Occupational Cancer Epidemiology

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Goal

To identify chemical & physical agents in the workplace that cause cancer in humans.

Difficulty

How does one decide whether exposure to some agent is a cause of cancer in humans?

Issues

- **Latency**: solid tumours take ~10-20 years to develop
- **Multifactorial**: ≥1 exposures can cause cancer (interactions)
- **Timing of exposures**: multistage and two-stage models; can be very complicated

Issues (continued)

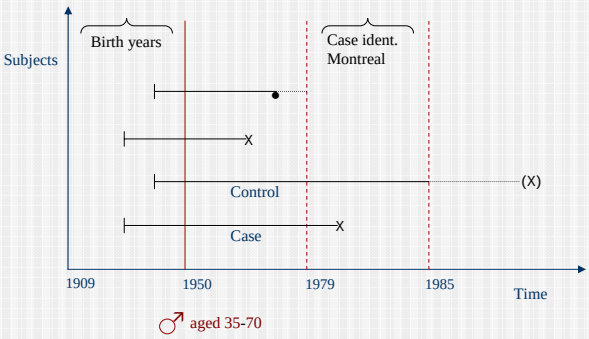
- **Hereditary:** non-sporadic cancers; functional genetic polymorphisms
- **Cellular mechanisms**: host factors and their interaction with exogenous factors likely to be important
- **Measurement of exposure**: difficult to characterize and quantify

Available Data

- Occupational exposures
  - Cohort
  - Case-control
  - Cross-sectional
  - Ecologic
- Environmental exposures
  - Similar designs as in occupational studies
- Toxicological data
- Other experimental data

Example – Case-Control Studies

- Case-control study of occupational risk factors for cancer on men
  (Siemiatycki, "Risk factors for cancer in the workplace", CRC Press, 1991)



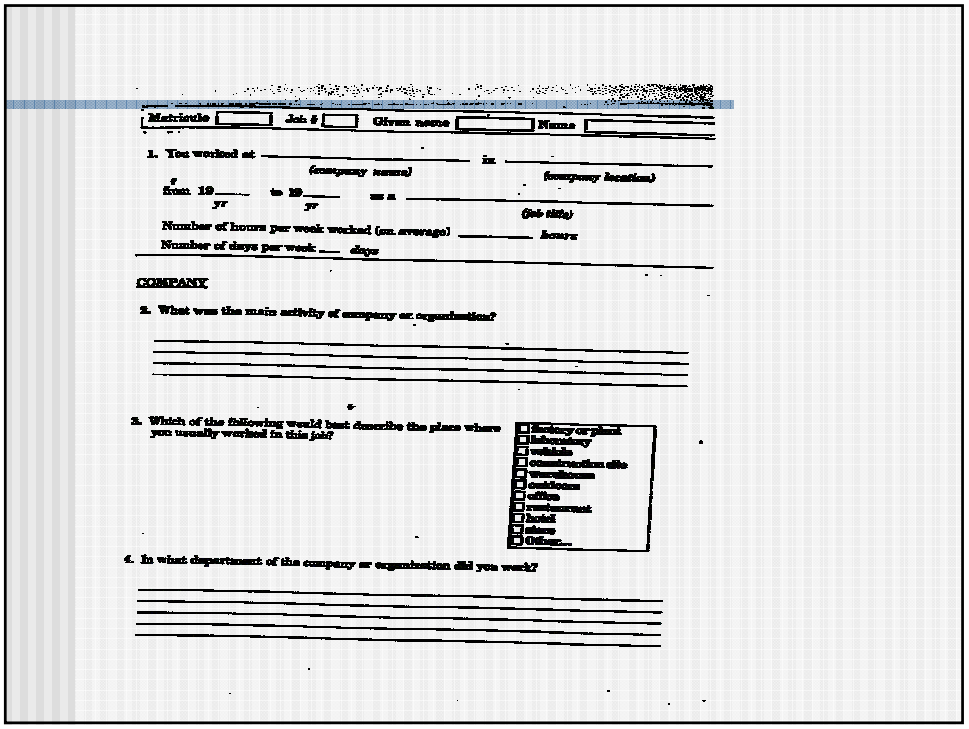
Characteristics of the study design

- ♂, age 35-70, living in Montreal between 1979 & 1985
- ~20 sites of cancer, <u>confirmed histologically</u>
- Small (~350) population-based series of control subjects

- Interviewer-administered questionnaire for non-occupational risk factors and lifetime occupational histories

Occupational questionnaire

- General questionnaire about each job each subject ever had
- Supplemented with specific questionnaires for selected jobs (e.g. welders)



Matricule ☐ Job # ☐ Given name ☐ Name ☐

1. You worked at _____ in _____
(company name) (company location)
from 19__ to 19__ as a _____
yr yr (job title)
Number of hours per week worked (on average) _____ hours
Number of days per week ___ days

