

Table 2.11.1: Cohort study on relationship of endocrine disruptors with sperm count

Author and publishing year	Location and subject studied	Chemical agent	Results
Leary, 1984	U.S. Exposed group/unexposed group = 828/676 (Semen check conducted on 110/95)	DES	Logarithmic mean of sperm concentration (x 10 <sup>6</sup> ml) Exposed/unexposed = 3.788/3.759

Table 2.7.3: Synchronic studies on relationship of endocrine disruptors with thyroid functions

Region and subjects	Compound	Measure of effects	Findings	P trend
		Frequency of normal thyroid gland (%)	Employed for 21-35 years: 33.6, employed for 11-20 years: 49.3 Employed for 21-35 years: 33.6, matched controls 46.1	P<0.05 P<0.025
Mazhitova, 1998				
Kazakhstan Region near Aral Sea 12 Hospitalized children, 7.5-15 years of age Schoolchildren in Stockholm as controls	PCB	Thyroid hormone TSH		No significant difference No significant difference
Nagayama, 1998				
Japan 36 Infants 1 year of age	PCDD, PCDF, Co-PCB	Thyroid functions		
Sala, 1999				
Catalonia, Spain Areas with high atmospheric HCB levels 1800 Residents of villages around an electrochemical plant including employees of the plant Average serum HCB level (ng/ml) of 608 residents: 54.6 for current male employees 27.1 for male ex-employees 9.0 for men without employment history 14.9 for current female employees 22.2 for female ex-employees 13.5 for women without employment history	HCB	Hypothyroidism  Others	Women: With employment history 1/62, never employed 17/952 Men: With employment history 1/445, never employed 0/341  Natural miscarriage: With employment history 8/60, never employed 143/396 Low body weight of newborn: With employment history 2/46, never employed 51/719 Congenital malformation: With employment history 1/46, never employed 26/719	
Guo, 1999				
Taiwan Yusho patients studied 13 years after onset		Thyroid adenoma	High frequency (20%)	

Table 2.11.2: Nested case-control study on relationship of endocrine disruptors with sperm count

Author and publishing year	Location and subject studied	Chemical agent	Results
Kurinczuk, 2001	England Case (infertility)/control = 1606/1013	Organic solvents Not specified	Ratio for cases Leather industry: 1.10 (p=0.99) Handling organic solvent: 1.73 (p<0.001) Ratio for leather industry workers Oligospermia: 1.20 (p=0.73) Abnormal spermatozoa: 1.65 (p=0.51)

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Guo, 1999				
Taiwan Yusho patients studied 13 years after onset		Thyroid adenoma	High frequency (20%)	

Table 2.11.3: Case-control studies on relationship of endocrine disruptors with sperm count

Author and publishing year	Location and subject studied	Chemical agent	Results
Migliore, 2002	Italy Exposed group*/unexposed group** = 46/27 * Employees of a reinforced plastic processing plant ** Healthy male volunteers living near the plant	Styrene	No significant difference between the two groups in usual semen check results Sperm nuclear DNA fragmentation ratio by Comet method: exposed/unexposed = 10.9/7.4 (p < 0.001)
Tan, 2003	China Exposed group*/unexposed group** = 32/46 + 22 * Occupationally exposed employees of a pesticide plant ** 46 Internal controls, 22 external controls	Fenvalerate	Significant difference in average sperm count (x 10 <sup>6</sup> /ml): exposed/unexposed (internal/external) = 53.96*/(89.45/113.24) (* significant with respect to internal and external controls, p < 0.05) Ratios of abnormality of viscosity, coagulation and concentration of sperm of exposed group significantly higher than internal and external controls (p < 0.05)
Naccarati, 2003	Tuscany, Italy Exposed group*/unexposed group** = 18/13 * Employees of a reinforced plastic processing plant ** Unexposed men living in the same region (Semen is normal in both groups)	Styrene	No significant difference in aneuploidy and diploidy frequencies between the two groups in FISH test of sperm chromosomes Other factors (age, smoking) involved in numerical abnormality of sperm nuclear chromosomes
Hsu, 2003	Taiwan Exposed group*/unexposed group** = 40/28 * Yusho patients ** Residents in the same region	PCB/PCDF	Ratio of normal sperm morphology: exposed/unexposed = 27.5/23.3, p = 0.04 Ratio of oligospermia: exposed/unexposed = 9/1, p = 0.04 Ratio of oocyte penetration by sperm: exposed/unexposed = 16.2/32.4, p < 0.01 Ratio of combined hamster oocytes: exposed/unexposed = 1.6/2.7, p < 0.01
Marmol-maneiro, 2003	Spain Exposed group*/unexposed group** = 29/30 * 29 Men (20-54 years of age) occupationally exposed to pesticides ** Unexposed men of matched ages	Cholinesterase inhibitor-based pesticides	Significant differences between exposed and unexposed groups in average concentration, motility and survival rate of sperm (p=<0.05)
Duty, 2003-2	U.S. 168 Outpatients of male infertility Exposed group*/unexposed group** = 91/77 * With any of sperm concentration, motility and morphology less than standard ** With all of these parameters above standard	Phthalate metabolites in urine: MEP, MMP, MEHP, MBP, MBZP, MOP, MINP, MCHP,	Dose-response relationships: Odds ratios assuming 1.0 for the group of lowest of three groups by urinary exposure level: MBP with sperm motility MBP with sperm concentration MBzP with sperm concentration

