The IARC Monographs Programme

The Identification of Human Carcinogens

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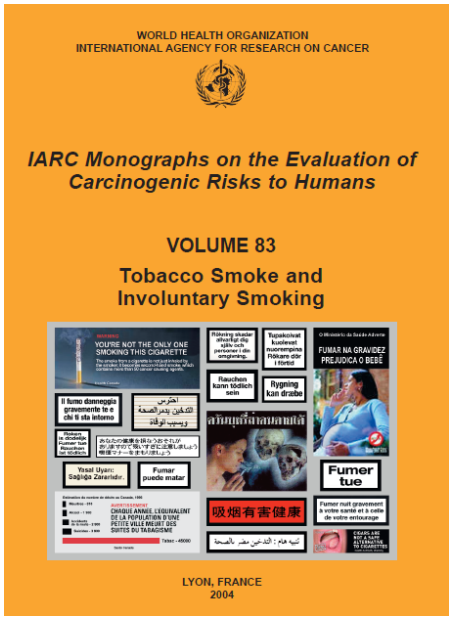
International Agency for Research on Cancer
Lyon, France

WCC, Melbourne, 4 Dec 2014

Global burden and control of cancer



- **Rising burden of cancer**: estimates by 2025 19.3 million new cases/a compared to 14.1 million in 2012
- Majority of the increase in cancer burden expected in **low- and middle-income countries** (LMIC)
- **Prevention** probably the **single most effective response** to these challenges, particularly in LMIC where health services are least able to meet the impending challenge.
- The first step in cancer prevention is to **identify the causes of human cancer**

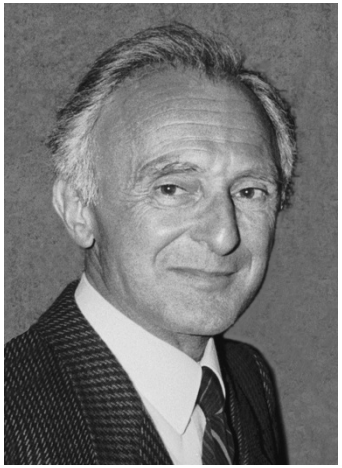
International Agency for Research on Cancer

World Health Organization

"The encyclopaedia of carcinogens"

The *IARC Monographs* evaluate

- Chemicals
- Complex mixtures
- Occupational exposures
- Physical and biological agents
- Lifestyle factors



Lorenzo Tomatis
1929-2007

More than 950 agents have been evaluated

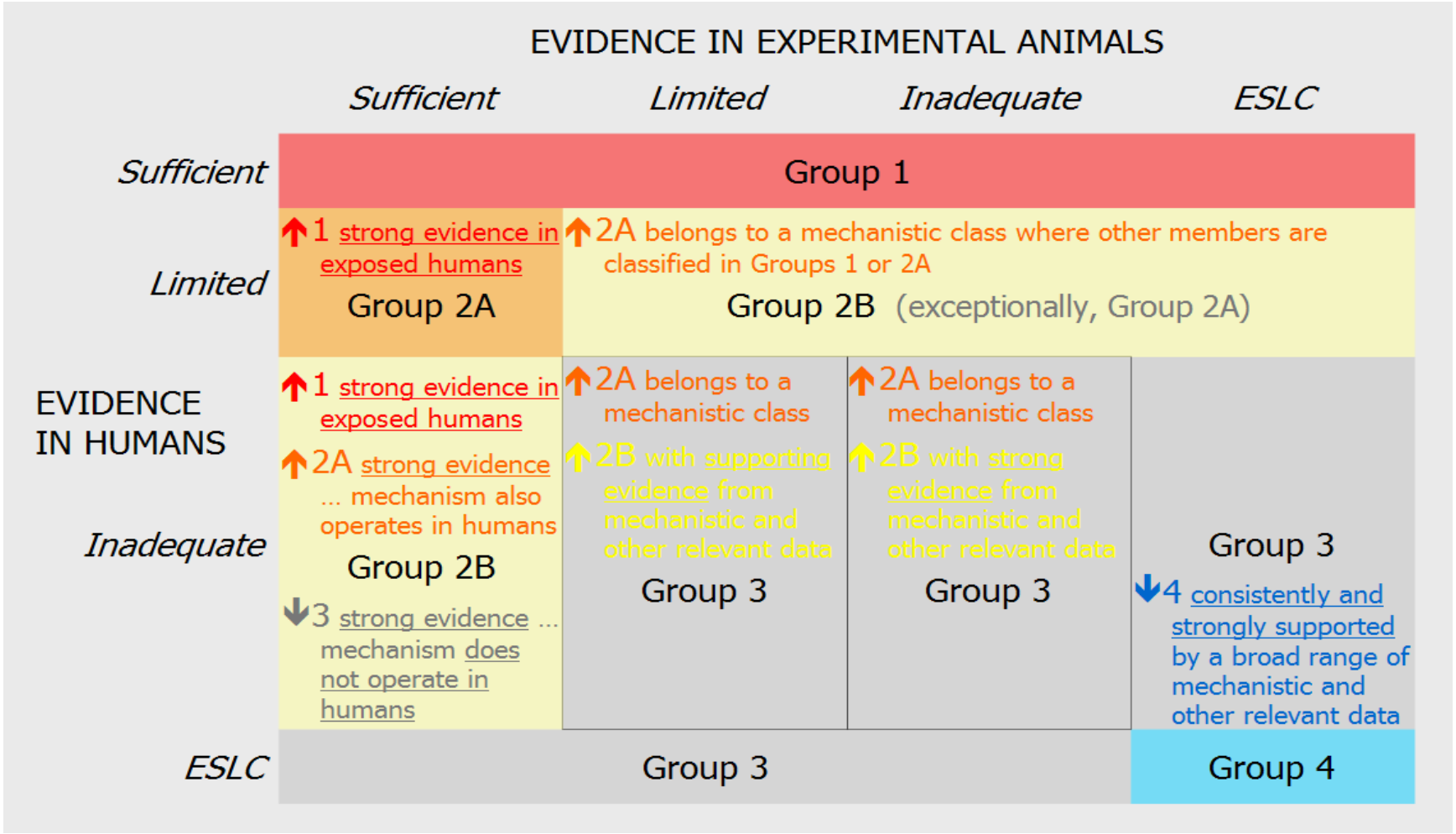
- 114 are *carcinogenic to humans* (Group 1)
- 69 are *probably carcinogenic to humans* (Group 2A)
- 283 are *possibly carcinogenic to humans* (Group 2B)

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

You are part of a worldwide endeavour that since 1971 has involved over 1000 scientists from over 50 countries

Overall carcinogenicity evaluation



IARC Monographs, Volume 100
A Review of Human Carcinogens

- Scope of volume 100
  - Update the critical review for each carcinogen in Group 1
  - Identify tumour sites and plausible mechanisms
  - Compile information for subsequent scientific publications
- The volume was developed over the course of 6 meetings
  A. *Pharmaceuticals* (23 agents, Oct 2008)
  B. *Biological agents* (11 agents, Feb 2009)
  C. Metals, particles and fibres (14 agents, Mar 2009)
  D. Radiation (14 agents, June 2009)
  E. Lifestyle factors (11 agents, Sept 2009)
  F. Chemicals and related occupations (34 agents, Oct 2009)

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Preventable Exposures Associated With Human Cancers