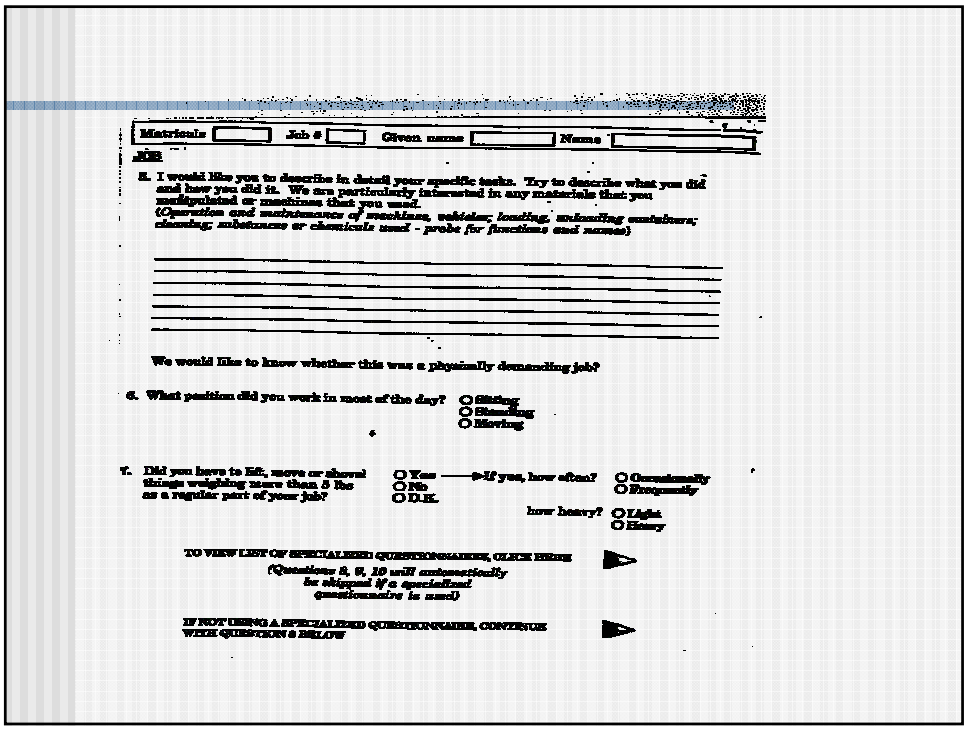
COMPANY

2. What was the main activity of company or organization?

3. Which of the following would best describe the place where you usually worked in this job?

- ☐ factory or plant
- ☐ laboratory
- ☐ vehicle
- ☐ construction site
- ☐ warehouse
- ☐ outdoors
- ☐ office
- ☐ restaurant
- ☐ hotel
- ☐ store
- ☐ Other...

4. In what department of the company or organization did you work?



Materiels ☐ Job # ☐ Given name ☐ Name ☐

JOB

5. I would like you to describe in detail your specific tasks. Try to describe what you did and how you did it. We are particularly interested in any materials that you manipulated or machines that you used.
(*Operation and maintenance of machines, welding, loading, unloading containers; cleaning; substances or chemicals used - probe for functions and names*)

We would like to know whether this was a physically demanding job?

6. What position did you work in most of the day?
- ○ Sitting
- ○ Standing
- ○ Moving

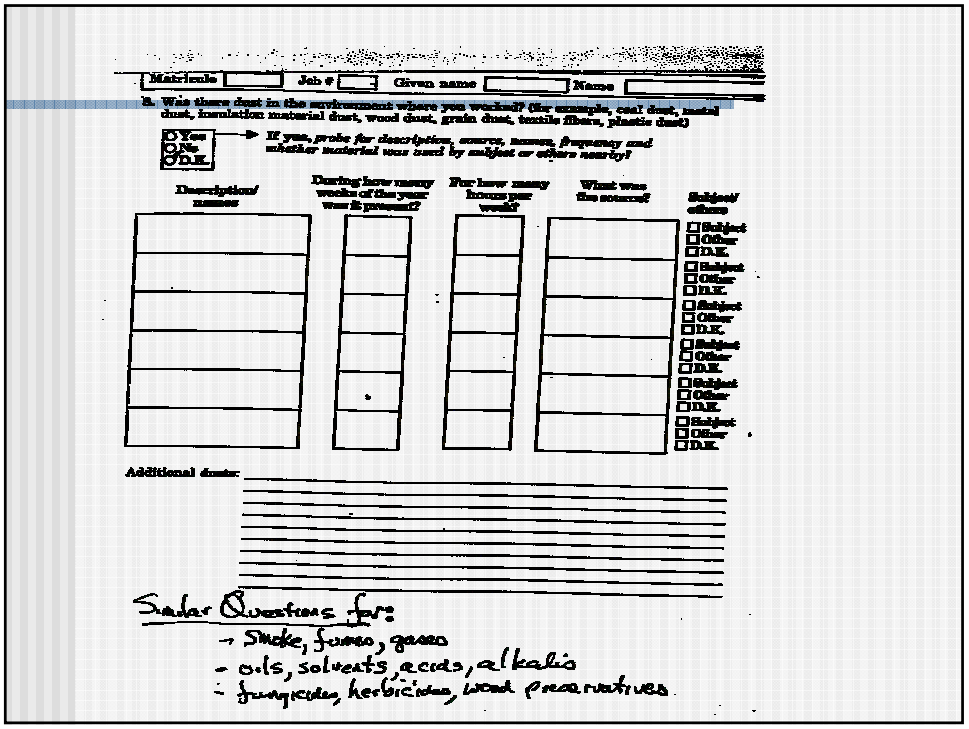
7. Did you have to lift, move or shovel things weighing more than 5 lbs as a regular part of your job?
- ○ Yes ——▶ If yes, how often? ○ Occasionally ○ Frequently
- ○ No
- ○ D.K.

