Arbeitsbedingte Krebserkrankungen
Einstufung und Bewertung

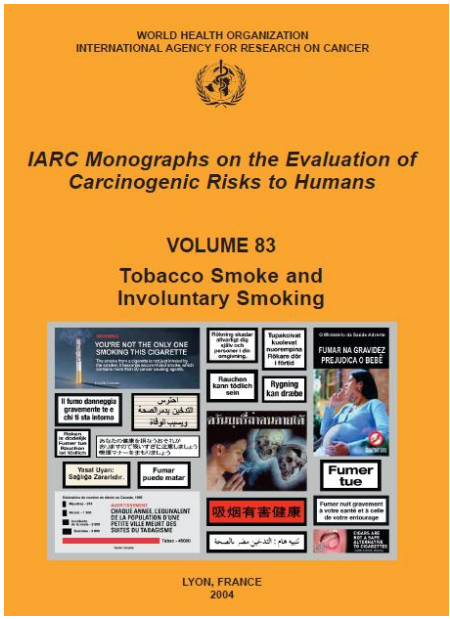
Kurt Straif, MD MPH PhD

Head, IARC Monographs Section

International Agency for Research on Cancer
Lyon, France

Jahrestagung, Österreichische Gesellschaft für Arbeitsmedizin, Zell am See, 22-24 Sept 2016

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** http://monographs.iarc.fr/ and **what works in cancer prevention** http://handbooks.iarc.fr/

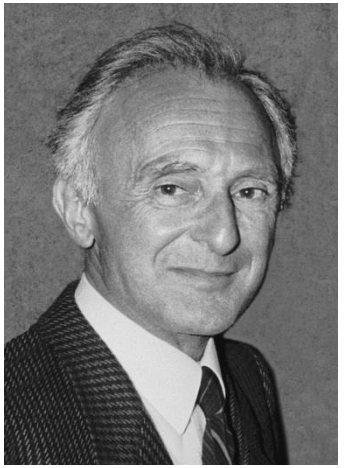
International Agency for Research on Cancer

World Health Organization

“The encyclopaedia of carcinogens”

The *IARC Monographs* evaluate

- Chemicals
- Complex mixtures
- Occupational exposures
- Physical and biological agents
- Personal habits



Lorenzo Tomatis
1929-2007

Almost 1000 agents have been evaluated

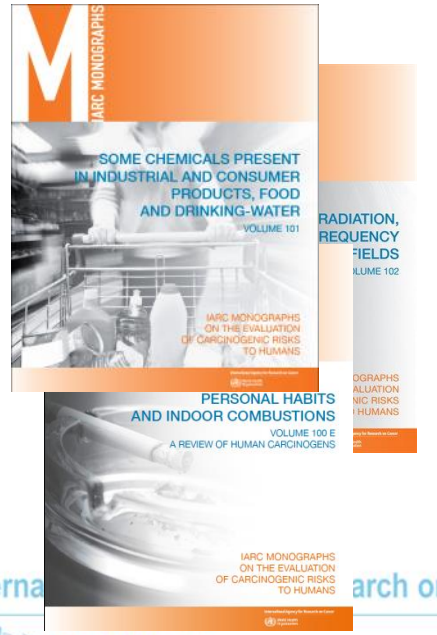
- 118 are *carcinogenic to humans* (Group 1)
- 79 are *probably carcinogenic to humans* (Group 2A)
- 291 are *possibly carcinogenic to humans* (Group 2B)

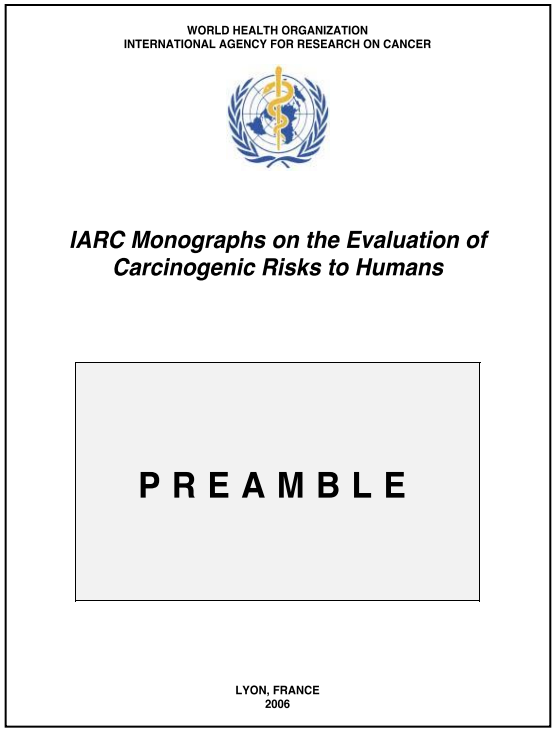
National and international health agencies use the *Monographs*

- 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

How are Evaluations Conducted?

