# Current knowledge on adverse effects of ambient air pollution: Approaches for evidence synthesis

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# Outline

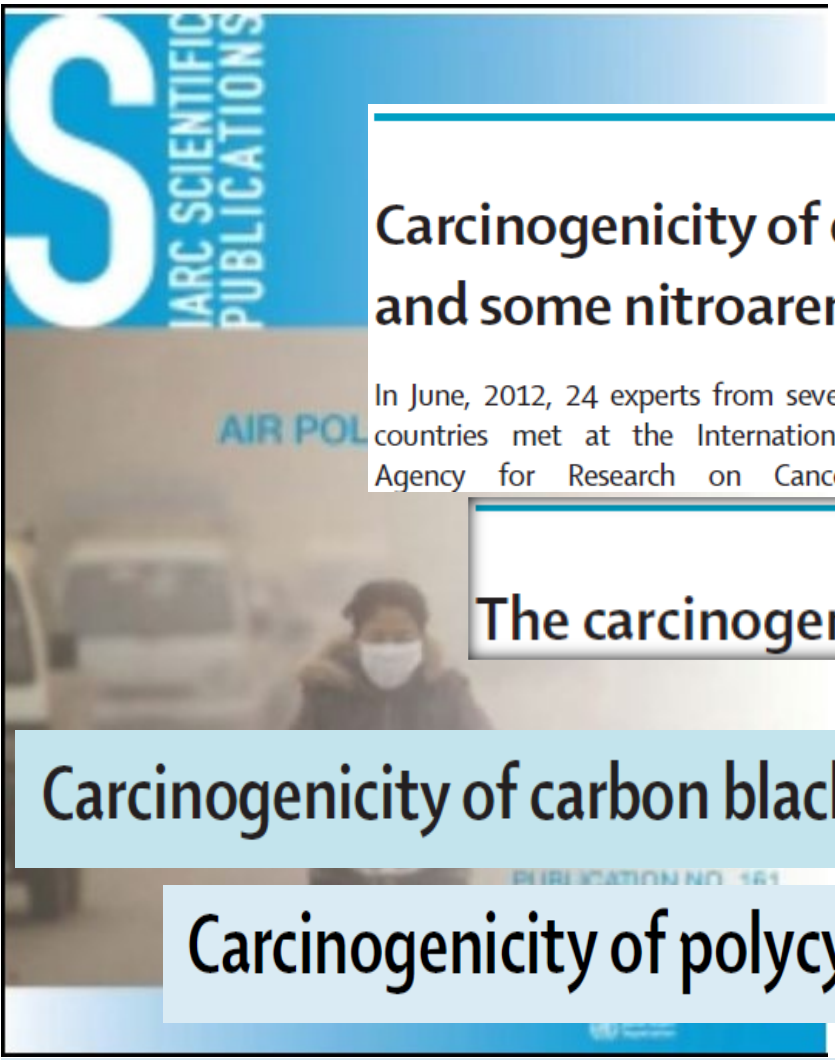
- The IARC Monographs on Air pollution
- History of causal inference
  - Biomedicine
  - Bradford Hill
  - The IARC Monographs (Preamble, examples)
- Current discussions
  - Randomized controlled vs observational studies
  - GRADE
  - Risk of bias tools
  - “Manipulative science” and the “Transparency rule”
- Recent evolution
  - Concepts: Triangulation
  - Tools: DAGs, Mendelian Randomisation
- Conclusion and Questions for policy makers

# The IARC Monographs on Air pollution


AG Priorities, 02/2003, "Air pollution" recommended as high priority for evaluation – the complexity of the topic requires a dedicated planning meeting

AG on Air pollution and Cancer, 12/2004, Recommended a series of Monographs related to the topic of air pollution

# The IARC Monographs on Air pollution




THE LANCET Oncology

## Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes

In June, 2012, 24 experts from seven countries met at the International Agency for Research on Cancer

The most influential epidemiological studies assessing cancer risks associated with diesel-engine exhausts

with 20 years of employment roughly doubling the risk after adjusting for tobacco smoking. When this study

## The carcinogenicity of outdoor air pollution

News

## Carcinogenicity of carbon black, titanium dioxide, and talc

## Carcinogenicity of polycyclic aromatic hydrocarbons

Published Online
June 15, 2012

## Carcinogenicity of household solid fuel combustion and of high-temperature frying

# Outdoor air pollution, IARC Vol 109

- A complex mixture with many manmade and natural sources
- Determined by local, regional and global sources and atmospheric processes
- Transport, industry, power generation, agriculture, home heating & cooking are important sources
- Often measured by levels of regulated pollutants: particulate matter, nitrogen-oxides, sulfur-dioxide, etc
- $PM_{2.5}$ global range of annual average concentrations from < 10 to >>100 μg/$m^3$.
- In many areas WHO and national air quality guidelines for $PM_{2.5}$ and other air pollutants are substantially exceeded.