how heavy? ○ Light ○ Heavy

TO VIEW LIST OF SPECIALIZED QUESTIONNAIRES, CLICK HERE ▶

(*Questions 8, 9, 10 will automatically be skipped if a specialized questionnaire is used*)

IF NOT USING A SPECIALIZED QUESTIONNAIRE, CONTINUE WITH QUESTION 8 BELOW ▶



Matricule ____ Job # ____ Given name ____ Name ____

13. Was there dust in the environment where you worked? (for example, coal dust, metal dust, insulation material dust, wood dust, grain dust, textile fibers, plastic dust)

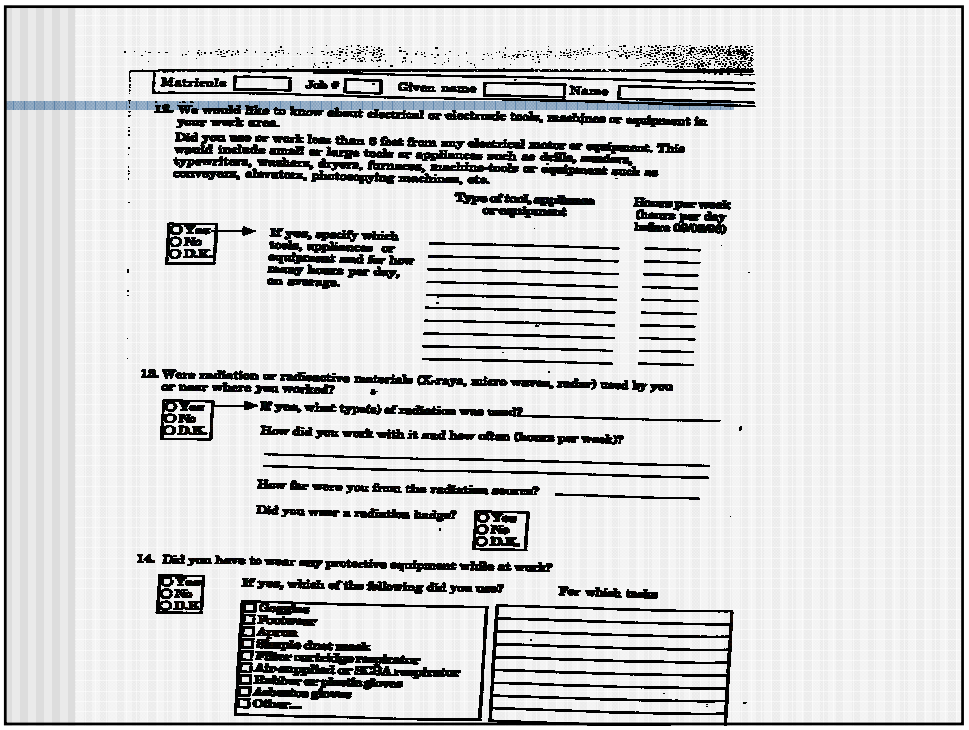
☐ Yes
☐ No
☐ D.K.

→ *If yes, probe for description, source, nature, frequency and whether material was used by subject or others nearby!*

Description/ names	During how many weeks of the year was it present?	For how many hours per week?	What was the source?	Subject/ others
				☐ Subject ☐ Other ☐ D.K.
				☐ Subject ☐ Other ☐ D.K.
				☐ Subject ☐ Other ☐ D.K.
				☐ Subject ☐ Other ☐ D.K.
				☐ Subject ☐ Other ☐ D.K.
				☐ Subject ☐ Other ☐ D.K.

