222 spina bifida cases, 764 controls (hospital- and community-based)	Self-reported paternal occupational exposures <3 months before conception or <1 mth after conception; duration of exposure (hr/wk)		Population controls matched for commun size and region; adj for parental parenal smoking, alcohol, fam history of NTDs and maternal use of fertility drugs, OCs, parity

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, self-reported paternal occupational pesticide exposure, mod or high vs nil	Mod/high exposure 1.7, 0.7-4.0					
(Kristensen and others 1997), Norway	Retrospective cohort	Linked national registry of all deliveries at GW ≥ 16 since 1967 to 5 agricultural and horticultural censuses; 192,417 births of farmers (1967-91); comparison group of 61,351 births to non-farmers in agricultural municipalities	287 infants of farmers and 90 infants of non-farmers had CNS birth defects	Census info on farm ownership and expenditures on pesticides in 1968, possession of tractor pesticide spraying equipment in 1979; focused on data for yr closest to child's YOB but also used other data if available	Exposure data for prenatal period limited to younger children; 57% of men and 34% women worked at least 500 hr/yr on farm	Year of birth, maternal age, geog region, parental consanguinity
Farm vs non-farm parents	Total CNS defects 0.94, 0.73-1.20 Anencephaly 1.10, 0.68-1.79 Spina bifida 0.76, 0.51-1.13	Tractor spraying equipment	Total CNS defects 1.27, 0.93-1.73 Spina bifida 1.56, 0.92-2.66	Tractor spraying equipment on farm with orchards or greenhouses	Total CNS defects 2.30, 1.31-4.04 Spina bifida 2.76, 1.07-7.13	
(Croen and others 1997), California	2 case-control studies	Population-based, 1989-1991; cases identified from Calif	507 live born or stillborn NTD cases, 517 live birth controls,	Mother-reported periconceptual residence history;	Categorized chemicals and potential for	Various combinations of maternal

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		Birth Defects Monitoring Program		assessed maternal residence prox to 764 hazardous waste disposal sites incl 105 National Priority List (NPL) sites	human exposure at nearby residences	race/ethnicity, education, alcohol, family income, periconceptual vitamin supplement use, neighbourhood educational attainment, employment status, infant sex
OR, NTDs, maternal residence <1.6 km of NPL site containing pesticides	2.2, 0.9-5.2					
(Shaw and others 1999), California	Case-control	Live births and fetal deaths (GW ≥20) with selected birth defects, California except LA and SF metro areas, 1987-89; cases identified from Calif Birth Defects Monitoring Program	265 late fetal deaths and infants with NTDs, 734 healthy controls	Self-reported maternal pesticide exposure at work or home (incl residence prox to crops) in mth before conception and 1 st trimester, paternal exposure at conception ±3 months		Maternal periconceptual vitamin use, smoking, education, race
OR, NTDs, maternal	Likely	Prof pesticide applic	Residence prox to crops	OR, paternal	0.9, 0.5-1.7	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
pesticide exposure	occupational exposure 0.9, 0.2-3.8 Maternal applic garden pesticide 2.9, 1.3-6.7	in home 1.6, 1.1-2.5 Pet flea treatments 1.0, 0.7-1.4	1.5, 1.1-2.1 Residence prox to crop pesticide use 1.6, 1.1-2.6	occupational pesticide exposure		
(Irgens and others 2000), Norway	Retrospective cohort	Birth record info for 1.2 million births in Norway, 1970-1993; birth registry info on all birth defects diagnosed within 1 st wk after delivery	45 NTDs with paternal occupation in agricultural	Birth record info on paternal occupation		Maternal age
RR, paternal occupation in agricultural vs general population	NTDs 0.91, 0.67-1.21	Anencephalus 0.71, 0.39-1.20				
(Brender and others 2002), Texas	Case-control	Mexican-American mothers in 14 counties along Texas-Mexico border; 1995-2000; multi-source active case surveillance incl induced abortion, live births, stillbirths	Infants with NTDs (n=184), healthy infant controls (n=225)	Self-reported parental occupational exposures from 1 yr before to 3 months after conception		Household income

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, NTDs, parental periconceptual occupational pesticide exposure	Maternal 1.2, 0.3-4.8	Paternal 1.2, 0.5-2.8				
(Orr and others 2002), California	Case-control	Cases 1983-88 identified from State birth defect registry	13,938 minority infants with major structural birth defects, 14,463 minority healthy infant controls	Maternal residence in census tract with any of the 84 NPL hazardous waste sites in California		
OR, CNS defects, maternal residence in census tract with NPL site containing pesticides	CNS 1.02, 0.68-1.55					
(Schreinemachers 2003), Minnesota, Montana, N Dakota, S Dakota, USA	Retrospective cohort	Counties with at least 50% rural population and at least 20% of land in crops; linked birth and vital stats records 1995-97	62 infants with CNS birth defects among total of 43,634 births	1992 US agricultural census info; crop acreage by county and herbicide use by state	Compared 74 high- and 73 low-wheat rural counties (>85% of spring and durum wheat acreage treated with chlorophenoxy herbicides such as 2,4-D and MCPA)	Mothers in high- and low-wheat counties similar re age, education, marital status, parity, prenatal care, previous preterm or IUGR birth, prenatal smoking and alcohol use, infant sex, time of conception (April-June vs other)

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, CNS defects, residence in high- vs. low-wheat rural county	0.81, 0.46-1.42					
(Blanco Munoz and others 2005), Mexico	Case-control	Population-based, 3 states, 2000-2001; cases identified from stillbirth and neonatal death records	151 anencephaly cases, 151 controls	Mother-reported periconceptual occupation		Controls matched on state, maternity service and DOB; adj for maternal education, age, fam income, previous adverse pregnancy outcome
OR, maternal occupation in agricultural	6.5, 1.4-29.6					
(Rull and others 2006), California	Pooled analysis of two case-control studies	Most counties of California, 1987-1991; cases identified from Calif Birth Defect Monitoring Program	731 NTD cases, 940 controls	Record-based maternal residence prox (<1 km) to applications of specific pesticides or physicochemical groups of pesticides during early gestation	Data on specific pesticides and dates and amounts applied from Calif Pesticide Reporting System	Study population, maternal ethnicity, educal level, cigarette smoking, vitamin use
OR, NTDs, 1 st trimester agricultural	Amides (herbicides)	Ureas (herbicides)	Organophosphates (insecticides)	Benzimidazoles (fungicides)		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
pesticide use within 1 km of maternal residence, by pesticide chemical class	2.2, 1.0-5.3 Substituted benzenes (herbicides) 0.8, 0.3-1.8 Triazines/triazoles (herbicides) 0.9, 0.4-1.8	0.9, 0.4-2.1 Halogenated organics (insecticides) 0.9, 0.6-1.3 Methyl carbamates (insecticides) 1.5, 1.0-2.3	1.3, 0.9-1.8 Phthalimides (insecticides) 0.8, 0.3-1.5 Pyrethroids/pyrethrins (insecticides) 0.9, 0.5-1.6	2.2, 1.1-4.7 Dicarboximides (fungicides) 1.1, 0.6-2.1 Dithiocarbamates (fungicides) 0.7, 0.3-1.5		
OR, NTDs, 1 st trimester agricultural pesticide use within 1 km of maternal residence	1 pesticide 1.2, 0.9-1.7 2-5 pesticides 1.7, 1.3-2.3 ≥6 pesticides 1.4, 1.0-2.1	Benomyl (benzimidazole fungicide) 2.3, 0.9-5.6 1,3-dichloropropene (soil fumigant) 1.8, 0.8-4.3 Carbaryl (carbamate insecticide) 1.7, 0.8-3.9	Methomyl (a methylcarbamate insecticide) 1.4, 0.8-2.5 Glyphosate (organophosphorus herbicide) 1.5, 0.8-2.9 Naled (OP insecticide) 2.7, 0.9-8.2	Malathion (OP insecticide) 1.0, 0.4-2.7 Chlorpyrifos (OP insecticide) 1.3, 0.7-2.3	Oxydemeton-methyl (OP insecticide) 3.4, 0.8-14.3 2,4-D and derivatives (chlorophenoxy herbicides) 1.5, 0.8-2.7	
(Lacasana and others 2006), Mexico	Case-control	See Blanco-Munoz et al 2005 above; cases identified from stillbirth and neonatal death records	151 anencephaly cases (20+ gestation wk), 151 matched controls, 2000-01	Maternal and paternal-reported exposure info incl occupational pesticide use esp during 3 months before and 1 month		Matched for

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
				after conception		
OR, anencephaly, parental work in agricultural during periconceptual period (3 months before and 1 mon after conception)	Maternal workers 4.57, 1.05-19.96 Paternal applicators 2.50, 0.73-8.64					

Summary: Neural tube defects, original studies published since 1996

Maternal exposure, chlorophenoxy herbicides, inadequate evidence

A retrospective cohort study in 4 U.S. states reported no association between CNS birth defects and prenatal residence in high-wheat counties (a proxy for agricultural use of chlorophenoxy herbicides including 2,4-D and MCPA) (high- vs low-wheat counties, OR=0.81, 95% CI 0.46-1.42) (Schreinemachers 2003). A pooled analysis of 2 case-control studies in California revealed a statistically non-significant elevated NTD risk related to prenatal residence less than 1 km from areas with documented agricultural use of 2,4-D or derivatives (OR=1.5, 95% CI 0.8-2.7, in a multi-pesticide model) (Rull and others 2006).

Maternal exposure, other herbicides, inadequate evidence

In the California pooled analysis, NTDs were associated with prenatal residential proximity to agricultural applications of amide herbicides (OR=2.2, 95% CI 1.0-5.3) and a statistically non-significant association with glyphosate use (OR=1.5, 95% CI 0.8-2.9) (Rull and others 2006).

Maternal exposure, insecticides, inadequate evidence

In the California pooled analysis, NTDs were not associated with prenatal residential proximity to agricultural applications of halogenated organic insecticides (OR=0.9, 95% CI 0.6-1.3) but elevated NTD risks were related to organophosphate (OR=1.3, 95% CI 0.9-1.8), methyl carbamate insecticides (OR=1.5, 95% CI 1.0-2.3) and specific carbamates including carbaryl (OR=1.7, 95% CI 0.8-3.9) and methomyl (OR=1.4, 95% CI 0.8-2.5) (Rull and others 2006). This study also reported statistically non-significant associations between NTDs and specific organophosphate insecticides including naled (OR=2.7, 95% CI 0.9-8.2) and oxydemeton-methyl (OR=3.4, 95% CI 0.8-14.3) but not with malathion (OR=1.0, 95% CI 0.4-2.7) or chlorpyrifos (OR=1.3, 95% CI 0.7-2.3).

Maternal exposure, fungicides, inadequate evidence

In the California pooled analysis, NTDs were associated with prenatal residential proximity to agricultural applications of fungicides in the benzimidazole chemical class (OR=2.2, 95% CI 1.1-4.7) but not with dicarboximides (OR=1.1, 95% CI 0.6-2.1) or dithiocarbamates (OR=0.7, 95% CI 0.3-1.5) (Rull and others 2006). This study observed an association of borderline statistical significance with the benzimidazole fungicide benomyl (OR=2.3, 95% CI 0.9-5.6).

Maternal exposure, unspecified pesticides, inadequate evidence

Reviewers noted limited epidemiologic evidence for an association between NTDs (anencephaly, spina bifida) and prenatal occupational pesticide exposure (Sever and others 1997). Among Norwegian farm families, CNS birth defect risk was not elevated (compared to non-farm families, OR=0.94, 95% CI 0.73-1.20) but was associated with farm use of tractor pesticide spraying equipment for orchards or greenhouses (OR=2.30, 95% CI 1.31-4.04) (Kristensen and others 1997). Combined analysis of two case-control studies in California revealed an association between NTDs and maternal residential proximity to NPL sites containing pesticides (<1 vs ≥1 mile, OR=2.2, 95% CI 0.9-5.2) (Croen and others 1997). A California study revealed associations between NTDs and prenatal professional pesticide use in homes (OR=1.6, 95% CI 1.1-2.5) and maternal use of garden pesticides (OR=2.9, 95% CI 1.3-6.7) but not with pet flea treatments (Shaw and others 1999). Two reports of a Mexican case-control study of anencephaly revealed strong associations with self-reported periconceptual maternal occupation in agriculture; in the more recent report, the odds ratio was 4.57 (95% CI 1.05-20.0) (Blanco Munoz and others 2005). A Finnish case-control study found no association between NTDs and maternal 1st trimester work in agriculture (OR=1.2, 95% CI 0.6-2.4); among the 38 exposed case mothers, half were considered lightly exposed (Nurminen and others 1995). NTDs were associated with prenatal occupation in agriculture in a case-control study in the Netherlands (OR=3.4, 95% CI 1.3-9.0); however, among the few women employed in agriculture, similar proportions of case (4/9) and control (5/10) mothers reported pesticide exposure (Blatter and others 1996). NTDs were not associated with self-reported periconceptual maternal occupational pesticide exposure in case-control studies in California (OR=0.9, 95% CI 0.2-3.8) (Shaw and others 1999) or Texas (OR=1.2, 95% CI 0.3-4.8) (Brender and others 2002). In a California case-control study, CNS defects were not associated with prenatal residence in a census tract with a NPL site containing pesticides (OR=1.02, 95% CI 0.68-1.55) (Orr and others 2002). The heterogeneous and non-specific exposure indices preclude strong inferences.

Paternal occupational exposure, TCDD-contaminated chlorophenoxy herbicides and chlorophenate wood preservatives, limited evidence

A case-control study in Atlanta reported no association between anencephaly or spina bifida and self-reported paternal exposure to Agent Orange in Vietnam (respective ORs=0.80 and 1.19, CIs not stated) (Erickson and others 1984). In a retrospective cohort study of Vietnam veterans and partners, there was an elevated risk of CNS defects of borderline statistical significance among offspring of men with a history of elevated serum TCDD levels compared to offspring of men with background levels (OR=4.18, 95% CI 0.96-21.3, calculated from data in paper, 5 exposed case fathers) (Wolfe and others 1995). Among male sawmill workers in British Columbia, NTDs were associated with maximum preconceptional chlorophenate exposure intensity (hr/yr) (75th vs 25th percentile, OR=2.35, 95% CI 1.1-5.3) and less strongly with cumulative exposure (hr) during the 3 mos before conception (75th vs 25th percentile, OR=1.27, 95% CI 0.8-2.0) (Dimich-Ward and others 1996). The latter findings are consistent with a role for cumulative exposure to PCDD and PCDF contaminants that bioaccumulate in body lipids. Reviewers noted inadequate epidemiologic evidence for an association between NTDs and paternal TCDD exposure (Longnecker and others 1997). A subsequent review concluded that there was limited epidemiologic evidence for an association between spina bifida and paternal exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid (the main herbicides used by the U.S. military in Vietnam) (National Academy of Sciences 2007).

Paternal occupational exposure, unspecified pesticides, inadequate evidence

Reviewers found limited epidemiologic evidence for an association between NTDs and paternal occupational pesticide exposure (Sever and others 1997). Among studies published before the latter review, CNS birth defects were associated with farm use of tractor pesticide spraying equipment for orchards or greenhouses (OR=2.30, 95% CI 1.31-4.04) (Kristensen and others 1997). Statistically non-significant elevated risks were observed in Texas (anencephaly, paternal occupations likely exposed to pesticides, OR=1.28, 95% CI 0.77-2.13; occupation as farm or ranch workers, OR=1.73, 95% CI 0.84-3.55) (Brender and Suarez 1990), Minnesota (CNS defects, paternal occupation as licensed pesticide applicator, RR=1.10, 95% CI 0.50-2.40, 6 exposed case fathers) (Garry and others 1996) and the Netherlands (spina bifida, moderate to high vs no periconceptual paternal occupational pesticide exposure, OR=1.7, 95% CI 0.7-4.0) (Blatter and others 1997). The Minnesota study also noted increased risks of NTDs among non-farm families (neither parent was a licensed pesticide applicator) living in agricultural regions (e.g., residence in corn/soybean vs non-crop regions, OR=1.42, 95% CI 1.09-1.86; wheat/sugar beet/potato regions, OR=1.49, 95% CI 0.92-2.40); the crude exposure indicator and inability to adjust for potential confounders preclude strong inferences (Garry and others 1996). Among recently reported studies, a country-wide Norwegian retrospective cohort study reported no association between NTDs and paternal occupation in agriculture (based on census records) (OR=0.91, 95% CI 0.67-1.21) (Irgens and others 2000). NTDs were not associated with self-reported paternal periconceptual occupational pesticide exposure in case-control studies in California (OR=0.9, 95% CI 0.5-1.7) (Shaw and others 1999) or Texas (OR=1.2, 95% CI 0.5-2.8) (Brender and others 2002). Anencephaly risk was elevated (but not statistically significant) among offspring of men with partner-reported periconceptual occupation in agriculture in Mexico (OR=2.50, 95% CI 0.73-8.64) (Lacasana and others 2006). The inconsistent findings and the heterogeneity of exposure indices precludes firm conclusions.

7. Cardiac defects

Reviews

Author	Scope of review	Findings
(Loffredo 2000), USA	Review of literature on epidemiologic studies of cardiovascular birth defects	Scant and inconsistent evidence of association between cardiovascular birth defects and prenatal pesticide exposure

Cardiac defects: Original studies since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Shaw and others 1999), California	Case-control	Live births and fetal deaths (GW ≥20) with selected birth defects, California except LA and SF metro areas, 1987-89; cases identified from Calif Birth Defects Monitoring Program	207 fetal deaths GW ≥20 and live births with cardiac defects, 734 healthy controls	Self-reported maternal pesticide exposure at work or home (incl residence prox to crops) in mth before conception and 1 st trimester, paternal exposure at conception ±3 months		Maternal periconceptual vitamin use, smoking, education, race
OR, conotruncal cardiac birth defects, maternal prenatal pesticide exposure at home or work	1.2, 0.8-1.8	Mother applied garden pesticides 3.1, 1.3-7.3 Professional pesticide application in home 1.2, 0.7-2.0	Pet flea treatments 1.2, 0.8-1.8	Residence prox to crops 1.4, 0.9-2.0	Residence proximity to crops treated with pesticides 1.2, 0.7-1.9	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Paternal occupational exposure, 3 months before or after conception	1.0, 0.6-1.9					
(Loffredo and others 2001), Baltimore-Washington Infant Study	Case-control	Liveborn infants with cardiac birth defects diagnosed up to age 1, Maryland, DC, northern Virginia, 1981-89; case diagnoses by pediatric cardiologists, hospital pathology reports, infant death records	1001 cases of cardiovascular birth defects, 771 controls	Self-reported info on maternal pesticide exposure at conception \pm 3 months		Race, SES, maternal age, smoking, alcohol, diabetes, solvent exposures, paternal pesticide exposure, family history of heart defects
Maternal periconceptual exposure	Transposition of great arteries Any pesticide 2.0, 1.2-3.4	herbicides 3.6, 1.6-8.2 rodenticides 5.1, 1.7-14.9	insecticides 1.5, 0.9-2.6	Maternal periconceptual exposure	Endocardial cushion defect Any pesticide 1.5, 0.9-2.4 herbicides	rodenticides insecticides
(Orr and others 2002), California	Case-control	Cases during 1983-88 identified from State birth defect registry	13,938 minority infants with major structural birth defects, 14,463 minority healthy infant controls	Maternal residence in census tract with any of the 84 NPL hazardous waste sites in California		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, cardiac defects, maternal residence in census tract with NPL site containing pesticides	Cardiovasc 0.83, 0.56-1.25					
(Schreinemachers 2003), Minnesota, Montana, N Dakota, S Dakota, USA	Retrospective cohort	Counties with at least 50% rural population and at least 20% of land in crops; linked birth and vital stats records 1995-97	55 infants with cardiac birth defects among total of 43,634 births	1992 US agricultural census info; crop acreage by county and herbicide use by state	Compared 74 high- and 73 low-wheat rural counties (>85% of spring and durum wheat acreage treated with chlorophenoxy herbicides such as 2,4-D and MCPA)	Mothers in high- and low-wheat counties similar re age, education, marital status, parity, prenatal care, previous preterm or IUGR birth, prenatal smoking and alcohol use, infant sex, time of conception (April-June vs other)
OR, cardiac defects, residence in high- vs. low-wheat rural county	1.23, 0.70-2.17					
(Shaw and others 2003), California	Case-control	Live births and fetal deaths (GW \geq 20) with selected birth defects, California except LA and SF metro areas, 1987-89; cases identified from Calif Birth Defects Monitoring Program	207 conotruncal defect cases, 734 healthy infant controls, 1987-1989	Self-reported maternal pesticide exposure at work or home (incl residence prox to crops) in mth before conception and 1 st trimester,		Assessed maternal race/ethnicity, education, folic acid supplement use during periconceptual period

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
				paternal exposure at conception \pm 3 months		
OR, conotruncal defects, maternal periconceptual occupational exposure	Insecticides 2.1, 0.8-5.1	Other pesticides 1.0, 0.5-2.2				

Summary: Cardiac defects

Review

A reviewer found scant and inconsistent evidence of association between cardiovascular birth defects and prenatal pesticide exposure (Loffredo 2000).

Original studies since 1998

Maternal exposure, chlorophenoxy herbicides, inadequate evidence A retrospective cohort study found no association between cardiac birth defects and prenatal residence in high-wheat counties, a proxy for agricultural use of chlorophenoxy herbicides (high- vs low-wheat counties, OR=1.23, 95% CI 0.70-2.17) (Schreinemachers 2003).

Maternal exposure, unspecified herbicides, inadequate evidence

The Baltimore-Washington case-control study noted an association between transposition of great arteries and self-reported periconceptual maternal herbicide exposure at home or work (OR=3.6, 95% CI 1.6-8.2) (Loffredo and others 2001). Further studies are needed to assess this finding and to explore specific herbicides and dose-response relationships.

Maternal exposure, insecticides, inadequate evidence

In a California case-control study, conotruncal defects were not associated with prenatal pet flea treatments (OR=1.2, 95% CI 0.8-1.8) or professional indoor pesticide application (OR=1.2, 95% CI 0.7-2.0) (Shaw and others 1999). There were statistically non-significant elevated risks in case-control studies in Baltimore-Washington (transposition of great arteries, self-reported maternal periconceptual insecticide exposure at home or work, OR=1.5, 95% CI 0.9-2.6) (Loffredo and others 2001) and California (conotruncal defects, self-reported prenatal occupational insecticide exposure, OR=2.1, 95% CI 0.8-5.1) (Shaw and others 2003).

Maternal exposure, unspecified pesticides, inadequate evidence

Conotruncal defects were associated with prenatal residential proximity to crops (OR=1.4, 95% CI 0.9-2.0) or garden pesticide application (OR=3.1, 95% CI 1.3-7.3) in California (Shaw and others 1999). The Baltimore-Washington case-control study reported an association between transposition of great arteries and self-reported maternal periconceptual exposure at home or work to rodenticides (OR=5.1, 95% CI 1.7-14.9) (Loffredo and others 2001). The Baltimore-Washington case-control study reported a statistically non-significant elevated risk of total anomalous pulmonary vein return defects related to self-reported periconceptual maternal pesticide exposure at home or work (OR=2.06, 95% CI 0.82-5.15) (Correa-Villasenor and others 1991). A retrospective cohort study revealed a statistically non-significant elevated congenital heart defect risk (as evidenced by heart murmurs) related to prenatal pesticide exposure in Colombian greenhouses (crude OR=2.16, 95% CI 0.69-6.54, calculated from data in paper) (Restrepo and others 1990). A subsequent report of the California study revealed an association between conotruncal defects and prenatal occupational exposure to insecticides (as noted above) but not to pesticides other than insecticides (OR=1.0, 95% CI 0.5-2.2) (Shaw and others 2003). In another California case-control study, limited to minority groups, cardiovascular birth defects were not associated with prenatal residence in a census tract with a NPL site containing pesticides (OR=0.83, 95% CI 0.56-1.25) (Orr and others 2002). The heterogeneity of these studies with regard to type of cardiac defect evaluated and non-specific exposure indices precludes strong inferences.

Paternal occupational exposure, TCDD-contaminated phenoxy herbicides or chlorophenolate wood preservatives, inadequate evidence

A case-control study of cardiovascular birth defects in Atlanta revealed no overall association with exposure to Agent Orange (based on self-reports and military records) (OR=0.97, CI not reported) but noted elevated risks of transposition of the great vessels (OR=1.49) and coarctation of the aorta (OR=1.89) (Erickson and others 1984). In a retrospective cohort study of Vietnam veterans and partners, there was an elevated risk of cardiovascular birth defects among offspring of men with low (OR=2.39, 95% CI 1.02-5.24) but not high serum TCDD levels (OR=0.95, 95% CI 0.28-2.65) (TCDD categories defined above) (Wolfe and others 1995). Among offspring of male sawmill workers, conotruncal and septal defects were not associated with preconceptional chlorophenolate exposure intensity (per 100 hr exposure during peak exposure year up to 3 mos before conception, OR=0.95, $p>.05$) or with cumulative exposure during the 3 mos before conception (per 100 hr exposure, OR=0.94, $p>.05$) (Dimich-Ward and others 1996). A recent review concluded that there was inadequate evidence for an association between birth defects other than spina bifida and paternal exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid (the main herbicides used by the U.S. military in Vietnam) (National Academy of Sciences 2007).

Paternal occupational exposure, unspecified pesticides, inadequate evidence

There was an increased risk of cardiorespiratory birth defects among offspring of male licensed pesticide applicators in Minnesota (RR=1.69, 95% CI 1.04-2.76); this study did not present data separately for cardiac defects (Garry and others 1996). Among other residents of agricultural counties (after excluding licensed applicators), there were increased cardiorespiratory birth defect risks in areas with corn/soybeans (RR=1.43, 95% CI 1.17-1.76) or wheat, sugar and/or potatoes (RR=1.90, 95% CI 1.37-2.63). In the Norwegian farm cohort study, cardiac birth defect risk was not elevated among offspring of farmers (compared to non-farm families, RR=0.83, 95% CI 0.68-1.02); 57% of fathers and 34% of mothers worked at least 500 hr/yr on their farms (Kristensen and others 1997). A California case-control study reported no association between cardiac birth defects and periconceptual paternal occupational pesticide exposure (OR=1.0, 95% CI 0.6-1.9) (Shaw and others 1999).

8. Orofacial defects

Reviews

Author	Scope of review	Findings
(Nurminen 1995), Finland	Review of epidemiologic studies of maternal pesticide exposure and adverse pregnancy outcome published during 1979 until early 1995	Limited but inconclusive evidence for associations between orofacial birth defects and maternal occupational pesticide exposure

Orofacial defects: Original studies since 1995

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Nurminen and others 1995), Finland	Case-control	National population-based study of parental occupation and birth defects, 1976-82; cases identified from national birth defect registry; covers stillbirths >600 g and infants up to age 1	1,306 case-control pairs incl 581 orofacial clefts	Self-reported work history incl pesticide exposure	158 mothers had worked in agricultural during the 1 st trimester	Maternal age, birth order 3+, 2+ induced abortions, previous fetal death, previous late fetal death, previous malformed infant, prenatal smoking/alcohol, 1 st trimester drug use, 1 st trimester cold or fever
OR, orofacial clefts, 1 st trimester maternal work in agriculture vs other work	1.9, 1.1-3.5					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners; 1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; cases identified from parent-reported info, medical records	12 ear/face/neck defects among infants of potentially exposed fathers, 11 among infants of comparison fathers	Paternal serum TCDD	Serum TCDD levels categorized as background (current level ≤ 10 ng/L), low (current level > 10 and initial level ≤ 110 ng/L) and high (current level > 10 and initial level > 110 ng/L)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia
Relative risk, ear, face or neck defects, high or low vs comparison group	Low or high 1.23, 0.43-3.44	(calc from data in paper)				
(Kristensen and others 1997), Norway	Cohort	Linked national birth registry of all deliveries at GW ≥ 16 since 1967 to 5 agricultural and horticultural censuses; 192,417 births of farmers (1967-91); comparison group of 61,351 births to non-farmers in agricultural municipalities	Numbers of birth defects among offspring of farmers and non-farmers included: isolated cleft palate (92 and 32), cleft lip (285 and 96)	Agricultural census info on farm ownership and expenditures on pesticides in 1968	Possession of tractor pesticide spraying equipment in 1979; focused on data for yr closest to child's YOB but also used other data if available; exposure data for prenatal period limited to younger children; 57% of men and 34% women worked at least 500 hr/yr on farm	Year of birth, maternal age, geog region, parental consanguinity

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Farm vs non-farm parents	Isolated cleft palate 0.93, 0.60-1.43	Total cleft lip 0.94, 0.74-1.20				
(Croen and others 1997), California	2 case-control studies	Population-based, 1989-1991; cases identified from Calif Birth Defects Monitoring Program	439 oral cleft defect cases 455 live birth controls	Mother-reported periconceptual residence history; assessed maternal residence prox to 764 hazardous waste disposal sites incl 105 National Priority List (NPL) sites	Categorized chemicals and potential for human exposure at nearby residences	Various combinations of maternal race/ethnicity, education, alcohol, family income, periconceptual vitamin supplement use, neighbourhood educational attainment, employment status, infant sex
OR, oral clefts, maternal residence <1.6 km of NPL site containing pesticides	0.5, 0.1-1.5 Only 4 exposure case mothers					
(Shaw and others 1999), California	Case-control	Live births and fetal deaths (GW \geq 20) with selected birth defects, California except LA and SF metro areas, 1987-89; cases identified from Calif Birth Defects Monitoring Program	662 late fetal deaths and infants with orofacial clefts, 734 healthy controls	Self-reported maternal pesticide exposure at work or home (incl residence prox to crops) in mth before conception and 1 st trimester, paternal exposure at conception \pm 3		Maternal periconceptual vitamin use, smoking, education, race

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
				months		
OR, isolated cleft lip with or without cleft palate vs 1 st trimester maternal exposure	Occupational exposure 1.1, 0.6-2.0 Maternal garden pesticide use 1.2, 0.5-2.8	Prof insectic applic in home 0.9, 0.6-1.3 Pet flea treatments 0.8, 0.6-1.2	Residence prox to crops 1.2, 0.9-1.6 Pesticides applied to crops 0.9, 0.6-1.4	OR, isolated cleft palate, paternal occupational pesticide exposure at conception \pm 3 months	1.1, 0.8-2.1	
(Orr and others 2002), California	Case-control	Cases during 1983-88 identified from State birth defect registry	13,938 minority infants with major structural birth defects, 14,463 minority healthy infant controls	Maternal residence in census tract with any of the 84 NPL hazardous waste sites in California		
OR, oral clefts, maternal residence in census tract with NPL site containing pesticides	0.89, 0.45-1.74					
(Schreinemachers 2003), Minnesota, Montana, N Dakota, S Dakota, USA	Retrospective cohort	Counties with at least 50% rural population and at least 20% of land in crops; cases identified by linking birth and vital stats records 1995-97	62 infants with cleft lip/palate defects among total of 43,634 births	1992 US agricultural census info; crop acreage by county and herbicide use by state	Compared 74 high- and 73 low-wheat rural counties (>85% of spring and durum wheat acreage treated with chlorophenoxy	Mothers in high- and low-wheat counties similar re age, education, marital status, parity, prenatal care, previous preterm or

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					herbicides such as 2,4-D and MCPA)	IUGR birth, prenatal smoking and alcohol use, infant sex, time of conception (April-June vs other)
Residence in high- vs. low-wheat rural county	Cleft lip/cleft palate 1.12, 0.62-2.01					
(Shaw and others 2003), California	Case-control	Live births and fetal deaths (GW \geq 20) with selected birth defects, California except LA and SF metro areas, 1987-89; cases identified from Calif Birth Defects Monitoring Program	662 cleft lip with or without cleft palate cases, 734 healthy infant controls	Self-reported maternal prenatal (1 month before and 3 months after conception) occupational exposures	Expert assessment of potential chemical exposures	Assessed maternal race/ethnicity, education, folic acid supplement use during periconceptual period
OR, cleft lip with or without cleft palate, maternal periconceptual occupational exposure	Insecticides 0.9, 0.4-2.2 Other pesticides 1.0, 0.6-1.7					

Summary: Orofacial defects

Review

A reviewer found limited but inconclusive evidence for associations between orofacial birth defects and maternal occupational pesticide exposure (Nurminen 1995).