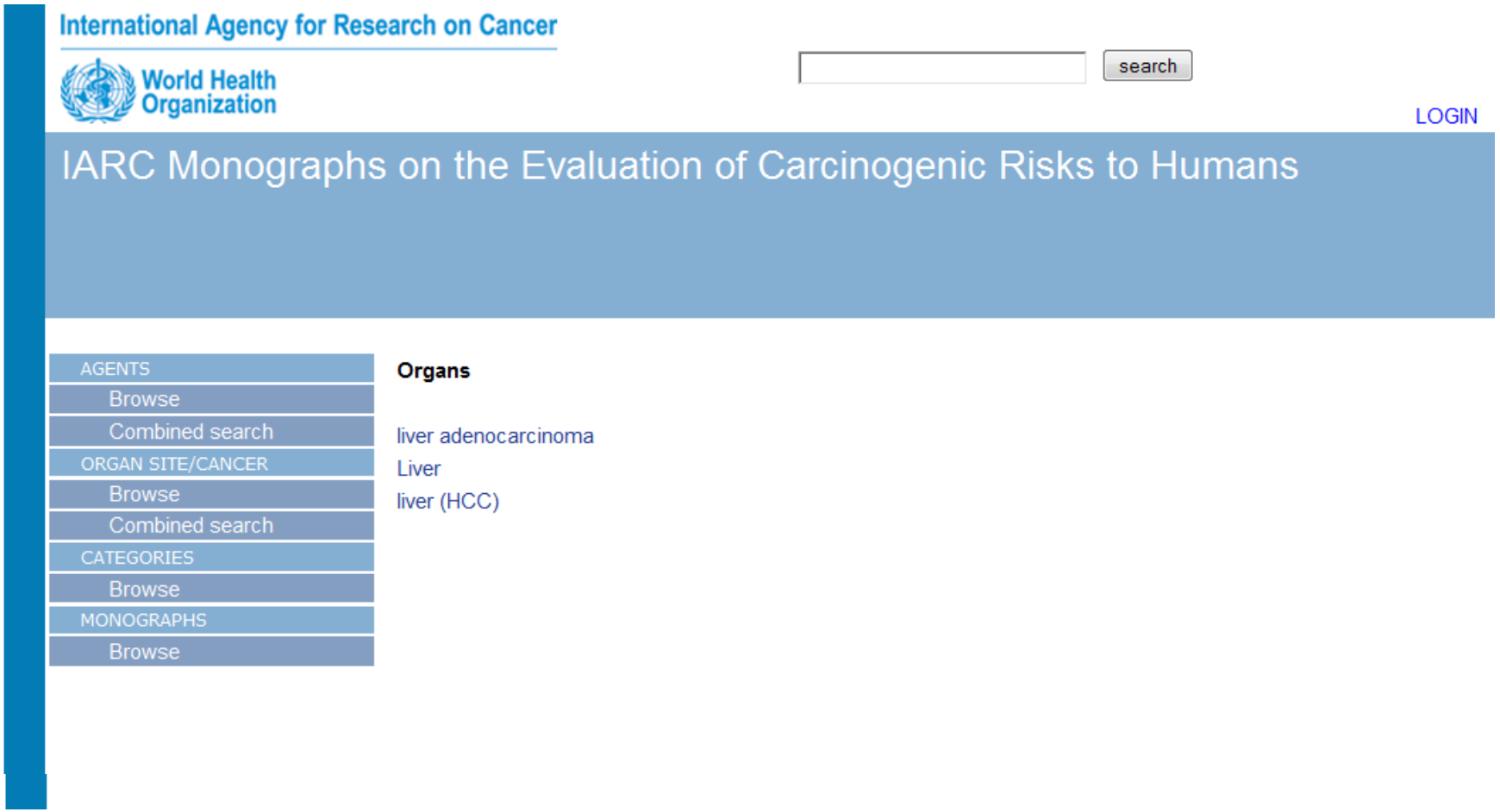
Vincent James Cogliano, Robert Baan, Kurt Straif, Yann Grosse, Béatrice Lauby-Secretan, Fatiha El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Crystal Freeman, Laurent Galichet, Christopher P. Wild

Known and suspected causes of cancer

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 108*

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Lung	Aluminum production Arsenic and inorganic arsenic compounds Asbestos (all forms) Beryllium and beryllium compounds Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade) Cadmium and cadmium compounds Chromium(VI) compounds Coal, indoor emissions from household combustion Coal gasification Coal-tar pitch Coke production Engine exhaust, diesel	Acid mists, strong inorganic Art glass, glass containers and pressed ware (manufacture of) Biomass fuel (primarily wood), indoor emissions from household combustion of Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work Carbon electrode manufacture

Dissemination of information



http://monographs.pubcan.org/organ.php

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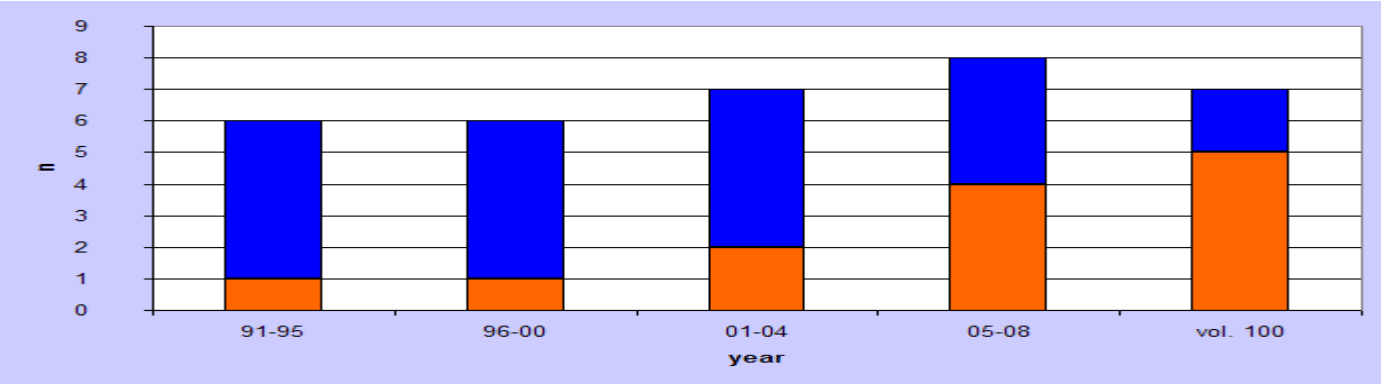
Mechanisms Involved in Human Carcinogenesis

New research continues to find additional human carcinogens &
Use of mechanistic data to identify carcinogens is accelerating



Total new Group 1
Mechanistic up-grades to Group 1

Types of mechanistic upgrades

Ethylene oxide: Dose-related increase in the frequency of SCE, CA, and MN in lymphocytes of exposed workers.

DNA adducts and A:T→T:A transversions in TP53 identified **aristolochic acid** as the carcinogen in herbal remedies -> environmental exposures: cereal fields in the Balkans where *Aristolochia* plants grow as weeds

Benzidine-based dyes: Metabolism results in the release of free benzidine in humans and in all experimental animal species studied.

More known human carcinogens

THE LANCET Oncology

News

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

In June, 2012, 24 experts from seven countries met at the International

The most influential epidemiological studies assessing cancer risks

with 20 years of employment roughly doubling the risk after adjusting for

Published Online

News

Carcinogenicity of trichloroethylene, tetrachloroethylene, some other chlorinated solvents, and their metabolites

News

Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls

News

The carcinogenicity of outdoor air pollution

World Health Organization

Diesel engine exhaust: exposure (1)

- Diesel engines are used for on-road and non-road transport (eg, trains, ships) and (heavy) equipment in various industrial sectors (eg, mining, construction), and in electricity generators, particularly in developing countries.
- Emissions from these engines are complex, with varying composition.
- The gas phase consists of carbon monoxide, nitrogen oxides, and volatile organic compounds such as benzene and formaldehyde.
- Particles consist of elemental and organic carbon, ash, sulfate, and metals.
- Polycyclic aromatic hydrocarbons and nitroarenes are distributed over the gas and the particle phase.

Diesel engine exhaust: exposure (2)

- The qualitative and quantitative composition of exhausts depends on the fuel, the type and age of the engine, the state of its tuning and maintenance, the emission control system, and pattern of use.
- In the past two decades, progressively tighter emission standards for on-road vehicles, introduced in North America, Europe, and elsewhere, have triggered advances in diesel technology that resulted in lower emission of particulate matter, nitrogen oxides, and hydrocarbons.
- Emission standards in non-road applications are lagging and therefore are still largely uncontrolled today.
- In many less developed countries standards are not in place for both on-road and non-road use of diesel and gasoline engines.

Diesel engine exhaust and lung cancer

- In a large US miners study diesel engine exhaust was quantified via estimated elemental carbon as a proxy of exposure
- Cohort and nested case–control analyses adjusted for tobacco smoking showed positive trends in lung cancer risk with increasing exposure to diesel exhaust, with 2–3-fold increased risk in the highest categories of cumulative or average exposure. (Attfield et al 2012, Silverman et al 2012).
- In US railroad workers exposed to diesel exhaust a 40% increased risk for lung cancer was observed.
- A large cohort study in the US trucking industry reported a 15–40% increased lung cancer risk
- Findings of above cohort studies were supported by those in other occupational groups and by case–control studies including various occupations involving exposure to diesel-engine exhaust.