Author and publishing year	Location and subject studied	Chemical agent	Results
Swan, 2003	<p>Missouri and Minnesota, U.S.            Spouses of pregnant women            Exposed group*/unexposed group** = 34a/52b            * With any of sperm concentration, motility and morphology less than standard            ** With all of these parameters above standard            a34 = 25 (Missouri) + 9 (Minnesota)            b52 = 25 (Missouri) + 27 (Minnesota)</p>	<p>Pesticides:            alachlor, IMPY, atrazine, metolachlor,            2,4-dichlorophenoxyacetic acid (2,4-D), DEET, acetochlor</p>	<p>Pesticides associated with semen quality            Missouri cases showed significantly higher average concentrations of alachlor, atrazine and IMPY than controls (p = 0.0007, 0.012 and 0.0004, respectively)            Frequency of high levels of these pesticide was significantly higher (odds ratios 30.0, 11.3 and 16.7, respectively)            Missouri men showed significantly higher frequency of alachlor, IMPY, atrazine and metolachlor levels above detection limit than Minnesota men (p &lt; 0.0001, 0.001, 0.004 and &lt; 0.0001, respectively)            Minnesota men showed no significant difference in pesticide levels between case and control</p>
Hauser, 2003	<p>U.S.            212 Outpatients of male infertility            Exposed group*/unexposed group** = 114/98            * With any of sperm concentration, motility and morphology less than standard            ** With all of these parameters above standard</p>	<p>PCB,DDE</p>	<p>Dose-response relationships:            Odds ratios assuming 1.0 for the group of lowest of three groups by urinary exposure level:            PCB-138 with motility            PCB-138 with morphology</p>
Wong, 2003	<p>Holland            Case*/control** = 73/92            *Infertile men with sperm counts 5-20 million/ml            **Men with fertility confirmed</p>	<p>Many factors (including occupation, environment, life style, etc.)</p>	<p>Exposure factors as oligospermia risk:            Pesticides (OR = 8.4, CI = 1.3-52.1), welding industry (OR = 2.8, CI = 0.9-8.7), antibiotics use (OR = 15.4, CI = 1.4-16.3), mumps (OR = 2.9, CI = 1.3-6.7), gastrointestinal symptoms (OR = 6.2, CI = 1.4-26.8), insufficient intake of fruits (OR = 2.3, CI = 1.0-5.1), insufficient intake of vegetables (OR = 1.9, CI = 0.7-5.0), female reproductive diseases as family history (OR = 8.4, CI = 1.7-41.9)</p>

Table 2.11.4: Synchronic studies on relationship of endocrine disruptors with sperm count

Author and publishing year	Location and subject studied	Chemical agent	Results
Padungtod, 1999	China Exposed/unexposed = 32/43 (chromosome and semen check conducted for 13/16)	Organophosphate pesticides ethylparathion methamidophos	Median sperm count: 52.8/53.1 ( $\times 10^6$ /ml) Sperm motility: 50.5/61.3(%) Ratio of abnormal sperm morphology: 59/61.5(%) Risk of sperm chromosome abnormality 1.51 times higher for exposed group than for unexposed group
Tomenson , 1999	U.S. 272 Workers in pesticide manufacture and processing industry High exposure: Working period in manufacture and processing Low exposure: Non-working period	Pesticides Molinate S-ethyl hexahydro- 1H-asepene-1- carbothioate	Changes in semen findings and endocrine hormone level not associated with exposure level
Juhler, 1999	Denmark 256 Farmers (conventional 171, organic farming 85)	40 Pesticides	Median sperm count ( $\times 10^6$ /ml) N/M/H: 62/44/75 p=0.40
Padungtod, 2000	China Exposed/unexposed = 32/43 (Semen check conducted for 20/32)	Organophosphate pesticides ethylparathion methamidophos	Linear regression analysis Sperm count Motility
Selevan, 2000	Czech Republic Exposed/unexposed = 215/193 (Semen check conducted for 154/118)	Effects of air pollution PM10, PM-TSP, SO2, NOx, CO	Mean (median) sperm count 61.7(49.5)/60.6(39.0) ( $\times 10^6$ /ml)

