Occupational causes of cancer

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Historic eras in occupational cancer research

<1900

- Clinical cluster observations

1900-1950

- Animal carcinogenesis experimentation
- Clinical cluster observations followed by fairly primitive cohort studies
- Legal recognition of occupational cancer

1950-1970

- Modern epidemiology develops
- Environmentalism
- Development of active epidemiologic surveillance

Historic eras in occupational cancer research

1970-1990

- IARC
- Increasing numbers of trained epidemiologists
- Development of “short-term” tests
- Increasing coordination of animal experimentation
- Sharp increase in numbers and quality of epidemiologic studies
- Case-control methods used, as well as cohort
- Attention to exposure assessment, dose-response, internal analyses, biases
- Intense debates on PARP

>1990

- Increasing experimental work on mechanisms
- Epidemiology research plateaus, maybe wanes
- Molecular epidemiology and GxE interactions
- Internationalization

IARC Evaluations

- **Substances chosen on basis of two criteria:**
  - Humans exposed
  - Suspicion of cancer risk
- **Working groups**
  - Composition
  - Functioning
- **Evaluations**
  - Dimensions (human Ca, animal Ca, other)
  - Overall (1, 2A, 2B, 3, 4)
  - Limitations (target organ, quantification, validity)

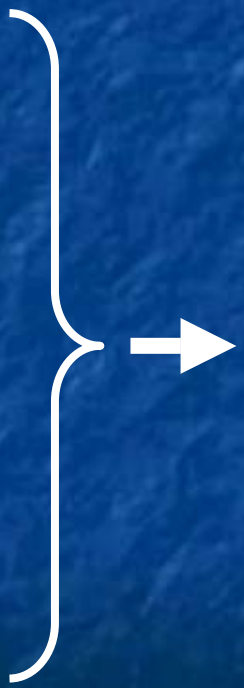
IARC Evaluations
Dimensions and Groups

Types of evidence

Human

Animal

Other
- mutagenicity
- genotoxicity
- metabolism
- etc.



Group

1	Carcinogenic to humans
2A	Probably carcinogenic to humans
2B	Possibly carcinogenic to humans
3	Not classifiable
4	Not carcinogenic to humans

Number of IARC group 1 carcinogens by main source of exposure

Exposure	N
Occupation	37
Environment	3
Biological agents	10
Medications	23
Radiation	12
Lifestyle factors	8

What is an occupational exposure?

- (Bis)chloromethylether
- Vinyl chloride monomer
- Coke oven emissions
- PAHs
- Asbestos
- Radon gas
- Passive smoking
- Pesticides
- Dyes & pigments
- Solar radiation
- Aflatoxins
- Medications

Occupational carcinogens: operational definition

- An agent to which **substantial** numbers of workers are or have been exposed at **significant** levels of exposure.

- Substantial: > 10,000 workers
- Significant: As much as, or more than, in general environment

Siemiatycki et al, Environ Hlth Persp, 2004, http://www.ehponline.org

Numbers of occupational carcinogens and high risk occupations and industries designated by the IARC Monograph Programme, 1971-2003

Group		Numbers
1	(definite)	40
2A	(probable)	30
2B	(possible)	117

Numbers of occupational carcinogens and high risk occupations and industries designated by the IARC Monograph Programme, 1971-2003

Group		Mixtures & Agents	Occupations & Industries
1	(definite)	28	12
2A	(probable)	27	3
2B	(possible)	113	4

Siemiatycki et al, Environ Hlth Persp, 2004, http://www.ehponline.org

Number of IARC occupational "carcinogens" by type and group (1/2)

Substance or mixture	Group 1	Group 2A	Group 2B
Physical agents (radiation)	2	1	1
Respirable dusts & fibers	5	0	7
Metals & metal compounds	5	0	5
Fuels & by-products of wood & fossil fuels	5	2	10
Monomers	1	5	8
Intermediates in plastics & rubber manufacturing	1	2	8
Aromatic amine dyes	3	3	13

Siemiatycki et al, Environ Hlth Persp, 2004, http://www.ehponline.org

Number of IARC occupational "carcinogens" by type and group (2/2)

Substance or mixture	Group 1	Group 2A	Group 2B
Pesticides	2	3	17
Polyaromatic hydrocarbons	0	3	9
Chlorinated hydrocarbons	0	4	7
Intermediates in the production of dyes	0	1	7
Azo dyes	0	0	10
Nitro compounds	0	0	10
Others	3	6	10

Siemiatycki et al, Environ Hlth Persp, 2004, http://www.ehponline.org

Current (2003) IARC Group 1 occupational carcinogens: Target organs (1/3)

Agent	Definite	Probable
Physical agents		
Ionizing radiation	Br, Leuk, Li, Lu	Others
	Th, Bone	
Solar radiation	NMS, Mel	
Respirable dusts & fibres		
Asbestos	Lu, Meso	Lar, GI
Talc containing asbestos fibres	Lu, Meso	
Silica, crystalline	Lu	
Wood dust	Nose	

Current (2003) IARC Group 1 occupational carcinogens: Target organs (2/3)

Agent	Definite	Probable
Metals & metal compounds		
Arsenic & arsenic cmpds	NMS, Lu	Li
Beryllium & beryllium cmpds	Lu	
Cadmium & cadmium cmpds		
Chromium cmpds, hexavalent	Lu	Lu, Nose
Nickel & nickel cmpds	Lu, Nose	
Fuels & by-products of wood & fossil fuels		
Benzene	Leuk	
Coal tars & pitches	NMS, Lu	Bl
Mineral oils, untreated/mildly treated	NMS	Lu, Bl, Nose
Shale oils or shale-derived lubricants	NMS	
Soots	NMS, Lu	Eso