Original studies since 1995

Maternal exposure, chlorophenoxy herbicides, inadequate evidence

A retrospective cohort study found no association between cleft lip and/or palate and prenatal residence in high-wheat counties, a proxy for chlorophenoxy herbicide exposure (high- vs low-wheat counties, OR=1.12, 95% CI 0.62-2.01) (Schreinemachers 2003).

Maternal exposure, organophosphate insecticides, inadequate evidence

A small nested case-control study in San Francisco reported a statistically non-significant association between orofacial defects and prenatal residence <1 km from areas sprayed with malathion (OR=3.35, 95% CI 0.61-18.5) (Thomas and others 1992).

Maternal exposure, unspecified insecticides, inadequate evidence

In a California case-control study, there was no association between isolated cleft lip with or without cleft palate and 1st trimester professional indoor insecticide application (OR=0.9, 95% CI 0.6-1.3) or pet flea treatments (OR=0.8, 95% CI 0.6-1.2) (Shaw and others 1999). Further analysis of this study revealed no association with maternal periconceptual occupational insecticide exposure (OR=0.9, 95% CI 0.4-2.2) (Shaw and others 2003).

Maternal exposure, unspecified pesticides, inadequate evidence

In a large Finnish case-control study, orofacial clefts were associated with maternal 1st trimester employment in agriculture (compared to other work, OR=1.9 95% CI 1.1-3.5) (Nurminen and others 1995). In the California study, there was no association between isolated cleft lip with or without cleft palate and 1st trimester maternal occupational pesticide exposure (OR=1.1, 95% CI 0.6-2.0), maternal application of garden pesticides (OR=1.2, 95% CI 0.5-2.8) or residential proximity to crops treated with pesticides (OR=0.9, 95% CI 0.6-1.4) (Shaw and others 1999). Further analysis of this study revealed no association with maternal periconceptual occupational exposure to pesticides other than insecticides (OR=1.0, 95% CI 0.6-1.7) (Shaw and others 2003). In another California case-control study, limited to minority groups, oral clefts were not associated with prenatal residence in a census tract with a NPL site containing pesticides (OR=0.89, 95% CI 0.45-1.74) (Orr and others 2002). The inconsistent findings and the heterogeneous and non-specific exposure indices preclude strong inferences.

Paternal exposure, TCDD-contaminated phenoxy herbicides or chlorophenolate wood preservatives, inadequate evidence

In a retrospective cohort study of Vietnam veterans and partners, there was no association between ear, face or neck defects and paternal serum TCDD categories (low or high serum TCDD vs unexposed or serum TCDD <10 pg/g lipid, OR=1.09, 95% CI 0.42-2.62 (calculated from data in paper)) (Wolfe and others 1995). A recent review concluded that there was inadequate evidence for an association between birth defects other than spina bifida and paternal exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid (the main herbicides used by the U.S. military in Vietnam) (National Academy of Sciences 2007).

Paternal occupational exposure, unspecified pesticides, inadequate evidence A cohort study of Norwegian farm families found no increased risks of cleft lip with or without cleft palate (compared to non-farm families, OR=0.94, 95% CI 0.74-1.20) (Kristensen and others 1997). Cleft palate was not associated with periconceptual paternal occupational pesticide exposure in a large California case-control study (OR=1.1, 95% CI 0.8-2.1) (Shaw and others 1999).

9. Musculoskeletal defects

Reviews

Author	Scope of review	Findings
(Nurminen 1995), Finland	Review of epidemiologic studies of maternal pesticide exposure and adverse pregnancy outcome published during 1979 until early 1995	Limited but inconclusive evidence for associations between limb reduction birth defects and maternal occupational pesticide exposure
(Sever and others 1997), USA	Literature review, epidemiologic literature on occupational pesticide exposure and reproductive/ developmental effects	Limited evidence for associations between limb reduction birth defects and maternal and paternal pesticide exposures

Musculoskeletal defects: Original studies since 1996

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Garry and others 1996), Minnesota	Cohort and ecologic studies	34,772 licensed agricultural pesticide applicators; linked state birth and birth defect registry records; cases identified from birth and birth defect registry records	30 musculoskeletal birth defects among offspring of pesticide applicators; also assessed birth defect rates in general population by agricultural region	Occupation as certified applicators of restricted-use pesticides; <10% were females and they were excluded		Maternal age
Paternal pesticide applicator vs general population	Musculoskeletal defects Maternal age <30 0.94, 0.52-1.71 Maternal age	General pop: parental residence crop vs non-crop region; excludes registered agricultural pesticide applicators	Corn/soybean region 1.36, 1.18-1.58	Wheat/sugar beet/potato region 1.75, 1.37-2.22		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	≥30 2.52, 1.58-4.01					
(Marshall and others 1997), New York State	Case-control	Population-based, NY State minus NY City, 1983-1986; cases identified from NY State Congenital Malformations Registry, defects diagnosed up to age 2	473 CNS and 3,305 musculoskeletal birth defects, 12,436 normal births	Maternal residential proximity at delivery to hazardous waste sites	1. maternal residence <1 mi of NPL and other hazardous waste sites 2. potential exposure to pesticides, metals and solvents 3. TRI data on industrial air emissions 4. drinking water THM levels ≥100 µg/L	Adjusted as necessary for maternal age, race, education, population density, parity, delayed prenatal care, infant sex
OR, musculoskel defects vs maternal prob pesticide from haz waste site	0.80, 0.51-1.26 adj for residence <1.6 km from NPL site	OR, musculoskel defects vs maternal res ≤1.6 vs >1.6 km from a TRI site releasing pesticides	1.12, 0.93-1.35			
(Kristensen and others 1997), Norway	Cohort	Linked national birth registry of all deliveries at GW ≥16 since 1967 to 5 agricultural and horticultural censuses; 192,417 births of farmers (1967-91);	69 infants of farmers and 26 infants of non-farmers had limb reduction birth defects	Census info on farm ownership and expenditures on pesticides in 1968	Possession of tractor pesticide spraying equipment in 1979; focused on data for yr closest to child's YOB but also used other data if	Year of birth, maternal age, geog region, parental consanguinity

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		comparison group of 61,351 births to non-farmers in agricultural municipalities			available; exposure data for prenatal period limited to younger children; 57% of men and 34% women worked at least 500 hr/yr on farm	
Risk of limb reduction defects: farm vs non-farm parents	0.84, 0.51-1.37	Expenditure on pesticides	All farms 1.79, 0.98-3.26 Farms with grain crops 2.50, 1.06-5.90			
(Shaw and others 1999), California	Case-control	Live births and fetal deaths (GW \geq 20) with selected birth defects, California except LA and SF metro areas, 1987-89; cases identified from Calif Birth Defects Monitoring Program	165 late fetal deaths and infants with limb anomalies, 734 healthy controls	Self-reported maternal pesticide exposure at work or home (incl residence prox to crops) in mth before conception and 1 st trimester, paternal exposure at conception \pm 3 months		Maternal periconceptual vitamin use, smoking, education, race
Self-reported 1 st	Mother applied	Pet flea treatments	Paternal			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
trimester maternal exposure; ORs for limb reduction birth defects	<p>garden pesticides 1.5, 0.5-4.6</p> <p>Professional applied garden pesticides 3.5, 1.2-9.9</p> <p>Professional pesticide application in home 1.6, 1.0-2.7</p>	<p>0.9, 0.6-1.4</p> <p>Residence prox to crops 0.9, 0.5-1.3</p> <p>Pesticides applied to crops 1.0, 0.6-1.8</p>	<p>occupational pesticide exposure, 3 months before and 3 months after conception 1.2, 0.6-2.2</p>			
(Irgens and others 2000), Norway	Retrospective cohort	Birth record info for 1.2 million births in Norway, 1970-1993; cases identified from birth registry info on all birth defects diagnosed within 1 st wk after delivery	22 limb reduction defects with paternal occupation in agricultural	Birth record info on paternal occupation		Maternal age
Self-reported paternal occupation in agricultural	Limb reduction defects 0.89, 0.56-1.33					
(Engel and others 2000), Washington State	Retrospective cohort	Washington State births, 1980-1993; cases identified from birth records	9 limb reduction defects among 4,466 births to women employed in	Parental occupation recorded on birth certificates		In trivariate analyses, inclusion of maternal age, marital status,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			agricultural, 19 such defects among 23,512 births with neither parent employed in agricultural and 4 such defects among 5,994 births with father employed in agricultural	and potentially exposed to agricultural pesticides		alcohol, smoking, parity, prenatal care, residence, gestation length or infant sex made little difference in OR estimates
Maternal occupation in agricultural (vs neither parent employed in agricultural)	Unadjusted 2.5, 1.1-5.4 parity-adjusted 2.8, 1.2-6.3					
(Orr and others 2002), California	Case-control	24 California counties, 1983-88; cases identified from State birth defect registry	13,938 minority infants with major structural birth defects, 14,463 minority healthy infant controls	Maternal residence in census tract with any of the 84 NPL hazardous waste sites in California		Preliminary analyses excluded child sex, maternal age, race/ethnicity and prenatal care as potential confounders
OR, musculoskel defects, maternal residence in census tract with NPL site containing pesticides	1.19, 0.92-1.54					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Shaw and others 2003), California	Case-control	Live births and fetal deaths (GW \geq 20) with selected birth defects, California except LA and SF metro areas, 1987-89; cases identified from Calif Birth Defects Monitoring Program	165 limb reduction cases, 734 healthy infant controls	Self-reported maternal prenatal (1 month before and 3 months after conception) occupational exposures	Expert assessmt of potential chemical exposures	Assessed maternal race/ethnicity, education, folic acid supplement use during periconceptual period
OR, limb reduction defects, maternal periconceptual occupational exposure	Insecticides 0.7, 0.2-3.4 (2 exposure case mothers)	Other pesticides 0.7, 0.3-1.9				
(Schreinemachers 2003), Minnesota, Montana, N Dakota, S Dakota, USA	Retrospective cohort	Counties with at least 50% rural population and at least 20% of land in crops; cases identified from linkage of birth and vital stats records 1995-97	212 infants with musculoskeletal defects, 33 with poly- or syndactyly, 42 with clubfoot among total of 43,634 births	1992 US agricultural census info; crop acreage by county and herbicide use by state	Compared 74 high- and 73 low-wheat rural counties (>85% of spring and durum wheat acreage treated with chlorophenoxy herbicides such as 2,4-D and MCPA)	Mothers in high- and low-wheat counties similar re age, education, marital status, parity, prenatal care, previous preterm or IUGR birth, prenatal smoking and alcohol use, infant sex, time of conception (April-June vs other)

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Residence in high- vs. low-wheat rural county	Polydactyly or syndactyly 2.43, 1.26-4.71	Clubfoot 0.84, 0.39-1.80	Total musculoskeletal 1.50, 1.06-2.12			

Summary: Musculoskeletal defects

Reviews

A reviewer found limited evidence for an association between limb reduction birth defects and maternal occupational pesticide exposure (Nurminen 1995). Other reviewers concluded that there was limited evidence for associations between limb reduction birth defects and maternal or paternal pesticide exposures (Sever and others 1997).

Original studies since 1996

Maternal exposure, chlorophenoxy herbicides, inadequate evidence

A retrospective cohort study found an association between musculoskeletal birth defects and maternal residence in high-wheat counties, a proxy for agricultural chlorophenoxy herbicide use (high- vs low-wheat counties, OR=1.50, 95% CI 1.06-2.12) (Schreinemachers 2003). There was also an association between such exposure and polydactyly/syndactyly (OR=2.43, 95% CI 1.26-4.71) but not clubfoot (OR=0.84, 95% CI 0.39-1.80).

Maternal exposure, unspecified herbicides, inadequate evidence

A case-control study in New York State reported no association between limb reduction defects and maternal residence in counties with high agricultural herbicide use (high vs low acres treated (1987 census), OR=0.82, 95% CI 0.41-1.64 (Lin and others 1994).

Maternal exposure, organophosphate insecticides, inadequate evidence

The San Francisco study observed a statistically non-significant association between limb defects and 1st trimester maternal residence in areas sprayed with malathion (OR=1.73, 95% CI 0.87-3.46) (Thomas and others 1992).

Maternal exposure, unspecified insecticides, inadequate evidence

A case-control study in New York State reported no association between limb reduction defects and maternal residence in counties with high agricultural insecticide use (high vs low acres treated (1987 census), OR=0.68, 95% CI 0.34-1.36 (Lin and others 1994). In a California case-control study, limb reduction defects were associated with self-reported 1st trimester professional indoor insecticide application at the maternal residence (OR=1.6, 95% CI 1.0-2.7) but not with pet flea insecticide use (OR=0.9, 95% CI 0.6-1.4) (Shaw and others 1999). Further analysis of this study revealed no association with periconceptual maternal occupational insecticide exposure (OR=0.7, 95% CI 0.2-3.4, only 2 exposed case mothers) (Shaw and others 2003).

Maternal exposure, unspecified pesticides, inadequate evidence

Among women prenatally exposed to pesticides in Colombian semi-enclosed greenhouses, there was an elevated risk of congenital dislocated hip (crude OR=2.90, 95% CI 1.19-6.99, calculated from data in paper) (Restrepo and others 1990). A retrospective cohort study in Minnesota observed increased risks of musculoskeletal defects in families (neither parent was a licensed pesticide applicator) living in regions with corn/soybean (compare to non-crop regions, OR=1.36, 95% CI 1.18-1.58) or wheat/sugar beet/potato crops (OR=1.75, 95% CI 1.37-2.22) (Garry and others 1996). In a California case-control study, limb reduction defects were associated with self-reported 1st trimester professional (OR=3.5, 95% CI 1.2-9.9) but not maternal application of garden pesticides (OR=1.5, 95% CI 0.5-4.6, 5 exposed case mothers) (Shaw and others 1999). Further analysis of this study revealed no association with prenatal residential proximity to crops treated with pesticides (OR=1.0, 95% CI 0.6-1.8) or occupational exposure to insecticides or non-insecticide pesticides (OR=0.7, 95% CI 0.3-1.9, only 5 exposed case mothers) (Shaw and others 2003). In a cohort study of women employed in agriculture in Washington State, limb reduction defect risk was elevated (compared to neither parent in agriculture, OR=2.8, 95% CI 1.2-6.3) (Engel and others 2000). In a California case-control study, limb reduction defects were not associated with parental employment in agriculture (either parent vs neither, OR=0.9, 95% CI 0.4-1.7) but were related to intensity of restricted agricultural pesticide use in counties of maternal residence (high vs minimal use, OR=1.9, 95% CI 1.2-3.1, p-trend=0.02) (Schwartz and LoGerfo 1988). A case-control study in New York State reported no association between limb reduction defects and maternal occupations likely exposed to pesticides (OR=0.7, 95% CI 0.4-1.5) or with maternal residence in counties with high per capita acreage in farms (high vs low acreage, OR=1.49, 95% CI 0.53-4.23, calculated from data in paper) (Lin and others 1994). A Finnish case-control study revealed no association between skeletal defects and 1st trimester maternal employment in agriculture (OR=0.8, 95% CI 0.4-1.7, only 3 exposed case mothers) (Nurminen and others 1995). In New York State, musculoskeletal defects were not associated with maternal residence within 1.6 km of a hazardous waste disposal site known to contain pesticides (OR=0.80, 95% CI 0.51-1.26) or a TRI industrial site known to emit pesticides into air (OR=1.12, 95% CI 0.93-1.35) (Marshall and others 1997). Another California case-control study, limited to racial or ethnic minority populations, revealed no association between musculoskeletal defects and prenatal residence in a census tract with a NPL site containing pesticides (OR=1.19, 95% CI 0.92-1.54) (Orr and others 2002). The inconsistent findings and the heterogeneous and non-specific exposure indices and the variable scope and great heterogeneity of musculoskeletal defects preclude strong inferences.

Paternal occupational exposure, TCDD-contaminated phenoxy herbicides or chlorophenate wood preservatives, inadequate evidence

In a retrospective cohort study of Vietnam veterans and partners, there was no association between musculoskeletal birth defects and paternal serum TCDD levels categorized as low (current level >10 and initial level ≤110 pg/g lipid, OR=1.08, 95% CI 0.72-1.60) or high (current level >10 and initial level >110 pg/g lipid, OR=0.89, 95% CI 0.58-1.32, calculated from data in paper) (Wolfe and others 1995). A recent review concluded that there was inadequate evidence for an association between birth defects other than spina bifida and paternal exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid (the main herbicides used by the U.S. military in Vietnam) (National Academy of Sciences 2007).

Paternal occupational exposure, unspecified pesticides, inadequate evidence

Among infants of women age 30 or older, musculoskeletal defects were associated with paternal occupation as licensed pesticide applicators in Minnesota (OR=2.52, 95% CI 1.58-4.01); there was no association among offspring of younger mothers (OR=0.94, 95% CI 0.52-1.71) (Garry and others 1996). A case-control study in New York State found no association between limb reduction defects and paternal occupations likely exposed to pesticides (OR=0.9, 95% CI 0.5-1.6) or the subgroup employed as farmers (OR=1.1, 95% CI 0.5-2.7) (Lin and others 1994). Limb reduction defect risk was not elevated among all infants in Norwegian farm families (OR=0.84, 95% CI 0.51-1.37) but was elevated on all farms reporting pesticide expenditures during agricultural censuses (OR=1.79, 95% CI 0.98-3.26) and the subgroup of grain farms with such expenditures (OR=2.50, 95% CI 1.06-5.90) (Kristensen and others 1997). A retrospective cohort

study of the general Norwegian population reported no association between limb reduction defects and paternal occupation in agriculture, based on birth certificates (OR=0.89, 95% CI 0.56-1.33) (Irgens and others 2000). A case-control study in California found no association between limb reduction defects and self-reported periconceptual paternal occupational pesticide exposure (OR=1.2, 95% CI 0.6-2.2) (Shaw and others 1999).

10. Urinary tract defects

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Erickson and others 1984), Atlanta, USA	Case-control	Atlanta births, 1968-80; cases identified from Metropolitan Atlanta Congenital Birth Defects Program	7133 cases of major structural birth defects, 4246 healthy live birth controls	Self-reported info on Vietnam military service incl Agent Orange exposure; review of military records	Subjective ratings of opportunity for exposure	Matched for race, year of birth, hospital of birth; adj for maternal age, education, alcohol use and family history of birth defects yielded similar results
OR, urinary tract defects, self-reported exposure vs non-exposure; paper did not report CIs or p-values	0.21, n=214					
(Li and others 1986), China	Retrospective cohort	6,173 pregnancies in region with MATDA-treated rice, 10,145 in same region before contamination, 3,326 in unexposed region, 1977-83; cases identified from self-reported pregnancy history, death records	23 + 31 + 15 genitourinary birth defects in 3 groups	Ratio of amount of N, N'-methylene-bis-(2-amino-1,3,4-thiadiazole) (MATDA), an animal teratogen to weight of rice yield in maternal residence region		5% of each group interviewed re potential confounders

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, maternal residence in region with MATDA-treated rice vs unexposed comparison region	1.22, 0.69-2.15 (calc'd from data in paper)	OR, exposed vs same region before MATDA use	0.82, 0.41-1.65			
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners; 1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; cases identified from parent-reported info and medical records	17 urinary tract defects among infants of potentially exposed fathers, 12 among infants of comparison fathers	Paternal serum TCDD	Serum TCDD levels categorized as background (current level ≤ 10 ng/L), low (current level > 10 and initial level ≤ 110 ng/L) and high (current level > 10 and initial level > 110 ng/L)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia
Relative risk, urinary tract defects, TCDD exposure category vs comparison group	Background 1.16, 0.31-3.90 Low 2.06, 0.68-5.98	High 2.17, 0.76-5.98	(calc from data in paper)			
(Garry and others 1996), Minnesota	Cohort and ecologic studies	34,772 licensed agricultural pesticide applicators; cases identified from linkage of state birth and birth defect registry records	20 urogenital birth defects among offspring of pesticide applicators; also assessed birth defect rates in	Occupation as certified applicators of restricted-use pesticides; $< 10\%$ were females and they were excluded from record linkage		Maternal age

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			general population by agricultural region			
Relative risk, paternal pesticide applicator vs general population	Urogenital 1.69, 1.06-2.64	General pop: parental residence crop vs non-crop region; excludes registered agricultural pesticide appliers	Corn/soybean region 1.56, 1.29-1.89	wheat/sugar beet/potato region 2.25, 1.67-3.03		
(Kristensen and others 1997), Norway	Cohort	Linked birth registry and five agricultural and horticultural censuses; 192,417 births of farmers (1967-91); comparison group of 61,351 births to non-farmers in agricultural municipalities; cases identified from national birth registry of all deliveries at GW \geq 16 since 1967	74 urinary system defects among offspring of farmers and 34 among non-farmers	Census info on farm ownership and expenditures on pesticides, tractor pesticide spraying equipment	Focused on data for yr closest to child's YOB but also used other data if available; 57% of men and 34% women worked at least 500 hr/yr on farm	Year of birth, maternal age, geog region, parental consanguinity
OR, farm vs non-farm parents	0.82, 0.53-1.27	Farm families, OR, pesticide purchases, yes/no	1.33, 0.75-2.35	Farm families, OR, pesticide purchase and orchards/greenhouses, yes/no	2.94, 1.19-7.29	
(Schreinemachers 2003), Minnesota, Montana, N Dakota, S	Retrospective cohort	Counties with at least 50% rural population and at least 20% of land	33 infants with male genital birth defects,	1992 US agricultural census info; crop acreage by county and herbicide	Compared 74 high- and 73 low-wheat rural	Mothers in high- and low-wheat counties similar

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Dakota, USA		in crops; cases identified from linkage of birth and vital stats records 1995-97	135 infants with other GU defects among total of 43,634 births	use by state	counties (>85% of spring and durum wheat acreage treated with chlorophenoxy herbicides such as 2,4-D and MCPA)	re age, education, marital status, parity, prenatal care, previous preterm or IUGR birth, prenatal smoking and alcohol use, infant sex, time of conception (April-June vs other)
Residence in high- vs. low-wheat rural county	Genitourinary birth defects (either sex) other than male genital anomalies 1.01, 0.65-1.55					

Summary: Urinary tract defects

Review

None available.

Original studies

Maternal exposure, chlorophenoxy herbicides, inadequate evidence

A retrospective cohort study of Minnesota and 3 adjacent states found no association between genitourinary defects and maternal residence in high-wheat regions, a proxy for chlorophenoxy herbicide exposure (high- vs low-wheat rural counties, OR=1.01, 95% CI 0.65-1.55) (Schreinemachers 2003).

Paternal occupational exposure, TCDD-contaminated phenoxy herbicides or chlorophenate wood preservatives, inadequate evidence

In a retrospective cohort study of Vietnam veterans and partners, urinary tract birth defects were associated with paternal serum TCDD levels categorized as low (OR=1.97, 95% CI 0.70-4.97) or high (OR=2.12, 95% CI 0.81-5.12) (calculated from data in paper) (Wolfe and others 1995). These findings preclude firm inferences as the odds ratios were not statistically significant (there were only 17 cases among the 3 exposure categories) and there was no testing or

adjustment for potential confounders. A review concluded that early gestational exposure to relatively low doses of TCDD and dioxin-like chemicals can cause ureteral hyperplasia and hydronephrosis in experimental animals (Birnbaum 1995). A recent review concluded that there was inadequate evidence for an association between birth defects other than spina bifida and paternal exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid (the main herbicides used by the U.S. military in Vietnam) (National Academy of Sciences 2007).

Paternal occupational exposure, unspecified pesticides, limited evidence

Among offspring of male licensed pesticide applicators in Minnesota, there was an increased risk of urogenital birth defects compared to the general population (OR=1.69, 95% CI 1.06-2.64) (Garry and others 1996). This study also found increased risks of these defects among offspring of women living in high-crop regions of Minnesota (high corn/soybean vs non-crop regions, OR=1.56, 95% CI 1.29-1.89; high wheat/sugar beet/potato regions, OR=2.25, 95% CI 1.67-3.03). A cohort study of Norwegian farm families reported an association between kidney and other urinary tract birth defects and pesticide expenditures on farms with orchards and/or greenhouses (OR=2.94, 95% CI 1.19-7.29); there was no increased risk of such defects among all farm families (OR=0.82, 95% CI 0.53-1.27) (Kristensen and others 1997). The heterogeneity of exposure indices precludes firm conclusions.