Additional dusts: _____

Solar Questions for:
- Smoke, fumes, gases
- oils, solvents, acids, alkalis
- fungicides, herbicides, wood preservatives



Matricule ____ Job # ____ Given name ____ Name ____

12. We would like to know about electrical or electronic tools, machines or equipment in your work area.

Did you use or work less than 6 feet from any electrical motor or equipment. This would include small or large tools or appliances such as drills, sanders, typewriters, washers, dryers, furnaces, machine-tools or equipment such as conveyors, elevators, photocopying machines, etc.

Type of tool, appliance or equipment	Hours per week (hours per day before brackets)

☐ Yes
☐ No
☐ D.K.

→ If yes, specify which tools, appliances or equipment and for how many hours per day, on average.

13. Were radiation or radioactive materials (X-rays, micro waves, radar) used by you or near where you worked?

☐ Yes
☐ No
☐ D.K.

→ If yes, what type(s) of radiation was used? _____

How did you work with it and how often (hours per week)?

How far were you from the radiation source? _____

Did you wear a radiation badge? ☐ Yes ☐ No ☐ D.K.

14. Did you have to wear any protective equipment while at work?

☐ Yes
☐ No
☐ D.K.

If yes, which of the following did you use? For which tasks

- ☐ Goggles
- ☐ Earplugs
- ☐ Apron
- ☐ Simple dust mask
- ☐ Filter cartridge respirator
- ☐ Air-supplied or SCBA respirator
- ☐ Rubber or plastic gloves
- ☐ Asbestos gloves
- ☐ Other...

Matricule [ ] Job # [ ] Given name [ ] Name [ ]

15. Did you ever have to replace someone else?

- O Yes → If yes, how often and what were your tasks? ______
- O No
- O D.K.

We would like to know about your main worksite or work area or office or the most typical if there were many.

16. What was the size of the area?

Rooms
- ☐ Living room/Salon
- ☐ Metro/Provigo
- ☐ Club Price
- ☐ >> Club Price

Ceilings
- ☐ Low(house)/Bas (maison)
- ☐ High (Club Price)/Hauts (Club Price)

17. How many people were performing the same tasks as you in your work area? ______ *number of people*

18. What other work was being done around you? ______

19. What machines or processes were used by others in your work area? ______

20. Were lift trucks used in your work area?

- O Yes → If yes, how were the lift trucks powered?
  - ☐ Gasoline
  - ☐ Propane
  - ☐ Diesel
  - ☐ Electric
- O No
- O D.K.

How many lifts were operating at the same time in your work area? ______ *lifts*

Did you ever drive the trucks yourself?
- O Yes
- O No
- O D.K.

Matricule [ ] Job # [ ] Given name [ ] Name [ ]

21. What was the temperature of your work area, on average? ______

22. What type of ventilation did your work area have?
- O No ventilation
- O Open doors and windows
- O Ventilation fan with outlet to outside
- O Air conditioning
- O Fume hood with fan and air filters
- O D.K.

23. How effective was the ventilation of your usual work area?
- O Aucune efficacité
- O Modérément efficace
- O Très efficace
- O N.S.P.
- O Other...

24. We would like to know about tobacco smoke in your workplace.

On average, how many people around you smoked at work regularly, apart from yourself? ______ *people*

If None: Skip to Question 27

On average, how many hours per day were you exposed to tobacco smoke at work? ______ *hours*

How much tobacco smoke was there in your usual work area?
- O None
- O Slight
- O Moderate
- O Very smoky
- O D.K.

Were people smoking around you when you were on break or at lunch?
- O No
- O A little
- O A lot
- O D.K.

Comments

______

Occupational Coding

- Team of chemists & industrial hygienists reviewed each job history & attributed exposure to ~300 agents

- Coded:
  - Lifetime occupations (as coded by job and industry titles)
  - Lifetime exposure to ~300 agents in the workplace

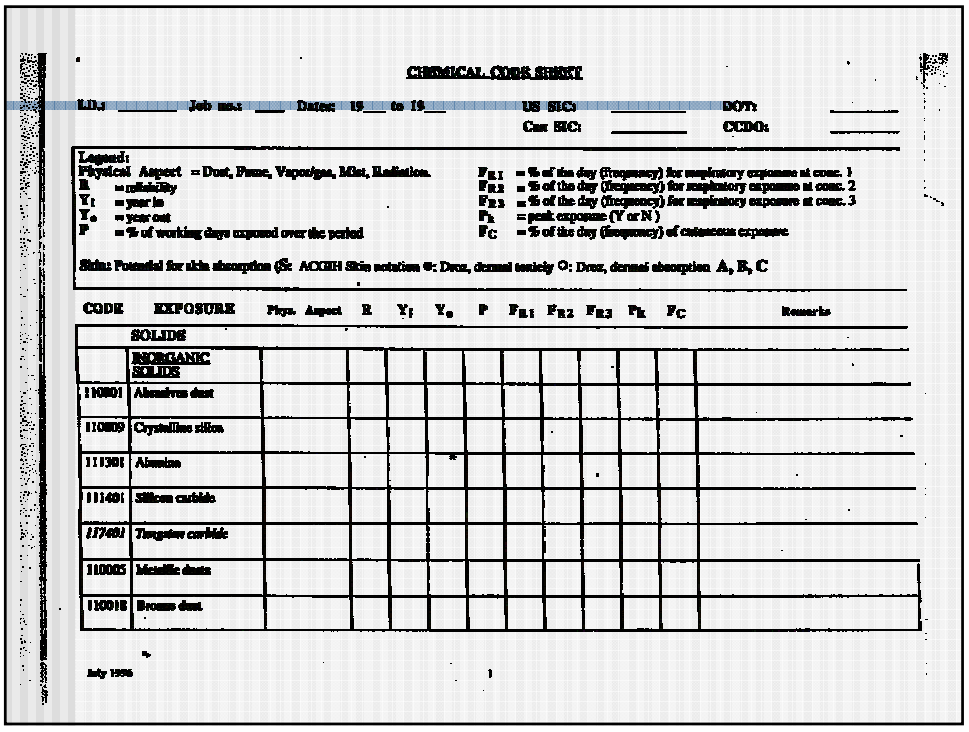
- Exposure variables
  - Start/end dates of job; duration
  - Concentration, coded on a 4-level ordinal scale

None	
Low	- Background exposure
Medium	- In between
High	- Handling product in concentrated form

- Frequency, coded on 4-level interval scale

None	
Low	- 1-5%
Medium	- 5-30%
High	- >30%

- Route of exposure, nominal
  - Respiratory
  - Cutaneous
  - Both
- Confidence of exposure, ordinal
  - “Possible”
  - “Probable”
  - “Certain”



CHEMICAL CODES SHEET

I.D.: _____ Job no.: ____ Dates: 19___ to 19___ US SIC: _____ DOT: _____

Can SIC: _____ CCDO: _____

Legend:
Physical Aspect = Dust, Fume, Vapor/gas, Mist, Radiation.
R = reliability
Y_i = year in
Y_o = year out
P = % of working days exposed over the period
F_{R1} = % of the day (frequency) for respiratory exposure at conc. 1
F_{R2} = % of the day (frequency) for respiratory exposure at conc. 2
F_{R3} = % of the day (frequency) for respiratory exposure at conc. 3
P_k = peak exposure (Y or N)
F_C = % of the day (frequency) of cutaneous exposure

Skin: Potential for skin absorption (S: ACGIH Skin notation ⊕: Dose, dermal toxicity ○: Dose, dermal absorption A, B, C

CODE	EXPOSURE	Phys. Aspect	R	Y_i	Y_o	P	F_{R1}	F_{R2}	F_{R3}	P_k	F_C	Remarks
	SOLIDS											
	INORGANIC SOLIDS											
110801	Aluminum dust											
110809	Crystalline silica											
111301	Alumina											
111401	Silicon carbide											
117401	Tungsten carbide											
110005	Metallic dusts											
110018	Bronze dust											

July 1996

Statistical Analysis

- Logistic regression (unconditional) using selected sites of cancer & population controls as reference
- Adjusted for measured risk factors

- Exposure indices
  - Duration at medium/high concentrations
  - Cumulative = $\sum_{\text{jobs}} \text{conc} * \text{freq} * \text{duration}$
  - "Substantial$_1$" - { conc ≥ medium (2); freq ≥ high (3) }
  - " Substantial$_2$" - { conc * freq > 3; duration > 5 y prior to 5 years before dx }

Coding:
conc= {0,…,3}
freq= {0,…,3}

Selected Results

Site	Agent	OR (subst$_2$)	90% CI
Lung	Crysotile ashestod	1.9	1.1-3.2
	Crystaline silica	1.4	1.0-1.8
	Wood dust	1.3	1.0-1.7
Rectum	Rayon fibres	3.5	1.6-7.8
Stomach	Co	2.4	1.6-3.7
Rectum	Synthetic fibres	2.5	1.1-5.7

Aspects of the design

Strengths

- Population-based
- Relatively large case series
- Histological confirmation
- Control subjects
- Lifetime exposure data
- Confounders

Limitations

- Low prevalence of exposure
- Control subjects
- Confounders

Example: Postmenopausal Breast Cancer and Occupational Exposures to Extremely Low Frequency Magnetic Fields

Relative Risks for Exposure to Magnetic Fields

Index	No. of exposed cases	No. of exposed controls	Age-adjusted OR	Adjusted OR	95% CI
Ever	437	450	1.12	1.17	0.82-1.67
Confidence: >Low	427	426	1.17	1.18	0.83-1.69
Intensity: >Low	134	151	1.07	1.55	0.93-2.60
Confidence & Intensity: >Low	134	148	1.10	1.58	0.94-2.65

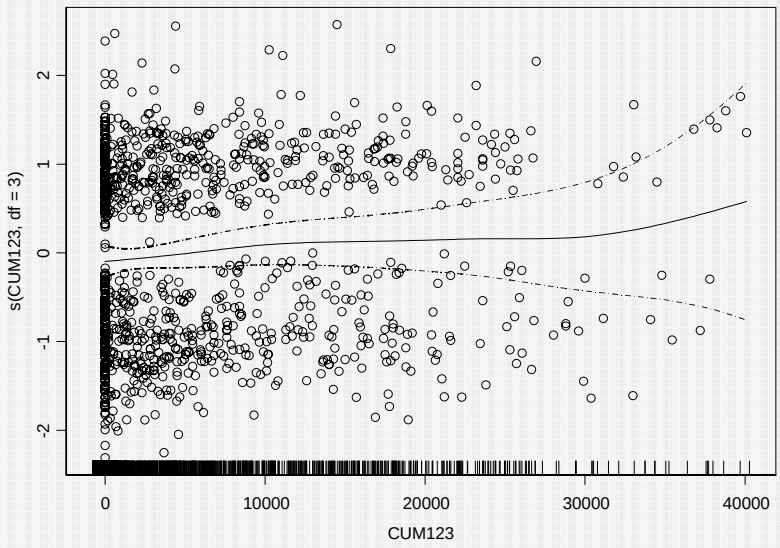
Duration of Exposure (per 1 Year Increase)

Index	Age-adjusted OR	Adjusted OR	95% CI
Ever	1.01	1.03	0.99-1.06
Confidence>Low	1.02	1.03	0.99-1.07
Intensity > Low	1.01	1.05	0.98-1.12
Confidence & Intensity > Low	1.01	1.05	0.97-1.12

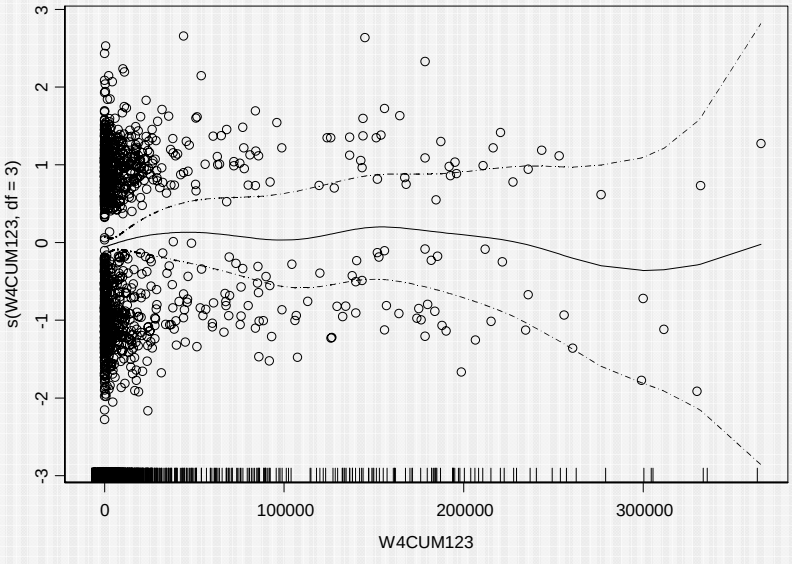
Continuous Indices of Exposure

Duration/level	IQ	OR_A	OR_F	95% CI
Lifetime exposures				
Duration	6000	1.05	1.08	0.96 – 1.20
Cumulative	12000	0.99	1.00	0.97 – 1.04
Latency of 10 years before diag.				
Duration	6000	1.07	1.12	0.99 – 1.28
Cumulative	12000	0.99	1.02	0.98 – 1.06
Exposures at age ≤ 35 years				
Duration	6000	1.14	1.27	0.99 – 1.62
Cumulative	12000	1.01	1.04	0.97 – 1.12

Dose-response for Lifetime Duration of Occupational Exposures to Magnetic Fields, at any Intensity

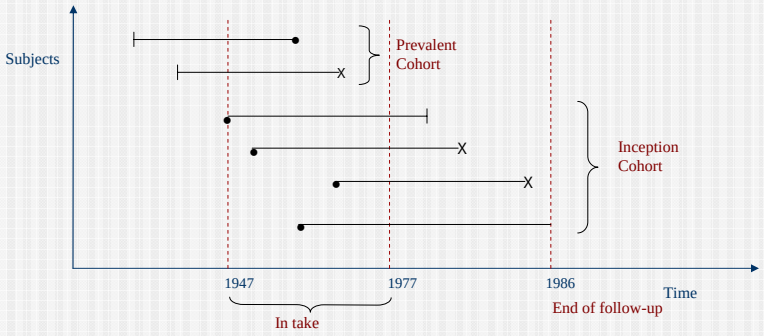


Dose-response for Cumulative Occupational Exposure to Magnetic Fields



Example – Cohort Studies

- Cohort study of synthetic textiles workers (Goldberg & Thériault, *Am J Indust Med* 1994; 25: 889-922)