# Cancer in humans

- Lung cancer positively associated with indicators of air pollution in most studies
- Most consistent associations with particulate matter; $PM_{2.5}$ often ranged from 10 to 30 $\mu g/m^3$
- Similar effects in non-smokers
- Risk increases with increasing exposure

There is *sufficient evidence* in humans for the carcinogenicity of outdoor air pollution.

There is *sufficient evidence* in humans for the carcinogenicity of particulate matter in outdoor air pollution.

# Cancer in experimental animals

- *sufficient evidence* in experimental animals for the carcinogenicity of organic solvent-extracted material from particles collected from outdoor air pollution.
- *sufficient evidence* in experimental animals for the carcinogenicity of particulate matter in OAP
- *sufficient evidence* in experimental animals for the carcinogenicity of OAP.
- For the 2nd evaluation, the WG considered the data on solvent-extracted material from particles collected from outdoor air and the evidence on carcinogenicity of diesel engine exhaust particles. The 3rd evaluation was based on findings of studies in experimental animals exposed to polluted outdoor air (Sao Paolo)

# Other relevant data

- Studies of people exposed occupationally to outdoor air pollution have demonstrated enhanced frequencies of chromosome aberrations and micronuclei in lymphocytes
- Studies of people exposed to polluted outdoor air in occupational settings or urban and industrial areas show altered expression of genes involved in DNA damage and repair, cell cycle control, inflammation, and the response to oxidative stress
- Observations of cytogenetic damage, DNA damage and mutations in cells of animals, birds and plants exposed to outdoor air pollution.

# Overall evaluation

- Outdoor air pollution is *carcinogenic to humans* (Group 1)
- Particulate matter in outdoor air pollution is *carcinogenic to humans* (Group 1)
- Overall evaluation also strongly supported by other relevant data showing that exposures are associated with increases in genetic damage that have been shown to be predictive of cancer in humans.

# A short history of causal inference in Biomedical research and public health (I)

Causation cannot be observed directly

Philosophers developed constructs and heuristics by which to define a "cause" operationally.

These constructs typically have two components:

- an associational one, determined empirically from variations in the probability of disease occurrence, and
- an explanatory one, based on a proposed underlying mechanism.

All causal claims rest on these twin pillars.

- For biomedical research, the first criteria came following the discovery of bacteria during the nineteenth century.
- Method needed for judging if an organism caused a particular disease.

**Henle-Koch Postulates**

1. The parasite occurs in every case of the disease in question and under circumstances that can account for the pathologic changes of the disease.
2. It occurs in no other disease as a fortuitous and non-pathogenic parasite.
3. After isolation from the body and grown in pure culture, it can induce the disease anew.

# A short history of causal inference in Biomedical research and public health (II)

Criteria are necessarily different for **chronic diseases**, with **multiple causes**, heterogeneous clinical features and much longer induction periods than in infectious diseases.

Bradford Hill: "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non."

Rather, in support of causal explanations, or

as evidence against, competing non-causal explanations,
- chance;
- selection bias;
- residual or unmeasured confounding;
- errors in measurement of exposure, confounders, or outcome.

5 of these viewpoints also used in 1964 Surgeon General's report, as the criteria for causal judgment

**Bradford Hill's Viewpoints for assessing causality**

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

# The IARC Monographs

Since its inception in 1971, the Monographs programme has evaluated >1000 agents (Chemicals, Complex mixtures, Physical and biological agents, Personal habits)

Guided by the Preamble, the general principles and procedures for scientific review and evaluation