??





- Published guidelines for participant selection, conflict of interest & stakeholder involvement
- Criteria for data eligibility
- Guidelines for review of human, animal and mechanistic evidence
- Decision process for overall evaluations

Interna arch on Cancer

World Health Organization

http://monographs.iarc.fr/ENG/Preamble/index.php

The IARC Monographs, a worldwide endeavour that since 1971 has involved over 1000 scientists from over 50 countries

WHO Declaration of Interests

To ensure public confidence that interested parties do not have links to the WG, IARC strives to identify and avoid real or apparent conflicts of interests

- Before official invitation WG have to declare employment, research, and financial interests
- At the opening of the meeting they are asked to update their Declaration

Pertinent interests are disclosed

- To meeting participants
- To the public, before the meeting (http://monographs.iarc.fr/)
- In the published volume of *Monographs*

Meeting participants

Working Group Members

- Write the critical reviews and develop the evaluations
- Serve as individual scientists, not representatives of any organization

Invited Specialists assist in the WG

- Have similar knowledge, but also a conflicting interest
- Do not serve as chair, draft text that describes or interprets cancer data, or participate in the evaluations

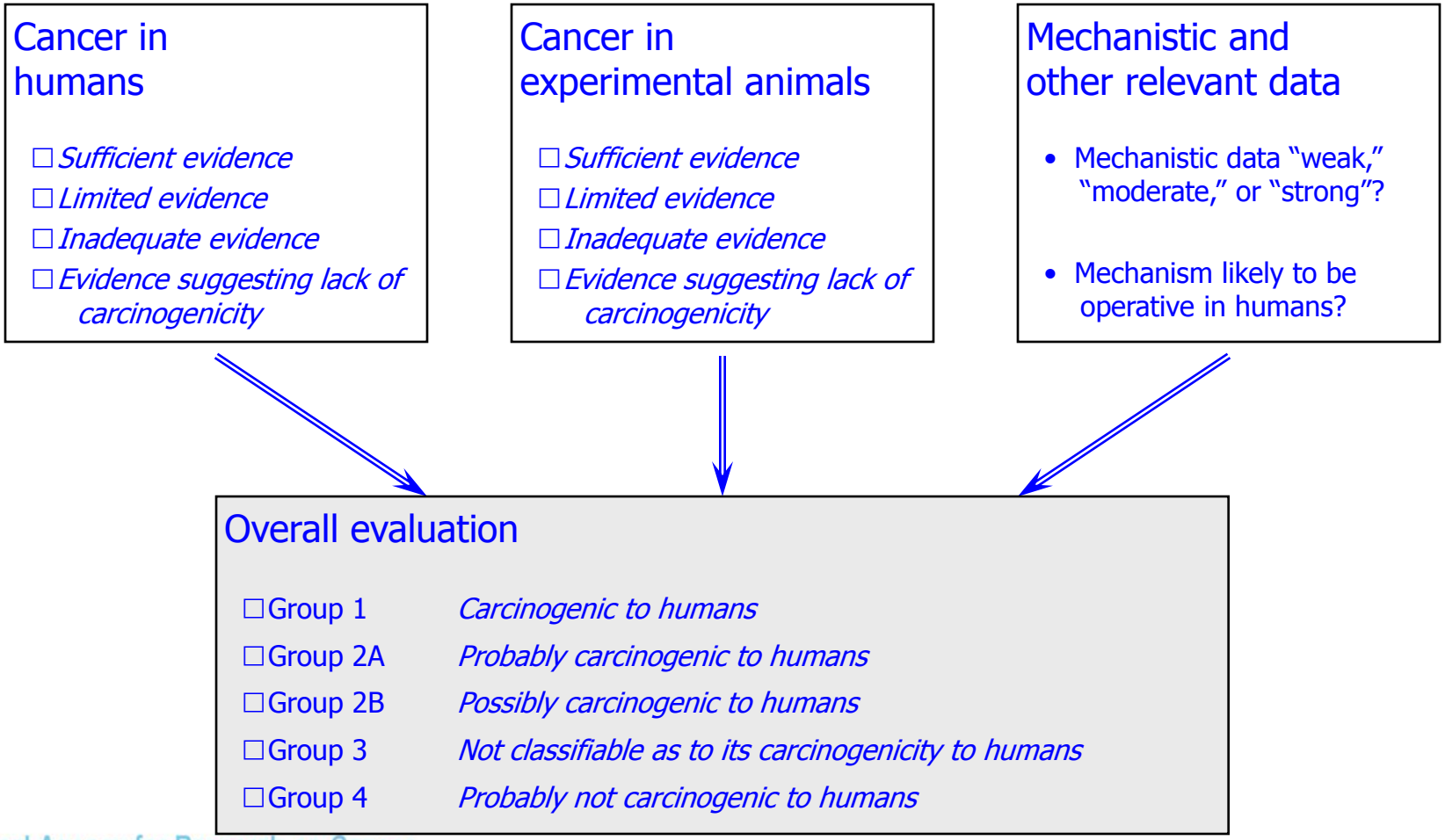
Representatives of national and international health agencies