- ≥ 1 yr service at plant
- 7422 ♂ [217,000 person-years]
  2720 ♀ [89,000 p-y]
- 15 different "exposure areas"
  - Cellulose acetate 1927-
  - Cellulose triacetate 1957-78
  - Polypropylene 1959-70
  - Textiles & weaving 1927-
  - Dyeing & finishing 1927-
  - Power plant/maintenance 1927-

- Tracing & ascertainment of vital status

  Statistics Canada's Mortality Data Base ~98% identifying correctly vital status
  [Goldberg et al., *Can J Pub Health* 1993; 84:201-4.]

  ♂ : 1663 deaths [22.4%]

  ♀ : 238 deaths [8.8%]

- Analysis
  - Cause-specific SMRs by province, "non-urban" Quebec, Eastern Townships
  - Analysis by "occupational unit", by duration of employment
  - Case control analysis by extent & duration of exposure to ~150 occupational agents

SMRs for selected causes of death, 1947-86

Cause	Number of deaths	SMR & 95% CI
MEN		
All causes	1663	0.71 0.68-0.74
All neoplasms	414	0.73 0.66-0.80
Colorectal cancer	49	0.68 0.51-0.91
WOMEN		
All causes	238	0.75 0.66-0.85
All neoplasms	107	0.97 0.80-1.17
Colorectal cancer	14	0.95 0.52-1.59

SMRs for colorectal cancer among men according to length of service at the plant

Length of service	No. of deaths	SMR	RR	95% CI
1-4	5	0.32	1	
5-9	10	0.82	2.55	0.79-9.55
10-19	9	0.55	1.72	0.52-6.58
20+	25	0.90	2.81	1.06-9.45
Total	49	0.68		

Chi-square for test for linear trend: 3.64 (p=0.06)

Results of case-control analyses for colorectal cancer among men

POLYPROPYLENE and CELLULOSE TRIACETATE EXTRUSION UNIT

Duration of employment	Number of exposed cases	ctrls	Unadjusted OR	95%
0	52	742	1	
>0-4	1	11	1.55	0.19-12.8
5+	2	5	3.55	0.49-25.6
Total	55	758		

Results of case-control analyses for colorectal cancer and occupational agents

Exposure	Number of exposed Cases	Ctrls	Unadjusted OR	95%CI
Pyrolysis fumes from cellulose triacetate/polypropylene	8	73	1.05	0.98-1.14
Cellulose acetate dust	6	57	3.54	0.77-16.3

Contrasting Cohort & C-C Studies

	Cohort	C-C
End point: Mortality	<	____
Incidence	>	>
Covariates:	Age, sex calendar yr.	>
Exposure: Duration	Only in target cohort	Lifetime
Accuracy	>	<
Reference group:	Gen. popn.; within cohort	Population-based; hospital-based; etc

	Cohort	C-C
Analysis:	SMR; Poisson Cox; c-c-w-cohort	M-H; logistic
Sources for bias & msmt. error		
Endpoints	<	>
Selection	Entry, exit [HWE]	popn ←response
		Hosp ←?
Response	>	<
Confounding	<	>
Exposure	>	< (recall bias)

Causality

Philosophies

- Causes are not observable directly, but can only be inferred through the observed statistical associations
  - **Deductive reasoning (Popper):** an hypothesis remains that until refuted
  - **Inductive reasoning:** weight of the evidence suggests that the exposure is a cause
  - **Prediction:** lack of prediction is one of the strongest tests in all of the sciences (including physics)

Guidelines for Judging Causality (Bradford–Hill)

- Temporality
  - Event occurs after cause
- Strength of Association
  - No confounding principle
- Consistency/coherency
  - Are results "similar" across studies
- Exposure-response
  - Does the response (e.g., RR) reflect a plausible relationship with exposure

Judging Causality (continued)

- Experimental evidence — Rarely available
- Specificity — Beware! Can be misleading
- Plausibility