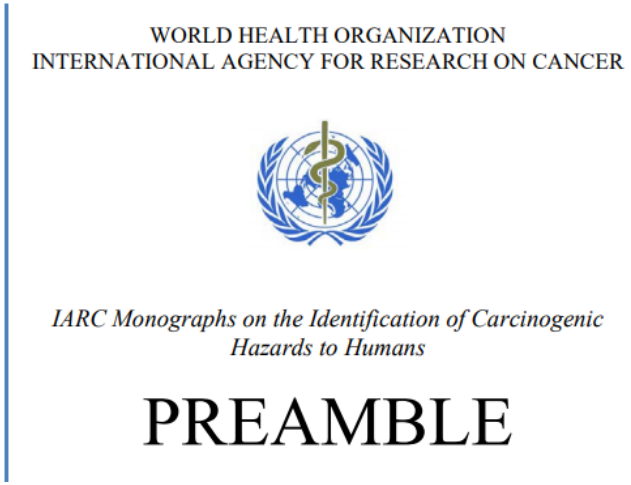
- Independent experts perform review and evaluations
- Systematic gathering and review of the published evidence
- Formal evaluation of quality of published studies
- Integration of different streams of evidence

Strength of evidence with a focus on hazard identification as the first step in risk assessment

- National and international health agencies use the Monographs
- As a source of scientific information on known or suspected carcinogens
- As scientific support for their actions to prevent exposure to known or suspected carcinogens

Methods and knowledge in cancer hazard identification evolve over time…

# Monographs Preamble Update, 2018


**Key features:**

- Strong procedures for conflict of interest management, public engagement and stakeholder involvement
- Robust **systematic review methodology**, including mechanistic data & facilitated by "key characteristics"
- New section on critical review of **exposure methods** in epidemiologic studies of cancer and mechanisms
- Consideration of **Informativeness of studies** - ability of a study to show a true association, if there is one:
  - adequate exposure contrast
  - sufficient time from exposure to outcome;
- Refined **evaluation criteria for mechanistic evidence**
- Rigorous and transparent **integration** of human cancer, animal bioassay and mechanistic **evidence streams**

# Strength of Association: Not so strong association

## IARC Monographs Vol 83, 2002

## Lung Cancer Risk in Involuntary Smokers

- Spouses of smokers who had never smoked had a significant and consistent increase in lung cancer risk when exposed to second-hand tobacco smoke.
- Husbands of women who smoked experienced a 30% increase in risk of lung cancer.
- Wives of men who smoked experienced a 20% increase in risk of lung cancer.
- Risk increased with increasing exposure.

# Experiment (or RCT) vs Ecologic studies

## IARC Monographs Vol 84, 2002

For arsenic in drinking-water, ecological studies provide important information on causal inference, because of

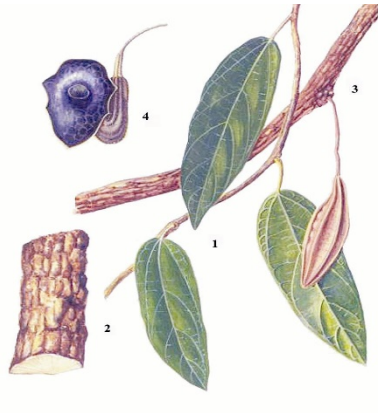
- large exposure contrasts and limited population migration.
- As a consequence of widespread exposure to local or regional water sources, ecological measures provide a strong indication of individual exposure.
- Moreover, in the case of arsenic, the ecological estimates of relative risk are often so high that potential confounding with known causal factors cannot explain the results."

# Aristolochic acid

IARC Monograph Vol 82, 2002

- Case reports: 2 Brussels, Belgium, 1 Taiwan, 1 U.K.
- Among 10 renal-grafted Chinese herb nephro-pathy patients 4 cases of multifocal carcinoma in situ
- Among 39 patients with end-stage renal disease 18 cases of urothelial carcinomas

Herbal remedies containing plant species of the genus Aristolochia, Group 1
Aristolochic acid, Group 2A



IARC Monograph Vol 100A, 2008

DNA adducts and A:T→T:A transversions in TP53 identified aristolochic acid as the carcinogen in herbal remedies

Aristolochic acid Group 1

# Randomized controlled vs observational studies

RCTs rarely used in natural sciences, such as physics; likewise, most important public health questions (e.g. global climate change, smoking) cannot be studied

Observational studies have potential to suffer from biases theoretically avoided by RCTs

GRADE states : "Evidence from randomized controlled trials starts at high quality and, because of residual confounding, evidence that includes observational data starts at low quality."