Observers

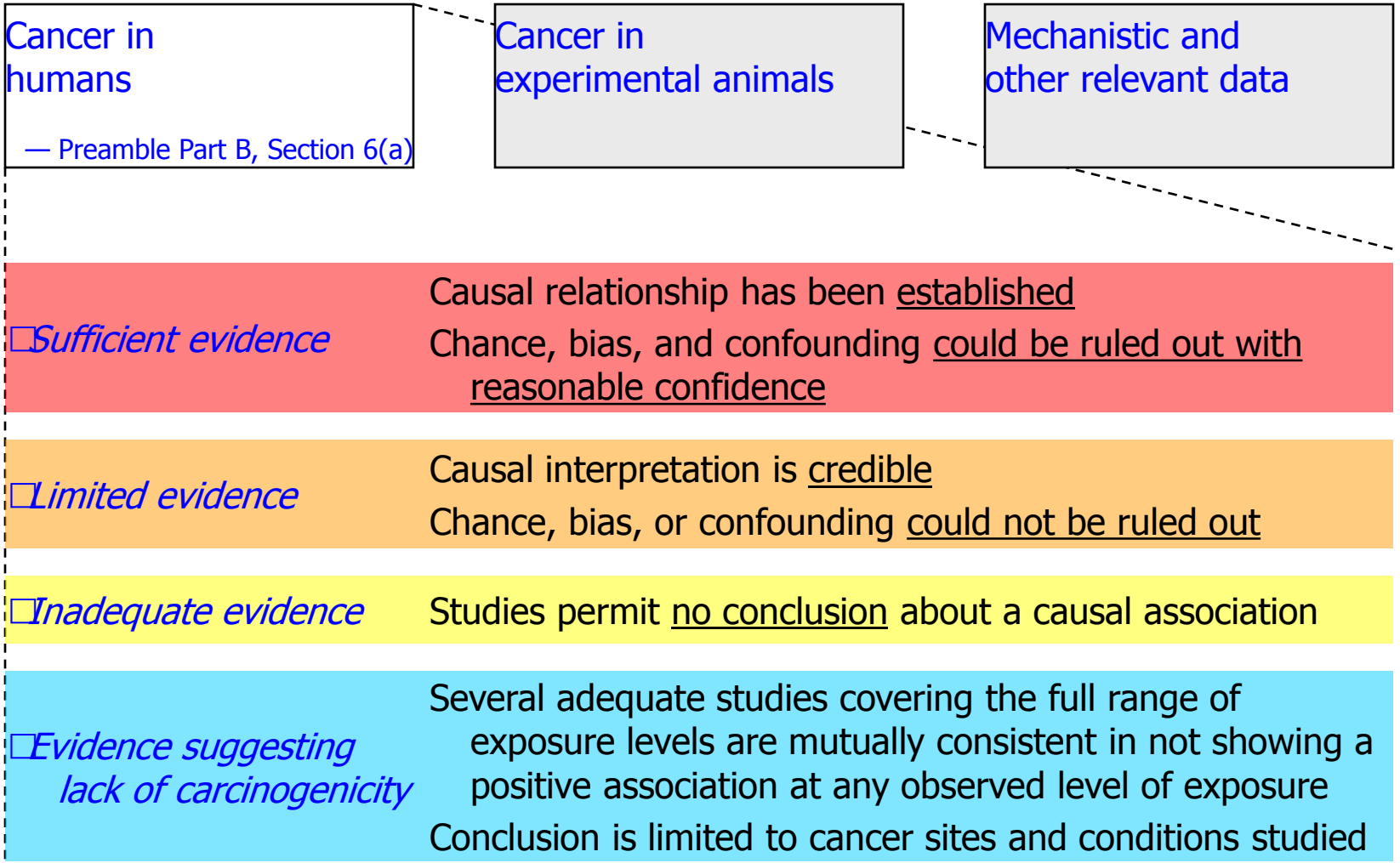
- Here to *observe* the meeting, *not to influence* its outcome
- All participants agree to respect the *Guidelines for Observers*