Diesel engine exhaust, cancer bioassays Evaluation

- The Working Group concluded that there was "sufficient evidence" in experimental animals for the carcinogenicity of whole diesel-engine exhaust, of diesel-engine exhaust particles and of extracts of diesel-engine exhaust particles.

DEE, mechanisms of carcinogenicity

- DEE, DEE particles, DEE condensates, and organic solvent extracts of DEE particles induced in vitro and in vivo, various forms of DNA damage
- Increased expression of genes involved in xenobiotic metabolism, oxidative stress, inflammation, antioxidant response, apoptosis, and cell cycle regulation in mammalian cells was observed.
- Positive genotoxicity biomarkers of exposure and effect were also observed in humans exposed to diesel engine exhaust.

The Working Group concluded that there is "strong evidence" for the ability of whole diesel-engine exhaust to induce cancer in humans through genotoxicity.

Diesel engine exhaust
Overall Evaluation

- There is sufficient evidence for the carcinogenicity in humans of diesel engine exhaust. Diesel engine exhaust causes lung cancer. Also, a positive association between diesel engine exhaust and bladder cancer has been observed.
- There is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust.

Overall evaluation

- Diesel engine exhaust is carcinogenic to humans (Group 1).

Joint IARC, NIOSH-NORA, ACS, US NIEHS and NCI Workshop

Review

Research Recommendations for Selected IARC-Classified Agents

Elizabeth M. Ward,[1] Paul A. Schulte,[2] Kurt Straif,[3] Nancy B. Hopf,[4] Jane C. Caldwell,[5] Tania Carreón,[2] David M. DeMarini,[5] Bruce A. Fowler,[6] Bernard D. Goldstein,[7] Kari Hemminki,[8] Cynthia J. Hines,[2] Kirsti Husgafvel Pursiainen,[9] Eileen Kuempel,[2] Joellen Lewtas,[10] Ruth M. Lunn,[11] Elsebeth Lynge,[12] Damien M. McElvenny,[13] Hartwig Muhle,[14] Tamie Nakajima,[15] Larry W. Robertson,[16] Nathaniel Rothman,[17] Avima M. Ruder,[2] Mary K. Schubauer-Berigan,[2] Jack Siemiatycki,[18] Debra Silverman,[17] Martyn T. Smith,[19] Tom Sorahan,[20] Kyle Steenland,[21] Richard G. Stevens,[22] Paolo Vineis,[23] Shelia Hoar Zahm,[17] Lauren Zeise,[24] and Vincent J. Cogliano[3]

Acetaldehyde
Atrazine
Carbon black
Chloroform
Cobalt metal with tungsten carbide
Dichloromethane
Diesel engine exhaust
Di-2-ethylhexyl phthalate
Formaldehyde
Indium phosphide
Lead and lead compounds
Polychlorinated biphenyls (PCB)
Propylene oxide
Refractory ceramic fibers
Shiftwork that involves nightwork
Styrene
Tetrachloroethylene
Titanium dioxide
Trichloroethylene
Welding fumes

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IARC Workshop: Defining 'Shift Work' for epidemiological Studies of Cancer

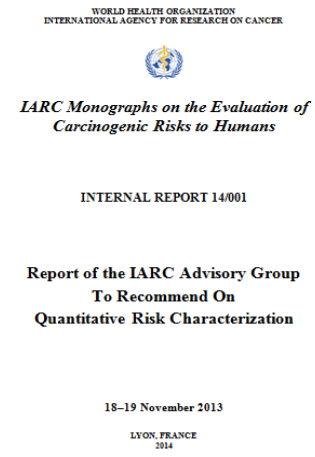
Working time	Workhours/week
Night work	At least 3 hrs of work between midnight and 5 am
Duration	Years employed in non-day shift work
Intensity	Number of non-day shifts per month/year
Cumulative exp.	Duration times intensity over the work history
Permanent shift	# consecutive days of night work, followed by # days off
Rotating type	Continuous (365 days/year) or dis-continuous
Direction of rotation	Forward (morning → afternoon/evening → night) backward (afternoon/evening → morning → night)
Rate of rotation	Daily change, 2-3-4 day change, weekly, etc.
Morning shift	# consecutive days of early morning shift (before 6 am)
Start/end time	Displacement from solar day, duration of the working hours
Rest after shift	Number of rest-days after night shifts
Jetlag	No of time zones crossed; eastward vs. westward
Sleep	Sleep duration &
Light at night	During sleep peri
Characteristics of the individual	Diurnal type (mor

Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report

Richard G Stevens,[1] Johnni Hansen,[2] Giovanni Costa,[3] Erhard Haus,[4] Timo Kauppinen,[5] Kristan J Aronson,[6] Gemma Castaño-Vinyals,[7] Scott Davis,[8] Monique H W Frings-Dresen,[9] Lin Fritschi,[10] Manolis Kogevinas,[11] Kazutaka Kogi,[12] Jenny-Anne Lie,[13] Arne Lowden,[14] Beata Peplonska,[15] Beate Pesch,[16] Eero Pukkala,[17] Eva Schernhammer,[18] Ruth C Travis,[19] Roel Vermeulen,[20] Tongzhang Zheng,[21] Vincent Cogliano,[22] Kurt Straif[22]

AG Quantitative Risk Characterization, Nov. 2013

- Suggestions for enhancements of the *Monographs* that would be likely to result in contributions to QRC
  - review cancer burden and other risk scenarios from the literature
  - summarize exposure–response relationships seen in epidemiological studies
  - should not formally review existing national risk assessments
- Additional resources will be needed to pursue QRC to the point of developing risk estimates, combining these risks with exposures and predicting cancer burden.


WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

INTERNAL REPORT 14/001

Report of the IARC Advisory Group To Recommend On Quantitative Risk Characterization

18–19 November 2013

LYON, FRANCE
2014

International Agency for Research on Cancer

World Health Organization

Future priorities for the IARC Monographs

News

An Advisory Group of 21 scientists from 13 countries met in April, 2014, to recommend topics for assessment in 2015–19 and to discuss strategic matters for the International Agency for Research on Cancer (IARC) Monographs programme. IARC periodically convenes such advisory groups to ensure that the Monographs reflect the current state of priorities for public health.

The Advisory Group assessed the responses to a call for nominations on the IARC website and recommended a broad range of agents and exposures for assessment with high or medium

Panel: Agents recommended by the IARC Advisory Group for assessment

High priority

Acrylamide, furan, and 5-(hydroxymethyl) furfural—commonly found in cooked foods; cancer bioassay data are available

Aspartame and sucralose—widespread use and concern about their potential carcinogenicity

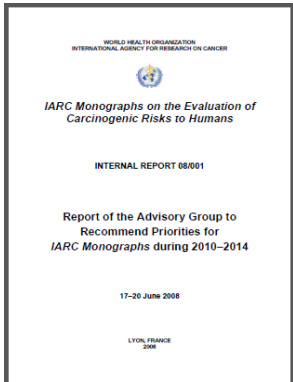
Lancet Oncol 2014

Published Online
May 6, 2014

- Beta-carotene
- Bisphenol A
- Disinfected water
- Dimethylformamide
- HCMV
- Indium-tin oxide
- Iron, dietary
- Mate & coffee drinking
- MTBE, ETBE
- Nicotine
- Obesity , Physical inactivity
- Opium
- Phenyl and octyl tin compounds
- Pesticides
- Shift work
- Styrene
- Welding

International Agency for Research on Cancer

World Health Organization



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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

INTERNAL REPORT 08/001

Report of the Advisory Group to Recommend Priorities for *IARC Monographs* during 2010–2014

17–20 June 2008

LYON, FRANCE
2008

Upcoming Meetings

Meeting 111: Some Nanomaterials and Some Fibres (30 September – 7 October 2014)

Preliminary List of Agents
Call for Data (closing date 3 September 2014)
Preliminary List of Participants
Call for Experts (closed 30 January 2014)
Request for Observer Status (closed 3 June 2014)
WHO Declaration of Interests for this volume

Meeting 112: Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos (3–10 March 2015)

Call for Data (closing date 3 February 2015)
Call for Experts (closing date 30 July 2014)
Request for Observer Status (closing date 3 November 2014)
WHO Declaration of Interests for this volume

Meeting 113: Some Organochlorine Insecticides and Some Chlorphenoxy Herbicides (2–9 June 2015)

Acknowledgements

The *IARC Monographs* are supported by grants from

- **U.S. National Cancer Institute (since 1982)**
- **European Commission, DG Employment, Social Affairs and Inclusion (since 1986)**
- **U.S. National Institute of Environmental Health Sciences (since 1992)**

International Agency for Research on Cancer

World Health Organization

IARC - priority areas for research

Describing occurrence

Establishing causes

Evaluating prevention

Supporting implementation

Education and training

International Agency for Research on Cancer

World Health Organization

Vol. 100 Workshops

- *Tumour (Site) Concordance between Humans and Animals*
  - Increase understanding of the correspondence across species
  - Identify human cancer sites without good animal models

- *Mechanisms Involved in Human Carcinogenesis*
  - Organized by mechanism to facilitate joint consideration of agents that act through similar mechanisms
  - Identify biomarkers that could be influential in future studies
  - Identify susceptible populations and developmental stages
  - Promote research that will lead to more confident evaluations

REVIEW

Preventable Exposures Associated With Human Cancers

Vincent James Cogliano, Robert Baan, Kurt Straif, Yann Grosse, Béatrice Lauby-Secretan, Fatiha El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Crystal Freeman, Laurent Galichet, Christopher P. Wild

Tumour (Site) Concordance between Humans and Animals

Sites	lip	nose	oral cavity	tongue	pharynx	larynx	trachea	lung	mesothelium	salivary gland	digestive tract	liver	gallbladder	bile ducts (intrahepatic & ext	pancreas	CNS	adrenal medulla	adrenal gland NOS	eye (squamous cell carcinor	pituitary gland	thyroid	kidney	urinary tract/urothelium	haematopoietic tissue	lymphoid tissue	leukaemia NOS	hard connective tissue	soft connective tissue	skin	breast	endometrium	lower reproductive tract	uterus	ovary	testis	prostate	solid tumours	solid tumours aside from lu	all cancers combined
agent	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9	Z10	Z11	Z12	Z13	Z14	Z15	Z16	Z17	Z18	Z19	Z20	Z21	Z22	Z23	Z24	Z25	Z26	Z27	Z28	Z29	Z30	Z31	Z32	Z33	Z34	Z35	Z36	Z37	Z38	Z39
Azathioprine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	##	0	0	0	0	0	0	0	0	0	0
Chlorambucil	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	##	0	0	0	0	0	0	0	0	0	0	0	0	0
Combined oral contraceptives	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	##	##	0	0	0	0	0	0
Cyclophosphamide	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	##	##	0	0	0	##	0	0	0	0	0	0	0	0	0
Diethylstilbestrol	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	##	##	##	##	0	##	0	0	0	0
Estrogen only menopausal therapy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	##	0	0	0	0	##	##	##	##	##	0	0	0	0	0
Methoxsalen in combination with UV	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0
Phenacetin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Plants containing aristolochic acid	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tamoxifen	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0
Thiotepa	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	##	0	0	0	0	0	0	0	0	0	0	0	0	0
Arsenic and Arsenic Compounds	0	0	0	0	0	0	0	##	0	0	0	##	0	0	0	0	0	0	0	0	0	##	##	0	0	0	0	0	##	0	0	0	0	0	0	##	0	0	0
Asbestos	0	0	0	0	0	##	0	##	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0
Beryllium and Beryllium compounds	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cadmium and cadmium compounds	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	##	0	0	0	0	0	0	0	##	0	0	0
Chromium (VI) compounds	0	##	##	##	0	0	0	##	0	0	##	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	##	0	0	0	0	0	0	0	##	0	0	0
Erionite	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nickel and nickel compounds	0	##	0	0	0	0	0	##	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0
Silica dust, crystalline (quartz or crys	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fission products including Sr-90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	##	0	0	0	0	0	0	0	0	0	##	0	0
Neutrons	0	0	0	0	0	0	0	##	0	0	0	##	0	0	0	0	0	##	0	##	0	1	0	##	##	0	0	0	0	##	0	0	0	##	0	0	0	0	0
Solar radiation	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0
X rays, Gamma rays	0	0	0	0	0	0	0	##	0	##	##	##	0	0	##	##	0	0	0	##	##	##	##	##	##	##	##	##	##	##	0	0	0	##	0	##	0	0	##
alpha particle emitters (Am-241)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0
alpha particle emitters (Cf-249)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0
alpha particle emitters (Cf-252)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0
alpha particle emitters (Cm-244 and	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0
alpha particle emitters (Cm-244)	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
alpha particle emitters (Np-237)	0	0	0	0	0	0	0	##	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
alpha particle emitters (Po-210)	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Human S + Any Animal							0	0

Human L + Any Animal

Human S but No Animal

Animal Only

International Agency for Research on Cancer

World Health Organization

Key Characteristics of Carcinogens

- Electrophilicty and Metabolic activity
  - electron-seeking molecules that commonly form addition products, commonly referred to as adducts
  - binds with DNA, RNA and proteins
- Genotoxicity
  - induces DNA damage
- Altered repair and genomic instability
  - alters DNA replication fidelity
- Chronic inflammation
  - disrupts local tissue homeostasis and alters cell signaling
- Oxidative stress
  - creates an imbalance in reactive oxygen formation and/or alters their detoxification

Carcinogenesis vol.34 no.9 pp.1955–1967, 2013
doi:10.1093/carcin/bgt212
Advance Access publication June 7, 2013

REVIEW

Towards incorporating epigenetic mechanisms into carcinogen identification and evaluation

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during development and contribute to the lineage-specific epigenome that is maintained over the lifetime of an organism.

Epigenetic mechanisms are essential for the stable propagation of

Key Characteristics of Carcinogens (2)

- Receptor-mediated
  - acts act as ligands via nuclear and/or cell-surface and/or intracellular receptors
- Altered cellular proliferation and/or death
  - alterations in cellular replication and/or cell-cycle control resulting in escape from growth control or mutations or inflammation
- Immunosuppression
  - reduces the capacity of the immune system to respond effectively to antigens on tumour cells
- Epigenetic alterations
  - Induces stable and heritable changes in gene expression and chromatin organization that are independent of the DNA sequence itself
- Immortalization
  - DNA and RNA viruses that produce viral-encoded oncoproteins targeting the key cellular proteins that regulate cell growth

Mechanisms of Carcinogenesis in Future Cancer-Hazard Evaluations

- Link between concordance of tumours and mechanisms of carcinogenesis
  - ✓ **Concordance confirmed by mechanistic data**
  - ✓ **Discordance explained by mechanistic data**
- Use of mechanistic data can help identify additional cancer sites
- Use of mechanistic data can help identify whether the carcinogenic potential is limited to certain dose levels
- Mechanistic data may help understand interactions of multiple factors acting jointly, and thus may help identify new carcinogens
- Identify populations and developmental stages that may be more susceptible

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) in conjunction with updating and confirming previous pertinent evaluations

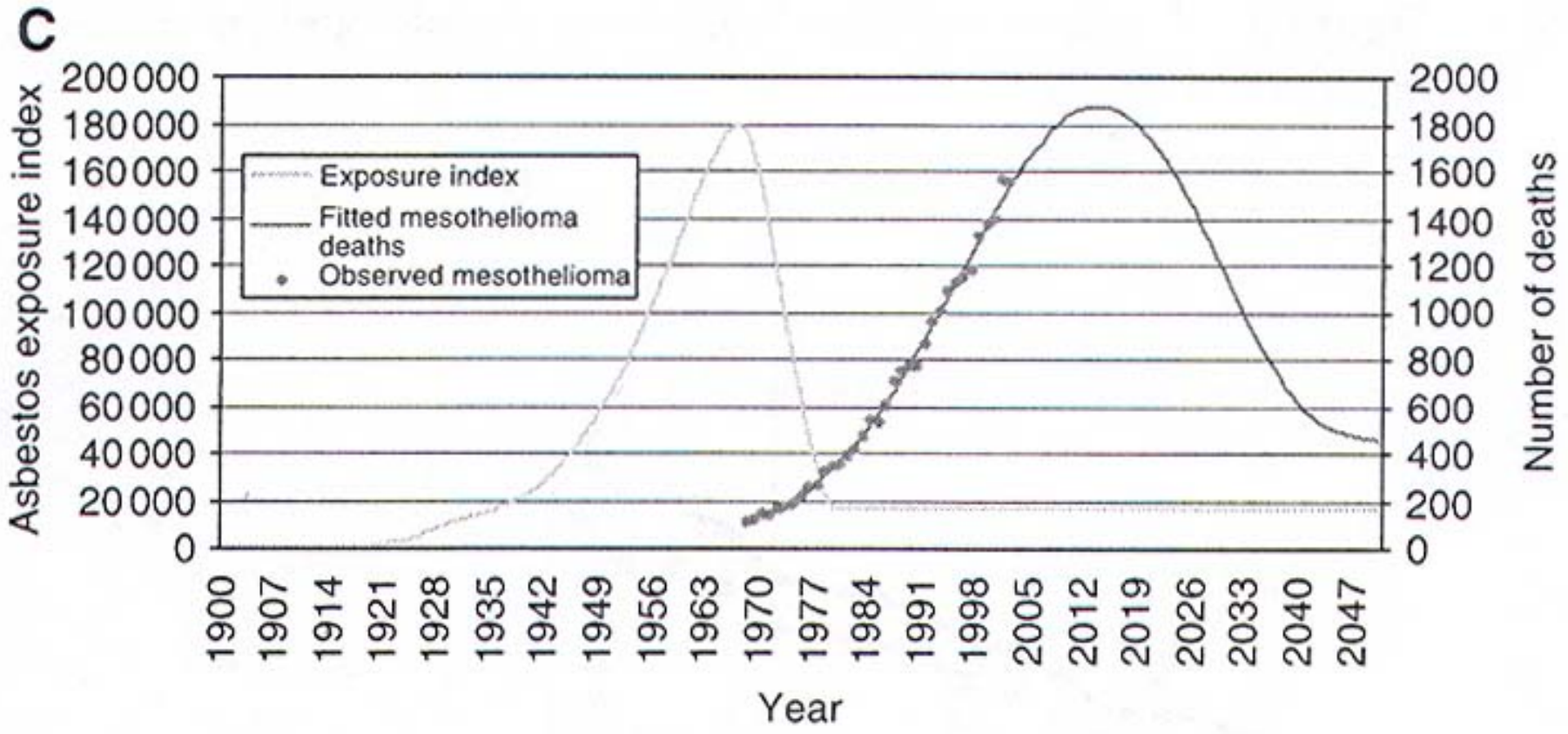
Other relevant data

- 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.
- Atmospheric mutagenic activity varies > 5 orders of magnitude across locations and increased activity is quantitatively related to increased levels of atmospheric PM

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.

Asbestos exposure index and observed and fitted mesothelioma mortality in Great Britain



Adapted from Hodgson et al, 2005

Asbestos, Vol 100C: Carcinogenic to humans

- **There is *sufficient* evidence in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite). All forms of asbestos cause mesothelioma and cancers of the lung, larynx and ovary.**
- **The Working Group classified the evidence for colorectal cancer as *limited* although the Members were evenly divided as to whether the evidence was strong enough to warrant classification as *sufficient*.**
- **There is *limited* evidence in humans for cancers of the pharynx and of the stomach.**

Silica Group 1 Human Carcinogen, V68, 1997

- Among silicotics, consistent excess lung cancer risk across countries, industries and time periods
- Sufficient evidence of carcinogenicity in animals for quartz
- Mechanistic data: most genotoxicity studies negative; oxidative stress , inflammatory response, carcinogenicity may depend on inherent characteristics of the crystalline silica, or external factors affecting its biological activity
- Vol. 100C IARC WG reaffirmed carcinogenicity of crystalline silica dust. Increased risk of lung cancer observed across various industries.

Ionising radiation

- One of the best studied and most ubiquitous carcinogens in our general environment
  - Radon: high lung cancer rates in miners reported since 16th century
  - X-rays : first animal experiments: 1903-1904
  - Cancers among pioneer radiologists
  - Cancers among survivors of atomic bombs
- Evaluations of health effects
  - US NAS – BEIR / BEAR since 1956
  - IARC Monographs:
    radon (vol 43,1988),
    external radiation(75,2000),
    internally deposited radionuclide (78,2001)

IARC Monographs, vol 100D, 2009

Dose-response analyses of occupational and residential radon exposure and lung cancer

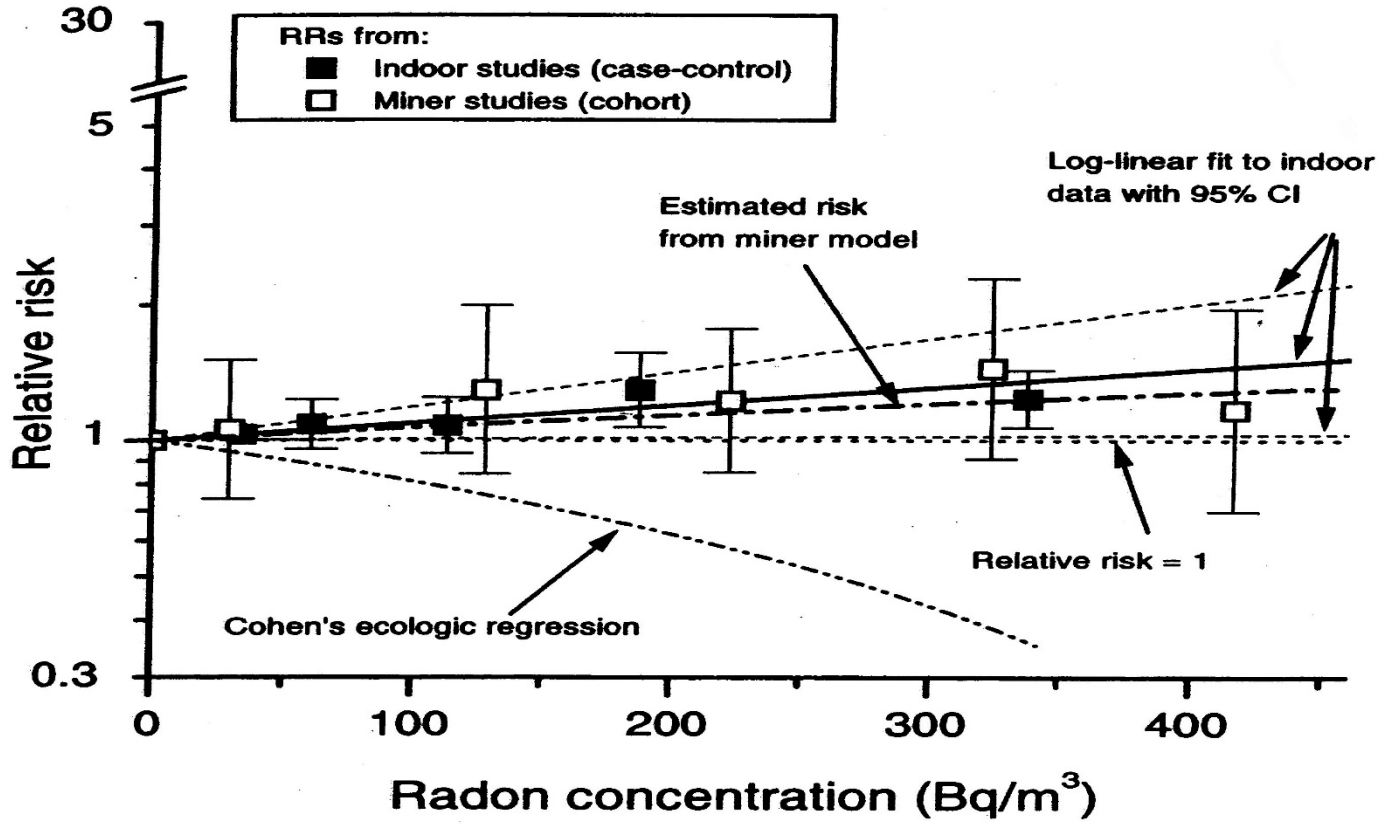


FIGURE 3-2 Summary relative risks (RR) from meta-analysis of indoor-radon studies and RRs from pooled analysis of underground-miner studies, restricted to exposures under 0.175 Jhm^{-3} (50 WLM). Included are RR of 1, fitted exposure-response and its 95% confidence interval from indoor-radon studies, and estimated linear RR based on ecologic analysis by Cohen (1995).