RCTs may be a useful theoretical starting point to think about potential bias,
but they do NOT provide the gold standard for environmental studies

- RCTs typically involve limited sample sizes and a short follow-up time, inadequate for observing chronic disease or rare outcomes.
- Observational studies often involve rare outcomes with long latencies
- RCTs deliver the exposure (e.g., medication) at the beginning of follow-up, typically in a limited number of dose levels
- Yet, in real life exposures are often present before follow-up begins, occur at many different levels, and often change over time
- RCT may involve highly selective study groups, which have little generalizability to other populations

# Problematic developments in systematic review methodology and causal inference

Systematic review and causal inference concepts as developed by the IARC Monographs have matured as an authoritative source of cancer hazard identification **well before** risk assessment paradigms evolved.

Approaches more recently developed in clinical medicine (e.g., Cochrane Collaboration, 1993; GRADE, 2000) now try to impose their methodology on evidence synthesis in public health.

Annals of Internal Medicine IDEAS AND OPINIONS

## GRADE Methods for Guideline Development: Time to Evolve?

Susan L. Norris, MD, MPH, MSc, and Lisa Bero, PhD

"not currently applicable to many questions that guideline developers face, including those about assessing risk and causality, establishing risk thresholds, or assessing animal studies."

"have low interrater reliability when assessing complex bodies of evidence consisting of different study designs".

Other ongoing assessments (e.g. WHO/ILO Global burden of occupational diseases project) do not follow GRADE procedures

# Carcinogenicity of consumption of red and processed meat

In October, 2015, 22 scientists from ten countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of the consumption of red meat and processed meat. These assessments will be published in

more than 200 g per person per day.[4] Less information is available on the consumption of processed meat.

The Working Group assessed more than 800 epidemiological studies that investigated the association of cancer with consumption of red meat

day of red meat and an 18% increase (95% CI 1·10–1·28) per 50 g per day of processed meat.[12]

Data were also available for more than 15 other types of cancer. Positive associations were seen in cohort studies and population-based case-

FINANCIAL TIMES

November 24, 2015 5:55 pm

## A false alarm on red meat and cancer

Gordon Guyatt

Share Author alerts Print Clip

Two large trials have tested for evidence and the WHO ignored both of them, writes Gordon Guyatt

"So the WHO leaned heavily on the third source: epidemiological data. ... Unless relative risks are greater than five, epidemiological studies typically provide only low-quality evidence."

REVIEW

Annals of Internal Medicine

# Patterns of Red and Processed Meat Consumption and Risk for Cardiometabolic and Cancer

A Systematic Review

Robin W.M. Vernooij, PhD*; D

CLINICAL GUIDELINE

Annals of Internal Medicine

ption: Dietary
ecommendations

udia Valli, MSc;

## CORRECTION: NUTRITIONAL RECOMMENDATIONS (NUTRIRECS) ON CONSUMPTION OF RED AND PROCESSED MEAT

On the author disclosure forms accompanying recent related articles on red and processed meat consumption and health outcomes (1-6), Bradley Johnston did not indicate a grant from Texas A&M AgriLife Research to fund investigator-driven research related to saturated and polyunsaturated fats.

thebmj

NEWS

# New red meat guidelines are undermined by undisclosed ties and faulty methods, say critics

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

New "guidelines" say continue red meat consumption habits, but recommendations contradict evidence

Red and processed meat still pose cancer risk, warn global health experts

World Cancer Research Fund International

# So-called "guidelines" on meat consumption

Weighting evidence from **RCTs** more heavily than observational studies, but

- small exposure contrasts and short follow-up of the trials
- combined red meat and processed meat

**Observational studies** categorized as providing low or very low "certainty"

- despite showing strong evidence of dose-response gradient,
- selection of most-adjusted parameter estimate (overadjustment)
- RoB approach, all sources of bias considered as equally important,
- high RoB if 2 or more elements rated as having high RoB, regardless of the direction or impact of the likely bias
- Risk estimates for consumption of red meat and processed meat and overall cancer similar to those used by authoritative health organizations

However, estimates considered as of low-to-very low certainty due to their origin in observational studies

# Risk of bias (ROB)

- Increasing use of various tools for evaluating epidemiological studies
- Here, risk of bias (ROB) assessments tools, such as various ROBINS, or within GRADE

**A risk of bias instrument for non-randomized studies of exposures: A users' guide to its application in the context of GRADE**