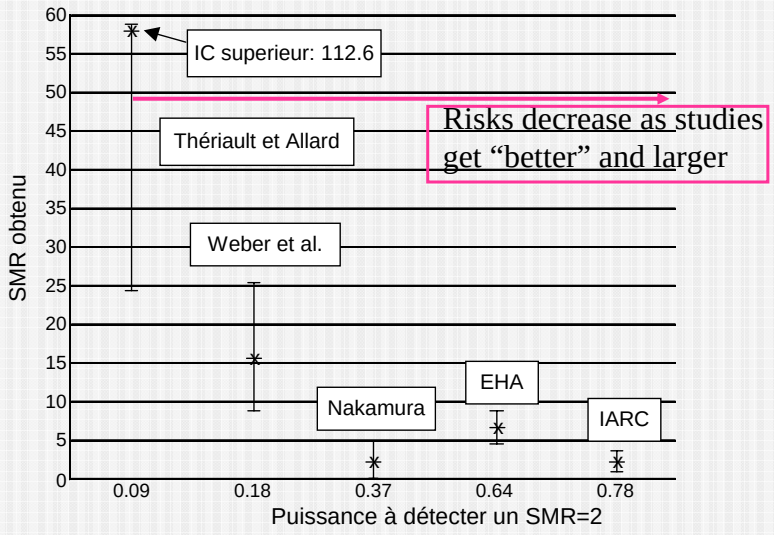
Some “accepted” carcinogens

- Ionizing radiation
- Asbestos
- Radium
- Vinyl chloride monomer
- Benzidine dyes
- Coal tar pitch volatiles
- Arsenic

Making Decisions About Causal Associations

The example of vinyl chloride monomer as a human carcinogen

SMRs for liver and biliary cancers for workers exposed to vinyl chloride monomer



Number of observed deaths in five cohorts of workers exposed to vinyl chloride monomer

Reference	Type of cancer	No. of observed deaths	Confirmed angiosarcomas
Thériault et Allard, 1981 Thériault, 1982	Liver	8	NM[1]
Weber et al., 1981	Liver	12	4
Nakamura, 1983	Liver	6	1
EHA, 1986	Liver and gallbladder	37	15
Simonato et al., 1991	Liver	24	22
Total		87	42

[1] NM, Not mentioned

Exposure-response relationships for liver cancer in various occupational mortality studies of vinyl chloride monomer

Reference	Exposure metric	Exposure Unit of exposure	Category	N[1]	SMR or RR[2]	95%CI
Liver cancer						
Weber et al., 1981	Duration employment	Years	<1	0	0	
			1-5	2	8.7	1.1-31.4
			6-10	3	15.3	3.2-44.7
			>10	7	25.3	10.2-52.3
Nakamura, 1983	Duration employment	Years	1-14	3	1.4	0.3-4.1
			>14	3	1.7	1.6-22.5
Simonato et al., 1991	Duration employment	Years	1-9	4	0.9	0.3-2.4
			10-14	5	3.3	1.1-7.6
			15-19	4	3.1	0.8-7.9
			20-24	6	7.1	2.6-15.5
			>24	5	11.1	3.6-25.9
Simonato et al., 1991	Cumulative exposure	ppm-years	<500		1	
			500-1999		1.2	0.1-11.4
			2000-5999		4.6	1.0-21.0
			6000-9999		12.2	2.5-59.6
			>10,000		17.1	3.1-93.6
Liver and gallbladder cancer						
EHA, 1986	Duration employment	Years	<10	6	1.8	0.7-3.9
			10-20	20	12.4	7.6-19.2
			20 +	11	12.9	6.5-23.1
Angiosarcoma						
Simonato et al., 1991	Cumulative exposure	ppm-years	<2000		1	
			2000-5999		6.8	1.1-41.7
			6000-9999		24.7	4.1-150.1
			>9999		45.4	7.3-281.1

International Agency for Research on Cancer (IARC)

- IARC working group of experts declared that vinyl chloride monomer is a Class 1 human carcinogen
  - This decision process was based on a “weight-of-the-evidence” approach (inductive reasoning)
  - It uses human and experimental data
  - The conclusion was a consensus decision

IARC Classification System for Carcinogens (Monograph Series)

1	Sufficient evidence in humans
2	Limited A. Probably carcinogenic B Possibly carcinogenic (animal studies)
3	Insufficient evidence
4	Lack of carcinogenicity

Other Processes

- Consensus conferences (NIH)
- Governmental law/decree

Resources

Sources for carcinogencity information

International Agency for Research on Cancer (IARC)

U.S. National Toxicology Program

U.S. Environmental Protection Agency

NIOSH

Web sites

- EPA server:
  listserver@unixmail.rtpnc.epa.gov
- Health Canada: www.hc-sc.ca
- U.S. NCI: www.nci.nih.gov
- U.S. NIEHS: www.niehs.nih.gov
- WHO: www.who.org
- IARC: www.iarc.fr
- CDC: www.cdc.gov

U.S. NTP

ntp-server.niehs.nih.gov

Annual Report on Carcinogens

U.S. EPA

www.epa.gov/ngispgm3/iris/index.html

IRIS – Integrated Risk Information System

NIOSH

“Pocket Guide to Chemical Hazards”

www.cdc.gov/niosh/homepage.html

“Current Intelligence Bulletins”

And other databases

Exposure Limit Values

- TLV – ACGIH (www.acgih.org)
- Quebec: Gazette, No 50, 1 Dec 1993, Part 2

Where to get this lecture

- http://www.epi.mcgill.ca
  - Under Faculty
  - Under Courses
  - Occupational Cancer Lecture