11. Male genital defects

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Erickson and others 1984), Atlanta, USA	Case-control	Atlanta births, 1968-80; cases identified from Metropolitan Atlanta Congenital Birth Defects Program	7133 cases of major structural birth defects, 4246 healthy live birth controls	Self-reported info on Vietnam military service incl Agent Orange exposure	Review of military records, subjective ratings of opportunity for exposure	Matched for race, year of birth, hospital of birth; adj for maternal age, education, alcohol use and family history of birth defects yielded similar results
OR, hypospadias, self-reported exposure vs non-exposure; paper did not report CIs or p-values	0.99, n=583					
(Restrepo and others 1990), Colombia	Retrospective cohort	2951 men and 5916 women employed at least 6 months in floriculture, interviewed 1981; cases identified from self- or partner-reported pregnancy history	2320 pregnancies of female workers, 1130 pregnancies of wives of male workers, 8161 pregs among female and 2373 among male	Exposed to 127 types of pesticides in semi-enclosed greenhouses; most often used – captan, propineb, mancozeb, zineb, chlorothalonil, benomyl, dicofol, dienochlor, oxycarboxin, tetradifon	Measured airborne captan in 2 companies; self-rep use in relation to pregnancy – rated exposure highest for sorters and	Matched for maternal age and parity; adjusted for maternal x-rays, diazepam use, other drugs, pregnancy test, alcohol,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			workers before occupation in floriculture; 16 cases cryptorchidism, 443 healthy controls		packers; survey of pesticides used by each company (n=58) – assessed wt pesticide used per unit area	smoking, paternal pesticide exposure
OR, cryptorchidism, prenatal maternal pesticide exposure	5.08, 1.67-15.7					
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners; 1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; cases identified from parent-reported info, medical records	15 genital defects among infants of potentially exposed fathers, 18 among infants of comparison fathers	Paternal serum TCDD	Serum TCDD levels categorized as background (current level ≤10 ng/L), low (current level >10 and initial level ≤110 ng/L) and high (current level >10 and initial level >110 ng/L)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia
Relative risk, high or low vs comparison group	Low 1.84, 0.72-4.53	High 1.23, 0.43-3.31	(calc from data in paper)			
(Garcia-Rodriguez and others 1996), Spain	Case-control	Hospital-based, single hospital serving 15 health care districts in southern Granada province, 1990-	131 cases of cryptorchidism, 243 hospital controls with	Pesticide exposure inferred from residence in health care districts	4-point scale for pesticide use intensity based on expert rating	Age, health care district population

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		91; cases identified from hospital records	other diagnoses, age 1-16		of crops grown in each region of maternal residence	
Cryptorchidism vs agricultural pesticide use in region of maternal residence	Lowest exposure region 1.0 (ref) Exposure level 1 0.93, 0.43-2.01	Exposure level 2 1.56, 0.72-3.38 Exposure level 3 2.32, 1.26-4.29				
(Dimich-Ward and others 1996), British Columbia	Nested case-control	Cohort of 19675 offspring of 9512 men exposed for at least one yr in a sawmill using chlorophenate wood preservatives; cases identified from linkage of cohort birth and stillbirth records	57 cases cryptorchidism, 5 controls per case	Father's exposure to chlorophenate wood preservatives known to be contaminated with PCDDs incl TCDD	Exposure level estimated from job titles and duration of employment in each job	Sex, parental ages
OR per 100 hr exposure, any genital defect, 75 th vs 25 th percentile of exposure index	Up to 3 months before conception 1.08, 0.9-1.3	Hours exposure, 3 preconceptual months 1.29, 0.9-1.5	Hours exposure during pregnancy 1.3, 1.0-1.7	Highest hr/yr up to 3 months before conception 1.03, 0.8-1.4		
OR, cryptorchidism, 75 th vs 25 th percentile of exposure index	Hours exposure, up to 3 months before conception 1.19, 0.9-1.5	Hours exposure, 3 preconceptual months 1.16, 0.8-1.6	Hours exposure during pregnancy 1.4, 1.0-1.9	Highest hr/yr up to 3 months before conception 1.25, 0.8-1.9		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Kristensen and others 1997), Norway	Cohort	Linked national birth registry of all deliveries at GW ≥ 16 since 1967 to 5 agricultural and horticultural censuses; 192,417 births of farmers (1967-91); comparison group of 61,351 births to non-farmers in agricultural municipalities	577 genital defects among offspring of farmers and 208 among non-farmers	Census info on farm ownership and operations	Expenditures on pesticides, tractor pesticide spraying equipment; focused on data for yr closest to child's YOB but also used other data if available; 57% of men and 34% women worked at least 500 hr/yr on farm	Year of birth, maternal age, geog region, parental consanguinity
OR, genital defects, farm vs non-farm births	All genital defects 0.94, 0.80-1.12	cryptorchidism 0.77, 0.58-1.03 Hypospadias 1.00, 0.75-1.34	OR, farm families, pesticide purchase	Cryptorchidism Pesticide purchase 1.70, 1.16-2.50 pesticide purch + field vegetables 2.32, 1.34-4.01	Hypospadias Tractor spray equip 1.38, 0.95-1.99 trac sp equip + grain 1.51, 1.00-2.26	
(Weidner and others 1998), Denmark	Case-control	Country-wide; ; cases identified from linkage of national birth, hospital surgical, tax and Danish Malformation Registry (up to age 1) records	4226 cases of surgically confirmed cryptorchidism, 650 cases surgically confirmed	Assessed parental occupation in farming or gardening industry as recorded on tax records for year of conception		Year of birth, birth weight

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			hypospadias, 23,273 healthy live birth controls			
OR, cryptorchidism (surgical cases only), parental occupation in farming or gardening, yes vs no	Maternal 1.36, 1.05-1.77 Paternal 1.08, 0.94-1.23	Hypospadias vs parental occupation in farming or gardening	Maternal 0.90, 0.42-1.92 Paternal 1.15, 0.83-1.58			
(Hosie and others 2000), Mannheim, Germany	Case-control	Cases identified from hospital pediatric surgical cases	18 cases cryptorchidism, 30 controls	Measured infant adipose tissue organochlorine levels	Median and ranges of contaminants ($\mu\text{g}/\text{kg}$ lipid) in controls: PCBs – 561, 52-2965; ρ,ρ' -DDE – 170, 31-1384; HCB – 20, 4.6-156; heptachlor epoxide – 2.4, 0.3-23	
Median adipose tissue organochlorine levels, cases vs controls	ρ,ρ' -DDE 265 vs 170 $\mu\text{g}/\text{kg}$ lipid, $p>0.05$	Heptachlor epoxide 5.2 vs 2.4 $\mu\text{g}/\text{kg}$ lipid, $p=.01$	HCB 61 vs 20 $\mu\text{g}/\text{kg}$ lipid, $p=.01$			
(Irgens and others 2000), Norway	Retrospective cohort	Birth record info for 1.2 million births in Norway, 1970-1993; cases identified from birth	10 hypospadias cases with paternal occupation in	Info on paternal occupation during 3 censuses		Maternal age

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		registry info on all birth defects diagnosed within 1 st wk after delivery	agricultural			
Self-reported paternal occupation in agricultural (10 exposed case fathers)	Hypospadias 0.68, 0.34-1.23					
(Longnecker and others 2002), Collaborative Perinatal Project, USA	Nested case-control	About 42000 women recruited during early pregnancy, 1959-1965, 12 US study centres, 55000 infants born during study; cohort ltd to women with prenatal serum DDE measured; cases identified from mother-reported pregnancy history and hospital/clinic records	219 cases cryptorchidism, 199 cases hypospadias, 167 cases polythelia, 552 healthy controls	Measured maternal serum DDE	Median DDE levels in stored maternal serum samples: mothers of cryptorchidism, hypospadias and polythelia cases and controls, respectively, were 4.3, 4.2, 6.3 and 4.2 µg/g lipid	Race, serum triglyceride and cholesterol levels
OR, cryptorchidism by maternal serum DDE quintile (µg/g lipid)	Q1 1.0 (ref) Q2 0.9, 0.6-1.2 Q3 1.1, 0.7-1.7	Q4 0.8, 0.4-1.4 Q5 1.3, 0.7-2.2 per 2.67 µg/g 1.07, 0.97-1.18	OR, hypospadias by maternal serum DDE (µg/g lipid)	Q1 1.0 (ref) Q2 0.9, 0.6-1.4 Q3 0.9,0.6-1.5	Q4 0.7, 0.3-1.3 Q5 1.0, 0.6-1.9 per 2.67 µg/g 1.01, 0.90-1.16	
(Wang and Wang	Case-control	Hospital-based; abstract	99 cases		Parent-reported	Controls were

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
2002), China [only abstract in Eng] (excluded)		does not describe case verification	cryptorchidism, 198 controls		pesticide exposure	matched (abstr does not state for which cov.s)
OR, paternal occupational pesticide exposure	Cryptorchidism 12.8, 2.90-56.4					
(Flores-Luevano and others 2003), Mexico [only abstr in Eng]	Case-control	Hospital-based, Mexico City, 1997-99; cases identified from hospital records	41 cases hypospadias, 28 controls, age <19		Maternal plasma DDT/DDE levels	Maternal age, paternal age
OR, hypospadias vs maternal plasma DDT	DDT <30 µg/g lipid 1.0 30-49 2.23, 0.47-3.05 50-133 1.13, 0.24-5.29	OR, hypospadias vs maternal plasma DDE	DDE ≤ 840 µg/g lipid 1.0 850-9580 µg/g lipid 0.48, 0.15-1.60			
(Vrijheid and others 2003), UK	Proportional incidence	29250 total birth defect cases in England and Wales during 1980-1996; cases identified from National Congenital Anomaly System, birth and stillbirth records, voluntary notifications by doctors and midwives	2794 cases hypospadias	Record-based maternal occupation; JEM; assessed likely exposure to pesticides and other potential endocrine modulators		Maternal age, social class, region, year of birth, paternal social class

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, hypospadias, probable maternal occupational pesticide exposure	0.84, 0.50-1.41					
(Schreinemachers 2003), Minnesota, Montana, N Dakota, S Dakota, USA	Retrospective cohort	Counties with at least 50% rural population and at least 20% of land in crops; cases identified from linkage of birth and vital stats records 1995-97	33 infants with male genital birth defects, 135 infants with other GU defects among total of 43,634 births	1992 US agricultural census info	Crop acreage by county and herbicide use by state; compared 74 high- and 73 low-wheat rural counties (>85% of spring and durum wheat acreage treated with chlorophenoxy herbicides such as 2,4-D and MCPA)	Mothers in high- and low-wheat counties similar re age, education, marital status, parity, prenatal care, previous preterm or IUGR birth, prenatal smoking and alcohol use, infant sex, time of conception (April-June vs other)
OR, residence in high- vs. low-wheat rural county	Male genital 1.03, 0.51-2.09					
(Pierik and others 2004), the Netherlands	Nested case-control	Within cohort of 8695 boys born in Rotterdam during 1999-2001; examined at birth by physicians trained in	78 cases cryptorchidism, 56 cases hypospadias, 313 healthy controls	Self-reported job history incl spec exposures, JEM	Assessed 1 st trimester maternal and periconcep exposure	Maternal age, education, ethnicity, health status, preterm birth, diet

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		standard genital examination; cases identified by examination by trained physicians				
Univariate OR, paternal occupational pesticide exposure, yes vs no	Cryptorchidism Prob exposure (JEM) 4.5, 1.4-13.9 Self-rep'd 2.8, 0.8-8.5	Hypospadias <5 exposure case fathers	Multivar OR, paternal occupational pesticide exposure, yes vs no	Cryptorchidism Prob exposure (JEM) 3.8, 1.1-13.4	Hypospadias <5 exposure case fathers	<5 exposed case mothers for either defect
(Bhatia and others 2005), San Francisco, USA	Nested case - control	Child Health and Development Studies cohort, 20,754 pregnancy women enrolled during 1959-1967; cases identified from SF Kaiser Permanente Health Plan maternal and pediatric records up to age 5	75 cases cryptorchidism, 66 cases hypospadias, 283 healthy controls, age <6	Measured maternal serum DDT/DDE	4 th quartile prenatal maternal serum DDT/DDE levels were ≥ 20.0 and ≥ 61.0 $\mu\text{g/L}$	Maternal cholesterol, triglyceride, race
OR, prenatal maternal serum DDE or DDT 4 th vs 1 st quartile, p-trend	Cryptorchidism DDE 1.34, 0.51-3.48 p-trend=.75 DDT 1.01, 0.44-2.28 p-trend=.38	ORs by prenatal maternal serum DDE or DDT quartile (2 nd to 4 th vs 1 st)	Hypospadias DDE 1.18, 0.46-3.02 p-trend=.82 DDT 0.79, 0.33-1.89 p-trend=.30			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Carbone and others 2007), Sicily	Case-control	Population-based, agricultural area of Ragusa, 1998-2002; cases identified from diagnoses by pediatricians and surgeons	90 cases with hypospadias or cryptorchidism, 203 controls, age <6	Parent-reported (both parents) occupational and residence exposures at conception \pm 3 months		
OR, maternal occupation in agricultural	Cryptorchidism 2.97, 0.77-11.5 Hypospadias 0.37, 0.04-3.22	OR, prob maternal prenatal occupational or domestic pesticide exposure	Cryptorchidism 2.74, 0.72-10.4 Hypospadias 0.42, 0.05-3.56			
Paternal occupation in agricultural	Cryptorchidism 2.45, 0.63-9.59 Hypospadias 1.61, 0.29-9.01	OR, prob paternal preconceptional occupational or domestic pesticide exposure	Cryptorchidism 0.60, 0.21-1.74 Hypospadias 1.07, 0.42-2.73			
(Meyer and others 2006), Arkansas, USA	Case-control	Population-based, eastern Arkansas; cases identified by the state birth defect registry (Arkansas Reproductive Health Monitoring System)	354 cases of hypospadias, 1998-2002, 727 controls	Detailed state-wide database on pesticide use	Data on lb of pesticide active ingredients applied or persisting within 500 m of subject's home during GW 6-16; estimated timing of pesticide applic based on crop	Assessed 38 of the 116 pesticides used on crops based on toxicologic evidence of repro, devmt, or endocrine toxicity

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					and published records; birth certif. occupation info + JEM	
OR, hypospadias vs agricultural pesticide use <0.5 km from maternal residence during GW 6-16	All pesticides Per 0.5 lb applied 0.82, 0.70–0.96	Diclofop-methyl (herbicide) ≥0.3 vs 0 lb 2.33, 1.02-5.31 Trifluralin ≥8.5 vs 0 lb 0.60, 0.23-1.56	Alachlor >0 vs 0 lb 0.56, 0.35–0.89 Diuron (urea herbicide) >0 vs 0 lb 0.78, 0.37-1.62	Atrazine ≥3.6 vs 0 lb 1.02, 0.58-1.79 Dicamba ≥0.04 vs 0 lb 0.91, 0.38-2.14	Permethrin >0 vs 0 lb 0.37, 0.16–0.86 Carbaryl >0 vs 0 lb 0.80, 0.20-3.18	Note: GW 6-16 = period of genital devmt
(Damgaard and others 2006), Finland and Denmark	Case-control	Nested within birth cohort recruited 1997-2001; cases identified by examination by trained physicians at birth and again at age 3 months	62 cases cryptorchidism at birth (diagnosed by specially trained MDs), 68 healthy controls	Measured 27 breast milk organochlorine pesticides, milk collected as pools 1-3 months after delivery	Median levels (ng/g lipid): DDE (97.3), HCH (13.6), HCB (10.6)	Country, maternal age, gestation length, parity, birth weight, maternal BMI
Mean breast milk pesticide concentration (ng/g lipid), cryptorchidism cases vs controls	DDT + DDE 140.4 vs 116.3, p=.27 HCB 10.6 vs 8.8, p=.12	Pentachlorobenzene 0.27 vs 0.28, p=.04 α-endosulfan 6.95 vs 6.66, p=.06	trans-chlordane 0.06 vs 0.04, p=.01 Oxychlordane 4.52 vs 4.09, p=.21			
(Pierik and others 2007), Collaborative Perinatal Project,	Case-control	Nested within retrospective cohort of about 42000 women	219 cases cryptorchidism, 564 controls	Measured maternal serum heptachlor epoxide (HCE), HCB and		Triglycerides, cholesterol, study centre;

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
USA		recruited during early pregnancy, 1959-1966, 12 US study centres, 55000 infants born during study; cohort ltd to women with prenatal serum organochlorines measured; cases identified from mother-reported pregnancy history and hospital/clinic records		β-hexachlorocyclohexane (β-HCCH) in 1997-99		many other factors tested and dismissed as not potential confounders
Odds ratio, cryptorchidism, 90 th vs 10 th percentile maternal serum organochlorine level	Heptachlor epoxide 1.24, 0.59-2.64, p-trend=.56	β-hexachlorocyclohexane 1.60, 0.72-3.55, p-trend=.35	Odds ratio, cryptorchidism, 90 th vs 25 th percentile maternal serum organochlorine level	HCB 1.06, 0.57-1.98, p-trend=.96		

Summary: Male genital defects

Review

None available.

Original studies

Maternal exposure, chlorophenoxy herbicides, inadequate evidence

In a population-based case-control study in Arkansas, hypospadias (cases identified from state-wide registry) was associated with agricultural use of the herbicide diclofop-methyl within 0.5 km of the maternal residence during GW 6-16, the window of genital tract development (≥0.3 vs 0 lb active ingredient, OR=2.33, 95% CI 1.02-5.31) (Meyer and others 2006).

Maternal exposure, other herbicides, inadequate evidence

The Arkansas study found no association between hypospadias and use within 0.5 km of the maternal residence during GW 6-16 of alachlor (>0 vs 0 lb, OR=0.56, 95% CI 0.35-0.89), atrazine (≥ 3.6 vs 0 lb, OR=1.02, 95% CI 0.58-1.79), dicamba (≥ 0.04 vs 0 lb, OR=0.91, 95% CI 0.38-2.14), trifluralin (>8.5 vs 0 lb, OR=0.60, 95% CI 0.23-1.56) or diuron (>0 vs 0 lb, OR=0.78, 95% CI 0.37-1.62) (Meyer and others 2006).

Maternal exposure, DDT/DDE, inadequate evidence

In a case-control study nested within the U.S. Collaborative Perinatal Project pregnancy cohort, 3rd trimester maternal serum DDE levels were not associated with cryptorchidism (per natural log serum DDE ($\mu\text{g/g}$ lipid) increment, OR=1.07, 95% CI 0.97-1.18) or hypospadias (OR=1.01, 95% CI 0.90-1.16) (Longnecker and others 2002). There was no association in a Mexico City case-control study between cryptorchidism and maternal plasma DDE (>840 vs ≤ 840 $\mu\text{g/g}$ lipid, OR=0.48, 95% CI 0.15-1.60) or DDT levels (≥ 50 vs <50 $\mu\text{g/g}$ lipid, OR=1.13, 95% CI 0.24-5.29) (Flores-Luevano and others 2003). A case-control study nested within a California pregnancy cohort enrolled during 1959-1967 (when population serum DDT/DDE levels were much higher than recently) revealed no association between cryptorchidism and prenatal serum DDE (4th vs 1st quartile, OR=1.34, 95% CI 0.51-3.48, p-trend=.75) or DDT (OR=1.01, 95% CI 0.44-2.28, p-trend=.38) (Bhatia and others 2005). This study also found no association between hypospadias and maternal serum DDE (OR=1.18, 95% CI 0.46-3.02, p-trend=.82) or DDT (OR=0.79, 95% CI 0.33-1.89, p-trend=.30). A Finnish/Danish case-control study of cryptorchidism reported higher median breast milk DDT plus DDE concentrations in case compared to control mothers (140.4 vs 116.3 ng/g lipid, p=.27) (Damgaard and others 2006). A small German case-control study reported a statistically non-significant relationship between cryptorchidism and infant adipose tissue p,p'-DDE levels (median concentrations, cases vs controls, 265 vs 170 $\mu\text{g/kg}$ lipid, p>0.05) (Hosie and others 2000). DDE and other androgen receptor antagonists (vinclozolin, procymidone, linuron) produce feminization of prenatally exposed male rats with reduced anogenital distance and induced areolas at low doses and hypospadias, retained nipples, undescended testes and epididymal agenesis at higher doses (Gray and others 2001).

Maternal exposure, other organochlorine insecticides, inadequate evidence

A small German case-control study observed associations between cryptorchidism and infant adipose tissue heptachlor (median concentrations, cases vs controls, 5.2 vs 2.4 $\mu\text{g/kg}$ lipid, p=.01) and HCB levels (61 vs 20 $\mu\text{g/kg}$ lipid, p=.01) (Hosie and others 2000). The Finnish/Danish case-control study revealed higher median breast milk levels for 17 of 21 organochlorine pesticides in case compared to control mothers with differences being statistically significant for trans-chlordane (but not oxychlordane) and of borderline significance for HCB and α -endosulfan (Damgaard and others 2006).

Maternal exposure, other insecticides, inadequate evidence

The Arkansas study found no association between hypospadias and use within 0.5 km of the maternal residence during GW 6-16 of carbaryl (>0 vs 0 lb, OR=0.80, 95% CI 0.20-3.18) or permethrin (>0 vs 0 lb, OR=0.37, 95% CI 0.16-0.86) (Meyer and others 2006).

Maternal exposure, unspecified pesticides, inadequate evidence

Infants of women occupationally exposed to pesticides in Colombian semi-enclosed greenhouses had an elevated risk of cryptorchidism (OR=5.08, 95% CI 1.67-15.7) (Restrepo and others 1990). In a hospital-based case-control study in Spain, there was a dose-response relationship between cryptorchidism and expert-rated agricultural pesticide use intensity near the maternal residence (low vs no use, OR=0.93, 95% CI 0.43-2.01; medium use, OR=1.56, 95% CI 0.72-3.38; high use, OR=2.32, 95% CI 1.26-4.29) (Garcia-Rodriguez and others 1996). In a very large Danish case-control study, maternal occupation in farming or gardening was associated with cryptorchidism (OR=1.36, 95% CI 1.05-1.77) but not hypospadias (OR=0.90, 95% CI 0.42-1.92) (Weidner and others 1998). In a small

Sicilian case-control study, self-reported prenatal occupational or domestic pesticide exposure was related to a statistically non-significant elevated risk of cryptorchidism (OR=2.74, 95% CI 0.72-10.4) but not hypospadias (OR=0.42, 95% CI 0.05-3.56) (Carbone and others 2007). Although suggestive, the heterogeneity of exposure indices and inconsistent findings precludes firm conclusions. A proportional birth prevalence study in the U.K. revealed no association between hypospadias and maternal occupations likely exposed to pesticides (OR=0.84, 95% CI 0.50-1.41) (Vrijheid and others 2003). A retrospective cohort study in 4 Midwest states found no association between male genital tract defects and prenatal residence in high-wheat counties, a proxy for chlorophenoxy herbicide exposure (high- vs low-wheat counties, OR=1.03, 95% CI 0.51-2.09) (Schreinemachers 2003). In the Arkansas case-control study noted above, hypospadias was not associated with total agricultural pesticide use within 0.5 km of the maternal residence during GW 6-16 (per 0.5 lb pesticide active ingredient, OR=0.82, 95% CI 0.70-0.96) (Meyer and others 2006).

Paternal exposure, TCDD-contaminated phenoxy herbicides or chlorophenate wood preservatives, inadequate evidence

In a retrospective cohort study of Vietnam veterans, genital tract birth defects were not associated with paternal serum TCDD levels categorized as low or high (OR=1.66, 95% CI 0.41-6.10) calculated from data in paper) (Wolfe and others 1995). Among British Columbia sawmill workers exposed to chlorophenate wood preservatives known to be contaminated with TCDD and related toxicants, genital tract defects were weakly associated with hours of exposure during the 3 preconceptional months (75th vs 25th percentile, OR=1.29, 95% CI 0.9-1.5) (Dimich-Ward and others 1996). A recent review concluded that there was inadequate evidence for an association between birth defects other than spina bifida and paternal exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid (the main herbicides used by the U.S. military in Vietnam) (National Academy of Sciences 2007).

Paternal occupational exposure, unspecified pesticides, inadequate evidence

As noted above, a study of male licensed pesticide applicators in Minnesota reported an increased risk of urogenital birth defects compared to the general population but did not include data for urological and genital defects separately (Garry and others 1996). Among Norwegian farm families, cryptorchidism was associated with pesticide expenditure (yes/no, OR=1.70, 95% CI 1.16-2.50); the association was somewhat stronger for pesticide purchases on the subset of farms with field vegetables (OR=2.32, 95% CI 1.34-4.01) (Kristensen and others 1997). The latter study also reported associations between hypospadias and tractor spray equipment (OR=1.38, 95% CI 0.95-1.99) and the use of such equipment on farms with grain crops (OR=1.51, 95% CI 1.00-2.26). In a case-control study in the Netherlands, paternal employment in occupations with likely pesticide exposure was associated with cryptorchidism (OR=3.8, 95% CI 1.1-13.4) (Pierik and others 2004). In a very large Danish case-control study, paternal occupation in farming or gardening was not associated with cryptorchidism (OR=1.08, 95% CI 0.94-1.23) or hypospadias (OR=1.15, 95% CI 0.83-1.58) (Weidner and others 1998). A record-based retrospective cohort study in Norway revealed no association between hypospadias and paternal occupation in agriculture (OR=0.68, 95% CI 0.34-1.23) (Irgens and others 2000). A Sicilian case-control study revealed a statistically non-significant association between cryptorchidism and self-reported preconceptional paternal employment in agriculture (OR=2.45, 95% CI 0.63-9.59) but not with probable preconceptional pesticide exposure based on job title (OR=0.60, 95% CI 0.21-1.74) (Carbone and others 2007). This study also revealed no association between hypospadias and paternal employment in agriculture (OR=1.61, 95% CI 0.29-9.01) or likely pesticide exposure (OR=1.07, 95% CI 0.42-2.73).

12. Leukemia

Reviews

Author	Scope	Findings	
(Daniels and others 1997), USA	Literature review, 31 studies of occupational or residential pesticide exposure of parents or children and risk of childhood cancer published 1970-1996	Fairly consistent associations between childhood leukemia and parental occupational pesticide exposure indices: paternal exposure before conception and during pregnancy, maternal exposure during pregnancy	Fairly consistent associations between childhood leukemia and use of no-pest strips, pet pesticides and other home pesticides.
(Zahm and Ward 1998), USA	Literature review, epidemiologic studies of pesticides and childhood cancer	Leukemia – most of the 17 case-control studies and one cohort study reviewed found elevated risks among children of parents occupationally exposed to pesticides or who used pesticides in the home or garden; only one study measured levels of pesticides or their metabolites in biosamples	
(Olshan and van Wijngaarden 2003), USA	Review of epidemiologic literature on childhood cancer and paternal occupational; included reviews by Savitz and Chen (1990) and by Colt and Blair (1998) plus studies published since the latter review including 15 reports on leukemia/lymphoma and 7 reports on brain cancer	Leukemia/lymphoma: Reviews by Daniels et al (1997) and Zahm and Ward (1998) noted associations between childhood leukemia and paternal occupational pesticide exposure in 12 studies – several subsequent studies found similar associations; a few studies found associations between childhood lymphomas and paternal occupational pesticide exposure	
(Buffler and others 2005), USA	Reviewed recent epidemiologic studies on environmental factors and childhood leukemia; noted that confirmed clinical and epidemiologic associations explain <10% of such	Found growing evidence for association between childhood leukemia and pesticide exposure, especially prenatal and early childhood exposures	Most consistent evidence is for indoor use of insecticides, especially for ALL

Author	Scope	Findings	
	cases		
(Brown 2006), USA	Examines the timing of pesticide exposure and childhood leukemia	Risk from pesticide exposure seems to be greater during pregnancy	Maternal occupational exposure may of greater concern than paternal occupational exposure
Risk estimates for resid indoor use tend to be higher than outdoor use	Limited data on particular pesticides, genetic factors, critical windows of exposure during development vs different types of leukemia		
(Jurewicz and Hanke 2006), Poland	Review epidemiologic studies published during 1998-2005 to update the review by Zahm and Ward. Concluded that recent studies provide further evidence for an association between leukemia and pesticide exposure but level of evidence is still limited	Limitations of studies include exposure assessment, inadequate statistical power, small numbers of studies on specific relationships, uncertainty about critical windows of exposure	In the light of existing, although still limited evidence of adverse effects of pesticide exposure, it is necessary to reduce exposure to pesticides
(Infante-Rivard and Weichenthal 2007), Quebec	Reviewed 10 epidemiologic studies published during 1999-2004 to update the review by Zahm and Ward.	In general, new studies suggest an association between childhood leukemia and pesticide exposure with the greatest risks being from parental exposure before and during pregnancy and childhood exposure to household insecticides.	There may be a causal relationship between childhood leukemia and postnatal insecticide exposure.
(Emerenciano and others 2007), Brazil	Review of infantile acute leukemia (IAL) – before age 12-18 mos; included reports published 1990-2006	Chromosomal abnormalities (esp rearrangement of the MLL gene on chromosome 11q23 are common in IAL and appear to arise <i>in utero</i> ; topo-II inhibitor drugs cause MLL-positive leukemia; other	Foods linked to IAL include soybeans (genistein), tea/cocoa/wine (catechins, caffeine)

Author	Scope	Findings	
		<p>topo-II inhibitors include benzene metabolites, isoflavones, flavonoids, lignans, podophyllin resin, quinolone antibiotics, some pesticides.</p>	
<p>Noted international study by Alexander (2001) and a Brazilian sub-study by Pombo-de-Oliveira (2006) linking IAL to the insecticide propoxur and the drug dipyrone; the latter study also linked IAL to prenatal estrogen use (metabolites include semiquinones and quinines)</p>			
<p>(Wigle and others 2007), Canada</p>	<p>All 8 studies that examined prenatal residential^b indoor insecticide use reported elevated leukemia risks with evidence of dose-response gradients in 3 studies.</p>	<p>Seven of 8 studies of childhood residential indoor insecticide use revealed elevated leukemia risks with statistical significance apparent in 6 of these studies; there were exposure-risk gradients in 3 studies (statistically significant in 1 study).</p>	<p>All 5 studies of prenatal maternal residential herbicide exposure reported elevated childhood leukemia risks that were statistically significant in 2 studies and close to formal significance in 2 other studies; there were exposure-risk gradients in 2 studies.</p>

^b Residential exposure defined as indoor, garden or lawn pesticide use or residential proximity to agricultural or other pesticide use.