BEIR VI, 1999

Occupational exposure as a painter (Vol 100F)

Meta-analysis on lung cancer (Guha et al, EHP, 2010)

Cohort and linkage studies mRR, 1.36 (18 studies, 95% CI, 1.29-1.44)

Case-control studies mRR, 1.35 (29 studies, 95% CI, 1.22-1.51)

Pop.-based Case-control, smoking adjusted , mRR, 1.41 (95%CI, 1.23-1.61)

Among never & non-smokers, mRR, 1.96 (4 studies, 95%CI, 1.15-3.35)

Suggestive trend by duration of exposure

<20 years (mRR, 1.37; 95%CI, 0.89-2.13)

>20 years (mRR, 2.00; 95%CI, 1.01-3.92)

No particular causative agent could be identified from the available epidemiological studies

Increased mortality from mesothelioma noted in several studies.

o-toluidine (Vol 100F)

Cancer in humans : Sufficient evidence

- 5 EU and US cohort studies
- 4 studies reported highly elevated risk of bladder cancer
- confounding by other bladder carcinogens eliminated

Cancer in experimental animals: Sufficient evidence

Mechanistic data

- Acute toxicity and genotoxicity in mammalian systems *in vitro* and *in vivo*
- Haemoglobin adducts in prilocaine-treated patients (o-toluidine-based anesthetic)

Overall evaluation: Group 1

1,3-Butadiene (Vol 97)

Overall Evaluation

- Group 1 (*carcinogenic to humans)*
- *sufficient evidence* in humans that exposure to 1,3-butadiene causes an increased risk for leukaemias
- The Working Group refrained from mentioning a particular histological subtype of lymphatic and haematopoietic neoplasm because of the changes in coding and diagnostic practices that have occurred during the course of the epidemiological investigations
- *sufficient evidence* in experimental animals for the carcinogenicity of 1,3-butadiene and D,L-diepoxybutane

Shiftwork and circadian disruption (Vol 98)

Evaluation

Cancer in humans

- There is *limited evidence* in humans for the carcinogenicity of shiftwork that involves night work.

Cancer in experimental animals

- There is *sufficient evidence* in experimental animals for the carcinogenicity of light during the daily dark period (biological night).

Overall evaluation

- Shiftwork that involves circadian disruption is *probably carcinogenic to humans (Group 2A)*.

Carcinogenicity of trichloroethylene, Vol. 106

- TCE was widely used for degreasing metal parts until the 1990s, and in dry cleaning from the 1930s to 1950s, main current use is in chlorinated chemical production.
- A French case-control study in an area with high prevalence of occupational exposure to TCE, OR 2·16 (95% CI 1·02–4·60) for people with high cumulative exposure after adjusting for smoking and body-mass index (Charbotel 2006)
- In an eastern European study, OR 1·63 (95% CI 1·04–2·54) for any exposure to TCE and 2·34 (1·05–5·21) in the highest category of exposure intensity (Moore, 2010)
- Consistent with the importance of glutathione conjugation for kidney carcinogenesis, TCE-exposed people with an active GSTT1 enzyme had an increased risk (OR 1·88, 95% CI 1·06–3·33), but people without GSTT1activity did not (0·93, 0·35–2·44) (Boice, 2006)
- A meta-analysis also reported significant RRs of kidney cancer; 1·3 overall and 1·6 for high-exposure groups (Scott, 2011)

Sufficient evidence for carcinogenicity, Group 1

Vol 107, PCBs, Nomenclature

- 209 congeners

Chlorine position on each ring	2	3	4	2,3	2,4	2,5	2,6	3,4	3,5	2,3,4	2,3,5	2,3,6	2,4,5	2,4,6	3,4,5	2,3,4,5	2,3,4,6	2,3,5,6	2,3,4,5,6
None	1	2	3	5	7	9	10	12	14	21	23	24	29	30	38	61	62	65	116
2'	4	6	8	16	17	18	19	33	34	41	43	45	48	50	76	86	88	93	142
3'		11	13	20	25	26	27	35	36	55	57	59	67	69	78	106	108	112	160
4'			15	22	28	31	32	37	39	60	63	64	74	75	81	114	115	117	166
2',3'				40	42	44	45	56	58	82	83	84	97	98	122	129	131	134	173
2',4'					47	49	51	66	68	85	90	91	99	100	123	137	139	147	181
2',5'						52	53	70	72	87	92	95	101	103	124	141	144	151	185
2',6'							54	71	73	89	94	96	102	104	125	143	145	152	186
3',4'								77	79	105	109	110	118	119	126	156	158	163	190
3',5'									80	107	111	113	120	121	127	159	161	165	192
2',3',4'										128	130	132	138	140	157	170	171	177	195
2',3',5'											133	135	146	148	162	172	175	178	198
2',3',6'												136	149	150	164	174	176	179	200
2',4',5'													153	154	167	180	183	187	203
2',4',6'														155	168	182	184	188	204
3',4',5'															169	189	191	193	205
2',3',4',5'																194	196	199	206
2',3',4',6'																	197	201	207
2',3',5',6'																		202	208
2',3',4',5',6'																			209

Cancer in humans

- Excess risks for melanoma were noted consistently in occupational studies in different industries in North America and Europe, in studies of the general population, and with cohort and case-control designs.
- Excess risks for melanoma were reported in several cohort studies of workers in the manufacture of capacitors and transformers, and in electric power and equipment maintenance.
- A significant linear exposure–response trend was noted in the largest study.
- In a population-based case-control study that assessed exposure with PCB serum levels, the association persisted after control for sun sensitivity and exposure.

There is sufficient evidence in humans for the carcinogenicity of PCBs.

There is limited evidence for non-Hodgkin lymphoma and breast cancer.

Mechanisms, “Dioxin-like” PCBs

- 12 PCBs with a Toxicity Equivalency Factor (TEF) according to WHO :
  PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189
- PCB 126 classified in Group 1 in vol. 100F (IARC, 2012)
- *Sufficient evidence* of carcinogenicity in experimental animals (PCB 118, 126, 118 + 126)
- Activity identical to 2,3,7,8-TCDD for every step of the mechanism described for TCDD-associated carcinogenesis in humans :
  - Receptor binding activity
  - Changes in gene expression
  - Changes in protein activity
  - Increased cellular replication
  - Oxidative stress
  - Promotion in initiation-promotion studies
  - Complete carcinogens

Overall evaluations

CAS No	Agent	Group
001336-36-3	Polychlorinated biphenyls	1
	Polychlorinated biphenyls, dioxin-like, with a Toxicity Equivalency Factor (TEF) according to WHO (PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189) (NB: Overall evaluation upgraded to Group 1 with strong supporting evidence from other relevant data)	1
059536-65-1	Polybrominated biphenyls (NB: Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data, namely mechanistic similarity with polychlorinated biphenyls classified in Group 1)	2A

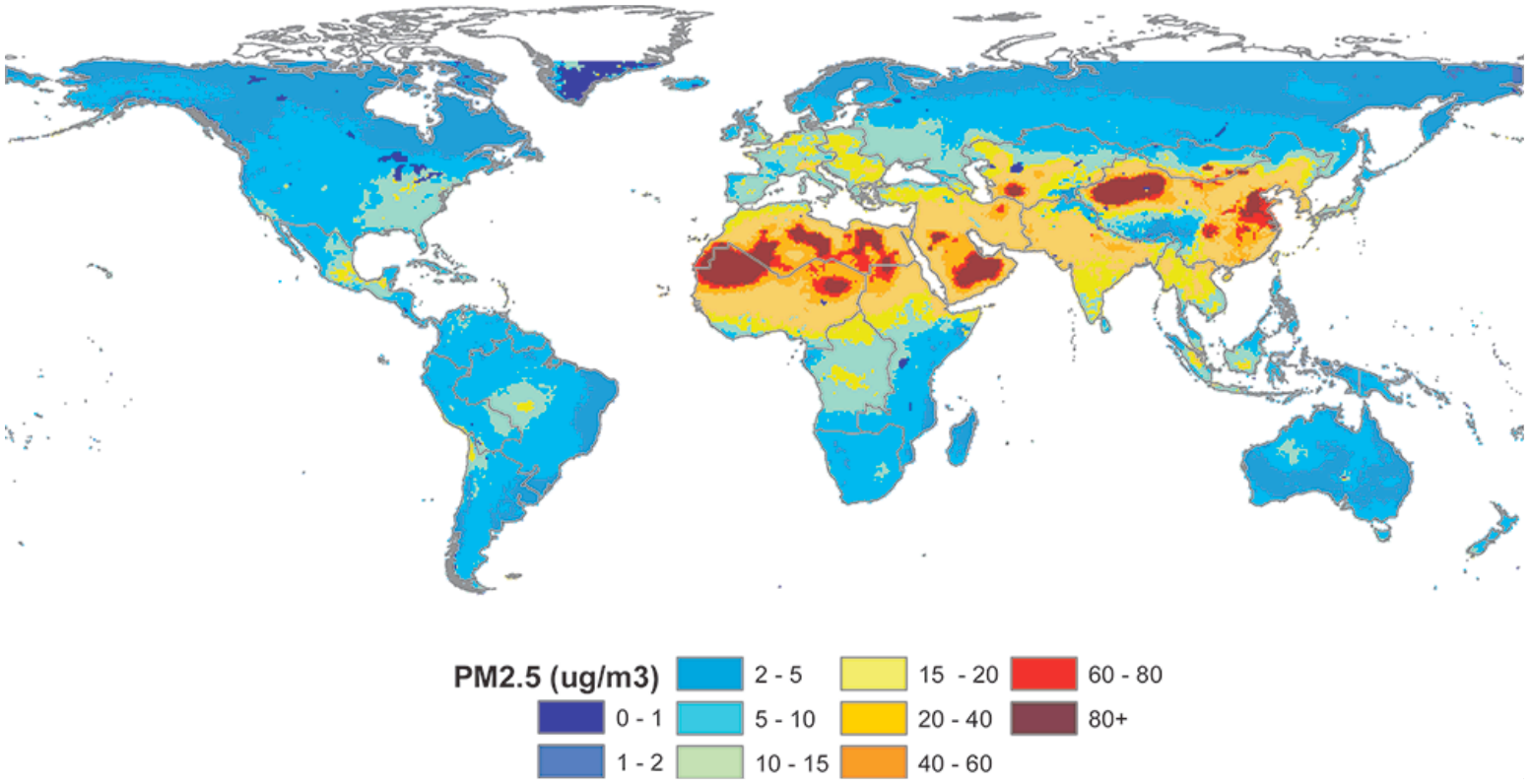
Cancer sites in experimental bioassays

- **Agents:** individual PCBs, binary mixtures, or fresh commercial products
- **Target organs ($p<0.05$ in at least one experiment):**
  - Rat: liver, biliary tract, thyroid gland, lung, oral mucosa, uterus
  - Rat offspring: mammary gland (benign + malignant)
  - Mouse: liver, lung, skin (topical)
  - Mouse offspring: lung (promotion)

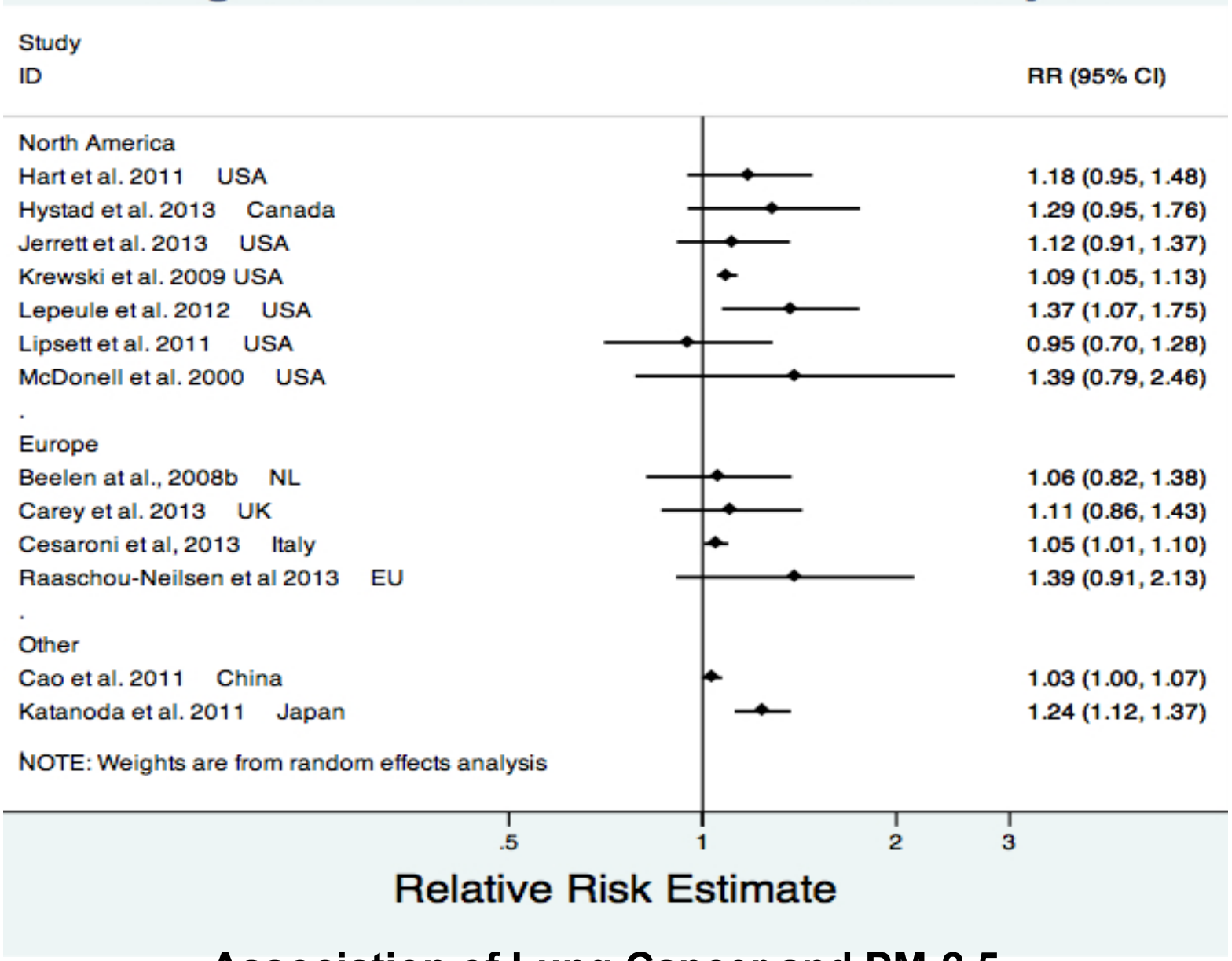
Carcinogenic mechanisms of PCBs

Metabolic activation	**Carcinogenic pathway**	**AhR**
CAR/PXR	**Receptor affinity**	AhR
CYP2B1/2	**Induction of xenobiotic metabolizing enzymes**	CYP1A1
Mutations, DNA strand-breaks, X aberrations	**Genetic and related effects**	DNA adduct formation
Liver	**Organ toxicity**	Liver, skin
Other, including metabolic activation	**Immunotoxicity**	AhR mediated
Driven by hydroxylated metabolites	**Endocrine effects**	AhR mediated (steroid hormones)
Initiator	**Initiation/promotion potential**	Promoter

Outdoor Air Pollution is Highly Variable



Source: Brauer et al. (2012). Environ Sci Technol 46:652-60



Association of Lung Cancer and PM-2.5

Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)

Ole Raaschou-Nielsen, Zorana J Andersen, Rob Beelen, Evangelia Samoli, Massimo Stafoggia, Gudrun Weinmayr, Barbara Hoffmann, Paul Fischer,

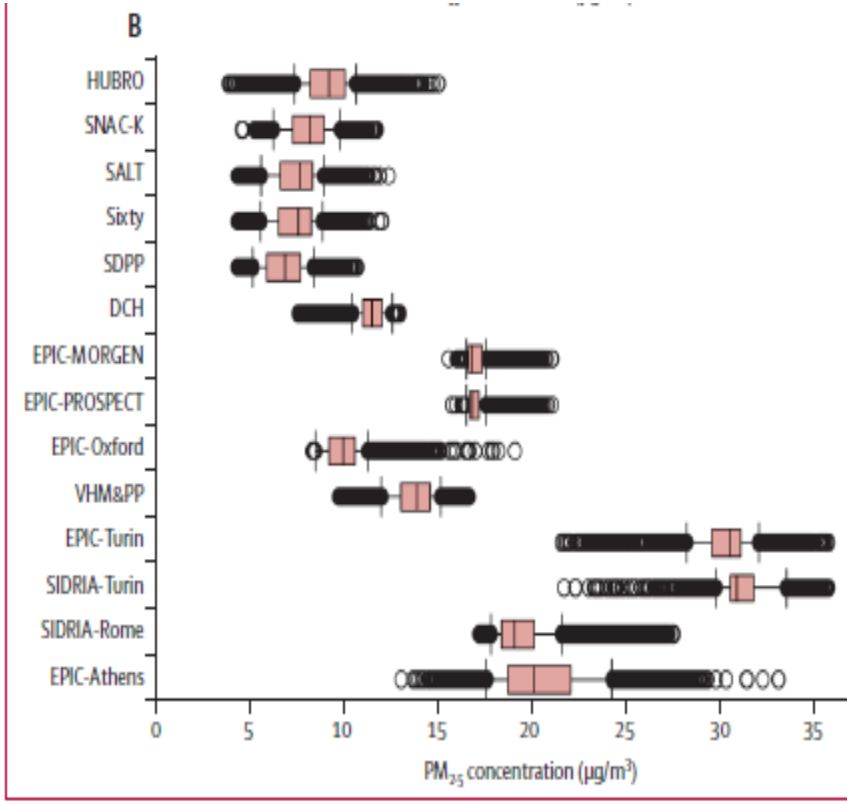


Figure 2: Distribution of particulate matter air pollution at participant addresses in each cohort

