

This work is licensed under a [Creative Commons Attribution-NonCommercial-ShareAlike License](https://creativecommons.org/licenses/by-nc-sa/4.0/). Your use of this material constitutes acceptance of that license and the conditions of use of materials on this site.



Copyright 2007, The Johns Hopkins University and Ronald Gray. All rights reserved. Use of these materials permitted only in accordance with license rights granted. Materials provided "AS IS"; no representations or warranties provided. User assumes all responsibility for use, and all liability related thereto, and must independently review all materials for accuracy and efficacy. May contain materials owned by others. User is responsible for obtaining permissions for use from third parties as needed.

Occupation and Reproductive Hazards

Reproductive Hazards and Occupational Exposures

- Maternal or paternal occupational exposures can affect reproduction, pregnancy outcome and infant health.
- **Potential hazards:**
 - chemicals,
 - physical agents (eg. radiation, lifting, heat),
 - psychosocial (stress)
- **Exposures**
 - Total number of persons with potential exposure is substantial, but numbers with specific exposures are often low due to small numbers of workers in high risk jobs
 - Multiple exposures are common and complicate identification of hazards
 - Animal toxicology studies have limited utility for predicting human reproductive hazards
 - Epidemiologic studies have serious limitations in establishing causality

Endpoints and Expected Frequencies

- Subfertility/Infertility (~ 9-10%)
- Early Pregnancy Loss (hCG detected ~ 23%)
- Spontaneous abortion (~ 10-15%)
- Stillbirth (~ 2%)
- Prematurity (~ 6-9%)
- Low Birthweight (5-7%)
- Major defects at birth (~ 3-4%)
- Hard to study in small populations due to lack of power

Healthy/Unhealthy Worker Effects

- **Selection effects** (“healthy/unhealthy”) worker effects
 - healthy workers may leave the workplace because of normal pregnancy /childbearing, causing over-representation of “unhealthy” workers
 - “Unhealthy” workers may leave job due to illness
 - Need to study voluntary terminated ex-employees of persons on leave of absence
 - Difficult to study long-term exposures due to selection

Employment during pregnancy

- **Effects of work in Pregnancy and PTD**
 - Studies contradictory
 - Selection: “unhealthy/healthy worker effect”
Socioeconomic benefits of employment
 - Most associations are with prolonged standing, heavy lifting, long working hours, shift work, work with industrial machines

Reconstructing Occupational Exposures

- **Job history is difficult**
 - Recall of jobs or chemicals poor (process information)
 - Job titles are non-specific (eg. lab technician)
 - Processes change over time
 - Timing of exposure relative to reproductive effects may be problematic (eg. subfertility), timing of exposure in relation to pregnancy
 - Hard to categorize jobs (job title, task analysis, processes) need to be linked to specific agents (Industrial Hygiene)
- **Exposure assessment**
 - Dose, duration and timing of exposures
 - Route of exposure (inhalation, dermal, ingestion)
 - Threshold effects (problem with quantifying exposure)

Regulation of exposures

- Regulatory:
 - Define “Threshold Limit Value” (TLV) lowest level of permitted exposure
 - NIOSH (National Inst Occupational Safety and Health) recommend TLVs
 - Legal and commercial factors affect TLV
 - OSHA (Occupational Safety and Health) regulates TLVs

Epidemiologic Study Designs

- **Retrospective Cohort or Case-control studies**
 - Problems of exposure/outcome timing
 - Recall of occupation and specificity of exposures poor
 - Job titles (nonspecific), processes, chemical/physical agents
 - Event frequency low (eg. specific birth defects)
 - Need medical record validation
 - Pregnancy outcome studies exclude infertility effects
- **Prospective Studies**
 - Recognized waiting time to conception/pregnancy loss (sample size, cost). Allow concurrent exposure assessment
 - Use of hCG to detect early losses or hormonal disturbances using daily urine samples. Sample size, cost, compliance

Evidence of Occupational Hazards

- Solvents
- Anticancer drugs
- Anesthetics
- Pesticides
- Herbicides
- Heavy metals
- Radiation
- Physical stressors

Fertility and Male Exposures

- Belgian studies of men in smelters and battery manufacturing, using biologic measurement of exposure (Gennant 1992)
 - Male fertility reduced with
 - High level cadmium
 - Lead at all levels
- Ethylene glycol ether metabolites in urine associated with infertility OR 3.1 (Veulemans 1993)
- DBCP Fungicide caused testicular atrophy
- Heat (outdoor work, lack of air conditioning) reduced fertility

Fertility and Female Exposures

- **Health Care Workers**
- Dental assistants exposed to nitrous oxide
 - Reduced fertility increased pregnancy loss (Rowland *NEJM* 1992)
- Anesthetics gases increase spontaneous abortion (RR = 1.5) Figa-Talamanca *Epi Reviews*;2000.
- Antineoplastic drugs increase spont abort, birth defects, menstrual dysfunction
- Microwave exposures increase SABs (Quellet-Hellstrom *Am J Edpid* 1993)

Work Stress

- Some association of night work or shift work with SABs
- High stress vs low stress jobs in nurses
(Hatch *Scand J Work Environ Hlth* 1999;25:144)
 - Long cycles OR = 4.3
 - Anovulation OR = 5.5
- Heavy lifting increase SABs (OR = 3.2. Florack *Epidemiol* 1993)

Solvents

- Microchip manufacturing
 - reduced fertility
 - increased spontaneous abortion
 - mainly in subgroups working with solvents such as short chain ethylene glycol ethers (EGEs)

Short Chain Ethylene Glycol Ethers (EGE)

- Were widely used (microchips, paint, printing, electronics)
- Low volatility (most exposure is dermal)
- Penetrate most rubber gloves
- Animal studies show reproductive and teratogenic effects
- Biological mechanism: Metabolized to alkoxy acetic acid which prevents DNA synthesis during cell division, detectable in urine (biomarker)

Three studies of Female EGE Exposures in Microchip manufacturing

- EGEs used in manufacture of microchips
- **Spontaneous abortions**
 - OR 2.4 (Pastides, 1988)
 - OR 2.8 (Gray 1996)
 - OR 2.3 (Swann, 1996)
- **Subfertility**
 - OR 4.6 (Gray 1996)

Cardiac Defects and Solvents

(Baltimore Washington Study, Ferencz 1993)

- Population based case-control study
- Type of exposure and type of defect varied
- **Aortic stenosis**
 - Any solvent OR = 3.2
 - Degreasing solvents OR = 12.5
- **Coarctation of the aorta**
 - Any solvent OR = 3.4
 - Degreasing solvents OR = 3.0
- Specific defects may result from highly specific exposures or from generalized exposures to a family of agents

Pesticide Exposures in Agriculture

- **Malformations**
 - Several organ systems (Nurminen, 1995)
- **Spontaneous Abortion**
 - Female agricultural workers, different exposures, seasonal. (Nurminen, 1995)
- **Stillbirths**
 - Agricultural workers in Sudan (Taha Gray)
- **Subfertility**
- **Female**
 - Agricultural workers, manufacturing
- **Male**
 - DBCP (testicular damage)

DDT and Reproduction

- Measure DDE (metabolite of DDT) in serum (Longnecker *Lancet* 2001;358:110)
 - PTD: Adjusted OR increased from 1.8 to 4.0 with DDE 15-29 ug/L to >60 ug/L (p<0.0001).
 - SGA: Adjusted OR increased 1.9 to 2.6 with increasing DDE (p = 0.04)

Sex ratio and exposures

- Seveso, Italy 1976. Explosion in herbicide plant released dioxin (Mocarelli Lancet 2000)
 - Men under 19 exposed at time of explosion subsequently fathered more girls than boys
 - sex ratio m/f = 0.38 CI 0.3-0.47
 - No effects in exposed females

Sex ratio and PCB exposure Taiwan

- PCB exposure via contaminated cooking oil
- Males <19, Sex ratio m/f = 0.85 (p = 0.04)
- Males >19 and females no effect
 - Similar effects observed in rats
 - Mechanism??
- Del Rio Lancet 2002;360:143
- Also observed oligospermia, abnormal sperm morphology and inability to penetrate oocyte in vitro (Huang JAMA 2003;289:2943)

Accidental Exposures

- Highest dose exposures often related to accidents
 - Spills
 - Explosions
 - Contamination of food and water
 - Hard to document

Health Protection

- Exclude from “high risk” jobs
- Move pregnant women to low risk jobs
- Problems:
 - Identify hazards (problematic); what is low risk
 - Identify limits of exposure Threshold limit value (TLV), known for < 13% of potential hazards
 - Protection of “average worker” versus vulnerable subgroups
 - **“Cautionary principle” (UN 1992), suspicion is sufficient, lack of scientific “certainty” should not be used to perpetuate exposures**
 - Economic costs, limitation of women’s choices?