Current (2003) IARC Group 1 occupational carcinogens: Target organs (3/3)

Agent	Definite	Probable
Monomers		
Vinyl chloride	AS	Li
Intermediates in plastics & rubber manufacturing		
BCME & CMME	Lu	
Aromatic amino dyes		
4-Aminobiphenyl	Bl	
Benzidine	Bl	
2-Napththylamine	Bl	
Pesticides & contaminants		
Ethylene oxide	Leuk	
TCDD	All	
Others		
Formaldehyde	NP	Leuk
Mustard gas	Lar	Lu
Strong inorganic acid mists	Lar	Lu
Passive smoking	Lu	

Current (2003) IARC Group 1 occupations and industries

- Aluminum production
- Auramine (manuf)
- Boot and shoe (manuf, repair)
- Coal gasification
- Coke production
- Furniture & cabinet making
- Haematite mining (underground)
- Iron and steel founding
- Isopropanol (manuf)
- Magenta (manuf)
- Painter
- Rubber industry

The evaluation might not apply to all exposure circumstances within the industry and it might reflect the risks from past exposure conditions

Selected current (2003) IARC Group 2A occupational carcinogens: Target organs (1/3)

Agent	Probable
Polyaromatic hydrocarbons	
Benz[a]anthracene	Lu, Bl, NMS
Benz[a]pyrene	Lu, Bl, NMS
Dibenz[a,h]anthracene	
Fuels & by-products of wood & fossil fuels	
Creosotes	NMS
Diesel engine exhaust	Lu, Bl
Intermediates in plastics & rubber manufacturing	
MOCA	Bl
Styrene-7,8-oxide	-

Selected current (2003) IARC Group 2A occupational carcinogens: Target organs (2/3)

Agent	Probable
Chlorinated hydrocarbons	
Alpha-chlorinated toluenes	Lu
Polychlorinated byphenyls	Li
Tetrachloroethylene	Cer, Eso, NHL
Trichloroethylene	Li, Kid, NHL
Monomers	
Acrylamide	Pan
1,3-Butadiene	NHL, Leuk
Epichlorohydrin	Lu, Br

Selected current (2003) IARC Group 2A occupational carcinogens: Target organs (3/3)

Substance or mixture	Probable
Aromatic amine dyes	
Benzidine-based dyes	Bl
4-Chlor-ortho-toluidine	Bl
Pesticides	
Captafol	-
Ethylene dibromide	-
Non-arsenical insecticides	Br, Leuk, Lu, NHL
Metals	
Inorganic lead compounds	Lu

Current (2003) IARC Group 2A occupations and industries

- Art glass manufacturing
- Cobalt metal manufacturing
- Hairdresser or barber
- Petroleum refining

Selected IARC Group 2B occupational carcinogens

- Refractory ceramic fibres
- Nickel alloys
- Carbon black
- Gasoline engine exhaust
- Gasoline
- Bitumens
- Styrene
- Acrylonitrile
- Chloroform
- Dichloromethane
- Some pesticides
- Welding fumes

Number of occupational carcinogens by site and strength of evidence

Site	++	+
Nose, NP	2	2
Nasopharynx	1	0
Esophagus	0	2
Liver	3	2
Pancreas	0	1
Larynx	2	1
Lung	12	11
Mesothelioma	2	0
Bone	1	0

Site	++	+
Melanoma	1	0
Non-melanoma skin	7	4
Bladder	3	10
Kidney	0	1
Cervix	0	1
Brain	1	2
Thyroid	1	0
NHL	0	4
Leukemia	3	3

Question

Q. Is the occupational environment an important source of human carcinogens?

A. Probably

Population attributable risk percent

Definition: Percentage of the diseased persons in the population whose disease would have been prevented had the exposure been absent.

Range of estimates: 2% - 10%

Reliability of estimates: Mediocre

The importance of occupational cancer epidemiology

- Nearly half of known human carcinogens are substances found essentially in the occupational environment
- While current estimates of attributable fractions are questionable, there are undoubtedly many cases of cancer attributable to occupational exposure
- Once identified, control measures are often feasible
- The discovery of occupational carcinogens has importance outside the factory walls
- Provides a basis for compensating victims
- Informs understanding of carcinogenesis

Trends in exposure to occupational carcinogens in developed countries

- Changing industrial / occupational structure
  - Blue collar → white collar & services
  - Increasing job mobility
  - Decreasing gender stratification
- Improving occupational hygiene
  - Most, but not all, monitored substances
  - Irrespective of known carcinogenicity

Exposure to occupational carcinogens in developing countries

- Economic development → "dirty" industries
- Documented evidence of high exposure levels of known carcinogens
- Ethical/political dimension of "exporting" dangerous industries
- Ethical/political dimension of "exporting" policies

Iceberg

- Most known occupational carcinogens were discovered by chance
- Is this the tip of an iceberg?
- Is it likely that there are many more?

Primary strategies for discovering carcinogens

- Epidemiology
- Animal experimentation (toxicology)
- Other biological effects
  - Mutagenesis
  - Genotoxicity
  - Etc.

Some challenges in occupational cancer epidemiology (1/3)

- Exposure assessment
- Exposure assessment
- Exposure assessment

Some challenges in occupational cancer epidemiology (2/3)

- Sample size
- Confounding
- Effect modification (including GxE)

More challenges (3/3)

- Manpower to conduct research
- Collaboration with exposure experts
- Access to human subjects/data/ethics
- Indifference of decision-makers

Selected take-home messages

- The legacy of occupational cancer research is rich
- Well-targeted occupational studies still present excellent opportunities for cancer etiology research
- Internationalization is good
- Sample sizes must be large enough
- Exposure assessment is essential
- Lobbying to prevent crippling effects of privacy laws
- Combat indifference of universities and funders