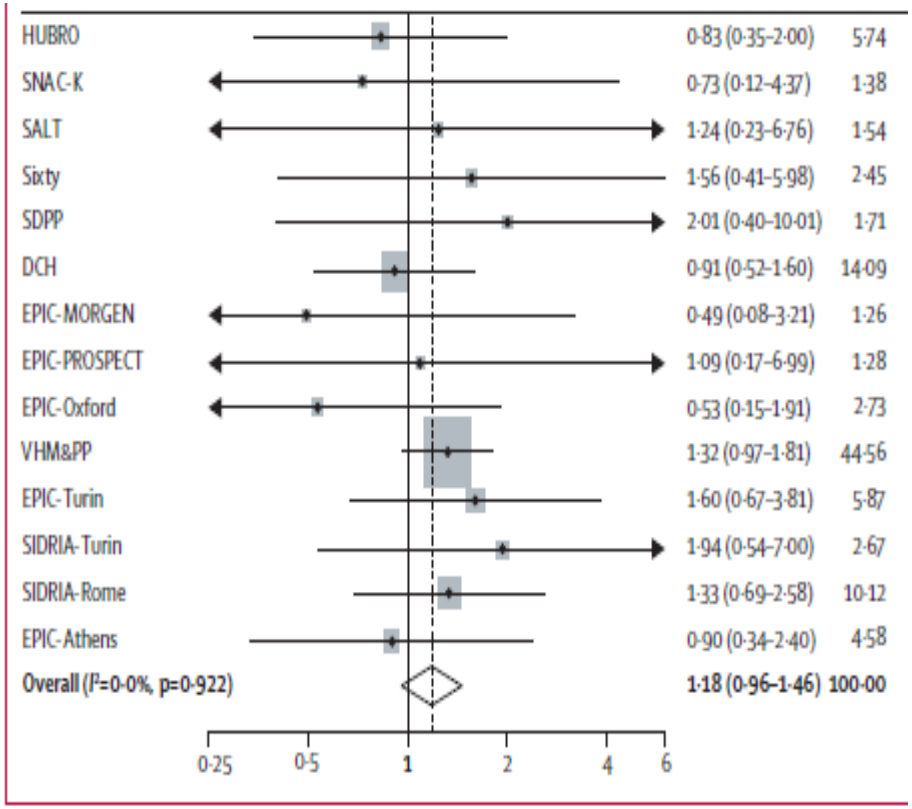


Figure 3: Risk for lung cancer according to concentration of particulate matter in each cohort study

International Agency for Research on Cancer

World Health Organization

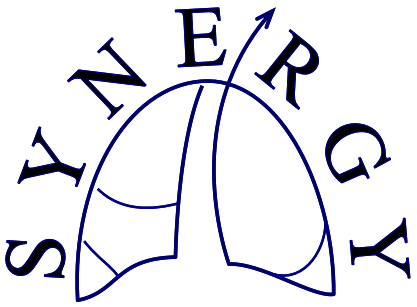
Evaluation: Cancer in humans

- There is *sufficient evidence* in humans for the carcinogenicity of **outdoor air pollution.** Outdoor air pollution causes cancer of the lung. A positive association has been observed for cancer of the urinary bladder.
- There is *sufficient evidence* in humans for the carcinogenicity of **particulate matter in outdoor air pollution**. Particulate matter in outdoor air pollution causes cancer of the lung.

Cancer in experimental animals

- Mice exposed to traffic-related outdoor air pollution from São Paulo showed an increase in the incidence of lung adenoma, promotion of urethane-induced adenomas and tumour multiplicity in a dose-dependent manner (
- Several studies in mice s.c. injected with organic solvent-extracted material from particles collected from outdoor air pollution showed increased incidences of injection site tumours, and pulmonary adenoma or adenocarcinoma

Pre- and post-Monograph meeting analyses of pooled datasets and meta-analyses



- 16 case-control studies from 16 countries
- 19,369 lung cancer cases; 23,670 controls
- SYN-JEM, routine measurement data for PAH asbestos, crystalline silica, chromium/nickel
- Lifetime smoking and occupational histories
- ~1,000 never smoking lung cancer cases
- ~20% Women

- Research platform for occupational lung cancer research
- Diesel engine exhaust: Olsson et al, 2011
- Meta-consortium with ILCCO: alcohol drinking & lung cancer?

Exposure to Diesel Motor Exhaust and Lung Cancer Risk in a Pooled Analysis from Case-Control Studies in Europe and Canada

Ann C. Olsson[1,2], Per Gustavsson[2], Hans Kromhout[3], Susan Peters[3], Roel Vermeulen[3], Irene Brüske[4],

Occupational cancer: AF

- Very divergent estimates <1% to 40%
  - Prevalence of risk factor & exposure level
  - Strength of evidence for causal association
- Doll & Peto 1981 4% of US cancers
- Simonato et al, 1988: 0.6 – 40% of lung cancers
- Leigh et al, 1997 „WHO Global Burden of Disease“ direct & indirect methods: 6-10%
- Nurminen & Karjalainen, 2001: 8% of cancers in Finns
- Steenland et al 2003: 2.4 – 4.8% of US cancers
- Rushton et al 2008, UK....

Occupational cancer: AF

"Occupational cancer, moreover, tends to be concentrated among relatively small groups of people among whom the risk of developing the disease may be quite large, and

such risks can usually be reduced or even eliminated, once they have been identified.

The detection of occupational hazards should therefore have a higher priority in any program of cancer prevention than their proportional importance might suggest."

Doll & Peto, 1981

UK Burden of Occupational Cancer

All IARC Group 1 and 2A carcinogens with "strong" or "suggestive" evidence for specific site in humans (Siemiatycki et al, 2004)

Cancer Site	AF (%)			Deaths (2005)			Registrations (2004)		
	M	F	Total	M	F	Total	M	F	Total
Mesothelioma	97.0	82.5	95.0	1699	238	1937	1699	238	1937
Sinonasal	46.0	20.1	34.4	29	10	40	102	32	134
Lung	22.2	5.5	15.2	4236	757	4993	4877	850	5727
Nasopharynx	11.1	2.5	8.3	7	1	8	16	1	17
Bladder	7.2	1.9	5.4	218	31	248	503	55	558
Breast		4.6	4.6		555	555		1971	1971
NMSC	7.0	1.2	4.6	20	2	23	2542	367	2909
Larynx	2.9	1.6	2.6	18	3	20	51	6	56
Oesophagus	3.3	1.1	2.5	157	28	185	160	29	189
STS	3.4	1.1	2.3	12	4	16	25	6	30
Stomach	3.0	0.3	2.0	102	6	108	150	9	159
NHL	2.1	1.1	1.7	49	23	71	110	51	161
Melanoma (eye)	2.9	0.4	1.6	1	0	1	6	1	7
Total	8.45	2.35	5.51	6588	1702	8290	10406	3703	14109

World Health Organization

Rushton et al, Occ Env Med; 2008. Straif, Occ Env Med, 2008

Impact of Monograph evaluations

Collaboration of IMO scientists with

- WHO and UN Interagency Committees
  - Global Collaboration in Chemical Risk Assessment
  - Conference of the Parties, WHO FCTC
  - Interagency Working Group WHO, ILO, UNEP, UNITAR, Rotterdam Convention and Basel Convention
- Global Burden of Disease 2010
- European Parliament, Debate on UV Radiation and Cancer
- National Agencies, e.g. NTP Report on Carcinogens, ANSES

Monographs directly used by other agencies or companies

- California Proposition 65, IARC Group 2B
- Denmark List of Occupational Diseases, shift-work
- Lawsuits, Tobacco Institute Australia v. Federation of Australian Consumer Societies
- Modifications of production processes (4-methylimidazole)