IARC Secretariat

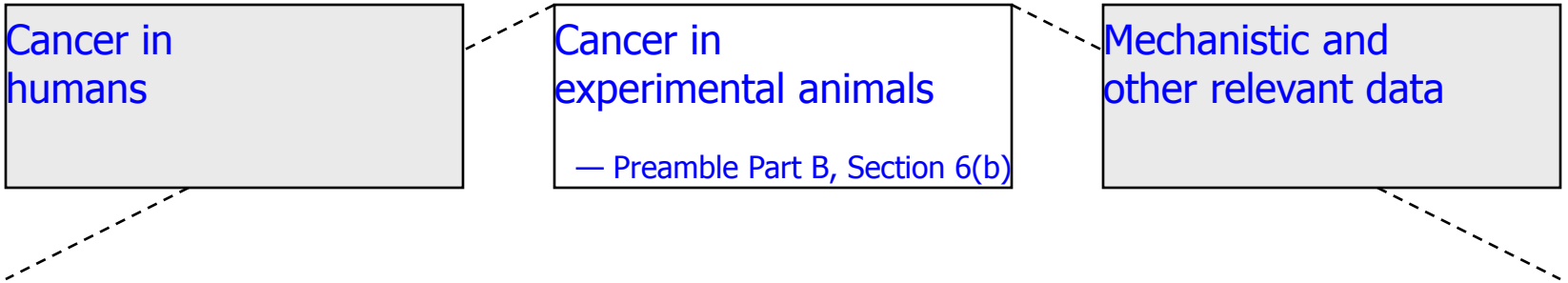
Subgroup work



Evaluating human data (Subgroup 2)



Evaluating experimental animal data (Subgroup 3)



☐*Sufficient evidence*	Causal relationship has been <u>established</u> through either: - <u>Multiple positive results</u> (2 species, studies, sexes of GLP) - <u>Single unusual result</u> (incidence, site/type, age, multi-site)
☐*Limited evidence*	Data <u>suggest</u> a carcinogenic effect but: (*e.g.*) single study, benign tumours only, promoting activity only
☐*Inadequate evidence*	Studies permit <u>no conclusion</u> about a carcinogenic effect
☐*Evidence suggesting lack of carcinogenicity*	Adequate studies in at least two species show that the agent is not carcinogenic Conclusion is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied

Evaluating mechanistic and other data (Subgroup 4)

Cancer in humans	Cancer in experimental animals	Mechanistic and other relevant data — Preamble Part B, Section 6(c)

- Are the mechanistic data "weak," "moderate," or "strong"?

Have the mechanistic events been established? Are there consistent results in different experimental systems? Is the overall database coherent?

Has each mechanism been challenged experimentally? Do studies demonstrate that suppression of key mechanistic processes leads to suppression of tumour development?

- Is the mechanism likely to be operative in humans?

Are there alternative explanations? Could different mechanisms operate in different dose ranges, in humans and experimental animals, or in a susceptible group?

Note: an uneven level of support for different mechanisms may reflect only the resources focused on each one

The plenary sessions will combine the human and experimental evaluations

EVIDENCE IN HUMANS \ EVIDENCE IN EXPERIMENTAL ANIMALS	*Sufficient*	*Limited*	*Inadequate*	*ESLC*
Sufficient	Group 1 *(carcinogenic to humans)*			
Limited	Group 2A *(probably carcinogenic)*	Group 2B *(possibly carcinogenic)* (exceptionally, Group 2A)		
Inadequate	Group 2B *(possibly carcinogenic)*	Group 3 *(not classifiable)*		
ESLC				Group 4

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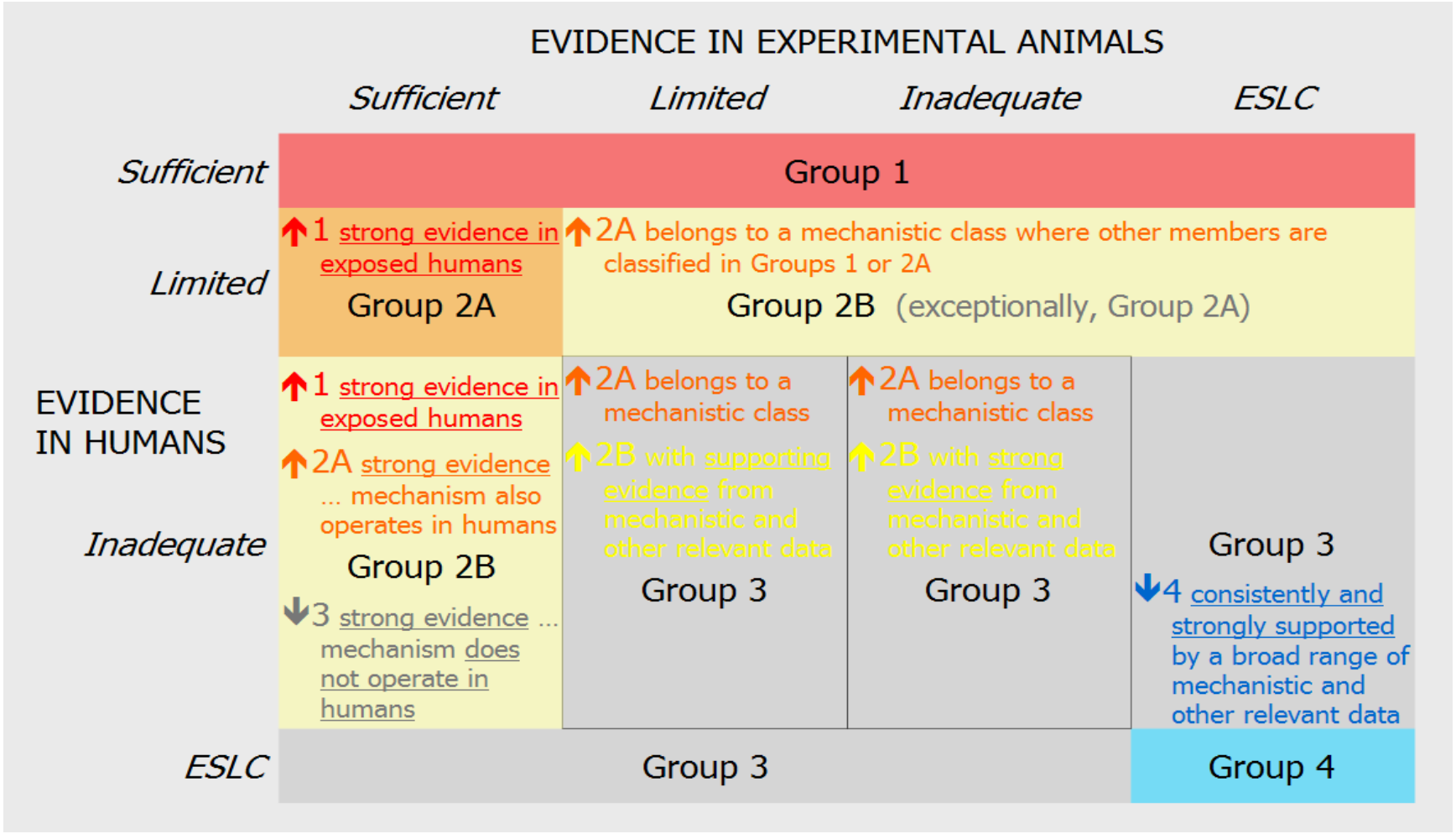
Overall carcinogenicity evaluation



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)

International Agency for Research on Cancer

World Health Organization

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 114*

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Lung	Acheson process, occupational exposures associated with 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	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 *alpha*-Chlorinated toluenes and

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

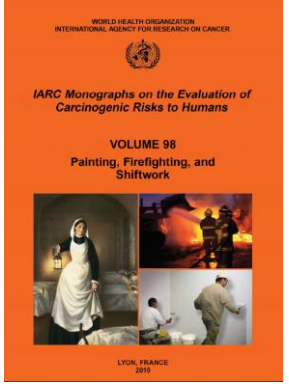
News

Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls

News

The carcinogenicity of outdoor air pollution

World Health Organization



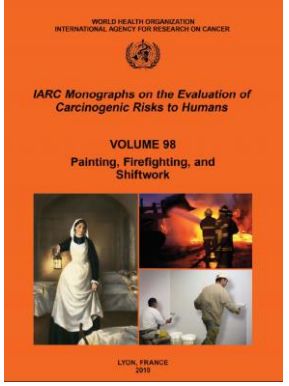
Shiftwork and circadian disruption (Vol 98)

Exposure

About **15-20%** of the working population **in Europe and USA** is engaged in **shift-work** that **involves night-work**

- most prevalent (above 30%) in the health-care, industrial manufacturing, mining, transport, communication, leisure, and hospitality sectors

Among the many different pattern of shift-work, those including **night-work** are the most disruptive for **the circadian clock**



Shiftwork and circadian disruption (Vol 98)

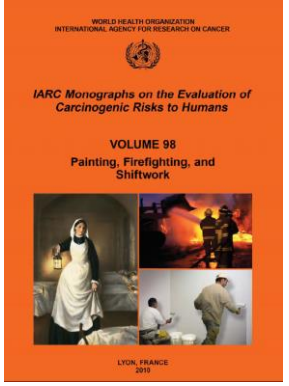
Cancer in Humans

6 of 8 studies from various geographical regions noted an increased risk of **breast cancer** among shift-workers

Cohort studies of *nurses* (3) and radio and telegraph operators (1) engaged in shift-work at night
Case-control study (1) and national linkage study (1) of occupations with high prevalence of shift-work.

Limitations of the studies
Inconsistent definition of shift-work
Limited number of studies
Studies often focused on single profession

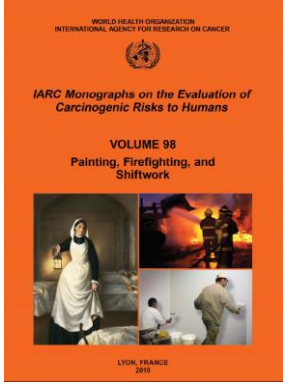
Shiftwork and circadian disruption (Vol 98)



Cancer in experimental animals

> 20 studies investigated the effect of **constant light, dim light at night, simulated chronic jet lag, or circadian timing of carcinogens**, and most showed a major increase in tumour incidence.

A similar number of studies investigated the effect of **reduced nocturnal melatonin concentrations or removal of the pineal gland** (where melatonin is produced) in tumour development and most showed increases in the incidence or growth of tumours



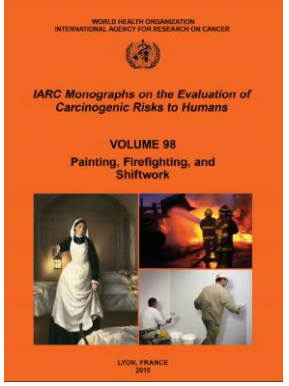
Shiftwork and circadian disruption (Vol 98)

Mechanisms of carcinogenicity (I)

Exposure to light at night disturbs the circadian system with alterations of sleep-activity patterns, suppression of melatonin production, and deregulation of circadian genes involved in cancer-related pathways.

Inactivation of the circadian Period gene, Per2, promotes tumour development in mice

In human breast and endometrial tumours, the expression of PERIOD genes is inhibited.



Shiftwork and circadian disruption (Vol 98)

Mechanisms of carcinogenicity (II)

In animals, melatonin suppression can lead to changes in the gonadotrophin axis.

In humans, sleep deprivation and the ensuing melatonin suppression lead to immunodeficiency.

Sleep deprivation suppresses natural killer-cell activity and changes the T-helper 1/T-helper 2 cytokine balance, reducing cellular immune defence and surveillance.

Shiftwork and circadian disruption (Vol 98)

Cancer in humans

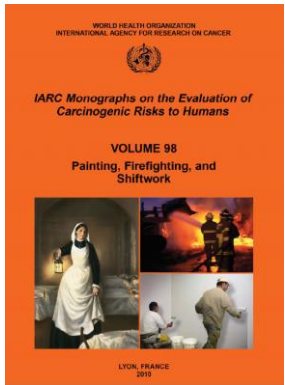
- There is *limited evidence* in humans for the carcinogenicity of shiftwork that involves night work.

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)*.



International Agency for Research on Cancer

World Health Organization

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

World Health Organization

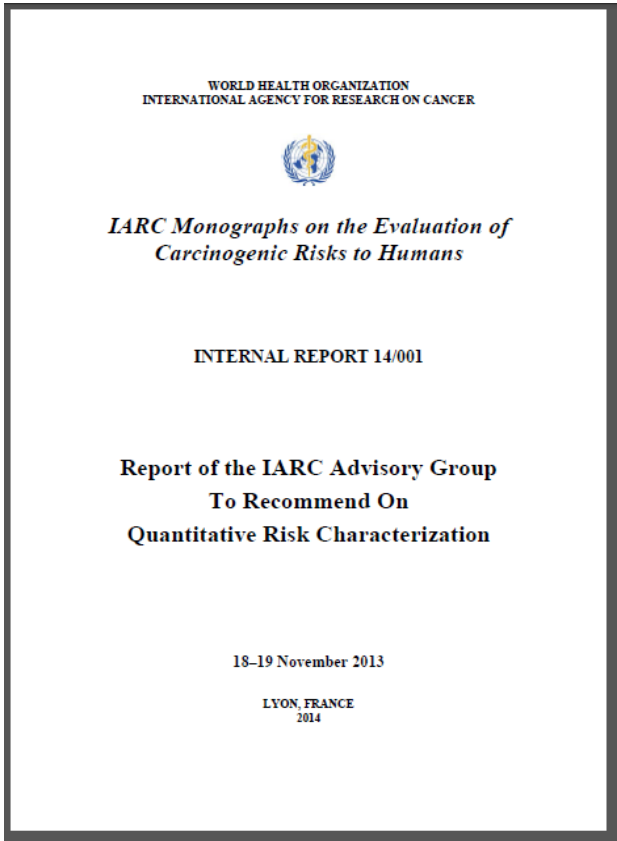
Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report

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


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

UK HSE Burden of occupational cancer

Occupational AF for cancers of lung, bladder, non-melan. skin, sinonasal cancers, leukaemia, mesothelioma:

All cancer deaths

- Group 1, 3.6% of (6% in men)
- Group 1 & 2A, 4.9% in total (8.0% in men)

Lung cancer

- Group 1, 16.5%
- Group 1 & 2A 21.6%

Lung cancer almost 70% of occupational cancers,
Asbestos > 50% of occupational cancer deaths

UK Burden of Occupational Cancer

All IARC Group 1 and 2A carcinogens with "sufficient" or "limited" evidence for specific site in humans

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

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

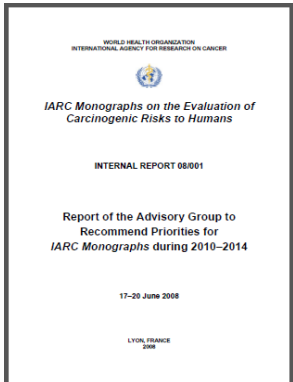
Lancet Oncol 2014

Published Online
May 6, 2014

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

International Agency for Research on Cancer

World Health Organization


WORLD HEALTH ORGANIZATION
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

IARC MONOGRAPHS - MEETINGS

Upcoming Meetings

Meeting 117: Pentachlorophenol and Some Related Compounds (4-11 October 2016)

Preliminary List of Agents
Preliminary List of Participants
Call for Data (closing date 5 September 2016)
Call for Experts (closing date 1 February 2016)
Request for Observer Status (closing date 6 June 2016)
WHO Declaration of Interests for this volume
Code of Conduct
Instructions for Authors

Meeting 118: Welding, Welding Fumes, and Some Related Chemicals (21-28 March 2017)

Preliminary List of Agents
Call for Data (closing date 17 February 2017)
Call for Experts (closing date 22 July 2016)
Request for Observer Status (closing date 25 November 2016)
WHO Declaration of Interests for this volume
Code of Conduct
Confidentiality Undertaking
Instructions for Authors

Meeting 119: Some Chemicals in Food and Consumer Products (6-13 June 2017)

Intern

9 years later…

PubMed: Almost 100 analytical studies on shiftwork and cancer, more than half on breast cancer

Many more positive studies, but increased complexity

- Exposure, type of shiftwork, duration, age at exposure
- Potential confounders and/or effect modifiers, chronotype, reproductive history, obesity, alcohol consumptions, vitamin D, societal context of shiftwork
- Outcome, pre-/post-menopausal breast cancer, hormone-receptor status
- Other cancers, prostate, colon, …

AG on Future Priorities: Shiftwork recommended as "high priority"

Body Fatness and Cancer — Viewpoint of the IARC Working Group

Béatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, Ph.D., Dana Loomis, Ph.D., Yann Grosse, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D.,

Table 2. Strength of the Evidence for a Cancer-Preventive Effect of the Absence of Excess Body Fatness, According to Cancer Site or Type.*

Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	Sufficient	1.3 (1.2–1.4)
Pancreas	Sufficient	1.5 (1.2–1.8)
Breast: postmenopausal	Sufficient	1.1 (1.1–1.2)§
Corpus uteri	Sufficient	7.1 (6.3–8.1)
Ovary	Sufficient	1.1 (1.1–1.2)
Kidney: renal-cell	Sufficient	1.8 (1.7–1.9)
Meningioma	Sufficient	1.5 (1.3–1.8)
Thyroid	Sufficient	1.1 (1.0–1.1)§
Multiple myeloma	Sufficient	1.5 (1.2–2.0)

Acknowledgements

The *IARC Monographs* and Handbooks are supported by grants from

- **U.S. National Cancer Institute (since 1982)**
- **EC, DG Employment, Social Affairs and Inclusion (since 1986)**
- **U.S. National Institute of Environmental Health Sciences (since 1992)**
- **Institut National du Cancer (INCa), France**
- **U.S. Center for Disease Control (CDC)**
- **American Cancer Society (ACS)**

International Agency for Research on Cancer

World Health Organization

straif@iarc.fr

Danke

Supportive epidemiological evidence for LAN and Breast cancer risk

- Flight attendants (shift work and jetlag):
  - Increased risk of **breast cancer** among *female flight attendants* (RR=1.9) who also experienced circadian disruption by frequently crossing time zones
  - Potential uncontrolled confounding by reproductive factors and cosmic radiation
- Breast cancer in the blind: reduced risk
- Sleep duration: longer sleep lower risk
- Ecological studies on LAN at population level

Night work acknowledged as an occupational disease (2007)

BBC NEWS

Night shifts spark cancer pay-out

By Kenneth Macdonald
BBC Scotland Special Correspondent

The Danish government has begun paying compensation to women who have developed breast cancer after long spells working nights.

It follows a ruling by a United Nations agency that night shifts probably increase the risk of developing cancer.

BMJ medical publication of the year

Search bmj.com
Advanced search

Published 18 March 2009, doi:10.1136/bmj.b1152
Cite this as: BMJ 2009;338:b1152

News

Danish night shift workers with breast cancer awarded compensation

Jacqui Wise

[1] London

Women in Denmark who developed breast cancer after many years of working night shifts have received compensation despite only limited research supporting the link. The ruling could have implications for compensation claims elsewhere in

CNNhealth.com

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Weather Forecast International Edition

Breaking News **Obama administration to beef up resources on the Mexico border to help with Mexico's war against violent drug cartels.**

Set your CNN.com Edition CNN U.S. CNN International

HEALTH MAIN LIVING WELL DIET & FITNESS MENTAL HEALTH CONDITIONS

vital signs

updated 1:00 p.m. EDT, Mon March 16, 2009

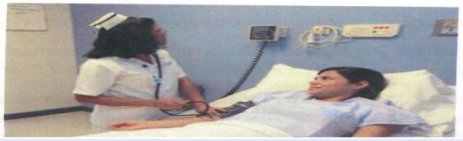
Payout for women who got breast cancer after night shifts

STORY HIGHLIGHTS
- Danish women who got breast cancer after night work get compensation
- Women must have worked at least one night a week for 20 to 30 years
- WHO have concluded that working night shifts "probably causes cancer"

Next Article in Health »

By Mark Tutton
For CNN

(CNN) -- Employers in Denmark have started paying compensation to women who have developed breast cancer after working night shifts.



Thirty-eight eight women have so far received payments via their employers' insurance companies, the Danish National Board of Industrial Injuries told CNN.

To qualify for compensation, women must have developed breast cancer after having worked at least one night shift a week for 20 to 30 years.

The amount of compensation depends on the severity of claimants' illness and their ability to work.

Criterias for night shiftwork and breast cancer acknowledgement, DK

- At least 25 (20) years of ‘night shift-work’ at least once a week”
  - Major part of night shifts between 11 pm. and 6 pm.
  - