Approaches to Determining Carcinogenic Risks in Humans

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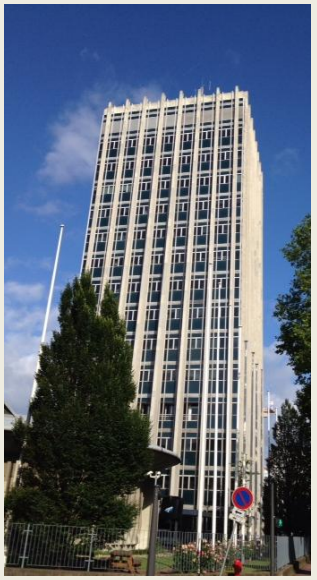
Outline

- International Agency for Research on Cancer (IARC) human carcinogenicity criteria
- Epidemiologic study design considerations
  - Population selection impact
  - Exposure assessment strategies
  - Outcome assessment strategies
  - Assessment of potential confounding
- Study design examples

International Agency for Research on Cancer



- Purpose is to identify human cancer causes
- Provides independent scientific opinion
- Expert working group reviews epidemiologic studies, cancer bioassays, exposure, mechanistic data
  - Group 1: Carcinogenic to humans
  - Group 2A: Probably carcinogenic to humans
  - Group 2B: Possibly carcinogenic to humans
  - Group 3: Not classifiable
  - Group 4: Probably not carcinogenic to humans

Evaluation of Carcinogenicity in Humans

- Sufficient: positive relationship between exposure and cancer; chance, bias and confounding is ruled out with reasonable confidence in studies.
- Limited: chance, bias or confounding could not be ruled out with reasonable confidence
- Inadequate: insufficient quality, consistency or statistical power to permit a conclusion
- Lack of risk: several adequate studies; bias and confounding be ruled out with reasonable confidence

IARC Overall Evaluation

- Group 1: sufficient evidence in humans OR sufficient evidence in animals and strong human evidence of a relevant mechanism (i.e. ethylene oxide, genotoxic)
- Group 2A: limited evidence in humans and sufficient evidence in animals OR sufficient evidence in animals and strong mechanistic considerations
- Group 2B: limited evidence in humans and less than sufficient evidence in animals OR inadequate evidence in humans but sufficient evidence in animals OR strong mechanistic and other data

IARC Assessment of Workshop Agents

Agent	Year	Human	Animal	Group
styrene	2002	Limited lymphatic, hematopoietic	limited	2B
naphthalene	2002	inadequate	sufficient	2B
ethylbenzene	2000	inadequate	sufficient	2B
cumene	2013	no data	sufficient	2B
coumarin	2000	no data	limited	3

Group 2B = possibly carcinogenic in humans
Group 3 = not classifiable

US National Toxicology Program

Workshop Agent Assessment

Reasonably anticipated to be human carcinogens

- styrene (2011): limited human evidence, sufficient animal evidence, supporting mechanistic data
- naphthalene (2004): sufficient animal evidence
- cumene (2013): draft document under review, proposed based on sufficient animal evidence

Challenge to Epidemiologists

- Human lung cancer takes >20 years or more to develop – prospective studies have not been feasible
- Reliance on occupational registries/work records not designed for health studies
- Ensuring quality linkage between job title or work records with quantitative or semiquantitive (categorical) exposure estimates
- Assessment of historical exposures
- Assessment of factors other than the agent of interest (smoking)

Impact of Population Selection

- General population based cancer/hospital registry
  - Large number of lung cancer cases, but potentially few with exposure of interest
  - Self reported exposure, or based on job title
- Industry specific cohort
  - Potential for small number of lung cancer cases unless industry is large
  - Opportunity to identify specific, long term exposures
  - Healthy worker effect - exposure effect underestimated or not detected if compared to general population (SMR)
  - Prevalent hires, healthier workers survive longer, may distort/invert relationship with exposure duration

Exposure Assessment

- Employment in a industry does not mean a worker has significant exposure to the agent under study
- Must determine linkage between job title and duties with current and historical exposures
- Approaches:
  - Industrial hygiene assessment to measure exposure in representative jobs, review historical exposure measures
  - Link exposure model to employment record
  - Alternative: job - exposure matrix to assign exposures based on job and expert review of industry

Outcome Assessment

- Mortality records detect majority of cases
- Death certificate detects ~95% compared to registry
- Approaches:
  - Retrospective industry-based occupational cohort study: job records linked to death certificate data (i.e., National Death Index), histology unavailable
  - Cancer/hospital based registry: histology available
- Tissue for molecular studies, biomarkers have not available as intermediate outcome
- Rarely, tissue retrieved from paraffin-embedded blocks for immunohistochemistry

Confounding

- Factor independently associated with lung cancer risk and agent of interest
- Often raised: cigarette smoking
- Not likely differentially related to exposure within an occupational cohort
- Others: family history, COPD history, other exposures
- Approaches:
  - Nested case-control study in an occupational cohort , obtain history from worker or next-of-kin
  - Survey of current workers
  - Interview of cancer/hospital registry cases/controls

Example: Diesel Exhaust Case-Control Study
Olsson et al. 2011

- 11 pooled lung cancer case-control studies Europe/Canada
- 13,304 cases/16,282 controls ~1990-2005
- Lifetime smoking history and occupational histories by interview (85% with person)
- Expert review (job exposure matrix)
  - intensity score (none=0,low=1,high=4)
  - ∑Cumulative exposure (intensity x duration)

Pooled Diesel Exhaust Case-Control Data Results and Effects of Smoking Adjustment

Cumulative Exposure/cases	Odds Ratio, Smoking Unadjusted*	95% CI	Odds Ratio, Smoking Adjusted**	95% CI
None (6954)	1.00		1.00	
Quartile 1 (1034)	1.05	0.96-1.15	0.98 **(↓7%)**	0.89-1.09
Quartile 2 (1091)	1.15	1.06-1.26	1.07 **(↓13%)**	0.97-1.18
Quartile 3 (1223)	1.28	1.17-1.39	1.10 **(↓14%)**	1.00-1.21
Quartile 4 (1412)	1.49	1.37-1.62	1.35 **(↓9%)**	1.23-1.49
Trend, P	<0.01		<0.01	

*Adjusted for age, gender, study,
**Additionally adjusted for pack-years, time since quitting smoking
N=11,714; excludes 1,590 persons in occupations known be associated with lung cancer.

Example: Retrospective Cohort Study and Exposure Assessment

- Retrospective cohort study to assess lung cancer mortality from diesel exhaust
  - 31,135 men with 1+ yrs of work employed in 1985 in 4 US trucking companies
  - Personnel files: all jobs, dates, terminal locations
- Mortality assessed through 2000
- Personnel files linked to US National Death Index to identify 779 lung cancer cases

Garshick et al. 2008, 2012

Exposure Assessment

- Elemental carbon (EC) is a marker of vehicle exhaust exposure, mainly from traditional diesel engines
- > 4000 shift/area samples of EC in $PM_{1.0}$ in 36 trucking terminals
- Terminal based worker exposure model:
  - *Personal EC (dock worker, mechanic*) *: f* (*Work area EC)*
  - *Area EC*: *f (*terminal characteristics, ventilation, terminal yard)
  - *Terminal yard (background) EC* : *f (*local temperature/wind , proximity to major road, %-industrial land, US region)
- Truck driver model: *f* (terminal background EC and temperature)
- Background linked to historical air pollution levels

Davis et al. 2006, 2007, 2009, 2011

Lung Cancer Mortality and Cumulative Exposure

Cumulative EC , 5-yr lag	**Employment duration adjusted***	
µg/m³-months	Lung cancer deaths	Hazard Ratio 95%CI
<371	122	**reference**
371 to < 860	191	**1.31 1.01, 1.71**
860 to <1803	202	**1.38 1.02, 1.87**
≥1803	226	**1.48 1.05, 2.10**
Trend		P=0.16

*Healthy worker survivor effect: lung cancer risk decreased with total employment duration

Garshick et al. 2012

Summary

- Epidemiologic study consideration
  - What is the nature of the exposure assessment?
  - How is job or cohort membership related to exposure intensity and duration?
  - Are workers followed for >20 to 30 years?
  - Appropriate comparison group?
  - Evidence of a healthy worker survivor effect?
  - Is confounding a concern?
- Mechanistic information may contribute to the assessment of human carcinogenicity potential