Leukemia: Original studies since 1997

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
(Infante-Rivard and others 1999), Montreal	Case-control	Population-based, Quebec except remote regions, 1980-90, Montreal only 1991-93	491 cases acute lymphoblastic leukemia (ALL), 491 controls, age <10; assessed polymorphisms in CYP1A1, CYP2D6, GSTT1 and GSTM1 genes	Hospital records	Self-reported home use of pesticides in and around house from 1 month before conception to diagnosis; ascertained mother's but not father's exposure to pesticides Pesticides used likely included chlorpyrifos, diazinon, dichlorvos, malathion, cygon, propoxur, chlordane and 2,4-D	Matched for age, sex, geog region; adjusted for maternal age and educ
OR, leukemia, indoor use of insecticides against:	Prenatal Cockroaches, ants, flies, bees, wasps 1.79, 1.34-2.40 Moths 2.47, 1.43-4.28 Mites, spiders 1.37, 0.73-2.58 Insects 1.59, 1.11-2.26	Childhood Cockroaches, ants, flies, bees, wasps 1.38, 1.07-1.77 Moths 2.13, 1.30-3.47 Mites, spiders 0.85, 0.50-1.49 Insects 1.99, 1.42-2.82 Termites	OR, leukemia, maternal use of pesticides for garden, yard or interior plants (OR, yes vs no)	Prenatal Herbicides 1.84, 1.32-2.57 plant insecticides 1.97, 1.32-2.94 for trees 1.70, 1.12-2.59 repellents and sprays for outdoor insects 0.70, 0.45-1.09 for slugs, snails	Childhood Herbicides 1.41, 1.06-1.86 plant insecticides 1.82, 1.31-2.52 for trees 1.41, 1.01-1.97 repellents and sprays for outdoor insects 0.65, 0.42-0.94 for slugs, snails	

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
	Termites 1.89, 0.56-6.37	1.27, 0.52-3.09		1.57, 0.43-5.62	2.23, 0.76-6.47	
OR, leukemia, maternal prenatal use of pesticides for garden, yard or interior plants (ORs)	Herbicides No use 1.0 1-5X 1.83, 1.31-2.57 >5X 3.72, 0.72-19.1	Plant insecticides No use 1.0 1-5X 1.89, 1.20-2.97 >5X 4.01, 1.12-14.3	For trees No use 1.0 1-5X 1.65, 1.07-2.54 >5X 3.27, 0.64-16.7	Repellents, sprays for outdoor insects No use 1.0 1-5X 0.47, 0.21-1.05 >5X 1.06, 0.52-2.13		
OR, leukemia, professional indoor extermination of ants and/or cockroaches	Prenatal 1.68, 0.87-3.25	1 yr before conception to date of diagnosis None 1.0 1-5X 1.26, 0.84-1.90 >5X 2.35, 0.89-6.17	OR, leukemia, exposure to single agents	Prenatal Insecticides against cockroaches, ants, flies, bees, wasps 1.15, 0.78-1.69 Herbicides 1.56, 0.96-2.55 Plant insecticides 1.10, 0.57-2.11 For trees 1.46, 0.53-3.99	Childhood Insecticides against cockroaches, ants, flies, bees, wasps 0.83, 0.60-1.16 Herbicides 0.88, 0.58-1.33 Plant insecticides 1.26, 0.70-2.28 For trees 0.61, 0.23-1.57	

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
				For outdoor insects 0.52, 0.30-0.89 ≥4 insecticides or rodenticides 2.17, 0.66-7.09	For outdoor insects 0.38, 0.23-0.64 ≥4 insecticides or rodenticides 2.08, 0.78-5.52	
OR, leukemia, prenatal and/or childhood use of insecticides on pets	Flea collar 0.84, 0.62-1.12 insecticide powder 0.88, 0.54-1.42 shampoo/soap 0.76, 0.53-1.09	OR, leukemia, indoor use of insecticides against cockroaches, ants, flies, bees and wasps among subset of cases with CYP1A1m2 polymorphism	Prenatal 4.73, 1.18-18.6 Childhood 3.95, 0.81-19.2	OR, leukemia, use of repellents and sprays for outdoor insects among subset of cases with CYP1A1m1 polymorphism; similar associations for use of rodenticides	Prenatal 5.55, 1.36-22.7 Childhood 3.64, 1.19-11.2	
(Infante-Rivard and Sinnett 1999), Montreal	Case-control	Population-based, Quebec except remote regions, 1980-90, Montreal only 1991-93	491 cases acute lymphoblastic leukemia (ALL), 491 matched controls, age <10	Hospital records	Self-reported paternal preconceptual occupational pesticide use	Matched for age, sex, geog region; adjusted for maternal age and educ
Paternal preconceptual occupational exposure to pesticides; ORs, CIs, numbers of exposed cases	Any pesticide 1.56, 1.02-2.40 (66) fungicides 5.11, 1.46-17.8 (15)	insecticides 1.38, 0.87-2.18 (50) herbicides 2.05, 0.93-4.56 (19)				

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
(Petridou and Dessypris 2000), Greece [letter to editor; 4 previous peer-reviewed articles on other risk factors]	Case-control	Population-based (nation-wide), 1993-94	153 cases leukemia, 300 matched controls, age <15	12 case and 10 control mothers reported non-negligible pesticide exposure during pregnancy	Self-reported "non-negligible" prenatal maternal pesticide exposure	Matched for age, sex, urban/rural region; adj for
OR, prenatal maternal pesticide exposure (does not specify home vs occupational)	Conditional logistic analysis 3.6, 1.2-10.8	Matched analysis 2.9, 0.9-9.9				
(Heacock and others 2000), British Columbia	Case-control	Nested within cohort of 23,829 workers in 11 softwood sawmills that used tetra- and pentachlorophenol; men worked at least 1 yr during 1950-85	11 cases of leukemia among offspring age <20 yr, 200 matched controls	Linked cohort file to B.C. marriage, birth and cancer records (including B.C. Cancer Registry database)	Assessed paternal occupational exposure to chlorophenol wood preservatives based on job title and work history Assessed exposure windows: first exposure to 3 mos before conception, 3 mos before conception, gestation, childhood, total)	Matched and adjusted for sex, YOB
Risk of leukemia among offspring similar to that in	1.0, 0.5-1.8	Cumulative paternal chlorophenolate exposure (hours)	<3000 1.0			

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
general population (SIR)			≥3560 0.8, 0.2-3.6 (5 exposed case fathers)			
(Meinert and others 2000), Germany	Case-control	Population-based, nation-wide (West Germany), 1992-94	1184 leukemia and 234 NHL cases, 2588 community controls, age <15	German Central Cancer Registry	Self-reported parental occupation and home exposures to pesticides and other hazards	Matched for sex, DOB, community
OR, parental occupation in farming, yes vs no	Maternal 1.3, 0.6-2.9 Paternal 1.5, 1.0-2.4	OR, paternal self-reported occupational pesticide exposure	Ever exposed 1.6, 1.1-2.3 During pregnancy 1.6, 1.1-2.3 Yr before pregnancy 1.5, 1.1-2.2 after pregnancy 1.3, 0.9-1.9	OR, maternal occupational pesticide exposure	Ever exposed 2.5, 1.3-4.7 During pregnancy 3.6, 1.5-8.8 Yr before pregnancy 2.1, 1.1-4.2 after pregnancy 2.5, 1.0-6.4	
OR, resid pesticide use during childhood (from birth to diagnosis)	Garden 1.0, 0.8-1.2 Farm 1.5, 1.0-2.2	OR, leukemia vs freq of indoor household use of insecticides during childhood, 1, 2-5, 6-10 and >10 vs <1X/yr	1.0, 0.7-1.5 1.0, 0.7-1.5 1.3, 0.7-2.4 1.8, 1.0-3.3 p-trend = 0.12	OR, indoor pesticide use by pest controller, during childhood	1.3, 0.8-2.3	

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
(Feychting and others 2001), Sweden	Birth cohort	235,635 children of married couples born soon after 2 censuses; linked national birth, census, death and cancer registry databases, 1976-93	522 cancer cases including 161 leukemia cases, age <15	Nationwide Swedish Cancer Registry	Census info on father's occupational/industry; JEM	Census year, sex, maternal age
OR, paternal occupations potentially exposed to pesticide	0.90, 0.37-2.19					
(Alexander and others 2001), international study	Case-control	Hospital-based, 7 countries, recruitment period not stated	136 cases infantile acute leukemia, 266 controls, age <18 mos; Southern blot assays for MLL gene rearrangements at 11q23 (these can be caused by topo-II inhibitors)	Hospital records	Self-reported maternal occupation and other exposures	Sex, geog region
OR, infantile leukemia vs prenatal maternal occupational pesticide exposure (15 exposed cases)	All cases 3.67, 1.54-8.74	AML 5.08, 1.84-14.0 ALL 2.53, 0.71-8.97	MLL-positive cases 4.96, 1.71-14.4 MLL-neg cases 1.87, 0.36-9.61	OR, infantile leuk vs prenatal maternal exposure to propoxur (a carbamate insecticide) or other mosquitocidals	All cases 5.14, 1.27-20.9 (7 exposed case mo)	

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
(Ma and others 2002), California	Case-control	Population-based, northern Calif, 1995-99	162 cases leukemia (including 135 ALL), 162 matched controls, age <15	Hospital and state-wide cancer registry records	Self-reported household pesticide use (no data on parental occupational exposure)	Matched for DOB, sex, maternal race and county of residence; adjusted for household income
OR, leukemia, resid pesticide use during infancy (birth to age 1)	Professional pest control 2.3, 1.1-4.9 Professional lawn service 0.9, 0.4-2.0 ant, fly, cockroach control products 1.1, 0.7-1.9 insect repellent 1.7, 0.6-4.4 slug, snail bait 1.5, 0.8-2.7	plant/tree pesticide use 0.8, 0.4-1.6 weed control products 0.7, 0.3-1.7 flea collars 0.6, 0.3-1.2 flea soaps, shampoos 0.8, 0.4-1.5 flea sprays, dusts, powders 1.0, 0.4-2.6	Combined exposure Insecticides 1.7, 1.0-2.9 Flea control products 0.8, 0.5-1.4 Herbicides 0.7, 0.4-1.2 Indoor pesticides 1.6, 1.0-2.7 Outdoor pesticides 1.2, 0.7-2.2	OR, leukemia, indoor household professional pesticide application	3 mos before pregnancy 1.7, 0.7-3.9 During pregnancy 2.2, 1.0-4.8 Birth-age 1 2.3, 1.1-4.9	age 1-2 3.6, 1.6-8.3 age 2-3 2.2, 1.0-4.7 3 mos before conception to age 3 2.8, 1.4- 5.7
OR, leukemia, indoor insecticide use (other	3 mos before pregnancy	OR, leukemia, indoor insecticide use, per	3 mos before pregnancy	OR, leukemia, household flea	3 mos before pregnancy 0.9, 0.5-1.7	age 1-2 0.9, 0.5-1.5

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
than flea control products)	1.8, 1.1-3.1 During pregnancy 2.1, 1.3-3.5 birth-age 1 1.7, 1.0-2.9 age 1-2 1.6, 1.0-2.7 age 2-3 1.2, 0.7-2.1 3 mos before conception to age 3 2.1, 1.1-4.3	increment in frequency of use	1.2, 1.0-1.5 During pregnancy 1.1, 1.0-1.2 birth-age 1 1.2, 1.0-1.4 age 1-2 1.1, 1.0-1.3 age 2-3 1.0, 0.9-1.2 3 mos before conception to age 3 1.0, 1.0-1.1	control product use	During pregnancy 0.8, 0.4-1.4 birth-age 1 0.8, 0.5-1.4	age 2-3 0.8, 0.4-1.4 3 mos before conception to age 3 0.9, 0.5-1.6
OR, leukemia, herbicide use	3 mos before pregnancy 1.8, 0.9-3.5 During pregnancy 1.6, 0.9-3.0 birth-age 1 0.7, 0.4-1.2	age 1-2 1.1, 0.7-2.0 age 2-3 1.1, 0.6-2.1 3 mos before conception to age 3 1.0, 0.6-1.8				

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
(Rodvall and others 2003), Sweden	Cohort	27,329 offspring of 20,245 male pesticide applicators, born during 1958-1994; licensed during 1965-1976; offspring followed for cancer incidence and mortality from 1958 to 1994	8 leukemia cases among offspring born during 1958-94	National cancer incidence and death records	Licensed pesticide applicators	Age, sex, calendar year
SIR, leukemia, offspring of male licensed pesticide applicators vs national	0.43, 0.19-0.86					
(McKinney and others 2003), UK Childhood Cancer Study	Case-control	Population-based, England, Scotland, Wales, 1991-96	1737 leukemia, 7629 matched controls, age <15	Cancer incidence and death records	Parent-reported info including occupations at conception, birth and cancer diagnosis; coded job titles and associated industries	Matched for sex, age, resid region at diagnosis
OR, leukemia, periconceptual occupations potentially exposed to agrochemicals, 5 exposed case mo, 36 exposed case fathers	maternal 0.81 (0.31-2.12) paternal 0.83 (0.58-1.19)	OR, periconceptual occupation in agriculture (7 exposed case mo, 29 exposed case fathers)	Maternal 1.41, 0.60-3.31 Paternal 0.90, 0.60-1.34			
(Flower and others	Cohort	17537 children of	50 cancers	Iowa Cancer Registry	Self-reported pesticide	Adjusted for age;

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
2004), Agriculture Health Study, USA		licensed agriculture pesticide applicators; limited to the Iowa sub-cohort recruited during 1993-97; the father was the applicator for over 99% of children	identified among children age 0-19, 1975-1998 (includes cases diagnosed before parent enrolled in cohort); 9 leukemia cases		use by licensed pesticide applicators	parental age at child's birth, child's sex, birth weight, parental smk, history of cancer and maternal history of early fetal death were tested and found to not be confounders
SIR, leukemia, children of male licensed pesticide applicators	0.91, 0.47-1.75					
(Reynolds and others 2005b), California	Case-control	State-wide, population-based, 1990-1997	837 cases childhood leukemia, 4335 controls, age <5 yr	Calif cancer registry	Prenatal exposure assessed using State-wide Pesticide Use Report database, percentiles of lb/acre within 0.5 mi buffer region	Race, gender, age
Propargite (organosulfite acaricide, percentile of lb/mi ²) <1 1-49 ≥50	OR 1.0 0.89, 0.53-1.51 0.96, 0.62-1.49	Methyl bromide (fumigant, percentile of lb/mi ²) <1 1-49 ≥50	OR 1.0 0.95, 0.65-1.40 0.89, 0.60-1.33	Simazine (triazine herbicide, percentile of lb/mi ²) <1 1-49 ≥50	OR 1.0 1.17, 0.74-1.85 1.29, 0.81-2.05	

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
Metam sodium (soil fumigant, percentile of lb/mi ²) <1 1-49 ≥50	Total leukemia OR 1.0 0.83, 0.36-1.91 2.05, 1.01-4.17 ALL only ≥50 th percentile 3.28, 1.37-7.86	Trifluralin (dinitroaniline herbicide, percentile of lb/mi ²) <1 1-49 ≥50	Total leukemia OR 1.0 1.06, 0.57-1.95 0.92, 0.51-1.65 ALL only ≥50 th percentile 1.35, 0.71-2.56	Chlorothalonil (chlorinated iosphthalic acid fungicide, percentile of lb/mi ²) <1 1-49 ≥50	OR 1.0 1.21, 0.77-1.89 1.33, 0.88-2.01	
Dicofol (organochlorine mitocide, percentile of lb/mi ²) <1 1-49 ≥50	Total leukemia OR 1.0 0.75, 0.36-1.55 1.83, 1.05-3.22 ALL only ≥50 th percentile 1.85, 0.98-3.52	Possible carcinogens percentile <1 1-49 ≥50	OR 1.0 1.16, 0.90-1.50 1.26, 0.99-1.61	Genotoxins percentile <1 1-49 ≥50	OR 1.0 1.02, 0.80-1.29 1.07, 0.85-1.35	
Probable carcinogens percentile <1 1-49 ≥50	OR 1.0 1.13, 0.85-1.49 1.17, 0.90-1.54	Devmtl/repro toxicants percentile <1 1-49 ≥50	OR 1.0 1.24, 0.97-1.57 1.05, 0.82-1.34	Organochlorines percentile <1 1-49 ≥50	Total leukemia OR 1.0 1.13, 0.72-1.79 1.29, 0.78-2.13	ALL only ≥50 th percentile 1.51, 0.85-2.69
Organophosphates percentile <1 1-49	OR 1.0 1.02, 0.79-1.32 1.22, 0.96-1.56	Carbamates percentile <1 1-49	OR 1.0 1.39, 1.04-1.86 1.08, 0.80-1.47	Dithiocarbamates percentile <1 1-49	OR 1.0 1.02, 0.71-1.46 1.01, 0.71-1.42	Odds ratio, high-use vs no use areas

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
≥50		≥50		≥50		
(Reynolds and others 2005a), California	Ecologic (see Reynolds et al 2002 above)	1938 statewide ALL cases, 1988-94, age <15	ALL incidence ratios (obs:exposed) by small geog area	Statewide cancer registry	Childhood exposure assessed using data from Pesticide Use Reporting system; assessed average lb/mi during 1991-94 for 8 chemical groupings and 7 specific high-use, highly toxic agents within 0.5 mi buffer region	Age, race and ethnicity, and gender
RR, ALL, childhood residence, 75 th vs <1 st percentile, lbs/mi ²	Prob carcinogens 0.99, 0.79-1.24 Genotoxins 1.00, 0.82-1.21	Organochlorines 0.73, 0.47-1.15 OPs 0.94, 0.77-1.14 Carbamates 0.87, 0.67-1.13 Dithiocarbamates 0.92, 0.70-1.19	Propargite 1.03, 0.76-1.39 Methyl bromide 1.16, 0.92-1.45 Metam sodium 0.88, 0.55-1.39 Trifluralin 0.81, 0.49-1.34	Simazine 1.21, 0.86-1.71 Dicofol 0.67, 0.40-1.12 Chlorothalonil 1.05, 0.78-1.43		
(Abadi-Korek and others 2006), Israel	Case-control	Hospital-based, 1984-2002	112 ALL cases, 1984-2002, 112 matched controls	Hospital records	Parent-reported info on occupational pesticide exposure in any job held for at least 6 mos from yr first worked to diagnosis	Matched for age, Jewish religion, sex
Parental occupational	2.35, 1.10-5.0					

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
pesticide exposure for at least 6 mos from yr first employed until diagnosis						
(Alderton and others 2006), USA and Canada	Case-control	Children's Oncology Group, cases and controls all had Down's syndrome, 1997-2002	158 acute leukemia cases (97 ALL, 61 AML), 173 controls with Down's syndrome but not leukemia, age <20	Hospital records	Mother-reported info on exposure to hhld chemicals during month before conception, pregnancy and while breastfeeding and child exposure up to 6 mos before diagnosis; incl frequency of exposure of mother or child during each time period to pesticides incl insecticides, herbicides, rodenticides, products to control moths, fleas/ticks, insect repellants	All ORs adj for
OR, leukemia, prenatal resid, freq of use	Any pesticide ALL <median vs 0 2.07, 0.97-4.44 ≥median vs 0 2.28, 1.07-4.84	Insecticides ALL <median vs none 1.56, 0.85-2.87 ≥median vs none 1.82, 0.94-3.52	Herbicides ALL <median vs none 0.96, 0.43-2.14 ≥median vs none 1.84, 0.91-3.73	Home exterminations ALL Any freq 2.25, 1.13-4.49 Freq <median vs none	Flea or tick control ALL 1.25, 0.59-2.65 p-trend=.29 AML 0.99, 0.34-2.91 p-trend=.69	

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
	<p>p-trend=.05</p> <p>AML <median vs 0 0.90, 0.40-2.01</p> <p>≥median vs 0 0.77, 0.33-1.79 p-trend=.54</p>	<p>p-trend=.05</p> <p>AML <median vs none 0.60, 0.26-1.38</p> <p>≥median vs none 0.85, 0.35-2.03 p-trend=.48</p>	<p>p-trend=.13</p> <p>AML na</p>	<p>3.44, 1.41-8.39</p> <p>Freq ≥median vs 0 1.28, 0.46-3.55 p-trend=.11</p> <p>AML</p> <p>Any freq 1.06, 0.43-2.61</p> <p><median vs 0 na</p> <p>Freq ≥median vs 0 1.85, 0.63-5.48 p-trend=.52</p>		
<p>OR, leukemia, childhood resid pesticide use, freq ≥median vs none</p>	<p>Any pesticide ALL <median vs 0 0.93, 0.43-2.01</p> <p>>median vs 0 1.63, 0.75-3.53 p-trend=.21</p> <p>AML <5 cases in each exposure</p>	<p>Insecticides ALL <median vs none 1.04, 0.53-2.06</p> <p>≥median vs none 1.63, 0.84-3.30 p-trend=.21</p> <p>AML <5 cases in each</p>	<p>Herbicides ALL <median vs none 1.53, 0.60-3.88</p> <p>≥median vs none 1.07, 0.42-2.67 p-trend=.66</p> <p>AML Na</p>	<p>Home extermination ALL <median vs 0 1.64, 0.69-3.89</p> <p>>median vs 0 1.25, 0.51-3.08 p-trend=.40</p> <p>AML na</p>		

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
	category	exposure category				
(Menegaux and others 2006), France	Case-control	Hospital-based, , 1995-99, hospitals in 4 major cities, controls mainly orthopedic and ER	280 acute leukaemia cases, 288 controls, age <15	Hospital records	Mother-reported info on parental occupational history, home and garden insecticide use, insecticidal treatment of pediculosis	Frequency matched on gender, age, hospital, ethnic origin
OR, leukemia, prenatal maternal pesticide use	Home insecticide use 1.8, 1.2-2.8 Garden use, any pesticide 2.5, 0.8-7.2 Garden use, insecticides 1.9, 0.6-6.5 Garden use, herbicides 5.9, 0.7-52 (6 exposure case mothers)	OR, leukemia, pesticide use during childhood	Home insecticides 1.7, 1.1-2.4 Garden use, any pesticide 1.7, 1.1-2.7 Garden insecticides 2.4, 1.3-4.3 Garden herbicides 1.4, 0.8-2.4 Garden fungicides 2.5, 1.0-6.2	OR, leukemia, childhood. insecticidal shampoo for lice	Any insecticide 1.9, 1.1-3.2 Pyrethroid only 2.2, 1.2-3.8 Lindane 2.1, 0.5-8.7 Malathion 0.7, 0.2-2.4	
(Pearce and others 2006), England	Case-control	Hybrid study, northern England; population-based cases age <25, 1968-2000; 2 sets of	1007 leukemia cases, age 0-24; 42,118 other cancer "controls", 95,099 live birth controls	Paternal occupation on birth certificates; occupations in farming, forestry, horticulture and		Matched for sex, YOB

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
		matched controls – other types of cancer, randomly selected from live birth records for Cumbria County (only has 16% of population of northern England)		gardening assumed to have pesticide exposure		
Odds ratio by type of leukemia, paternal occupation with likely pesticide exposure, yes vs no	Total leukemia Cancer control 0.86, 0.61-1.22 Live birth control 0.38, 0.27-0.55	Lymphoid leukemia Cancer control 0.76, 0.50-1.15 Live birth control 0.37, 0.24-0.57	Acute non-lymphocytic leukemia Cancer control 0.97, 0.45-2.09 Live birth control 0.36, 0.17-0.77	Chronic myeloid leukemia Cancer control 2.45, 0.72-8.15 Live birth control 0.59, 0.14-2.46		
(Walker and others 2007), Texas	Case-control	Population-based, cases from state-wide cancer registry, 1990-98; born during 1975-98	1178 leukemia cases, 3487 live birth controls, age <15	Ecological exposure indices: 1987, 1992 and 1997 Census of Agriculture info on % of land in crops and pesticide use in the county of birth (254 counties); pesticide use estimated from acres in specific crops and state data on pesticide use per acre; used EPA	3 exposure categories for both % of county land in cropland and county pesticide use	Adj for child's age, race/ethnicity, sex; eliminated birth weight, maternal age and paternal education as potential confounders

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
				carcinogenicity classification to categorize county pesticide use weighted by potential for carcinogenicity		
OR, leukemia, birth in counties with 25-49 or ≥50% vs <25% land in crops	0.9, 0.8-1.1 0.9, 0.7-1.3 p-trend=.44	OR, leukemia, birth in counties with medium or high vs low pesticide use	Total leukemia 0.9, 0.8-1.1 1.0, 0.8-1.2 p-trend=.71	ALL 0.9, 0.7-1.0 1.0, 0.9-1.3 p-trend=.92	AML 1.1, 0.8-1.5 1.0, 0.7-1.5 p-trend=.99	
(Rudant and others 2007) France	Case-control	Population-based, France, 2003-04	764 cases acute leukemia, 130 cases Hodgkin’s disease, 166 cases NHL, 1681 controls, age <15	Mother-reported household pesticide use during pregnancy and paternal use during pregnancy or childhood		All cancers: age, sex, degree of urbanization, type of housing Leukemia: also birth order
Odds ratio, leukemia vs maternal prenatal household pesticide use, ever vs never	Any pesticide Total leukemia 2.2, 1.8-2.6 ALL 2.3, 1.9-2.8 AML 2.2, 1.4-3.3	Insecticides Total leukemia 2.1, 1.7-2.5	Home insecticides Total leukemia 1.9, 1.6-2.3 ALL 2.2, 1.8-2.6 AML 2.1, 1.4-3.3	Pet insecticides Total leukemia 2.0, 1.5-2.5	Garden insecticides Total leukemia 1.5, 1.0-2.5 ALL AML	Herbicides Total leukemia 1.5, 1.0-2.2 ALL 1.7, 1.2-2.5 AML 1.2, 0.5-2.8

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
Fungicides Total leukemia 0.9, 0.5-1.7 ALL 1.1, 0.6-2.0 AML na	Mother in agricultural occupation during pregnancy 0.2, 0.1-0.8					
Odds ratio, leukemia vs paternal pesticide use during pregnancy or childhood, ever vs never	Any pesticide Total leukemia 1.5, 1.2-1.8 ALL 1.5, 1.2-1.9 AML 1.5, 0.9-2.4	Insecticides Total leukemia 1.4, 1.2-1.7 ALL 1.5, 1.2-1.9 AML 1.3, 0.8-2.0	Herbicide Total leukemia 1.2, 1.0-1.4 ALL 1.2, 1.0-1.5 AML 1.0, 0.7-1.7	Fungicides Total leukemia 0.9-1.4 ALL 1.1, 0.9-1.5 AML 1.1, 0.6-2.0	Pet insecticide use, ever vs never 1.3, 1.0-1.6 Home insecticide use, ever vs never 1.5, 1.3-1.8 Garden insecticide use, ever vs never 1.0, 0.7-1.3	Father in agricultural occupation during pregnancy 0.6, 0.4-1.1
Only mother used pesticides 2.7, 1.9-3.8	Only father used pesticides 1.3, 1.0-1.8	Both parents used pesticides 2.5, 2.0-3.2	Mother used insecticide, father did not use any pesticide 2.5, 1.7-3.7	Mother used herbicide, father did not use any pesticide 5.0, 1.3-19 (4 exposed case mothers)	Father used insecticide, mother did not use any pesticide 1.1, 0.6-1.8	Father used herbicide, mother did not use any pesticide 1.6, 1.0-2.4
(Monge and others 2007), Costa Rica	Case-control	Population-based, 1995-2000	334 cases leukemia, 579 controls, age	Face-to-face interviews of parents	Parent-reported exposures with focus on	Matched by YOB

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
			<15 yr	using a questionnaire	pesticide use by those in agricultural occupations; assessed yr before conception, 1 st T, 2 nd T, 3 rd T, age 0-1	
Odds ratio, leukemia vs maternal pesticide exposure during 1 st trimester	Any pesticide 22.0, 2.8, 172 Insecticides 6.9, 1.4-33.2	Herbicides 5.3, 1.4-20 Fungicides 7.8, 0.9-71	Organophosphates Total leukemia 3.5, 1.0-12.2 ALL 3.7, 1.0-13.1	Paraquat, chlorothalonil, glyphosate, other Total leukemia 3.7, 1.2-11.1 ALL 4.0, 1.8-12.3		
Odds ratio, leukemia vs maternal pesticide exposure during 1 yr before conception	Phenoxyacetic acids Total leukemia 1.3, 0.4-4.8 ALL na	Organophosphates Total leukemia 2.3, 0.9-6.0 ALL 2.5, 0.9-6.7	Paraquat, chlorothalonil, glyphosate, other Total leukemia 2.8, 1.1-7.2 ALL 3.1, 1.2-8.1	Odds ratio, leukemia vs maternal pesticide exposure during 1 st yr of child's life	Organophosphates Total leukemia 1.8, 0.6-4.9 ALL 1.8, 0.6-5.4	Paraquat, chlorothalonil, glyphosate, other Total leukemia 2.1, 0.8-5.3 ALL 2.5, 1.0-6.5
Odds ratio, leukemia vs paternal pesticide exposure during 1 yr before conception	Any pesticide 1.2, 0.9-1.8 Insecticides 1.4, 0.9-2.1	Herbicides 1.2, 0.8-1.7 Fungicides 1.6, 1.0-2.6	Phenoxyacetic acids 1.0, 0.6-1.6 Organophosphates 1.5, 1.0-2.2	Organochlorines 1.0, 0.4-2.5 Carbamates 1.3, 0.6-2.5	Dithiocarbamates 1.4, 0.7-2.7 Pyrethroids 1.2, 0.5-2.6	Benzimidazoles 2.1, 1.0-4.4 Chlorinated phthalides

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
						2.5, 0.7-9.4
Odds ratio, leukemia vs paternal pesticide exposure during 1 yr before conception	Malathion Boys 8.5, 1.1-74 n=5 exp fa Girls 0.9, 0.2-4.9 n=2 exp fa	Benomyl Boys 2.5, 1.1-6.0 n=13 exp fa Girls 0.9, 0.3-2.8 n=4 exp fa	Odds ratio, leukemia vs paternal pesticide use when child age 0-1, by age of child at diagnosis	Age 1-5 Any pesticide 0.9, 0.5-1.4 Herbicides 0.9, 0.5-1.6 Fungicides 1.6, 0.9-3.1	OPs 1.1, 0.6-1.9 Paraquat 1.1, 0.6-2.0	Age 6-15 Any pesticide 1.6, 1.0-2.5 Herbicides 1.8, 1.1-3.0 Fungicides 1.4, 0.7-2.8
OPs 1.7, 1.0-2.9 Paraquat 2.0, 1.2-3.5	Paternal 1 st trimester occupational exposure vs leukemia	Mancozeb Boys 3.1, 1.1-9.0 Girls 3 exp case fa				
(Urayama and others 2007), California 39	Case-control	Population-based, central and northern California, cases from major pediatric hospitals, controls from statewide birth registry; rr=86% for cases, 84% for controls; in-home interviews with primary caregiver	294 ALL cases, 369 matched controls, age <15; buccal cell samples for DNA, tested for 4 multiple drug resistant gene (MDR1) SNPs	Self-reported household pesticide use incl name of product, purpose, frequency of use, used during 3 mos before conception, pregnancy and years 1, 2 and 3; censored at 1 yr before diagnosis		Matched for DOB, sex, Hispanic status, mat race; conditional logistic regression analysis, adj for hhld income

Reference	Design	Study population	Outcomes	Outcome assmt	Exposure	Covariates
Indoor insecticide exposure during period from 1 yr before birth to age 3, excluding exposure during the 1 yr before diagnosis	All subjects 1.65, 1.10-2.47	Odds ratio, insecticide exposure plus given MDR1 haplotype vs no insecticide exposure and CGC- haplotype	Hap CGC- 3.03, 1.54-6.00 Hap CGC+ 2.09, 1.12-3.91	Hap CGC/insecticide interaction 0.37, 0.15-0.88		
Odds ratio, insecticide exposure plus given MDR1 haplotype vs no insecticide exposure and TTT- haplotype	Hap TTT- 1.46, 0.73-2.90 Hap TTT+ 1.68, 0.86-3.27	Hap TTT/ insecticide interaction 1.21, 0.53-2.74				

rr= % of eligible subjects who consented to participate.

Summary: Childhood leukemia

Reviews

A review of 18 epidemiologic studies published up to early 1998 noted that 13 studies reported increased childhood leukemia risk in relation to parental occupational or childhood pesticide exposure but did not clearly define the most critical exposures with regard to timing (preconceptual vs gestational vs childhood) or parent (maternal vs paternal) (Zahm and Ward 1998). A recent review noted that the 12 studies published since the Zahm and Ward paper generally support an association between childhood leukemia and pesticide exposure with the greatest risks being childhood exposure to household insecticides and parental exposure to pesticides before or during pregnancy (Infante-Rivard and Weichenthal 2007). Other reviewers reached similar conclusions (Buffler and others 2005; Brown 2006).

Original studies since 1997

Maternal exposure, herbicides, limited evidence

Leukemia was associated with prenatal residential herbicide application in case-control studies in Los Angeles (herbicides or other pesticides, OR=9.0, 95% CI 1.25-394; the high odds ratio was based on 9/1 discordant pairs^c in a matched-pairs analysis) (Lowengart and others 1987), Quebec (any herbicide use, OR=1.84, 95% CI 1.32-2.57; used more than 5 times vs no use, OR=3.72, 95% CI 0.72-19.1) (Infante-Rivard and others 1999), California (prenatal residential

^c Ratio of the number of matched pairs in which the case was exposed but not the control to the number of matched pairs in which the control was exposed but not the case.

herbicide use, OR=1.6, 95% CI 0.9-3.0) (Ma and others 2002), USA/Canada (frequency of use \geq median vs none, OR=1.84, 95% CI 0.91-3.73, p-trend=.13) (Alderton and others 2006) and France (prenatal outdoor use of herbicides, OR=5.9, 95% CI 0.7-52, 6 exposed case mothers) (Menegaux and others 2006). The Quebec study also reported an association between ALL and prenatal use of herbicides alone (OR=1.56, 95% CI 0.96-2.55) (Infante-Rivard and others 1999).

Maternal exposure, insecticides, limited evidence

Leukemia was associated with prenatal indoor insecticide use but not residential proximity to agricultural insecticide use. There were elevated risks in case-control studies in Los Angeles (≥ 1 vs 0 times/wk, OR=3.25, 95% CI 1.00-13.7) (Lowengart and others 1987), USA/Canada (≥ 1 /wk, OR=1.47, 95% CI 0.69-3.17, p-trend=.05) (Buckley and others 1989), Denver (prenatal use of insecticide pest strips in home, OR=3.0, 95% CI 1.6-5.7) (Leiss and Savitz 1995), Quebec (prenatal use of indoor insecticides for cockroaches, ants, flies, bees or wasps, all cases, OR=1.79, 95% CI 1.34-2.40, cases with CYP1A1m2 polymorphism, OR=4.73, 95% CI 1.18-18.6) (Infante-Rivard and others 1999), a 7-country study (leukemia before age 18 mos vs maternal use of the carbamate insecticide propoxur, OR=5.14, 95% CI 1.27-20.9) (Alexander and others 2001), California (prenatal indoor insecticide use, OR=2.1, 95% CI 1.3-3.5) (Ma and others 2002), USA/Canada (ALL, any prenatal home extermination, OR=2.25, 95% CI 1.13-4.49; cases and controls all had Down's syndrome) (Alderton and others 2006) and France (prenatal home use of insecticides, OR=1.8, 95% CI 1.2-2.8) (Menegaux and others 2006). Leukemia was associated with prenatal residential use of insecticides for interior or outdoor plants (any use, OR=1.97, 95% CI 1.32-2.94; used more than 5 times, OR=4.01, 95% CI 1.12-14.3) and with prenatal professional indoor insect extermination (OR=1.68, 95% CI 0.87-3.25) in Quebec (Infante-Rivard and others 1999). There was a dose-response relationship between leukemia and duration or frequency of prenatal indoor insecticide use in the first USA/Canada study (Buckley and others 1989). In a recent USA/Canada study, there was a non-monotonic relationship between ALL risk and frequency of prenatal home extermination ($<$ median vs none, OR=3.44, 95% CI 1.41-8.39; \geq median, OR=1.28, 95% CI 0.46-3.55) (Alderton and others 2006). There was no association between leukemia and prenatal occupational insecticide exposure in a Spanish case-control study (OR=1.40, 95% CI 0.44-4.41, 7 exposed case mothers) (Infante-Rivard and others 1991). Childhood leukemia was associated with prenatal use of tree insecticides in a Quebec case-control study (any use, OR=1.70, 95% CI 1.12-2.59; used more than 5 times, OR=3.27, 95% CI 0.64-16.7) (Infante-Rivard and others 1999). A French case-control study observed a statistically non-significant elevated leukemia risk related to prenatal garden insecticide use (OR=1.9, 95% CI 0.6-6.5) (Menegaux and others 2006).

Maternal exposure, unspecified pesticides, inadequate evidence

Elevated leukemia risks were related to prenatal occupational pesticide exposure in case-control studies in Shanghai (ALL, OR=3.5, 95% CI 1.1-11.2; ANLL, OR=2.4, 95% CI 0.5-11.0) (Shu and others 1988), USA/Canada (crude OR=2.85, 95% CI 0.82-10.8, calculated from data in paper) (Buckley and others 1989), Spain (occupation in farming, OR=1.80, 95% CI 0.60-6.64) (Infante-Rivard and others 1991), Germany (regional study, OR=2.59, 95% CI 0.45-20.4, only 4 exposed case mothers) (Meinert and others 1996), Greece (home or occupational exposure, OR=3.6, 95% CI 1.2-10.8) (Petridou and Dessypris 2000), Germany (nation-wide, OR=3.6, 95% CI 1.5-8.8) (Meinert and others 2000), a 7-country study (leukemia before age 18 mos, OR=3.67, 95% CI 1.54-8.74) (Alexander and others 2001) and Israel (occupational exposure of either parent, OR=2.35, 95% CI 1.10-5.0) (Abadi-Korek and others 2006). Elevated leukemia risk was also related to maternal outdoor pesticide use in case-control studies in Germany (prenatal or postnatal use, OR=2.76, 95% CI 1.26-6.30) (Meinert and others 1996) and France (prenatal, OR=2.5, 95% CI 0.8-7.2) (Menegaux and others 2006). There was no association in case-control studies in the Netherlands (prenatal occupational pesticide exposure, OR=0.7, 95% CI 0.2-2.5, only 4 exposed case mothers) (van Steensel-Moll and others 1985), Denver (prenatal outdoor herbicide or insecticide use, OR=1.1, 95% CI 0.6-1.9) (Leiss and Savitz 1995) or UK (periconceptual maternal occupations potentially exposed to agrochemicals, OR=0.81, 95% CI 0.31-2.12) (McKinney and others 2003). The consistency of findings are suggestive of an association but the heterogeneity of exposure

indices, the lack of demonstrated dose-response relationships and the relatively small numbers of exposed case mothers in most studies preclude firm conclusions.

Paternal occupational exposure, TCDD-contaminated phenoxy herbicides or chlorophenolate wood preservatives, inadequate evidence Among
 children of sawmill workers in British Columbia, Canada, leukemia was not associated with paternal chlorophenolate exposure duration (≥ 3000 vs < 3000 hours cumulated exposure, OR=0.8, 95% CI 0.2-3.6) (Heacock and others 2000). An expert panel found insufficient evidence for an association between paternal phenoxy herbicide exposure and childhood cancer (National Academy of Sciences 2003).

Paternal occupational exposure, major pesticide classes, inadequate evidence
 In the Quebec study, leukemia risk was elevated in relation to preconceptional paternal occupational exposure to herbicides (OR=2.05, 95% CI 0.93-4.56), insecticides (OR=1.38, 95% CI 0.87-2.18) and fungicides (OR=5.11, 95% CI 1.46-17.8) (Infante-Rivard and Sinnett 1999). Paternal occupational exposure, unspecified pesticides, inadequate evidence Elevated leukemia risk was associated with paternal occupational pesticide exposure in case-control studies in Italy (OR=5.6, 95% CI 1.3-24.3, 5 case fathers worked in farming) (Magnani and others 1990), USA/Canada (1-1000 days cumulated exposure vs none during period from 1 yr before birth to date of diagnosis, OR=1.0, 95% CI 0.4-2.4); > 1000 days vs none, OR=2.7, 95% CI 1.0-7.0, p-trend=.04) (Buckley and others 1989), UK (paternal occupation in farming, OR=1.98, 95% CI 0.66-5.96) (Gardner and others 1990) and Germany (occupational pesticide exposure in year before conception, OR=1.5, 95% CI 1.1-2.2) (Meinert and others 2000). Leukemia was not associated with paternal occupational pesticide exposure in case-control studies in Quebec (paternal work as farmer based on birth certificate information, OR=0.70, 95% CI 0.39-1.21) (Fabia and Thuy 1974), Netherlands (paternal work in agriculture, forestry or horticulture, OR=0.9, 95% CI 0.5-1.5; self-reported occupational pesticide exposure, OR=1.0, 95% CI 0.6-1.7) (van Steensel-Moll and others 1985), Germany (paternal occupational pesticide exposure in year before pregnancy, OR=1.29, 95% CI 0.46-3.62) (Meinert and others 1996), Sweden (OR=0.90, 95% CI 0.37-2.19) (Feychting and others 2001) or UK (periconceptional paternal occupations potentially exposed to agrochemicals, OR=0.83, 95% CI 0.58-1.19) (McKinney and others 2003). In a Norwegian retrospective cohort study, leukemia risk among offspring of farmers (84% of whom were males) was not elevated compared to non-farm children (all farm children, SIR=0.96, 95% CI 0.82-1.11; children on farms reporting pesticide expenditures, SIR=1.06, 95% CI 0.75-1.49) (Kristensen and others 1996). Two cohort studies reported normal leukemia risks among offspring of licensed pesticide applicators: a Swedish study (OR=0.43, 95% CI 0.19-0.86) (Rodvall and others 2003) and a U.S. study (OR=0.91, 95% CI 0.47-1.75) (Flower and others 2004). Despite the dose-response relationship observed in one study, the inconsistent findings, heterogeneous exposure indices and negative results of 2 cohort studies of licensed pesticide applicators provide inadequate evidence of an association.

Childhood TCDD exposure, inadequate evidence

Follow-up of Seveso residents age 0-19 at the time of the 1976 chlorophenol plant explosion revealed no overall excess of incident cancer by 1986 (obs=17, exp=13.6, SIR=1.2, 95% CI 0.7-2.1); there was a statistically non-significant excess of leukemia and other hematopoietic cancers (SIR=1.6, 95% CI 0.7-3.4) (Pesatori and others 1993). Much longer follow-up is needed to assess the risk of cancer after longer latent periods.

Childhood exposure, herbicides, inadequate evidence

The Quebec study reported an association between leukemia and childhood residential herbicide use (with or without residential use of other pesticides, OR=1.41, 95% CI 1.06-1.86) but not with residential use of herbicides alone (OR=0.88, 95% CI 0.58-1.33) (Infante-Rivard and others 1999). An ecologic study in

Maryland observed borderline associations between leukemia and residence at diagnosis <3.2 km from well water containing detectable levels of the herbicides atrazine (OR=1.43, 95% CI 0.89-2.30) and metolachlor (OR=1.48, 95% CI 0.93-2.36) but not simazine (OR=0.97, 95% CI 0.48-1.96) (Thorpe and Shirmohammadi 2005). There was a statistically non-significant elevated leukemia risk related to childhood residential herbicide use in a French case-control study (OR=1.4, 95% CI 0.8-2.4) (Menegaux and others 2006). An ecologic study in California found no association between total leukemia before age 15 and childhood residential proximity to agricultural use ($\geq 90^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi²) of the herbicides simazine (a triazine herbicide, OR=0.79, 95% CI 0.45-1.40) or trifluralin (a dinitroaniline herbicide, OR=0.87, 95% CI 0.46-1.63) (Reynolds and others 2002). Further analysis restricted to ALL before age 15 revealed a slightly elevated risk related to simazine use ($\geq 75^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi², OR=1.21, 95% CI 0.86-1.71) but not trifluralin (OR=0.81, 95% CI 0.49-1.34) (Reynolds and others 2005a). A California case-control study restricted to ALL before age 5 revealed elevated risks related to childhood residential proximity to agricultural use ($\geq 50^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi²) of simazine (OR=1.29, 95% CI 0.81-2.05) but not trifluralin (OR=0.92, 95% CI 0.51-1.65) (Reynolds and others 2005b). Leukemia was not associated with childhood residential herbicide use in Denver (OR=0.9, 95% CI 0.5-1.8) (Leiss and Savitz 1995), California (birth to age 1, OR=0.7, 95% CI 0.4-1.2; age 1-2, OR=1.1, 95% CI 0.7-2.0; age 2-3, OR=1.1, 95% CI 0.6-2.1) (Ma and others 2002) or in a USA/Canada study (\geq median frequency of use vs none, OR=1.07, 95% CI 0.42-2.67, p-trend=.66) (Alderton and others 2006).

Childhood exposure, insecticides, limited evidence

Leukemia was associated with childhood indoor residential use of insecticides but not residential proximity to agricultural insecticide use. Leukemia risk was elevated in relation to childhood indoor insecticide use in case-control studies in USA/Canada ($\geq 1\text{X}/\text{wk}$, OR=2.02, 95% CI 0.91-4.57, p-trend=.04) (Buckley and others 1989), Denver (insecticide pest strips^d in home, birth to 2 yr before diagnosis, OR=1.7, 95% CI 1.2-2.4; <2 yr before diagnosis, OR=2.6, 95% CI 1.7-3.9) (Leiss and Savitz 1995), Quebec (indoor insecticide use for cockroaches etc., all ALL cases, OR=1.38, 95% CI 1.07-1.77; ALL cases with CYP1A1m2 polymorphism, OR=3.95, 95% CI 0.81-19.2) (Infante-Rivard and others 1999), Germany (indoor insecticide use > 10 vs $< 1\text{X}/\text{yr}$, OR=1.8, 95% CI 1.0-3.3, p-trend=.12) (Meinert and others 2000), California (indoor insecticide use, birth to age 1, OR=1.7, 95% CI 1.0-2.9; age 1-2, OR=1.6, 95% CI 1.0-2.7; age 2-3, OR=1.2, 95% CI 0.7-2.1) (Ma and others 2002), USA/Canada (frequency of use \geq median vs none, OR=1.63, 95% CI 0.84-3.30, p=.21) (Alderton and others 2006) and France (indoor insecticide use, OR=1.7, 95% CI 1.1-2.4; childhood use of insecticide shampoo, OR=1.9, 95% CI 1.1-3.2) (Menegaux and others 2006). The French study also reported an association between leukemia and childhood use of insecticidal shampoos (OR=1.9, 95% CI 1.1-3.2) (Menegaux and others 2006). Dose-response relationships between leukemia and frequency of childhood residential indoor insecticide use were apparent in Germany (p-trend=.12) (Meinert and others 2000) and California (per increment in frequency of use, birth to age 1, OR=1.2, 95% CI 1.0-1.4; age 1-2, OR=1.1, 95% CI 1.0-1.3) (Ma and others 2002). Childhood indoor insecticide use was not associated with leukemia in the Denver case-control study (home extermination, <2 yr before diagnosis, OR=0.9, 95% CI 0.5-1.4) (Leiss and Savitz 1995). The apparent interaction between indoor insecticide exposure and the CYP1A1m2 polymorphism in the Quebec study may indicate a role for P-450 enzyme activation; however, this appears to be the only study of interactions between genetic polymorphisms and pesticide exposure in childhood cancer and more research is urgently needed. ALL was associated with childhood outdoor residential insecticide use in case-control studies in Quebec (tree insecticides, OR=1.41, 95% CI 1.01-1.97) (Infante-Rivard and others 1999), California (ALL age <5, childhood residential proximity, agricultural use of organophosphate insecticide, $\geq 50^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi², OR=1.22, 95% CI 0.96-1.56) (Reynolds and others 2005b) and France (OR=2.4, 95% CI 1.3-4.3) (Menegaux and others 2006). The California study also observed elevated risks of leukemia before age 5 related to childhood residential proximity to

^d Pest strips contained dichlorvos, a highly volatile organophosphate insecticide; it is a known mutagen and animal carcinogen causing leukemia and lung and mammary gland tumours.

agricultural use of the organochlorine miticide dicofol (OR=1.83, 95% CI 1.05-3.22) but not propargite (OR=0.96, 95% CI 0.62-1.49) or the broad classes of organochlorine (OR=1.29, 95% CI 0.78-2.13) or carbamate insecticides (OR=1.08, 95% CI 0.80-1.47) (Reynolds and others 2005b). An ecologic study in California found no association between total leukemia before age 15 and childhood residential proximity to agricultural use ($\geq 90^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi²) of organochlorine (OR=0.70, 95% CI 0.39-1.23), organophosphate (OR=0.91, 95% CI 0.70-1.18) or carbamate insecticides (OR=1.03, 95% CI 0.75-1.41) (Reynolds and others 2002). Further analysis restricted to ALL before age 15 revealed no association with agricultural use of organochlorine ($\geq 75^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi², OR=0.73, 95% CI 0.47-1.15), organophosphate (OR=0.94, 95% CI 0.77-1.14) or carbamate insecticides (OR=0.87, 95% CI 0.67-1.13) or propargite (OR=1.03, 95% CI 0.76-1.39) (Reynolds and others 2005a). The consistency of findings and evidence of dose-response relationships provide relatively strong evidence of an association.

Childhood exposure, fungicides, inadequate evidence

Leukemia was associated with childhood residential garden fungicide use in a French case-control study (OR=2.5, 95% CI 1.0-6.2) (Menegaux and others 2006). An ecologic study in California found no association between leukemia and childhood residential proximity to agricultural use ($\geq 90^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi²) of dithiocarbamate fungicides (OR=0.89, 95% CI 0.61-1.30) (Reynolds and others 2002). This study did report elevated leukemia risk related to agricultural use of the chlorinated isophthalic acid fungicide chlorothalonil (OR=1.27, 95% CI 0.90-1.80). Further analysis, restricted to ALL before age 15 and using different cut points of pesticide use intensity, revealed no association with agricultural use of dithiocarbamate fungicides ($\geq 75^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi², OR=0.92, 95% CI 0.70-1.19) (Reynolds and others 2005a). A California case-control study restricted to ALL before age 5 revealed no association with childhood residential proximity to agricultural use ($\geq 50^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi²) of dithiocarbamate fungicides (OR=1.01, 95% CI 0.71-1.42) and a statistically non-significant elevated risk related to childhood residential proximity to agricultural use of chlorothalonil (OR=1.33, 95% CI 0.88- 2.01) (Reynolds and others 2005b).

Childhood exposure, soil fumigants, inadequate evidence

An ecologic study in California found no association between total leukemia and childhood residential proximity to agricultural use ($\geq 90^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi²) of the soil fumigant metam sodium (OR=0.92, 95% CI 0.48-1.73) (Reynolds and others 2002). A subsequent case-control study restricted to ALL before age 5 revealed an association with childhood residential proximity to agricultural use ($\geq 50^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, lb/mi²) of metam sodium (OR=2.05, 95% CI 1.01-4.17) but not methyl bromide (OR=0.89, 95% CI 0.60-1.33) (Reynolds and others 2005b).

Childhood exposure, residential use of unspecified pesticides, inadequate evidence

A case-control study in northwestern Germany reported an association between leukemia and prenatal or childhood garden pesticide use (crude OR=2.76, 95% CI 1.26-6.30, calculated from data in paper) but did not distinguish between prenatal or childhood exposure (Meinert and others 1996). Childhood outdoor residential pesticide use was not associated with childhood leukemia in case-control studies in Denver (yard insecticide or herbicide use, OR=0.9, 95% CI 0.5-1.8) (Leiss and Savitz 1995) or a nation-wide German study (residential garden pesticide exposure use, OR=1.0, 95% CI 0.8-1.2) (Meinert and others 2000).

13. Lymphomas

Reviews

Author	Scope	Findings
(Zahm and Ward 1998), USA	Literature review, epidemiologic studies of pesticides and childhood cancer	Non-Hodgkin's lymphoma – 4 case-control studies and 1 cohort study found fairly consistent risk elevations related to parental or residence pesticide exposure indices
(Jurewicz and Hanke 2006), Poland	Reviewed epidemiologic studies published during 1998-2005 to update the review by Zahm and Ward.	Concluded that recent studies provide further evidence for an association between NHL and pesticide exposure but level of evidence is still limited
Limitations of studies include exposure assessment, inadequate statistical power, small numbers of studies on specific relationships, uncertainty about critical windows of exposure	In the light of existing, although still limited evidence of adverse effects of pesticide exposure, it is necessary to reduce exposure to pesticides	
(Infante-Rivard and Weichenthal 2007), Quebec	Reviewed 4 epidemiologic studies published since review by Zahm and Ward.	Concluded that recent studies support an association between childhood NHL and childhood residential pesticide exposure; 2 studies revealed exposure-risk gradients.

Lymphomas: Original studies since 1997

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Fear and others 1998), England and Wales (excluded)	Proportional mortality study	360,640 total deaths, age <15, England and Wales, 1959-63 plus 1970-90;	31 non-Hodgkin's lymphoma	Potential paternal exposure to pesticides based		Age, year of death, paternal social class

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Note: abstract only		cases identified from death records	deaths among 360,640 total deaths, age <15 yr	on occupation recorded on death certificate		
Paternal occupa potentially exposed to pesticides	PMR=0.87, 0.61-1.23					
(Buckley and others 2000), Children's Cancer Group, United States and Canada	Case-control	Population-based, 1986-90; cases identified from hospital records incl pathology	268 NHL cases, matched controls, age <20; identified B- and trimester-cell subtypes	Self-reported occupational and home exposure to pesticides during pregnancy and childhood	Categorized exposure intensity based on freq of use as 0, 1-2 and 3+d/wk	Matched for DOB, sex, race; adjusted for maternal education, race
OR, NHL, parental occupational pesticide exposure (no breakdown by maternal/paternal); p-trend based on frequency of use	1.74, 0.82-3.69 p-trend=.21	OR, NHL vs prenatal maternal indoor insecticide use, 1-2 and 3+ vs 0 d/wk	2.62 (0.96-7.18) 7.33 (0.84-63.9) p-trend=.05	OR, NHL, maternal insecticide applic around home, yes vs no, p-trend based on freq of use	2.98, 1.44-6.16 p-trend=.002	
OR, NHL, maternal use of garden sprays	Never 1.0 (referent) <1/mo 1.82, 0.61-5.45	≥1/mo 1.71, 0.67-4.37 p-trend=.29	OR, NHL, childhood direct contact with herbicides or insecticides, yes vs no	2.35, 1.37-4.03 p-trend=.001	OR, NHL, overall pesticide use score highest vs none; scores based on 1 point each for either parent with occupational	4.0, 1.8-8.3 p-trend=.0001

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					exposure, child freq exposed, insecticide use around home, use of garden sprays at least monthly, use of household insecticides at least weekly and an extra point if used daily	
(Meinert and others 2000), Germany	Case-control	Population-based, nationwide (West Germany), 1992-94; cases identified from German Central Cancer Registry	Population-based, 234 NHL cases, 2588 community controls, age <15	Self-reported parental occupational and home exposures to pesticides and other hazards		Matched for sex, DOB, community
NHL vs residence pesticide use during childhood (from birth to diagnosis)	Garden 0.8, 0.5-1.2 Farm 0.5, 0.2-1.4	Use of household insecticides 1, 2-5, 6-10 and >10 vs <1X/yr 1.3, 0.6-2.8 1.4, 0.7-2.9 1.5, 0.6-4.1 2.8, 1.1-7.2 p-trend = 0.02 Indoors, by pest controller 2.6, 1.2-5.7	Paternal occupational pesticide exposure	Ever exposed 1.9, 0.9-3.7 During pregnancy 1.6, 0.7-3.6 Yr before pregnancy 1.5, 0.7-3.1 after pregnancy 1.0, 0.4-2.5		
Maternal occupational	Ever exposed	During pregnancy				

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
pesticide exposure	4.1, 1.1-16 (4 exp case mo)	11.8, 2.2-64 (4 exp case mo)				
(Rodvall and others 2003), Sweden	Cohort	27,329 offspring of 20,245 male pesticide applicators, born during 1958-1994; licensed during 1965-1976; offspring followed for cancer incidence and mortality from 1958 to 1994; cases identified from national cancer incidence and death records	5 Hodgkin's disease, 3NHL cases, age <20	Licensed pesticide applicators		Age, sex, calendar year
Obs/exp Hodgkin's disease cases based on national incidence rates	SIR = 1.36, 0.44-3.17, n=5	Obs/exp NHL cases based on national incidence rates	SIR = 0.63, 0.13-1.83, n=3	Total lymphoma SIR	SIR = 0.94, 0.44-1.79	
(Flower and others 2004), Agricultural Health Study, USA	Cohort	17537 children of licensed agricultural pesticide applicators; limited to the Iowa subcohort recruited during 1993-97; the father was the applicator for over 99% of children; cases identified from Iowa Cancer Registry	50 cancers identified among children age 0-19 yr, 1975-1998 (includes cases diagnosed before parent enrolled in cohort)	Self-reported pesticide use by licensed pesticide applicators		Adjusted for age; parental age at child's birth, child's sex, birth weight, parental smoking, history of cancer and maternal history of early fetal death were tested and found to not be confounders

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
SIRs among children of licensed pesticide applicators	Total lymphomas (9 cases) 2.18, 1.13-4.19 NHL (2 cases) 1.18, 0.29-4.70	Hodgkin's disease (5 cases) 2.56, 1.06-6.14	Farm animals	Any farm animals 2.38, 0.30-19.0 Cattle 4.13, 0.86-19.9		
(Reynolds and others 2005a), California RE	Ecologic	Statewide cases – 258 Hodgkin's dis, 275 NHL, 99 Burkitt's lymphoma, 1988-94, age <15; cases identified from Statewide cancer registry	ALL incidence ratios (obs:exp) by small geog area	Childhood exposure assessed using data from Pesticide Use Reporting system	Assessed avg lb/mi during 1991-94 for 8 chemical groupings and 7 specific high-use, highly toxic agents within 0.5 mi buffer region	Age, race and ethnicity, and gender
RR, Hodgkin's disease, childhood residence, 75 th vs <1 st percentile, lbs/mi ²	Prob carcinogens 1.28, 0.75-2.18 Genotoxins 1.35, 0.90-2.03	Organochlorines 1.31, 0.70-2.46 OPs 1.12, 0.71-1.76 Carbamates 1.30, 0.77-2.20 Dithiocarbamates 1.38, 0.78-2.44	Propargite (organosulfite acaricide) 0.85, 0.39-1.86 Methyl bromide 1.24, 0.72-2.13 Metam sodium 1.17, 0.52-2.64 Trifluralin (dinitroaniline herbicide) 1.13, 0.40-3.17	Simazine (triazine herbicide) 0.59, 0.25-1.41 Dicofol (organochlorine miticide) 1.43, 0.70-2.95 Chlorothalonil (chlorinated iosphthalic acid fungicide) 0.98, 0.49-1.97		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
RR, NHL, childhood residence, 75 th vs <1 st percentile, lbs/mi ²	Prob carcinogens 0.56, 0.30-1.07 Genotoxins 0.74, 0.46-1.17	Organochlorines 1.11, 0.50-2.47 OPs 0.83, 0.50-1.37 Carbamates 0.84, 0.49-1.43 Dithiocarbamates 0.52, 0.23-1.19	Propargite 0.29, 0.09-0.96 Methyl bromide 0.86, 0.46-1.60 Metam sodium 0.24, 0.03-1.85 Trifluralin 0.47, 0.08-2.78	Simazine 0.76, 0.14-4.06 Dicofol 1.10, 0.43-2.79 Chlorothalonil 0.83, 0.42-1.67		
(Rudant and others 2007), France	Case-control	Population-based, France, 2003-04; nationwide cases from all pediatric oncology hospital departments and a national registry	764 cases acute leukemia, 130 cases Hodgkin's disease, 166 cases NHL, 1681 controls, age <15	Mother-reported household pesticide use during pregnancy and paternal use during pregnancy or childhood		All cancers: age, sex, degree of urbanization, type of housing Leukemia: also birth order
Odds ratio, Hodgkin's disease vs maternal pesticide use	Ever vs never 1.3, 0.9-2.0	Insecticide use, ever vs never 1.3, 0.9-2.0	Home insecticide use, ever vs never 1.4, 1.0-2.2 Pet insecticide use, ever vs never 1.3, 0.7-2.2	Garden insecticide use, ever vs never 0.5, 0.1-1.8 Herbicide use, ever vs never 1.1, 0.5-2.4	Fungicide use, ever vs never 1.9, 0.7-5.3	Mother in agricultural occup during pregnancy 3.2, 0.9-11.8
Odds ratio, Hodgkin's disease vs paternal	Ever vs never 1.0, 0.6-1.5	Insecticide use, ever vs never	Home insecticide use, ever vs	Garden insecticide use, ever vs never	Fungicide use, ever vs never	Father in agricultural occup

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
pesticide use		0.9, 0.6-1.4	never 1.1, 0.7-1.7 Pet insecticide use, ever vs never 1.2, 0.8-2.0	0.9, 0.5-1.5 Herbicide use, ever vs never 1.1, 0.7-1.6	1.3, 0.8-2.2	during pregnancy 0.6, 0.1-3.1
Hodgkin's disease vs only mother used pesticides 3.4, 1.6-7.3	Only father used pesticides 1.2, 0.7-2.2	Both parents used pesticides 1.2, 0.7-2.1	Mother used insecticide, father did not use any pesticide 3.9, 1.7-9.2	Mother used herbicide, father did not use any pesticide na	Father used insecticide, mother did not use any pesticide 0.9, 0.2-3.1	Father used herbicide, mother did not use any pesticide 1.2, 0.4-3.2
Odds ratio, NHL vs maternal pesticide use	Ever vs never 1.9, 1.3-2.6	Insecticide use, ever vs never 1.8, 1.3-2.6	Home insecticide use, ever vs never 1.4, 1.0-2.0 Pet insecticide use, ever vs never 1.2, 0.7-1.9	Garden insecticide use, ever vs never 2.3, 1.1-4.9 Herbicide use, ever vs never 1.5, 0.8-2.7	Fungicide use, ever vs never 1.0, 0.3-2.9	Mother in agricultural occup during pregnancy na
Odds ratio, NHL vs paternal pesticide use	Ever vs never 1.7, 1.2-2.6	Insecticide use, ever vs never 1.5, 1.0-2.1	Home insecticide use, ever vs never 1.5, 1.1-2.1 Pet insecticide use, ever vs never	Garden insecticide use, ever vs never 1.3, 0.8-2.0 Herbicide use, ever vs never 1.5, 1.0-2.2	Fungicide use, ever vs never 1.5, 0.9-2.2	Father in agricultural occup during pregnancy 1.5, 0.6-3.6

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			1.2, 0.8-1.8			
NHL vs only mother used pesticides 3.3, 1.7-6.5	Only father used pesticides 1.8, 1.1-3.1	Both parents used pesticides 2.5, 1.6-4.1	Mother used insecticide, father did not use any pesticide 3.6, 1.7-7.3	Mother used herbicide, father did not use any pesticide na	Father used insecticide, mother did not use any pesticide 1.2, 0.4-3.5	Father used herbicide, mother did not use any pesticide 1.6, 0.7-4.0

Summary: Childhood lymphoma

Reviews

Among 7 studies published by early 1998, 3 reported increased childhood non-Hodgkin’s lymphoma (NHL) risks related to indoor insecticide use during pregnancy or childhood (2 studies) or residence on farms with relatively high pesticide exposures (1 study); the authors noted that each study had few exposed cases or case parents (Zahm and Ward 1998). A recent review of the 4 studies published since Zahm and Ward’s report concluded that they provided further evidence for an association between NHL and pesticide exposure, especially residential indoor insecticide use during pregnancy or childhood for which there were exposure-risk gradients (Infante-Rivard and Weichenthal 2007).

Original studies since 1997

Maternal exposure, insecticides, inadequate evidence

The USA/Canada case-control study reported a dose-response relationship between NHL and frequency of prenatal indoor insecticide use (1-2 vs 0 X/wk, OR=2.62, 95% CI 0.96-7.18; ≥3 X/wk, OR=7.33, 95% CI 0.84-64, p-trend=.05) (Buckley and others 2000). This study also reported a dose-response relationship between NHL and frequency of prenatal outdoor insecticide use (any use vs none, OR=2.98, 95% CI 1.44-6.16, p-trend=.002) (Buckley and others 2000). In the Denver case-control study, lymphoma was not associated with 3rd trimester home extermination (OR=1.2, 95% CI 0.4-3.9) or indoor use of insecticide pest strips (OR=1.4, 95% CI 0.7-2.5) (Leiss and Savitz 1995). Although suggestive, the findings of Buckley et al. require replication.

Maternal exposure, unspecified pesticides, inadequate evidence

The USA/Canada case-control study reported statistically non-significant elevated NHL risks related to occupational pesticide exposure of either parent (OR=1.74, 95% CI 0.82-3.69) and prenatal use of garden pesticide sprays (≥1/mo vs never, OR=1.71, 95% CI 0.67-4.37) (Buckley and others 2000). A German case-control study observed an association between NHL and self-reported prenatal occupational pesticide exposure (OR=11.8, 95% CI 2.2-64, 4 exposed case mothers) (Meinert and others 2000). In the Denver case-control study, lymphoma was not associated with 3rd trimester outdoor use of herbicides and/or insecticides (OR=0.5, 95% CI 0.2-1.2, 6 exposed case mothers) (Leiss and Savitz 1995). The small number of studies, heterogeneity of exposure indices and weak findings preclude firm conclusions.

Paternal occupational exposure, unspecified pesticides, limited evidence

There was a slightly elevated risk of Hodgkin's disease among Norwegian farm children (parents worked on farm at least 500 hr/yr, compared to non-farm families, SIR=1.17, 95% CI 0.85-1.56) (Kristensen and others 1996). There was also a dose-response relationship between NHL risk and pesticide expenditures on Norwegian farms (level 1 vs none, OR=1.30, 95% CI 0.49-3.42; level 2, OR=1.57, 95% CI 0.75-3.30; level 3, OR=2.50, 95% CI 1.02-6.15). In a U.S./Canada case-control study, there was a statistically non-significant elevated risk of NHL related to self-reported occupational pesticide exposure of either parent (OR=1.74, 95% CI 0.82-3.69) (Buckley and others 2000). A case-control study in Germany found a statistically non-significant elevated risk of NHL related to paternal occupational pesticide exposure in the year before conception (OR=1.5, 95% CI 0.7-3.1) (Meinert and others 2000). Among offspring of licensed pesticide applicators, lymphoma risk was not elevated in a Swedish study (SIR=0.94, 95% CI 0.44-1.79, 8 observed cases) (Rodvall and others 2003) but was increased in the AHS cohort (SIR=2.18, 95% CI 1.13-4.19, 9 observed cases) (Flower and others 2004). The relatively consistent findings, including the results of the AHS cohort (likely the best cohort study of pesticide risks ever done) and dose-response relationship provide limited evidence of an association.

Childhood exposure, residential use or proximity to agricultural use of herbicides, inadequate evidence

In the California ecologic study, there was no association between NHL and childhood residential proximity to agricultural use of the herbicides trifluralin ($\geq 75^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, OR=0.47, 95% CI 0.08-2.78) or simazine (OR=0.76, 95% CI 0.14-4.06) (Reynolds and others 2005a). Similarly, there was no association between Hodgkin's disease and childhood residential proximity to agricultural use of trifluralin (OR=1.13, 95% CI 0.40-3.17) or simazine (OR=0.59, 95% CI 0.25-1.41).

Childhood exposure, insecticides, inadequate evidence

In a case-control study in Denver, lymphoma was associated with childhood house extermination (OR=1.8, 95% CI 1.1-2.9) but not with indoor use of insecticide pest strips (OR=1.3, 95% CI 0.4-2.7) (Leiss and Savitz 1995). A German case-control study revealed a dose-response relationship between NHL and childhood indoor insecticide use (> 10 vs < 1 time/yr, OR=2.8, 95% CI 1.1-7.2, p-trend=.02) (Meinert and others 2000).

In a California-wide ecologic study, there was no association between childhood NHL and childhood residential proximity to agricultural use of organochlorine (75^{th} vs $< 1^{\text{st}}$ percentile, lb/mi², OR=1.11, 95% CI 0.50-2.47), organophosphate (OR=0.83, 95% CI 0.50-1.37) or carbamate insecticides (OR=0.84, 95% CI 0.49-1.43) (Reynolds and others 2005a). This study found statistically non-significant elevated risks of Hodgkin's disease related to organochlorine (OR=1.31, 95% CI 0.70-2.46) and carbamate insecticides (OR=1.30, 95% CI 0.77-2.20) and dicofol (1.43, 95% CI 0.70-2.95) but not organophosphate insecticides (OR=1.12, 95% CI 0.71-1.76) or propargite (OR=0.85, 95% CI 0.39-1.86).

Childhood exposure, fungicides, inadequate evidence

In the California ecologic study, there was no association between childhood residential proximity to agricultural use of dithiocarbamate fungicides and NHL (OR=0.52, 95% CI 0.23-1.19) but Hodgkin's disease risk was elevated (OR=1.38, 95% CI 0.78-2.44) (Reynolds and others 2005a). This study found no association between NHL or Hodgkin's disease and childhood residential proximity to agricultural use of soil fumigants (methyl bromide, metam sodium) or the fungicide chlorothalonil.

Childhood exposure, soil fumigants, inadequate evidence

The California ecologic study observed no association between NHL or Hodgkin's disease and childhood residential proximity to agricultural use of the soil fumigants methyl bromide or metam sodium (Reynolds and others 2005a).

Childhood exposure, unspecified pesticides, inadequate evidence

As noted above, children on Norwegian farms reporting pesticide expenditures had an increased risk of NHL (highest vs no expenditure, OR=2.50, 95% CI 1.02-6.15) with evidence of a dose-response relationship (Kristensen and others 1996). Given the design of the Norwegian study, farm pesticide exposures were indices of both prenatal parental and childhood exposures. NHL was associated with direct childhood exposure to herbicides or insecticides in a U.S./Canada case-control study (yes vs no, OR=2.35, 95% CI 1.37-4.03, p-trend=.001 based on exposure frequency); the report did not distinguish between indoor and outdoor exposure (Buckley and others 2000). In the Denver case-control study, lymphoma was not associated with postnatal outdoor use of herbicides and/or insecticides (OR=0.8, 95% CI 0.3-1.8) (Leiss and Savitz 1995). Although suggestive, the small number of studies and heterogeneous exposure indices preclude firm conclusions.

14. Brain tumours

Reviews

Author	Scope	Findings	
(Daniels and others 1997), USA	Literature review, 31 studies of occupational or residence pesticide exposure of parents or children and risk of childhood cancer published 1970-1996	Limited evidence of associations between childhood brain and other CNS tumours and paternal occupational exposure to pesticides before conception and during pregnancy	Fairly consistent associations between brain cancer and use of no-pest strips, pesticides used on pets and pesticide use in home
(Zahm and Ward 1998), USA	Literature review, epidemiologic studies of pesticides and childhood cancer	Out of 16 case-control studies and one cohort study of brain cancer, there was at least one association with a pesticide exposure index in 9 studies and non-significantly elevated risks in 5 additional studies	Most studies found stronger associations with prenatal as compared to childhood exposure
(Olshan and van Wijngaarden 2003), USA	Review of epidemiologic literature on childhood cancer and paternal occupation	Included reviews by Savitz and Chen (1990) and by Colt and Blair (1998) plus studies published since the latter review incl 15 reports on leukemia/lymphoma and 7 reports on brain cancer	4 of 7 studies reviewed by Zahm and Ward (1998) found associations between childhood brain cancer and paternal occupational pesticide exposure
2 of 5 subsequent studies found such associations (incl a high-quality Swedish study (Feychting et al 2001))			
(Baldwin and Preston-Martin 2004), USA	Many pesticides are intentionally neurotoxic and some are carcinogenic properties in animals; these 2 properties	Risk is most frequently elevated with residence use of pesticides, such as no-pest strips, flea and tick medications and pesticide bombs and with	Paternal occupational exposure during pregnancy, but not during childhood, is

	support biologic plausibility that pesticides may cause brain tumors in humans	exposures during or around pregnancy, compared to exposures during childhood	frequently associated with increased risk
A case-control analysis of CBT in 2223 children of farm workers in 7 countries (Efird et al. 2003) found associations with maternal exposure to pesticides in the 5 years before the index child's birth (OR=2.0, CI = 1.2–3.2)	A USA/Canada case-control study found slightly elevated ORs of 1.3-1.6 for astrocytoma related to paternal exposure to all 4 pesticide classes and for maternal exposure to all but agricultural fungicides; PNET risk was increased for paternal exposure to herbicides only		
(Jurewicz and Hanke 2006), Poland	Review epidemiologic studies published during 1998-2005 to update the review by Zahm and Ward. Concluded that recent studies provide further evidence for an association between brain cancer and pesticide exposure but level of evidence is still limited	Limitations of studies include exposure assessment, inadequate statistical power, small numbers of studies on specific relationships, uncertainty about critical windows of exposure	In the light of existing, although still limited evidence of adverse effects of pesticide exposure, it is necessary to reduce exposure to pesticides
(Infante-Rivard and Weichenthal 2007), Quebec	Reviewed 10 epidemiologic studies (4 case-control, 4 cohort and 2 ecological studies) published since review by Zahm and Ward.	3 of the 4 cohorts showed elevated brain cancer risks among offspring of men occupationally exposed to pesticides. The 4 case-control studies all showed associations with pesticide exposure, especially prenatal or household insecticide use.	Of the 3 studies that assessed exposure-risk gradients none showed a significant relationship; however, none of these studies had a strong measure of exposure level.

Brain tumours: Original studies since 1997

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Pogoda and Preston-Martin 1997), U.S. West Coast Childhood Brain Tumor Study	Case-control	Population-based, San Francisco-Oakland, Los Angeles County, Seattle-Puget Sound regions, 1984-91; cases identified from hospital records	224 brain cancer cases, 1984-1991, 218 matched controls, age <20	Mothers reinterviewed during 1988-1992 re pesticide exposures during pregnancy and childhood before Dx		Matched for YOB, sex
OR, brain ca, prenatal residence pesticide exposure	Any indoor insect use 1.3, 0.7-2.4 Indoor termiticide use 2.7, 0.5-14.2	Flea/tick insecticides All cases 1.7, 1.1-2.8 age <5 yr 2.5, 1.2-5.5	Maternal direct use of flea/tick insecticides All cases 2.2, 1.1-4.2 age <5 yr 5.4, 1.3-22.3	# pets treated for fleas/ticks, all subjects, relative to 0 1 pet 1.4, 0.9-2.4 >1 pet 2.0, 1.0-4.0 p-trend = .04	Herbicides 0.9, 0.1-6.1 (2 exposed case mothers)	
OR, brain cancer, childhood pesticide exposure	Flea/tick insecticides 1.0, 0.7-1.4	Any indoor insect use 1.2, 0.8-2.0 Indoor termiticide use 0.7, 0.4-1.3	Failure to leave house after pesticide applic 1.6, 1.0-2.6	Herbicides 1.2, 0.3-4.9 (4 exposed case mothers)		
(Cordier and others 1997), Italy, France, Spain	Case-control	Population-based, Paris, Milan, Valencia, 1983-90; cases	251 cases brain tumours, 601 matched controls,	Parent-reported occupational history for 5 yr before child's birth; JEM		Child's age, sex, ETS and ionizing radiation

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		identified from hospital records	age <16			exposure; maternal age, education, centre
OR, brain tumour, parental employment in agricultural	Paternal 2.0, 1.0-4.1 (17 exp case fa)	Maternal 0.5, 0.2-1.4 (5 exp case mo)				
(Fear and others 1998), England and Wales (excluded) Note: abstract only	Proportional mortality study	360,640 total deaths, age <15, England and Wales, 1959-63 plus 1970-90; cases identified from death records	109 brain and other CNS cancer deaths among 360,640 total deaths, age <15 yr	Potential paternal exposure to pesticides based on occupation recorded on death certificate		Age, year of death, paternal social class
Paternal occupies potentially exposed to pesticides	0.83, 0.69-1.00					
(Holly and others 1998), U.S. West Coast Childhood Brain Tumor Study	Case-control	Population-based, San Francisco-Oakland, Los Angeles County, Seattle-Puget Sound regions, 1984-91; cases identified from cancer registries in each region	540 brain tumour cases, 801 controls, age <20	Mother- and father-reported exposure incl agricultural-related (over 75% of fathers interviewed, an unusually good response rate)		Age, sex, birth year; other variables tested were not confounders
OR, brain tumour, maternal residence or work on a farm during pregnancy	1.6, 0.86-2.9	OR, brain tumour, maternal agricultural pesticide exposure during pregnancy	1.8, 0.77-4.2	OR, brain tumour, length of child's residence on a farm, ref = never on farm	≤1 yr 1.2, 0.58-2.6 >1 yr	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					1.7, 0.88-3.1	
OR, brain tumour, age child first lived on farm, ref = never on farm	age <6 months 1.9, 0.96-3.8 age ≥6 months 1.2, 0.59-2.4	No association with paternal occupation in agricultural (stated in paper without supporting data)				
(Heacock and others 2000), British Columbia	Case-control	Nested within cohort of 23,829 workers in 11 softwood sawmills that used tetra- and pentachlorophenol; men worked at least 1 yr during 1950-85; cases identified by linking cohort file to B.C. marriage, birth and cancer records (incl B.C. Cancer Registry database)	9 cases of brain cancer among offspring age <20 yr, 200 matched controls	Assessed paternal occupational exposure to chlorophenol wood preservatives based on job title and work history	Assessed exposure windows: first exposure to 3 months before conception, 3 months before conception, gestation, childhood, total)	Matched and adjusted for sex, YOB
Risk of brain cancer among offspring similar to that in general population (SIR)	1.3, 0.6-2.5	Cumulative paternal chlorophenolate exposure (hours)	<3000 1.0 ≥ 3560 1.5, 0.4-6.9			
(Cordier and others 2001), 7 countries No DR analyses	Case-control	Population-based, Sydney, Israel, Paris, Winnipeg, Milan, Valencia, Los Angeles,	1,218 cases brain or cranial nerve ca, 2,223 matched controls, age <20	Mother- and father-reported occupa and occupational exposures during 5 yr before child's		Child's age at interview, YOB, sex, study centre

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		San Francisco, Seattle; 1976-94; cases identified from hospital records, 90% histologically confirmed, remainder by radiology		birth		
OR, brain ca, paternal occupation in agricultural during 5 yr before birth	All brain ca 1.3, 1.0-1.8 PNET 1.1, 0.6-1.9	Astroglial 1.2, 0.8-1.8 Other glial 1.8, 1.0-3.5	OR, brain ca, maternal occupation in agricultural during 5 yr before birth	All brain ca 1.1, 0.7-1.9 PNET 1.5, 0.6-3.7	Astroglial 1.2, 0.6-2.3 Other glial 0.92, 0.2-3.9	
OR, brain ca, maternal occupation in agricultural	During pregnancy 1.4, 0.6-3.0	Before pregnancy 0.96, 0.5-2.0				
(Feychting and others 2001), Sweden	Birth cohort	235,635 children of married couples born soon after 2 censuses; linked national birth, census, death and cancer registry databases, 1976-93; cases identified from nationwide Swedish Cancer Registry	522 cancer cases incl 162 nervous system tumours, age <15 yr	Census info on father's occupation/industry; JEM		Census year, sex, maternal age

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Possible or probable paternal occupational pesticide exposure before conception	2.36, 1.27-4.39					
(Schuz and others 2001a), Germany	Case-control	Population-based, the former West Germany, 1988-94; cases identified from nationwide cancer registry	466 CNS tumour cases, 2,458 matched controls, age <15	Mother- and father-reported info on occupational and other exposures		Matched for YOB, sex; adj for family net income, parental education, urban/rural
OR, CNS tumour, annual freq of household insecticide use during childhood, ref = never	All brain ca 1/yr 1.38, 0.84-2.25 >1/yr 1.19, 0.81-1.77	Astrocytoma 1/yr 2.45, 1.09-5.47 >1/yr 0.58, 0.23-1.49	Medulloblastoma 1/yr 1.14, 0.44-2.95 >1/yr 1.06, 0.49-2.28	OR, CNS tumour, pesticide use during childhood	All brain cancer In garden 0.94 (0.68-1.29) On farms 0.41 (0.18-0.93)	Similar results for other histologic types
OR, CNS tumour, childhood residence use of wood preservatives	All brain ca 1.26, 1.00-1.59	Astrocytomas 1.91, 1.22-3.01	Medulloblastoma 1.15, 0.74-1.77			
(Reynolds and others 2002), California RE	Ecologic	State-wide childhood cancer incidence, 1988-94; cases identified from State-wide cancer registry	1,351 brain glioma cases age <15	State agricultural Pesticide Use Report database for 1991-94	Use of restricted pesticides (lb/sq mi) within 0.2 sq mi areas; no data on parental occupational or	Age, race, sex

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					residence pesticide use	
OR, brain cancer, residential prox to agricultural use of propargite, percentiles of lb/mi ² <1 1-74 75-89 ≥90	1.0 0.82, 0.66-1.02 1.04, 0.66-1.62 0.98, 0.54-1.76	Methyl bromide percentile (lb/mi ²) <1 1-74 75-89 ≥90	1.0 0.99, 0.84-1.16 0.77, 0.52-1.14 0.63, 0.38-1.05	Simazine percentile (lb/mi ²) <1 1-74 75-89 ≥90	1.0 1.02, 0.85-1.22 1.08, 0.72-1.60 1.12, 0.69-1.82	
Metam sodium percentile (lb/mi ²) <1 1-74 75-89 ≥90	1.0 0.87, 0.64-1.20 0.77, 0.35-1.67 0.37, 0.09-1.41	Trifluralin percentile (lb/mi ²) <1 1-74 75-89 ≥90	1.0 0.80, 0.65-0.98 0.75, 0.46-1.22 0.58, 0.27-1.25	Chlorothalonil percentile (lb/mi ²) <1 1-74 75-89 ≥90	1.0 0.95, 0.79-1.15 0.83, 0.52-1.33 0.47, 0.23-0.97	
Dicofol percentile (lb/mi ²) <1 1-74 75-89 ≥90	1.0 0.92, 0.71-1.20 0.52, 0.24-1.13 1.16, 0.60-2.22	Probable carcinogens percentile <1 1-74 75-89 ≥90	1.0 1.03, 0.91-1.17 0.74, 0.54-1.01 0.78, 0.545-1.12	Possible carcinogens percentile <1 1-74 75-89 ≥90	1.0 1.05, 0.93-1.18 0.84, 0.64-1.10 0.78, 0.54-1.12	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Genotoxins percentile <1 1-74 75-89 ≥90	1.0 1.09, 0.98-1.22 0.81, 0.64-1.03 0.71, 0.52-0.96	Devmtl/repro toxicants percentile <1 1-74 75-89 ≥90	1.0 1.04, 0.93-1.17 0.85, 0.66-1.10 0.76, 0.55-1.06	Organochlorines percentile <1 1-74 75-89 ≥90	1.0 0.87, 0.69-1.09 0.74, 0.42-1.30 0.86, 0.44-1.67	
Organophosphates percentile <1 1-74 75-89 ≥90	1.0 1.09, 0.97-1.22 0.80, 0.61-1.05 0.71, 0.50-1.02	Carbamates percentile <1 1-74 75-89 ≥90	1.0 1.12, 0.97-1.29 0.73, 0.50-1.06 0.76, 0.48-1.19	Dithiocarbamates percentile <1 1-74 75-89 ≥90	1.0 0.85, 0.71-1.01 0.93, 0.64-1.34 0.59, 0.33-1.04	
(Ebird and others 2003), 7 countries No DR analyses	Case-control	Population-based in San Francisco, Los Angeles, Seattle, Israel, Milan, Valencia, Sydney, Paris, Winnipeg, (SEARCH International Brain Tumour Study), 1976- 94; cases identified from hospital records and population-based cancer registries	1218 brain cancer cases, 2223 matched controls, age <20	Mother-reported exposure info		Matched for age, gender, geog region

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
All brain tumours						
OR, brain tumour, prenatal maternal residence on farm	1.3, 1.0-1.8	OR, brain tumour, maternal occupational exposure, <5 yr before child's birth	Any farm or agricultural 1.3, 0.80-2.2	General farm worker 3.8, 1.3-11	Agricultural pesticide use 2.0, 1.2-3.2	
OR, brain tumour, childhood residence on farm	1.3, 1.0-1.7 Starting before age 6 months 1.6, 1.1-2.2					
Astroglial brain tumours						
OR, brain tumour, residence on farm	Childhood 1.2, 0.84-1.7 Prenatal maternal 1.3, 0.90-2.0	OR, brain tumour, residence on farm before age 6 months	Childhood 1.4, 0.91-2.2	OR, brain tumour, on-farm animal exposure, any animal	Childhood 1.2, 0.85-1.8 Prenatal maternal 1.4, 0.92-2.1	
PNET tumours						
OR, brain tumour, residence on farm	Childhood 1.6, 0.97-2.5 Prenatal maternal 1.1, 0.61-1.9	OR, brain tumour, residence on farm before age 6 months	Childhood 1.6, 0.90-3.0	OR, brain tumour, on-farm animal exposure, any animal	Childhood 1.6, 0.93-2.6 Prenatal maternal 1.2, 0.91-1.5	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Rodvall and others 2003), Sweden	Cohort	27,329 offspring of 20,245 male pesticide applicators, born during 1958-1994; licensed during 1965-1976; offspring followed for cancer incidence and mortality from 1958 to 1994; cases identified from national cancer incidence and death records	17 brain tumour cases, age <20	Licensed pesticide applicators		Age, sex, calendar year
SIR, brain tumours (observed 17 cases, expected 16.4 cases)	1.03, 0.60-1.65					
(van Wijngaarden and others 2003), Children's Cancer Group, USA and Canada	Case-control	Population-based, 1986-89; cases identified through the Children's Cancer Group, a network of collaborating pediatric oncology hospitals	154 cases of astrocytoma and 158 cases of primitive neuroectodermal tumour (PNET) of brain, matched 321 controls, age <6	Mother- and father-reported job history and exposures	JEM to estimate exposure duration and intensity; for fathers, also estimated cumulative exposure: total, <2 yr before pregnancy, pregnancy, postnatal	Matched for race, YOB, telephone area code plus next 5 digits; adj for maternal age, education, hhld income

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
OR, brain ca, probable paternal occupational pesticide exposure, $\geq 50^{\text{th}}$ percentile of cumulative exposure-days vs unexposed, adjusted for other classes of pesticides	All brain ca Insecticides 0.7, 0.2-2.8 herbicides 1.6, 0.4-6.3 fungicides 0.7, 0.4-1.3	OR, brain ca, paternal occupational exposure, ever/never exposed	Astrocytomas Farm worker 1.1, 0.5-2.3 Insecticides 1.5, 0.9-2.4 herbicides 1.6, 1.0-2.7 fungicides 1.6, 1.0-2.6	PNET Farm worker 0.9, 0.5-1.7 Insecticides 1.1, 0.7-1.7 herbicides 1.5, 0.9-2.6 fungicides 1.1, 0.7-1.8		
OR, brain ca, preconceptual or prenatal maternal occupational exposure, $\geq 50^{\text{th}}$ percentile of cumulative exposure-days vs unexposed, adjusted for other classes of pesticides	All brain ca Insecticides 1.9, 1.0-3.8 herbicides 0.5, 0.1-2.2 fungicides 0.6, 0.3-1.0	OR, brain ca, preconceptual or prenatal maternal occupational exposure, ever/never exposed	Astrocytomas Insecticides 1.9, 1.1-3.3 herbicides 1.3, 0.5-3.7 fungicides 1.6, 0.9-2.7	PNET Insecticides 1.0, 0.6-1.7 herbicides 0.5, 0.2-1.5 fungicides 0.7, 0.4-1.2		
(McKinney and others 2003), UK Childhood Cancer Study	Case-control	Population-based, England, Scotland, Wales, 1991-96 Children's Cancer Group; cases identified from	687 CNS, 7629 matched controls, age <15	Parent-reported info incl occupies at conception, birth and cancer diagnosis; coded job titles and associated industries		Matched for sex, age, residence region at diagnosis

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		cancer incidence and death records				
OR, CNS tumour, periconceptual occurs potentially exposed to agrochemicals	Maternal 1.26, 0.38-4.17 (3 exp case mos0) Paternal 0.77, 0.44-1.36 (13 exp case fas)	OR, CNS tumour, periconceptual occupation in agricultural	Maternal 1.55, 0.46-5.19 (3 exp case months) Paternal 0.70, 0.35-1.38 (9 exp case fas)			
(Flower and others 2004), Agricultural Health Study, USA	Cohort	17537 children of licensed agricultural pesticide applicators; limited to the Iowa subcohort recruited during 1993-97; the father was the applicator for over 99% of children; cases identified from Iowa Cancer Registry	50 cancers identified among children age 0-19 yr, 1975-1998 (includes cases diagnosed before parent enrolled in cohort), 11 brain cancers	Self-reported pesticide use by licensed pesticide applicators		Parental age at child's birth, child's age, sex, birth weight, parental smoking, history of cancer and maternal history of early fetal death were tested and found to not be confounders
SIR, brain cancer, children of licensed pesticide applicators	1.60, 0.89-2.89					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Nielsen and others 2005), Washington State	Case-control	Population-based, Seattle-Puget Sound region, 1984-91; cases identified from population-based cancer registry	66 brain cancer cases, 236 matched controls, age <20	Mother-reported indoor insecticide use during pregnancy or childhood	Used archived neonatal DNA to detect PON1 polymorphisms; most common residence insecticides in use were chlorpyrifos and diazinon that are metabolized via the cytochrome P450/paraoxonase 1 (PON1) pathway	Matched for age and sex
OR, brain ca, PON1(-108TT) allele (inefficient polymorphism), relative to PON1(-108CC); subset whose mothers reported indoor insecticide use during pregnancy or childhood	Insecticide-exposed cases PON1 CC genotype 1.0 (ref) CT 2.6, 1.2-5.5 TT 6.6, 1.5-29.7	OR, brain ca, PON1(C-108TT) allele (inefficient polymorphism), relative to PON1(C-108CC)	2.1, 0.9-4.7 p-trend = 0.07			
(Reynolds and others 2005b), California	Case-control	State-wide, population-based, 1990-1997; cases identified from Calif cancer registry	352 cases CNS tumours, 4335 controls, age <5 yr, 1990-1997	Maternal res prox to agricultural pesticide use during pregnancy	Statewide database on agricultural pesticide use incl active ingredient, amt, date, acres	Race, gender, age

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					treated, location (sq mi sections); identified high-risk pesticides – propargite, methyl bromide, trifluralin, simazine, metam sodium, dicofol, chlorothalonil	
Propargite percentile (lb/mi ²) <1 1-49 ≥50	OR 1.0 0.71, 0.29-1.74 1.06, 0.50-2.28	Methyl bromide percentile (lb/mi ²) <1 1-49 ≥50	OR 1.0 1.59, 0.87-2.89 0.80, 0.44-1.46	Simazine percentile (lb/mi ²) <1 1-49 ≥50	OR 1.0 0.62, 0.24-1.59 1.06, 0.49-2.26	
Metam sodium percentile (lb/mi ²) <1 1-49 ≥50	OR 1.0 0.98, 0.29-3.29 0.91, 0.27-3.08	Trifluralin percentile (lb/mi ²) <1 1-49 ≥50	OR 1.0 0.98, 0.36-2.70 0.88, 0.26-2.98	Chlorothalonil percentile (lb/mi ²) <1 1-49 ≥50	OR 1.0 0.64, 0.28-1.42 1.18, 0.58-2.38	
Dicofol percentile (lb/mi ²) <1 1-49 ≥50	OR 1.0 0.99, 0.27-3.58 0.65, 0.27-1.61	Probable carcinogens percentile <1 1-49 ≥50	OR 1.0 0.89, 0.58-1.38 0.86, 0.54-1.36	Possible carcinogens percentile <1 1-49 ≥50	OR 1.0 0.92, 0.62-1.37 0.86, 0.57-1.29	
Genotoxins percentile <1 1-49	OR 1.0 1.00, 0.69-1.46	Devmtl/repro toxicants percentile <1	OR 1.0 0.97, 0.65-1.45	Organochlorines percentile <1 1-49	OR 1.0	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
≥50	0.93, 0.65-1.35	1-49 ≥50	0.84, 0.57-1.24	≥50	1.10, 0.50-2.41 0.73, 0.32-1.65	
Organophosphates percentile <1 1-49 ≥50	OR 1.0 0.89, 0.59-1.35 1.10, 0.74-1.66	Carbamates percentile <1 1-49 ≥50	OR 1.0 0.71, 0.43-1.19 0.93, 0.56-1.57	Dithiocarbamates percentile <1 1-49 ≥50	OR 1.0 0.99, 0.52-1.89 0.89, 0.49-1.64	
(Walker and others 2007), Texas	Case-control	Population-based, cases from state-wide cancer registry, 1990-98	1178 leukemia cases, 3487 live birth controls, age <15	Ecological exposure indices: 1987, 1992 and 1997 Census of Agriculture info on % of land in crops and pesticide use in the county of birth (254 counties); pesticide use estimated from acres in specific crops and state data on pesticide use per acre; used EPA carcinogenicity classification to categorize county pesticide use weighted by potential for carcinogenicity	3 exposure categories for both % of county land in cropland and county pesticide use	Adj for child's age, race/ethnicity, sex; eliminated birth weight, maternal age and paternal education as potential confounders
OR, brain cancer, birth in counties with 25-49 or ≥50% vs <25% land in crops	All brain cancers 0.9, 0.8-1.1 1.3, 0.9-1.8	Astrocytoma 1.0, 0.7-1.3 1.4, 0.8-2.2 p-trend=.69	PNET 1.0, 0.7-1.4 1.3, 0.7-2.5 p-trend=.41			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	p-trend=.55					
OR, brain cancer, birth in counties with medium or high vs low pesticide use	All brain cancers 0.9, 0.7-1.1 1.0, 0.8-1.3 p-trend=.83	Astrocytoma 1.0, 0.8-1.3 1.1, 0.7-1.5 p-trend=.80	PNET 1.2, 0.8-1.7 1.2, 0.7-1.8 p-trend=.42			

Summary: Childhood brain tumours

Reviews

A review found limited evidence of associations between childhood brain cancer and preconceptional paternal occupational pesticide exposure and prenatal maternal pesticide exposure at home or work (Daniels and others 1997). Exposure associated with brain cancer included residential insecticide use (no-pest strips, pet insecticides, other indoor insecticide use). Another review noted that 12 of 16 case-control studies published by early 1998 revealed increased childhood brain cancer risks related to pesticide exposure with statistically significant relationships in 7 studies (Zahm and Ward 1998). Risks were generally highest for parental pesticide use in the home, garden or on pets. Most studies found stronger associations with prenatal as compared to childhood exposure. The only cohort study observed an association with paternal employment in farming and one of the case-control studies found an association with prenatal household insecticide use or at least 1 year farm residence. A recent report reviewed the 10 epidemiologic studies (4 case-control, 4 cohort and 2 ecological studies) published since the 1998 review by Zahm and Ward (Infante-Rivard and Weichenthal 2007). The authors noted that 3 of the 4 cohorts showed elevated brain cancer risks among offspring of men occupationally exposed to pesticides and all 4 case-control studies found associations with pesticide exposure, especially prenatal or household insecticide use. Of the 3 studies that assessed exposure-risk gradients none showed a significant relationship; however, none of these studies had a strong measure of exposure level.

Original studies since 1997

Maternal exposure, herbicides, inadequate evidence

There was no association between brain cancer and prenatal residential herbicide use in Missouri (lawn herbicides, OR=1.1, 95% CI 0.5-2.5) (Davis and others 1993) or Denver (outdoor insecticide or herbicide use, OR=0.6, 95% CI 0.3-1.1) (Leiss and Savitz 1995). A large United States/Canada case-control study reported no association between maternal occupational herbicide exposure and astrocytoma (OR=1.3, 95% CI 0.5-3.7) or PNET (OR=0.5, 95% CI 0.2-1.5) (van Wijngaarden and others 2003). In a California case-control study, brain tumours before age 5 were not associated with prenatal residential proximity to agricultural use of the herbicides simazine ($\geq 50^{\text{th}}$ vs $< 1^{\text{st}}$ percentile of lb/mi², OR=1.06, 95% CI 0.49-2.26) or trifluralin (OR=0.88, 95% CI 0.26-2.98) (Reynolds and others 2005b).

Maternal exposure, insecticides, limited evidence

Prenatal residential insecticide use was related to elevated childhood brain tumour risks in Missouri (OR=1.8, 95% CI 0.8-4.0; insecticide pest strips in home, OR=5.2, 95% CI 1.2-22.2) (Davis and others 1993), France (OR=1.8, 95% CI 0.8-4.1) (Cordier and others 1994), USA/Canada (astrocytoma, any prenatal use, OR=1.5, 95% CI 0.8-2.7; used at least weekly, OR=2.2, 95% CI 0.6-7.4) (Bunin and others 1994), Australia (home extermination, OR=2.0, 95% CI 1.0-3.9) (McCredie and others 1994a), Denver (insecticide pest strips in home, OR=1.5, 95% CI 0.9-2.4; house extermination, OR=1.3, 95% CI 0.7-2.1) (Leiss and Savitz 1995) and western USA (direct prenatal use of flea/tick insecticides, all cases, OR=2.2, 95% CI 1.1-4.2; cases age <5, OR=5.4, 95% CI 1.3-22.3) (Pogoda and Preston-Martin 1997). The western USA study also revealed associations between brain cancer and prenatal number of pets treated with insecticides for fleas/ticks (1 pet, OR=1.4, 95% CI 0.9-2.4; >1 pet, OR=2.0, 95% CI 1.0-4.0, p-trend=.04). Among children in households with indoor insecticide use during pregnancy or childhood, brain cancer risk was strongly associated with inefficient polymorphisms at C-108 in PON1, the gene that encodes paraoxonase, an organophosphate detoxifying enzyme (CC, OR=1.0 (referent); CT, OR=2.6, 95% CI 1.2-5.5; TT, OR=6.6, 95% CI 1.5-29.7) (Nielsen and others 2005). There was no association between PNET and prenatal indoor insecticide use in the USA/Canada study (any prenatal use, OR=0.7, 95% CI 0.4-1.4; used at least weekly, OR=1.0, 95% CI 0.2-4.9) (Bunin and others 1994).

Prenatal outdoor residential insecticide use was related to elevated childhood brain tumour risks in Missouri (carbaryl, OR=1.5, 95% CI 0.7-3.3; diazinon, OR=4.6, 95% CI 1.2-17.9) (Davis and others 1993). A large United States/Canada case-control study reported an association between maternal occupational insecticide exposure and astrocytoma (OR=1.9, 95% CI 1.1-3.3) but not PNET (OR=1.0, 95% CI 0.6-1.7) (van Wijngaarden and others 2003). In a California case-control study, brain tumours before age 5 were not associated with prenatal residential proximity to agricultural use of organochlorine ($\geq 50^{\text{th}}$ vs $< 1^{\text{st}}$ percentile of lb/mi^2 , OR=0.73, 95% CI 0.32-1.65), organophosphate (OR=1.10, 95% CI 0.74-1.66) or carbamate insecticides (OR=0.93, 95% CI 0.56-1.57), propargite (OR=1.06, 95% CI 0.50-2.28) or dicofol (OR=0.65, 95% CI 0.27-1.61) (Reynolds and others 2005b). In sum, there were elevated brain cancer risks in 6 of 7 case-control studies of residential indoor insecticide use with statistical significance apparent in 4 studies, a dose-response relationship in 1 study and increased risk among children with inefficient polymorphisms at C-108 in PON1, the gene that encodes paraoxonase, an organophosphate detoxifying enzyme.

Maternal exposure, fungicides, inadequate evidence

A large United States/Canada case-control study reported an association between maternal occupational fungicide exposure and astrocytoma (OR=1.6, 95% CI 0.9-2.7) but not PNET (OR=0.7, 95% CI 0.4-1.2) (van Wijngaarden and others 2003). In a California case-control study, brain tumours before age 5 were not associated with prenatal residential proximity to agricultural use of dithiocarbamate fungicides ($\geq 50^{\text{th}}$ vs $< 1^{\text{st}}$ percentile of lb/mi^2 , OR=0.89, 0.49-1.64) or chlorothalonil (OR=1.18, 95% CI 0.58-2.38) (Reynolds and others 2005b).

Maternal exposure, other specified pesticides, inadequate evidence

In a California case-control study, brain tumours before age 5 were not associated with prenatal residential proximity to agricultural use of the soil fumigants dimethyl bromide (OR=0.80, 95% CI 0.44-1.46) or metam sodium (OR=0.91, 95% CI 0.27-3.08) (Reynolds and others 2005b).

Maternal exposure, unspecified pesticides, inadequate evidence

Elevated brain tumour risk was related to prenatal pesticide exposure in case-control studies in France (prenatal farm residence, OR=2.5, 95% CI 0.4-16.1, 4 exposed case mothers) (Cordier and others 1994), USA/Canada (farm residence, PNET, OR=3.7, 95% CI 0.8-23.9) (Bunin and others 1994), western U.S. States (prenatal agricultural pesticide use, OR=1.8, 95% CI 0.77-4.2) (Holly and others 1998) and a 7-country study (prenatal farm residence, OR=1.3, 95% CI 1.0-1.8; maternal agricultural pesticide use, OR=2.0, 95% CI 1.2-3.2) (Efird and others 2003).

In the USA/Canada study, astrocytomas were not associated with prenatal farm residence (OR=0.5, 95% CI 0.1-1.8, 4 exposed case mothers) (Bunin and others 1994). Brain cancer was not associated with prenatal pesticide exposure in Australia (maternal farm residence or farm work, OR=0.9, 95% CI 0.3-2.6) (McCredie and others 1994a), Europe (OR=0.5, 95% CI 0.2-1.4, 5 exposed case mothers) (Cordier and others 1997) or a 7-country study (maternal occupation in agriculture, during 5 yr before birth, OR=1.1, 95% CI 0.7-1.9; during pregnancy, OR=1.4, 95% CI 0.6-3.0) (Cordier and others 2001). The inconsistent findings, lack of statistical significance in most of the positive studies and the lack of demonstrated dose-response relationships comprise inadequate evidence for an association.

Paternal exposure, chlorophenolate wood preservatives, inadequate evidence

Among children of sawmill workers in British Columbia, Canada, there was a statistically non-significant elevated brain cancer risk related to paternal occupational chlorophenolate exposure duration (≥ 3560 vs < 3560 hours cumulated exposure, OR=1.5, 95% CI 0.4-6.9) (Heacock and others 2000).

Paternal exposure, broad pesticide classes, inadequate evidence

A large United States/Canada case-control study reported associations between astrocytoma brain tumours and paternal occupational exposure to herbicides (astrocytoma, OR=1.6, 95% CI 1.0-2.7), insecticides (OR=1.5, 95% CI 0.9-2.4) and fungicides (OR=1.6, 95% CI 1.0-2.6); PNET brain tumours were associated with paternal exposure to herbicides (OR=1.5, 95% CI 0.9-2.6) but not insecticides or fungicides (van Wijngaarden and others 2003). These findings require replication and exploration of dose-response relationships.

Paternal occupational exposure, unspecified pesticides, limited evidence

There was a dose-response relationship between non-astrocytic neuroepithelial brain tumours and pesticide expenditures in a Norwegian record-based cohort study of farm families (level 1 expenditures, OR=2.00, 95% CI 0.85-4.74; level 2, OR=2.93, 95% CI 1.54-5.60; level 3, OR=3.28, 95% CI 1.39-7.76) (Kristensen and others 1996). This study noted a particularly high risk of such tumours among children age < 5 on grain farms with pesticide purchases (OR=8.01, 95% CI 1.62-39.7). Because of the design of the Norwegian study, pesticide exposure indices reflect both prenatal parental and childhood exposures. Brain cancer risk was elevated among children of licensed pesticide applicators in the AHS cohort (SIR=1.60, 95% CI 0.89-2.89) (Flower and others 2004) but not in a Swedish record-based cohort (SIR=1.03, 95% CI 0.60-1.65) (Rodvall and others 2003). When paternal pesticide exposure was inferred from job titles, without other evidence of exposure, increased childhood brain cancer risk was noted in studies in Ohio (preconceptual paternal occupation in farming, brain cancer deaths, OR=2.0, 95% CI 1.0-4.1) (Wilkins and Koutras 1988), another Ohio study (preconceptual paternal occupation in farming, brain cancer incident cases, OR=2.7, 95% CI 0.8-9.1) (Wilkins and Sinks 1990), 3 U.S. States (preconceptual paternal occupation in agriculture, OR=1.8, 95% CI 0.6-6.0) (Kuijten and others 1992), France (preconceptual paternal occupation in agriculture (OR=2.0, 95% CI 1.0-4.1) (Cordier and others 1997), a 7-country study (paternal occupation in agriculture during 5 yr before birth, OR=1.3, 95% CI 1.0-1.8) (Cordier and others 2001) and Sweden (potential paternal preconceptual occupational pesticide exposure, RR=2.36, 95% CI 1.27-4.39) (Feychting and others 2001). There was no association in case-control studies in Quebec (occupation as farmer, OR=0.56, 95% CI 0.22-1.26) (Fabia and Thuy 1974) or UK (occupation in farming, OR=0.70, 95% CI 0.35-1.38) (McKinney and others 2003). The relatively consistent findings and dose-response relationship are suggestive of an association.

Childhood exposure, herbicides, inadequate evidence

Brain cancer was associated with childhood residential herbicide use in a case-control study in Missouri (OR=2.4, 95% CI 1.0-5.7) (Davis and others 1993) but not in Denver (use of herbicides or insecticides in yard, OR=0.5, 95% CI 0.2-0.9) (Leiss and Savitz 1995) or western USA (OR=1.2, 95% CI 0.3-4.9, 4 exposed case mothers) (Pogoda and Preston-Martin 1997). An ecologic study in California found no association between brain gliomas and childhood residential proximity to agricultural use of the herbicides simazine ($\geq 90^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, OR=1.12, 95% CI 0.69-1.82) and trifluralin (OR=0.58, 95% CI 0.27-1.25) (Reynolds and others 2002).

Childhood exposure, insecticides, limited evidence

Indoor residential insecticide use was associated with elevated brain cancer risks in case-control studies in Baltimore (household insect extermination, OR=2.29, 95% CI 0.96-5.95) (Gold and others 1979), Missouri (indoor use of insecticides, OR=3.4, 95% CI 1.1-10.6; indoor insecticidal pest strips, OR=3.7, 95% CI 1.0-13.7; Kwell insecticidal shampoo, OR=4.6, 95% CI 1.0-21.3) (Davis and others 1993), France (home extermination, OR=2.0, 95% CI 1.0-4.1) (Cordier and others 1994), Denver (insecticide pest strips, OR=1.4, 95% CI 0.7-2.9; house extermination, OR=1.4, 95% CI 0.6-2.7) (Leiss and Savitz 1995) and Los Angeles (failure to evacuate house after indoor insecticide use, OR=1.6, 95% CI 1.0-2.6) (Pogoda and Preston-Martin 1997). A German case-control study reported statistically non-significant and non-dose related elevated brain cancer risks related to indoor insecticide use (1X/yr vs 0, OR=1.38, 95% CI 0.84-2.25; >1/yr, OR=1.19, 95% CI 0.81-1.77) (Schuz and others 2001a). The western USA study found no association with any indoor insecticide use (OR=1.2, 95% CI 0.8-2.0) or flea/tick insecticide use (OR=1.0, 95% CI 0.7-1.4) (Pogoda and Preston-Martin 1997). An ecologic study in California found no association between brain gliomas and childhood residential proximity to agricultural use of organochlorine ($\geq 90^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, OR=0.86, 95% CI 0.44-1.67), organophosphate (OR=0.71, 95% CI 0.50-1.02) or carbamate insecticides (OR=0.76, 95% CI 0.48-1.19) (Reynolds and others 2002). The consistency of findings is suggestive of an association but further research is needed to explore dose-response relationships and specific insecticides or groups of toxicologically related insecticides.

Childhood exposure, fungicides, inadequate evidence

An ecologic study in California found no association between brain gliomas and childhood residential proximity to agricultural use of dithiocarbamate fungicides ($\geq 90^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, OR=0.59, 95% CI 0.33-1.04) or chlorothalonil (OR=0.47, 95% CI 0.23-0.97) (Reynolds and others 2002).

Childhood exposure, other specified pesticides, inadequate evidence

There was no association between brain cancer and childhood residential use of wood preservatives (OR=1.26, 95% CI 1.00-1.59) (Schuz and others 2001a). An ecologic study in California found no association between brain gliomas and childhood residential proximity to agricultural use of the soil fumigants methyl bromide ($\geq 90^{\text{th}}$ vs $< 1^{\text{st}}$ percentile, OR=0.63, 95% CI 0.38-1.05) and metam sodium (OR=0.37, 95% CI 0.09-1.41) (Reynolds and others 2002).

Childhood exposure, unspecified pesticides, limited evidence

Brain tumours were associated with outdoor residential pesticide use or proximity to agricultural pesticide use in case-control studies in Baltimore (childhood farm residence, OR=4.00, 95% CI 1.21-17.7) (Gold and others 1979), France (farm residence, OR=6.7, 95% CI 1.2-38.0) (Cordier and others 1994), USA/Canada (residence on farm for at least 1 yr, PNET, OR=5.0, 95% CI 1.1-46.8) (Bunin and others 1994), western States in the USA (farm residence before age 6 mos, OR=1.9, 95% CI 0.96-3.8; farm residence for over 1 yr, OR=1.7, 95% CI 0.88-3.1) (Holly and others 1998) and a 7-country study (childhood farm residence, OR=1.3, 95% CI 1.0-1.7; beginning before age 6 mos, OR=1.6, 95% CI 1.1-2.2) (Efird and others 2003). As noted above, there was a dose-response relationship between non-astrocytic neuroepithelial brain tumours and pesticide expenditures in a Norwegian record-based cohort study of farm families, especially among

children age <5 living on grain farms (Kristensen and others 1996). The design of the Norwegian study precluded clear distinction between prenatal parental and childhood pesticide exposures. No association was apparent in studies in Ontario (childhood pesticide exposure, OR=0.94, 95% CI 0.47-1.90) (Howe and others 1989), USA/Canada (childhood farm residence, OR=0.4, 95% CI 0.1-1.6) (Bunin and others 1994) or Australia (lived or worked on farm, OR=0.6, 95% CI 0.2-1.9, only 4 exposed cases) (McCredie and others 1994b). Although there was uncertainty about the timing of pesticide exposure in the Norwegian cohort, the observation of associations in the larger studies, the strength of associations (odds ratios in 3 studies exceeded 4) and the fact that 2 of the 3 studies with negative findings had less than 100 cases is suggestive of an association.

15. Neuroblastomas

Reviews

Author	Scope	Findings	
(Zahm and Ward 1998), USA	Literature review, epidemiologic studies of pesticides and childhood cancer	Neuroblastoma – the 4 case-control studies and one cohort study found little evidence for an association with pesticides; the elevated risk seen in the cohort study was based on only 7 cases	
(Jurewicz and Hanke 2006), Poland	Review epidemiologic studies published during 1998-2005 to update the review by Zahm and Ward. Concluded that recent studies provide further evidence for an association between neuroblastoma and pesticide exposure but level of evidence is still limited	Limitations of studies include exposure assessment, inadequate statistical power, small numbers of studies on specific relationships, uncertainty about critical windows of exposure	In the light of existing, although still limited evidence of adverse effects of pesticide exposure, it is necessary to reduce exposure to pesticides
(Infante-Rivard and Weichenthal 2007), Quebec	Reviewed 1 cohort and 3 case-control studies published since review by Zahm and Ward.	All 4 recent studies showed associations between neuroblastoma and parental occupational or residential pesticide use.	One recent study found an association between neuroblastoma and residential herbicide use.

Neuroblastomas: Original studies since 1997

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Olshan and others 1999), Children's Cancer Group, United States and Canada	Case-control	Population-based, cases from 139 hospitals in United States and Canada, 1992-94; cases	504 cases neuroblastoma, 504 matched controls, age <19	Mother- and father-reported occupational histories since age 18		Matched for DOB; adj for maternal age, race, education,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		identified from hospital records				household income
OR, neuroblastoma, paternal occupation	Farmer or farm worker 0.9, 0.4-1.8	Landscaper or groundskeeper 2.3, 1.0-5.2	OR, neuroblastoma, maternal occupation	Farmer or farm worker 2.2, 0.6-8.8 (7 exp case mo)	Florist or garden store worker 2.4, 0.6- 9.9 (6 exp case mo)	No DR analysis
(Kerr and others 2000), New York State	Case-control	Population-based, NY State minus NY City, 1976-87; cases identified from hospital records; all cases histologically confirmed	183 neuroblastoma cases, 372 controls, age <15	Mother-reported parental occupa and work-related exposures during pregnancy	Assessed exposure using a list of 25 potential workplace carcinogens	Child's age, parental age, education
OR, neuroblastoma, prenatal occupation in agricultural, yes/no	Maternal 0.8, 0.2-3.2 Paternal 1.0, 0.2-3.9	OR, neuroblastoma, prenatal occupational insecticide exposure, yes/no	Maternal 2.3, 1.4-3.7 Paternal 1.7, 1.0-2.7	OR, neuroblastoma, self-reported occupational insecticide exposure + expert-rated potential for such exposure vs neither	Maternal 2.6, 1.5-4.5 Paternal 1.8, 1.1-3.1	No DR analysis
OR, neuroblastoma, paternal occupational dioxin exposure	6.9, 1.3-68.4 (7 exp case fa)					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Daniels and others 2001), Children's Cancer Group, United States and Canada	Case-control	Population-based, cases from 139 hospitals in United States and Canada, 1992-94; cases identified from hospital records	390 cases of neuroblastoma, 296 matched controls; excluded subjects lacking paternal interviews (these were incl in Olshan et al 1999)	Mother- and father-reported home use of pesticides during month before conception through gestation and childhood		Matched for age and geog region; adj for age and household income
OR, neuroblastoma, indoor pesticide use (mainly insecticides), confirmed by both parents	Preconceptual/prenatal 1.3, 0.8-3.3 Childhood 1.4, 0.9-2.2	OR, neuroblastoma, indoor insecticide use for ants or roaches, confirmed by both parents	Prenatal or childhood 1.8, 1.0-3.1	OR, neuroblastoma, garden pesticide use confirmed by both parents	Preconceptual/prenatal 1.3, 0.8-2.0 Childhood 1.8, 1.0-3.1	
OR, neuroblastoma, indoor pesticide use (mainly insecticides), before or after birth, confirmed by both parents	Age <1 yr 1.2, 0.7-2.2 Age ≥1yr 1.9, 1.1-3.2	OR, neuroblastoma, garden insecticide use, before or after birth, confirmed by both parents	Age <1 0.8, 0.3-2.2 Age 1+ 1.7, 0.8-3.6	OR, neuroblastoma, herbicide use, before or after birth, confirmed by both parents	Age <1 1.2, 0.5-3.1 Age 1+ 2.2, 1.1-4.3	
OR, neuroblastoma, prenatal or childhood garden pesticide use by parent who did application	Maternal pesticide application 2.2, 1.3-3.8 Paternal application 1.1, 0.8-1.5	No DR analysis				
(Flower and others	Cohort	17537 children of	50 cancers	Self-reported		Adjusted for

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
2004), Agricultural Health Study, USA		licensed agricultural pesticide applicators; limited to the Iowa subcohort recruited during 1993-97; the father was the applicator for over 99% of children; cases identified from Iowa Cancer Registry	identified among children age 0-19 yr, 1975-1998 (includes cases diagnosed before parent enrolled in cohort)	pesticide use by licensed pesticide applicators		age; parental age at child's birth, child's sex, birth weight, parental smoking, history of cancer and maternal history of early fetal death were tested and found to not be confounders
SIRs among children of licensed pesticide applicators	Neuroblastoms 1.26, 0.40-3.89 (3 cases)					

Summary: Childhood neuroblastomas

Reviews

Among 5 studies of neuroblastoma published by early 1998, 2 reported associations with parental pesticide exposure through employment in agriculture and one with parental residential garden pesticide use during childhood (Zahm and Ward 1998). A review of the 1 cohort and 3 case-control studies published since review by Zahm and Ward noted that all 4 studies showed associations between neuroblastoma and parental occupational or residential pesticide use (Infante-Rivard and Weichenthal 2007). One recent study found an association between neuroblastoma and residential herbicide use.

Original studies since 1997

Maternal exposure, insecticides, inadequate evidence

A case-control study in New York State reported an association between neuroblastoma and maternal occupational insecticide exposure (OR=2.6, 95% CI 1.5-4.5) (Kerr and others 2000). In the USA/Canada case-control study, neuroblastoma was associated with prenatal or childhood indoor insecticide use for ants or

cockroaches (use confirmed by both parents, OR=1.8, 95% CI 1.0-3.1) and, among cases age 1 or older, with any indoor insecticide use (OR=1.9, 95% CI 1.1-3.2) (Daniels and others 2001).

Maternal exposure, unspecified pesticides, inadequate evidence

A large USA/Canada case-control study reported statistically non-significant elevated risks of neuroblastoma related to maternal occupation in farming (OR=2.2, 95% CI 0.6-8.8, 7 exposed case mothers) and florist/garden stores (OR=2.4, 95% CI 0.6-9.9, 6 exposed case mothers) (Olshan and others 1999). A subsequent report of this study revealed that neuroblastomas were associated with maternal application of garden pesticides (OR=2.2, 95% CI 1.3-3.8) (Daniels and others 2001). The few studies, limited sample size and heterogeneity of exposure indices preclude firm conclusions.

Paternal occupational exposure, insecticides, inadequate evidence

A case-control study in New York State reported an association between neuroblastoma and paternal occupational insecticide exposure (OR=1.8, 95% CI 1.1-3.1) (Kerr and others 2000).

Paternal occupational exposure, unspecified pesticides, inadequate evidence

In a Norwegian cohort study, neuroblastoma risk was increased among offspring of farmers (mainly male) who reported field vegetable farming and purchased pesticides (compared to farm families with neither trait, RR=2.51, 95% CI 1.03-6.13) (Kristensen and others 1996). A large USA/Canada case-control study reported that neuroblastoma was associated with certain potentially exposed paternal occupations (landscaping or grounds keeping, OR=2.3, 95% CI 1.0-5.2) but not farming (OR=0.9, 95% CI 0.4-1.8) (Olshan and others 1999). A later report of this study indicated that neuroblastomas were not associated with paternal application of garden pesticides (OR=1.1, 95% CI 0.8-1.5) (Daniels and others 2001). The AHS cohort revealed no association between neuroblastoma and paternal occupation as licensed agricultural pesticide applicators (SIR=1.26, 95% CI 0.40-3.89) but there were only 3 cases (Flower and others 2004). The findings of the Norwegian cohort and the large USA/Canada case-control study are suggestive of an association but further research is needed to clarify the role of specific pesticides or related groups of pesticides, critical exposure windows and dose-response relationships. Further follow-up of the AHS cohort would also be valuable.

Childhood exposure, herbicides, inadequate evidence

The USA/Canada case-control study also reported elevated neuroblastoma risk related to prenatal or childhood herbicide use (use confirmed by both parents, OR=2.2, 95% CI 1.1-4.3); there was no association among infants below age 1 (Daniels and others 2001).

Childhood exposure, insecticides, inadequate evidence

A recent report of the USA/Canada case-control study noted elevated neuroblastoma risk among children age 1 or older related to prenatal or childhood insecticide use indoors (OR=1.9, 95% CI 1.1-3.2) and in gardens (OR=1.7, 95% CI 0.8-3.6) (Daniels and others 2001).

16. Wilms' tumour

Reviews

Author	Scope	Findings
(Daniels and others 1997), USA	Literature review, 31 studies of occupational or residence pesticide exposure of parents or children and risk of childhood cancer published 1970-1996	Limited evidence of associations between Wilms' tumour and parental occupational pesticide exposure indices: paternal exposure before conception and during pregnancy, maternal exposure during pregnancy
(Zahm and Ward 1998), USA	Literature review, epidemiologic studies of pesticides and childhood cancer	Two recent case-control studies and a cohort study found associations between Wilms' tumour and paternal and maternal pesticide exposure
(Infante-Rivard and Weichenthal 2007), Quebec	Reviewed 1 cohort and 1 case-control study published since review by Zahm and Ward.	Both studies reported statistically non-significant increased Wilms' tumour risks related to maternal or paternal occupational pesticide exposure; these findings were based on only 2 or 3 exposed case parents.

Wilms' tumour: Original studies since 1997

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Fear and others 1998), England and Wales (excluded) Note: abstract only	Proportional mortality study	360,640 total deaths, age <15, England and Wales, 1959-63 plus 1970-90; cases identified from death records	42 Wilms' tumour and other kidney cancer deaths among 167,703 total deaths, age <15 yr	Potential paternal exposure to pesticides based on occupation recorded on death certificate		Age, year of death, paternal social class
Paternal occupies potentially exposed to pesticides, SMR (based on 42 deaths)	1.59, 1.18-2.15	Paternal occupation as farmers or market gardeners	1.74, 1.14-2.67			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Pearce and Parker 2000), England	Case-control	298,188 live births, Cumbria County, 1950-1993; cases identified from death records	21 kidney cancer deaths, 1367 `control`deaths from other causes, age <16	Paternal occupation from birth and death records		
OR, paternal occupation in agricultural	Age 1-15 0.88, 0.20-3.84	Age 1-4 1.05, 0.13-8.46 (9 exp case fa)	Age 5-15 0.76, 0.10-5.96			
(Schuz and others 2001b), Germany	Case-control	Population-based, former West Germany, 1988-97; cases identified from hospital records	177 cases Wilms' tumour, 2006 matched controls, age <10	Mother- and father-reported occupational and other exposures		Matched for community, sex, YOB
OR, Wilms'tumour, childhood exposure to pesticides	Farms 0.84, 0.32-2.25 Gardens 0.80, 0.44-1.47	OR, Wilms'tumour, parental occupational pesticide exposure,	Maternal, ever vs never 2.52, 0.50-12.6 (2 exp case mo) Paternal, postnatal exposure 0.97, 0.39-2.37 (6 exp case fa)	OR, Wilms'tumour, indoor use of insecticides, ≥1 vs <1/yr, prenatal or childhood	1.27, 0.78-2.08	
(Rodvall and others 2003), Sweden	Cohort	27,329 offspring of 20,245 male pesticide applicators, born during 1958-1994; licensed during 1965-1976; offspring followed for cancer incidence and mortality from 1958 to 1994; cases identified	1 kidney cancer case, age <20	Licensed pesticide applicators		Age, sex, calendar year

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		from national cancer incidence and death records				
SIR, kidney ca (observed 1 case, expected 3.7cases)	0.27, 0.00-1.52					
(Flower and others 2004), Agricultural Health Study, USA	Cohort	17537 children of licensed agricultural pesticide applicators; limited to the Iowa subcohort recruited during 1993-97; the father was the applicator for over 99% of children; cases identified from Iowa Cancer Registry	50 cancers identified among children age 0-19 yr, 1975-1998 (includes cases diagnosed before parent enrolled in cohort)	Self-reported pesticide use by licensed pesticide applicators		Adjusted for age; parental age at child's birth, child's sex, birth weight, parental smoking, history of cancer and maternal history of early fetal death were tested and found to not be confounders
SIRs among children of licensed pesticide applicators	Wilms' tumour 1.56, 0.50-4.84 (3 cases)					
(Tsai and others 2006), USA	Case-control	Population-based, 6 States (Calif, Florida, NJ, Mich, N Carolina, Penn), 1992-95; cases identified from State cancer registries, all cases histologically confirmed	303 cases Wilm's tumour, 575 matched controls, age <10	Parent-reported (usually mother) exposure info plus residence prox to National Priority List sites during 2 yr before birth		Matched for age, race
OR, Wilms' tumour, prenatal maternal	1.32, 0.83-2.09					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
residence or occupational pesticide use						

Summary: Wilms' Tumour

Reviews

A review of the 6 studies of Wilms' tumour published by early 1998 noted that the only study that examined household extermination (mainly insecticide use) observed an association and the 2 studies that focused on parental occupational exposures before birth both found associations; none of the 3 that assessed postnatal parental pesticide exposure (occupational use or residential gardening) found an association (Zahm and Ward 1998). A review of the 2 studies published since Zahm and Ward's report noted that both observed statistically non-significant increased risks related to parental occupational pesticide exposure based on only 2 or 3 exposed case parents (Infante-Rivard and Weichenthal 2007).

Original studies since 1997

Maternal exposure, herbicides, inadequate evidence

In a U.S./Canada case-control study, Wilms' tumour was not associated with residential herbicide use at any time during pregnancy or childhood (OR=1.0, 95% CI 0.7-1.4) (Cooney and others 2007).

Maternal exposure, insecticides, inadequate evidence

A German case-control study reported a statistically non-significant elevated risk of Wilms' tumour related to prenatal or childhood indoor residential insecticide use (≥ 1 vs < 1 X/yr, OR=1.27, 95% CI 0.78-2.08) (Schuz and others 2001b). In the U.S./Canada case-control study, Wilms' tumour was associated with indoor residential insecticide use at any time during pregnancy or childhood (OR=1.4, 95% CI 1.0-1.8) (Cooney and others 2007).

Maternal exposure, unspecified pesticides, inadequate evidence

A case-control study in Brazil, a country with relatively high Wilms' tumour incidence rates, revealed a dose-response relationship between this tumour and frequency of preconceptual/prenatal occupational exposure to agricultural pesticides (≥ 10 vs 0 times, OR=129, 95% CI 6.4-2570, 6 exposed case and 1 exposed control mothers, p-trend=.03) (Sharpe and others 1995). There were statistically non-significant elevated risks of Wilms' tumour in case-control studies in Germany (maternal occupational pesticide exposure, OR=2.52, 95% CI 0.50-12.6, 2 exposed case mothers) (Schuz and others 2001b) and the USA (prenatal residential or occupational pesticide exposure, OR=1.32, 95% CI 0.83-2.09) (Tsai and others 2006). In the U.S./Canada case-control study, Wilms' tumour was associated with indoor residential use of any pesticide at any time during pregnancy or childhood (OR=1.3, 95% CI 1.0-1.7) (Cooney and others 2007). Larger studies are needed to clarify the role of specific pesticides or related groups of pesticides, critical exposure windows and dose-response relationships.

Paternal occupational exposure, unspecified pesticides, inadequate evidence

The Brazil study revealed a dose-response relationship between Wilms' tumour and frequency of preconceptional paternal occupational exposure to agricultural pesticides (≥ 10 vs 0 times, OR=3.2, 95% CI 1.2-9.0, p-trend=.02) (Sharpe and others 1995). A Norwegian retrospective cohort study reported elevated risks of Wilms' tumour among offspring of farmers (mainly male) who reported ownership of pesticide spraying equipment (OR=2.54, 95% CI 0.98-6.58) and those with orchards or greenhouses and pesticide spraying equipment (OR=8.87, 95% CI 2.67-29.5) (Kristensen and others 1996). Although this study lacked detailed pesticide use information, it had the advantage of not relying on potentially biased parental recall of exposures. A mortality study in England found no association between Wilms' tumour and paternal occupation in agriculture (PMR=0.88, 95% CI 0.20-3.84) (Pearce and Parker 2000). The AHS cohort revealed a statistically non-significant elevated risk of Wilms' tumour related to paternal occupation as licensed agricultural pesticide applicators (SIR=1.56, 95% CI 0.50-4.84, only 3 cases) (Flower and others 2004). The 2 studies with negative findings are not compelling because one was a proportional mortality study limited to information on death records and the other was a cohort study with only 3 observed cases.

Childhood exposure, herbicides, inadequate evidence

In the U.S./Canada case-control study, Wilms' tumour was not associated with residential herbicide use at any time during pregnancy or childhood (OR=1.0, 95% CI 0.7-1.4) (Cooney and others 2007).

Childhood exposure, insecticides, inadequate evidence

The German study reported a statistically non-significant elevated risk of Wilms' tumour related to prenatal or childhood indoor residential insecticide use (≥ 1 vs < 1 X/yr, OR=1.27, 95% CI 0.78-2.08) (Schuz and others 2001b). In a U.S./Canada case-control study, Wilms' tumour was associated with indoor residential insecticide use at any time during pregnancy or childhood (OR=1.4, 95% CI 1.0-1.8) (Cooney and others 2007).

Childhood exposure, unspecified pesticides, inadequate evidence

The German study reported no association between Wilms' tumour and childhood residence on farms (OR=0.8, 95% CI 0.3-2.3), residential garden pesticide use (OR=0.8, 95% CI 0.4-1.5) or childhood paternal occupational pesticide exposure (OR=0.97, 95% CI 0.39-2.37) (Schuz and others 2001b). In the U.S./Canada case-control study, Wilms' tumour was associated with indoor residential use of any pesticide at any time during pregnancy or childhood (OR=1.3, 95% CI 1.0-1.7) (Cooney and others 2007).

17. Germ cell tumours

Original studies since 1995

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Shu and others 1995), Children's Cancer Group, Canada and United States	Case-control	Population-based, 35 centres in USA and Canada, 1982-89; cases identified from hospital records	105 cases germ-cell tumours (36 ovarian, 24 testicular, 45 non-gonadal), 639 community controls, age <15		Parent-reported occupational and other exposure info; only reported results for ever-exposure but found similar results for exposures before, during or after pregnancy but wider confidence intervals from smaller numbers	Age, sex, gestation length, maternal parity, education, prenatal smoking
OR, germ cell tumours, parental occupational or residence pesticide exposure	Maternal 2.4, 0.9-6.9	Paternal 1.8, 0.7-5.0		No analysis of testis germ cell vs pesticides		
(Rodvall and others 2003), Sweden	Cohort	27,329 offspring of 20,245 male pesticide applicators, born during 1958-1994; licensed during 1965-1976; offspring followed for cancer incidence and mortality from 1958 to 1994; cases identified from national cancer incidence and death records	2 testicular tumour cases, age <20	Licensed pesticide applicators		Age, sex, calendar year
SIR, testis ca (observed)	1.19, 0.13-4.28					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
2 cases, expected 1.7 cases)						
(Flower and others 2004), Agricultural Health Study, Iowa	Cohort	17537 children of licensed pesticide applicator-farmers in Iowa; recruited during 1993-97; the father was the applicator for over 99% of children; cases identified from Iowa Cancer Registry	50 cancers identified among children age 0-19 yr, 1975-1998 (includes cases diagnosed before parent enrolled in cohort)	Self-reported pesticide use by licensed pesticide applicators, 50 specific pesticides queried	Applicators were all men except for 76 women including the mother of one cancer case; 58% of women reported mixing or applying pesticides	Adjusted for age; parental age at child's birth, child's sex, birth weight, parental smoking, history of cancer and maternal history of early fetal death were tested and found to not be confounders
SIRs among children of licensed pesticide applicator-farmers	Germ cell (5 cases) 2.34, 0.88-6.24					
(Chen and others 2005), Children's Oncology Group, USA	Case-control	Population-based, 1996-2003; cases identified from hospital records	73 male and 180 female germ cell tumour cases, 394 controls, age <15	Mother- and father-reported info on pesticide and other exposures	Estimated cumulative pesticide exposure (mg), categorized as low (<50 th), medium (50-75 th) and high (>75 th percentile)	Matched for sex, YOB, geog region
OR, germ cell tumour, lifetime maternal occupational pesticide exposure, ref = never	low 1.2, 0.9-1.7 med/high 1.1, 0.8-1.6 p-trend=.36	OR, germ cell tumour, prenatal maternal occupational pesticide exposure	low 1.2, 0.7-2.1 med/high 0.9, 0.5-1.7 p-trend=.93	OR, germ cell tumour, maternal occupational pesticide exposure, ever vs never	Dysgerminoma 1.9, 0.9-4.2 Yolk-sac tumour 1.2, 0.8-1.8 Teratoma	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					1.1, 0.6-2.1	
OR, germ cell tumour, paternal lifetime occupational pesticide exposure, ref = never	low 0.9, 0.6-1.3 med 0.9, 0.5-1.4 high 0.6, 0.3-1.2 p-trend=.16	OR, germ cell tumour, paternal preconceptual occupational pesticide exposure	low 0.9, 0.6-1.3 med/high 0.9, 0.6-1.3 p-trend=.49	OR, germ cell tumour, paternal occupational pesticide exposure, ever vs never	Dysgerminoma 1.0, 0.4-2.5 Yolk-sac tumour 0.9, 0.5-1.4 Teratoma 1.1, 0.6-2.1	
(Chen and others 2006), USA	Case-control	See Chen et al 2005 above; cases identified from hospital records	83 male and 189 female cases germ cell tumours, age <15; 418 controls	Mother- and father-reported info on pesticide and other exposures		Matched for sex, YOB, geog region
OR, germ cell tumour, prenatal maternal residence insectic exposure	Yes vs no 1.0, 0.8-1.3	# types insecticides ≥ 2 vs none 1.2, 0.8-1.6 p-trend=.48	Cumulative exposure freq >5 vs never 1.1, 0.8-1.5 p-trend=.56	OR, germ cell tumour, prenatal parental residence herbicide exposure, ever vs never	Maternal 1.3, 0.9-1.7 Paternal 1.0, 0.7-1.3	
OR, germ cell tumour, paternal residence insectic exposure from	Yes vs no 1.0, 0.7-1.4	# types insecticides ≥ 2 vs none	Cumulative exposure freq >3 vs never			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
6 months before concept to age 1		1.1, 0.8-1.6 p-trend=.64	1.1, 0.7-1.5 p-trend=.66			
OR, germ cell tumour, childhood residence insectic exposure	Yes vs no 1.0, 0.7-1.4	Childhood # types insectic ≥2 vs none 1.0, 0.7-1.5 p-trend=.99	Cumulative exposure freq >8 vs 0 times 0.9, 0.6-1.3 p-trend=.50			

Summary: Germ cell tumours

Original studies since 1995

Maternal exposure, herbicides, insecticides, inadequate evidence

A U.S. case-control study revealed no association between germ cell tumours and prenatal residential use of indoor insecticides (used ≥2 vs 0 types of insecticides, OR=1.2, 95% CI 0.8-1.6, p-trend=.48) and a statistically non-significant, modestly elevated risk related to prenatal residential herbicide use (ever vs never, OR=1.3, 95% CI 0.9-1.7) (Chen and others 2006).

Maternal exposure, unspecified pesticides, inadequate evidence

A USA/Canada case-control reported elevated risks of germ cell tumours (ovarian, testicular, non-gonadal) related to maternal occupational or residential pesticide exposure (OR=2.4, 95% CI 0.9-6.9) (Shu and others 1995). In the AHS cohort study, children of licensed pesticide applicator-farmers (almost entirely men) had an increased risk of germ cell tumours (OR=2.34, 95% CI 0.88-6.24; 5 exposed case fathers); there was potential prenatal pesticide exposure because the women lived on farms and 58% of them reported mixing or applying pesticides (Flower and others 2004). In another U.S. case-control study, prenatal pesticide exposure at work was not associated with germ cell tumours (>50th percentile of cumulative exposure vs unexposed, OR=0.9, 95% CI 0.5-1.7, p-trend=0.93) but was related to an elevated risk of dysgerminoma, a specific histological type of germ cell tumour (ever exposed vs never, OR=1.9, 95% CI 0.9-4.2) (Chen and others 2005). Three studies observed elevated risks of germ cell tumours related to prenatal occupational or residential pesticide exposure. However, none of the relationships were statistically significant, one was limited to a histologic subtype and the role of maternal versus paternal exposure in the AHS cohort is not clear.

Paternal exposure, herbicides, insecticides, inadequate evidence

A U.S. case-control study revealed no association between germ cell tumours and preconceptual/perinatal paternal residential use of herbicides (ever vs never, OR=1.0, 95% CI 0.7-1.3) or insecticides (used ≥ 2 vs 0 types of insecticides, OR=1.1, 95% CI 0.8-1.6, p-trend=.64) (Chen and others 2006).

Paternal exposure, unspecified pesticides, inadequate evidence

The USA/Canada case-control reported elevated risks of germ cell tumours (ovarian, testicular, non-gonadal) related to paternal occupational pesticide exposure (OR=1.8, 95% CI 0.7-5.0) (Shu and others 1995). In the AHS cohort study, children of licensed pesticide applicator-farmers (almost entirely men) had an increased risk of germ cell tumours (OR=2.34, 95% CI 0.88-6.24; 5 exposed case fathers) (Flower and others 2004). In a U.S. case-control study, preconceptual paternal pesticide exposure at work was not associated with germ cell tumours (>50th percentile of cumulative exposure vs unexposed, OR=0.9, 95% CI 0.6-1.3, p-trend=0.49) or any histological subtype (Chen and others 2005). Two of the 3 studies observed statistically non-significant elevated risks of germ cell tumours related to self-reported paternal occupational pesticide exposure.

Childhood exposure, insecticides, inadequate evidence

A U.S. case-control study revealed no association between germ cell tumours and childhood residential indoor insecticide use (used ≥ 2 vs 0 types of insecticides, OR=1.0, 95% CI 0.7-1.5, p-trend=.99) (Chen and others 2006).

Childhood exposure, unspecified pesticides, inadequate evidence

In the AHS cohort study, children of licensed pesticide applicator-farmers (almost entirely men) had a statistically non-significant increased risk of germ cell tumours (OR=2.34, 95% CI 0.88-6.24; 5 exposed case fathers) (Flower and others 2004). Given their residence on farms known to use pesticides, and evidence that children of pesticide applicators have substantially higher urinary organophosphate insecticide metabolites compared to other children (Fenske and others 2005), there clearly was the potential for childhood pesticide exposure.

18. Bone cancer

Reviews

Author	Scope	Findings
(Daniels and others 1997), USA	Literature review, 31 studies of occupational or residence pesticide exposure of parents or children and risk of childhood cancer published 1970-1996	Limited evidence of associations between Ewing's sarcoma and paternal occupational exposure to pesticides before conception and during pregnancy
(Zahm and Ward 1998), USA	Literature review, epidemiologic studies of pesticides and childhood cancer	Ewing's sarcoma – 3 of the 4 case-control studies found associations with paternal pesticide exposure
(Infante-Rivard and Weichenthal 2007), Quebec	Reviewed 1 case-control study published since review by Zahm and Ward.	The single available new study found associations between childhood bone cancer and a father or at least one parent employed in a farm-related job at conception or during pregnancy.

Childhood bone cancer: Original studies since 1997

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Hum and others 1998), Ontario	Case-control	Population-based, 1980-88; cases identified from Ontario Cancer Registry	186 Ewing's sarcoma and osteosarcoma cases, 919 controls, age ≤25	Self-reported parental occupational histories		Matched for sex and age; adjusted for sex and age (several other variables were tested and were not confounders)
OR, bone ca, maternal occupation in farming	All bone ca 2.7, 0.8-9.3	OR, bone ca, paternal occupation in farming	All bone ca 1.4, 0.6-3.2	OR, bone ca, duration of parental employment in	Maternal 1-4 yr	Paternal 1-4 yr

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	Ewing's sarcoma 7.8, 1.9-31.7		Osteosarcoma 2.1, 0.8-5.7 Ewing's sarcoma 0.5, 0.1-3.9	farming 1-4 and ≥5 vs 0 yr	3.8, 0.6-23.3 5+ yr 2.9, 0.5-15.3	0.4, 0.1-3.3 5+ yr 2.4, 0.9-6.4
(Valery and others 2002), Australia	Case-control	Population-based, 1991-96; cases identified from cancer registries, hospital records	106 Ewing's sarcoma cases, 344 matched controls, age ≤20	Self- or parent-reported exposures from 6 months before pregnancy to age at diagnosis		Matched for age and state of residence; adjusted for sex, maternal education, state of residence
OR, Ewings` sarcoma, parental farm-related job at conception	Paternal 3.5, 1.0-11.9 Maternal 2.8, 0.5-15.8	OR, Ewings` sarcoma, parents ever handled pesticides	Paternal 2.0, 0.8-4.9 Maternal 2.3, 0.5-11.7	OR, Ewing's sarcoma, childhood residence on farm, yes vs no	2.0, 1.0-3.9	
(Rodvall and others 2003), Sweden	Cohort	27,329 offspring of 20,245 male pesticide applicators, born during 1958-1994; licensed during 1965-1976; offspring followed for cancer incidence and mortality from 1958 to 1994; cases identified from national cancer incidence and death records	2 bone tumour cases, age <20	Licensed pesticide applicators		Age, sex, calendar year
SIR, bone tumour (observed 2 cases,	0.54, 0.06-1.93					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
expected 3.7 cases)						
(Flower and others 2004), Agricultural Health Study, USA	Cohort	17537 children of licensed agricultural pesticide applicators; limited to the Iowa subcohort recruited during 1993-97; the father was the applicator for over 99% of children; cases identified from Iowa Cancer Registry	50 cancers identified among children age 0-19 yr, 1975-1998 (includes cases diagnosed before parent enrolled in cohort)		Self-reported pesticide use by licensed pesticide applicators	Adjusted for age; parental age at child's birth, child's sex, birth weight, parental smoking, history of cancer and maternal history of early fetal death were tested and found to not be confounders
SIRs among children of licensed pesticide applicators	Bone (4 cases) 2.19, 0.82-5.84					
(Moore and others 2005), USA	Case-control	Cases from 64 hospitals engaged in a clinical trial, 1983-85; cases identified from hospital records	196 cases Ewing's sarcoma, matched population controls	Mother-reported info on work history and other exposures	Expert-rated likelihood of occupational exposures	Matched for geog region, sex, ethnicity, YOB
OR, Ewings`sarcoma, household extermination during childhood	Boys age<16 3.0, 1.1-8.1 Girls age<14 1.1, 0.4-3.2	OR, Ewings`sarcoma, childhood farm residence	Boys age<16 Ever 0.9, 0.4-2.2 Always 2.3, 0.4-12.3 (8 exp cases) Girls age<14 ever 6.4, 0.7-58.4 (7	OR, Ewings`sarcoma, paternal occupational pesticide exposure during pregnancy	Any exposure 1.6, 0.7-3.5 Likely exposure 0.7, 0.2-2.9 (6 exp case fa)	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			exp cases) Always na (2 exp cases)			
OR, Ewings` sarcoma, postnatal parental occupational pesticide exposure	Any exposure 2.2, 0.9-5.4 Likely exposure 0.9, 0.2-3.7					
(Thorpe and Shirmohammadi 2005), Maryland	Ecologic	Maryland Cancer Registry, 63 bone, age <18, 1992-98; cases identified from Maryland Cancer Registry	Cancer incidence rates by small geog area	Residence within 2 mi of wells with detectable levels of 4 herbicides and nitrates based on US Geological Survey data for 834 wells	Detection limits were >0.15 or >0.5 µg/L for herbicides, >3 or >10 mg/L for nitrate	
RR, bone cancer, residence within 2 mi of a well with detectable levels in well water, yes vs no	Metolachlor 2.26, 0.97-5.24	Atrazine 1.89, 0.76-4.70				

Summary: Childhood bone cancer

Reviews

A review noted that 3 of the 4 studies of Ewing’s sarcoma published by early 1998 found elevated risks related to parental pesticide exposure (statistically significant in 2 studies) (Zahm and Ward 1998). A recent review noted that the only study published since the Zahm and Ward review found increased Ewing’s sarcoma risk related to agricultural employment of at least 1 parent (Infante-Rivard and Weichenthal 2007).

Original studies since 1997

Maternal exposure, unspecified pesticides, inadequate evidence

Maternal occupation in farming was associated with increased risk of childhood bone cancer in Ontario (2.7, 95% CI 0.8-9.3), especially among women with at least 5 years exposure (OR=2.9, 95% CI 0.5-15.3) and the subgroup of Ewing's sarcoma (OR=7.8, 95% CI 1.9-32) (Hum and others 1998). An Australian case-control study reported a statistically non-significant elevated risk of Ewing's sarcoma among children and young adults in relation to periconceptual maternal occupation in farming (OR=2.8, 95% CI 0.5-15.8) and ever-handling of pesticides (OR=2.3, 95% CI 0.5-12) (Valery and others 2002).

Paternal exposure, unspecified pesticides, limited evidence

Ewing's sarcoma was associated with paternal occupational pesticide exposure in a California case-control study (OR=8.8, 95% CI 1.8-42.7) (Holly and others 1992). The Ontario study showed that osteosarcoma risk was elevated in relation to paternal occupation in farming (OR=2.1, 95% CI 0.8-5.7) and bone cancer risk (any histologic type) was increased in relation to paternal work in farming for at least 5 years (OR=2.4, 95% CI 0.9-6.4) (Hum and others 1998). The Australian case-control study reported statistically non-significant elevated risks of Ewing's sarcoma related to periconceptual paternal occupation in farming (OR=3.5, 95% CI 1.0-11.9) and ever-handling of pesticides (OR=2.0, 95% CI 0.8-4.9) (Valery and others 2002). In the AHS cohort, there was a statistically non-significant increased risk of bone cancer among offspring of licensed pesticide applicators (SIR=2.19, 95% CI 0.82-5.84, based on 4 cases) (Flower and others 2004). A U.S. case-control study of Ewing's sarcoma observed no association with likely prenatal paternal pesticide exposure (OR=0.7, 95% CI 0.2-2.9) (Moore and others 2005).

Childhood exposure, insecticides, inadequate evidence

In a California case-control study, Ewing's sarcoma was not associated with childhood indoor insecticide use (OR=0.6, 95% CI 0.3-1.2) or residence on or next to a farm (OR=1.0, 95% CI 0.3-4.0) (OR=0.6, 95% CI 0.3-1.2) (Holly and others 1992). A U.S. case-control study of Ewing's sarcoma observed an association between childhood residential indoor insecticide use and Ewing's sarcoma among boys (OR=3.0, 95% CI 1.1-8.1) but not girls (OR=1.1, 95% CI 0.4-3.2) (Moore and others 2005).

Childhood exposure, unspecified pesticides, inadequate evidence

A U.S. case-control study reported statistically non-significant elevated risks of Ewing's sarcoma among girls who had ever lived on farms (OR=6.4, 95% CI 0.7-58.4) but not among boys (OR=0.9, 95% CI 0.4-2.2) and but not in relation to postnatal parental occupational pesticide exposure (OR=0.9, 95% CI 0.2-3.7) (Moore and others 2005).

19. Soft tissue sarcoma

Original studies since 1995

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Leiss and Savitz 1995), Denver, Colorado	Case-control	Population-based, Denver, 1976-83; cases identified from Colorado Central Cancer Registry, hospital records	252 childhood cancer cases, unspec number of soft tissue sarcoma cases, 222 matched controls, age <15	Parent-reported exposures; 4-33 exposed cases or case parents		Matched for age, sex, telephone exchange geog area; adj'd for age at diag, paternal education, per capita income, residence stability, maternal age and smoking, race, sex, wire code, year of diag found to be confounders in prelim analyses
Lawn herbicide use	Prenatal 0.8, 0.5-1.3	Birth to 2 yr before Dx 4.1, 1.0-16.0 (14 exposed cases)	2 yr before Dx 3.9, 1.7-9.2			
(Meinert and others 2000), Germany	Case-control	Population-based, nationwide (West Germany), 1992-94; cases identified from German Central Cancer Registry	137 soft tissue sarcoma cases, 2,588 community controls, age <15	Self-reported parental occupational and home exposures to pesticides and other hazards		Matched for sex, DOB, community
Soft tissue sarcomas associated with maternal occupational pesticide exposure before pregnancy	(data not shown in paper)					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Flower and others 2004), Agricultural Health Study, USA	Cohort	17537 children of licensed agricultural pesticide applicators; limited to the Iowa subcohort recruited during 1993-97; the father was the applicator for over 99% of children; cases identified from Iowa Cancer Registry	50 cancers identified among children age 0-19 yr, 1975-1998 (includes cases diagnosed before parent enrolled in cohort)	Self-reported pesticide use by licensed pesticide applicators		Adjusted for age; parental age at child's birth, child's sex, birth weight, parental smoking, history of cancer and maternal history of early fetal death were tested and found to not be confounders
SIRs among children of licensed pesticide applicators	Soft tissue sarcoma 1.17, 0.38-3.62 (3 cases)					

Summary: Soft tissue sarcoma

Original studies since 1995

Maternal exposure, herbicides, unspecified pesticides, inadequate evidence

A case-control study in Denver reported that childhood soft tissue sarcoma was not associated with prenatal residential herbicide use (OR=0.8, 95% CI 0.5-1.3) (Leiss and Savitz 1995). In a relatively large case-control study in Germany, childhood soft tissue sarcomas were associated with maternal occupational pesticide exposure (result stated without supporting data in paper) (Meinert and others 2000).

Paternal exposure, unspecified pesticides, inadequate evidence

The AHS cohort revealed no association between soft tissue sarcoma and paternal occupation as licensed agricultural pesticide applicators (SIR=1.17, 95% CI 0.38-3.62, only 3 cases) (Flower and others 2004).

Childhood exposure, herbicides, inadequate evidence

A case-control study in Denver reported that childhood soft tissue sarcoma was associated with postnatal lawn herbicide use (OR=4.1, 95% CI 1.0-16.0) (Leiss and Savitz 1995).

20. Eye tumours

Original studies since 1990

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Bunin and others 1990), Children's Study Group, USA	Case-control	34 hospitals in USA and Canada, 1982-85; cases identified from hospital records	201 retinoblastoma cases, 201 matched population controls; cases – 19 familial, 67 sporadic heritable, 115 nonheritable	Parent-reported exposure info		Matched for telephone area code and next 5 digits, YOB, race
OR, retinoblastoma, maternal grandfather occupation in farming, yes vs no	Non-heritable 10.0, 1.4-433 (10 case only and 1 control only exposed matched pairs)	Sporadic heritable 1.0, 0.1-7.5				
(Kristensen and others 1996), Norway	Cohort	Parents identified as farm holders during agricultural censuses, 1969-1989; 84% of owners were males; cases identified from linkage of census and national cancer registry records	323,292 offspring, 5.7 million person-years, 1275 incident cancers during 1965-1991, 4 exposed eye tumour cases	Census info on farm ownership and expenditures on pesticides in 1968, possession of tractor pesticide spraying equipment in 1979	Focused on data for yr closest to child's YOB but also used other data if available; exposure data for prenatal period limited to younger children; 57% of men and 34%	Age, sex

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
					women worked at least 500 hr/yr on farm	
Relative risk, parents who farmed field vegetables and purchased pesticides vs parents with neither trait	3.17, 0.93-10.9					
(Rodvall and others 2003), Sweden	Cohort	27,329 offspring of 20,245 male pesticide applicators, born during 1958-1994; licensed during 1965-1976; offspring followed for cancer incidence and mortality from 1958 to 1994; cases identified from national cancer incidence and death records	1 soft tissue sarcoma case, age <20	Licensed pesticide applicators		Age, sex, calendar year
SIR, soft tissue sarcoma (observed 1 case, expected 2.7 cases)	0.38, 0.00-2.09					
(Flower and others 2004), Agricultural Health Study, USA	Cohort	17537 children of licensed agricultural pesticide applicators; limited to the Iowa subcohort recruited during 1993-97; the father was the applicator for over 99% of children; cases	50 cancers identified among children age 0-19 yr, 1975-1998 (includes cases diagnosed before parent enrolled in	Self-reported pesticide use by licensed pesticide applicators		Adjusted for age; parental age at child's birth, child's sex, birth weight, parental smoking, history of cancer and maternal

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		identified from Iowa Cancer Registry	cohort)			history of early fetal death were tested and found to not be confounders
SIRs among children of licensed pesticide applicators	Retinoblastoma 1.63, 0.41-6.53 (2 cases)					

Summary: Eye tumour

Original studies since 1990

Maternal exposure, unspecified pesticides, inadequate evidence

A U.S. case-control study reported an association between non-heritable retinoblastoma and maternal grandparent occupation in farming (OR=10.0, 95% CI 1.4-433; based on 10 case-only and 1 control-only exposed matched pairs) (Bunin and others 1990).

Paternal exposure, unspecified pesticides, inadequate evidence

In a Norwegian retrospective cohort study, childhood eye tumours were associated with parental (mainly paternal) pesticide purchases for field vegetable farming (compared to no field vegetable farming and no pesticide purchases, RR=3.17, 95% CI 0.93-10.9) (Kristensen and others 1996). The AHS cohort revealed a statistically non-significant elevated retinoblastoma risk among children of licensed agricultural pesticide applicators (SIR=1.63, 95% CI 0.41-6.53, only 2 cases) (Flower and others 2004).

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