Author and publishing year	Location and subject studied	Chemical agent	Results
Wang, 2001	China Exposed/unexposed = 68/130 Control (Unexposed, non-smoking): 49 Unexposed, smoking: 81 Exposed, non-smoking: 23 Exposed, smoking: 45	Petrochemical products (gasoline, styrene, benzene, toluene, xylene, acetic acid, etc.) and smoking	Mean sperm count ( $\times 10^6/ml$ ) Control (unexposed, non-smoking): 60.07 Unexposed, smoking: 55.32 Exposed, non-smoking: 52.52 Exposed, smoking: 41.49* ( $p < 0.05$ )
Recio, 2001	Mexico 9 Healthy farm workers	Organophosphate pesticides (organophosphate metabolites: DMTP, DMDTP, DEP)	Association of sperm chromosome aneuploidy with organophosphate pesticide exposure: Frequency of null aneuploidy and urinary DEP level* Before pesticide spraying During pesticide spraying *(by Poisson regression analysis after adjustment for age, drinking and sperm count)
Hauser, 2002	25 U.S. 29 Outpatients of male infertility Semen finding: Abnormal*/normal = 11/18 * (Sperm count $< 20$ million/ml: 3, motility $< 50\%$ : 7, ratio of normal morphology $<$ 4%: 9, two or more of these parameters under standard: 6)	PCBs	Total PCB level: Motility $< 50\%$ /normal p,p'-DDE level: Motility $< 50\%$ /normal (significance not tested because of small number of cases)
Younglai, 2002	Canada 21 Couples who underwent in vitro fertilization	Blood and follicular fluid of women, contaminants in seminal plasma	Seminal plasma level of contaminants relatively low, with mirex detected most frequently (7 of 21 cases, 256-1455 pg/ml) Detected in all pregnant cases, correlation not known: Endosulfan, p,p'-DDE, PCB-99, PCB-138, PCB-153, PCB-180 found in women's sera Hexachlorethane, 1,2,4-trichlorobenzene, cadmium, mirex, conitine, p,p'-DDE, PCB-49, PCB-153, PCB-180, PCB-138 found in women's follicular fluids
Dallinga, 2002	Holland 65 Husbands of infertile couples MFS*/FFS = 34/31 * Abnormal semen findings ** Normal semen findings (feminine factors for infertility)	Organochlorine compounds in blood and seminal plasma: HCB, p,p'-DDT, PCB-118, PCB-153, PCB-138, PCB-180, total PCBs, PCB metabolites	No significant difference between the groups of organochlorine level Positive correlation of age with organochlorine metabolites in blood Correlation with blood organochlorine metabolites in FFS group: Sperm count Forward motility
Rozati, 2002	India Cases*/controls** = 21/32 * Outpatients for male infertility ** Men with fertility confirmed	Organochlorine compounds in seminal plasma PCBs Phthalic acid esters (PEs)	PCB level: case/control = 0/7.63 PE level: case/control = 0.06/2.03, $p < 0.05$ Correlation with PCB level (in cases) Semen volume Forward sperm motility Sperm survival rate Correlation with PE level (in cases) Ratio of normal sperm morphology Ratio of single-chain DNA in sperm



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Younglai, 2002	Canada 21 Couples who underwent in vitro fertilization	Blood and follicular fluid of women, contaminants in seminal plasma	Seminal plasma level of contaminants relatively low, with mirex detected most frequently (7 of 21 cases, 256-1455 pg/ml) Detected in all pregnant cases, correlation not known: Endosulfan, p,p'-DDE, PCB-99, PCB-138, PCB-153, PCB-180 found in women's sera Hexachlorethane, 1,2,4-trichlorobenzene, cadmium, mirex, conitine, p,p'-DDE, PCB-49, PCB-153, PCB-180, PCB-138 found in women's follicular fluids
Dallinga, 2002	Holland 65 Husbands of infertile couples MFS*/FFS = 34/31 * Abnormal semen findings ** Normal semen findings (feminine factors for infertility)	Organochlorine compounds in blood and seminal plasma: HCB, p,p'-DDT, PCB-118, PCB-153, PCB-138, PCB-180, total PCBs, PCB metabolites	No significant difference between the groups of organochlorine level Positive correlation of age with organochlorine metabolites in blood Correlation with blood organochlorine metabolites in FFS group: Sperm count Forward motility
Rozati, 2002	India Cases*/controls** = 21/32 * Outpatients for male infertility ** Men with fertility confirmed	Organochlorine compounds in seminal plasma PCBs Phthalic acid esters (PEs)	PCB level: case/control = 0/7.63 PE level: case/control = 0.06/2.03, p < 0.05 Correlation with PCB level (in cases) Semen volume (r=-0.682, p<0.001) Forward sperm motility (r=-0.477, p<0.05) Sperm survival rate (r=-0.791, p<0.001) Correlation with PE level (in cases) Ratio of normal sperm morphology (r=-0.7692, p<0.001) Ratio of single-chain DNA in sperm (r=-0.855, p<0.001)
Richthoff, 2003	Sweden 305 General young men (18-21 years of age)* * Recruited from health check subjects before military draft	Index substance for residual organochlorines: 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153)	Weak inverse correlation of CB-153 exposure level with sperm motility by CASA and with testosterone/SHBG ratio in blood (r = -0.13, p = 0.02 and r = -0.25, p < 0.001, respectively)
Duty, 2003-1	U.S. 141 Outpatients for male infertility	Phthalate metabolites in urine MEP, MMP, MEHP, MBP, MBZP, MOP, MINP, MCHP	Linear regression analysis revealed correlation of MEP level with sperm nuclear DNA damage parameter detected by comet assay: For an interquartile range increase in MEP level, the comet extent increased significantly by 3.6 $\mu$ m (95% CI = 0.74-6.47, p = 0.015), tail distribution moment also increased 1.2 $\mu$ m (95% CI = 0.05 -2.387, borderline significance) No association between other phthalate metabolites and comet parameters
Fenster, 2003	U.S. 164 Husbands of pregnant women	Trihalomethanes (THMs): total THM including chloroform, bromoform, bromodichloromethane and dibromochlorethane	Association of trihalomethane intake with semen findings: ratio of normal sperm morphology differed by -7.1 (95% CI = -12.7 to -1.6) between the groups of the highest and lowest third levels of THM intake.

Author and publishing year	Location and subject studied	Chemical agent	Results
Smith, 2004	U.S. 40 Healthy men Classified according to expected pesticide use in the season Exposed/unexposed = 20/20	Pesticides: herbicides, insecticides, fungicides (actual occupational exposure confirmed by questionnaire)	No significant difference between the groups of occurrence of sperm chromosome aneuploidy
Dalvie, 2004	Republic of South Africa 60 Pedi-speaking workers living around Malaria Control Center (semen check conducted for 48)	DDT	Blood DDT level not significantly related with semen volume, sperm concentration, total sperm count, motility or ratio of normal morphology
Sanchez-Pena, 2004	Mexico 33 Men in an agricultural community randomly chosen from 227 participants in an epidemiologic program	Organophosphate pesticides Dialkylthiophosphates in urine (DMDTP, DMTP, DEDTP, DETP, DMP, DEP)	Significant correlation of sperm nuclear DNA fragmentation index (DFI) with urine DETP level ( $r = 0.477$ , $p = 0.226$ ) Average DFI of subjects 58.48% (about 9% in unexposed population in the same area) 45% of subjects had DFIs over 30%, a measure of reduced male fertility
Kamijima, 2004	Japan Exposed*/unexposed** = 18/18 * Indoor pesticide spraying operators ** Volunteering students or doctors	Organophosphate pesticides	Reproductive capacity indicators which significantly differ between the groups: Testosterone level in winter Low linear motility in summer Nonlinear motility in summer No significant difference in other semen findings (semen volume, sperm concentration, total sperm count, sperm survival rate, sperm motility) as well as serum FSH and LH level

Table 2.11.5: Ecological study on relationship of endocrine disruptors with sperm count

Author and publishing year	Location and subject studied	Chemical agent	Results
Koifman, 2002	11 Cities in Brazil Chosen from Brazilian National Health Data System (20-59 years of age)	Pesticides: insecticides, herbicides, fungicides, acaricides, etc.	Pesticide sales in 1985 associated with reproductive diseases in 1990s Significant positive correlation of ratio of subjects who underwent semen check for suspected infertility with pesticide sales $r=0.6(-0.01-0.88)$