Rebecca L. Morgan[a], Kristina A. Thayer[b], Nancy Santesso[a], Alison C. Holloway[c], Robyn Blain[d], Sorina E. Eftim[d], Alexandra E. Goldstone[d], Pam Ross[d], Mohammed Ansari[e], Elie A Akl[a,f], Tommaso Filippini[g], Anna Hansell[h,i,j], Joerg J. Meerpohl[k], Reem A. Mustafa[a,l], Jos Verbeek[m], Marco Vinceti[g,n], Paul Whaley[o], Holger J. Schünemann[a,p,*], GRADE Working Group

- ROB assessments typically focus on whether specific biases (confounding, selection bias, and information bias) are present, but do not usually assess the direction, magnitude, or overall importance of the various types of bias.
- Information bias unlikely to explain positive findings of studies with non-differential exposure misclassification
- ROB tools typically evaluate bias in individual studies and consider individual studies out of context.
- Assessments often used to exclude “low-quality” studies from evidence synthesis.

# US EPA CASAC: “manipulative science”

US EPA Clean Air Scientific external Advisory Committee has traditionally used a weight-of-evidence approach to infer causation.

Dr. A. Cox, current chair of the CASAC, now argues

- all observational studies quantifying an exposure-response relationship are subject to critical bias
- all air pollution epidemiology studies lack adequate control for confounding, and are subject to high risk for potential bias

Therefore observational epidemiology studies should only be used in evidence integration if they can demonstrate ‘manipulative causation’ (largely intervention studies showing a direct health benefit of changing air pollution levels).

# "Strengthening Transparency or Silencing Science? The Future of Science in EPA Rulemaking"

**Hearing of the House Committee on Science, Space, and Technology, November 13, 2019**

Quotes from oral statement of Linda Birnbaum (Retired Former Director of NIEHS and NTP)

"EPA's proposed transparency rule will make it not only more difficult for human studies to be conducted ethically, but in many cases will make it impossible to use any information collected,…"

"EPA's proposed transparency rule in fact will block the use of the best science. It will prevent EPA from using the best available science in making policy. In fact, it will practically lead to the elimination of science from decision making. EPA's current proposal would silence science and block its ability to meet its mission of protecting human health and the environment."

# The future of evidence synthesis and causal inference


"Triangulation is the practice of obtaining more reliable answers to research questions through integrating results from several different approaches, where each approach has different key sources of potential bias that are unrelated to each other"

- Within the domain of observational studies, eg, estimating effects in different populations and study designs where the bias is likely to be in different directions (eg different types of controls in a case-control**).**
  Obviously, eliminating single studies (on the basis of ROB assessments) makes it impossible to conduct thoughtful triangulation analyses.

- Triangulation Across different streams of evidence (eg animal or mechanistic data) to support causal inference.

# Some new tools for facilitating causal inference

Directed acyclic graphs (DAGs) provided a tool for clearly specifying underlying causal pathways

Use of DAGs has enhanced our ability to think more clearly about confounding and intermediate variables

DAGs have triggered the use of new techniques for controlling confounding, such as instrumental variables in Mendelian randomization (MR)

MR studies have with their own strengths and weaknesses (missing instrumental variables for a certain question)

DAGs do not help in considering the importance of different exposure metrics;

DAGs contribute little about the likely direction or strength of possible biases.

# Conclusions

- Evidence synthesis and causal inference should include the use of classical considerations for judging causality, triangulation, and integration of animal and mechanistic data.
- Observational studies should be judged on their own merits, within the context of an optimal design for the exposure-outcome of interest, and in the broader evidence synthesis context.
- ROB assessments should try to identify and quantify possible biases, their direction, and their impacts on effect estimates.
- Risk of bias assessments should be done with knowledge of the specific context, rather than ruling out individual studies.
- Aspects of study informativeness - the ability of a study to show a true association, if there is one - need to be considered
- Evidence synthesis requires expert groups with the sufficient interdisciplinary subject matter expertise and
- Strong procedures for conflict of interest management, public engagement and stakeholder involvement

# Questions

- Ultimately, the question for policy makers and society is: how much evidence is enough to take action?
- The answer may vary by type of exposure and options for action
- Strong evidence of carcinogenicity in animals OR strong evidence of genotoxicity would normally be sufficient to stop re-licensing a pesticide according to pesticide regulations
- In the workplace, strong evidence of carcinogenicity in animals typically triggers the full hierarchy of controls, prominently including strict occupational exposure limits.

Thank you

Questions?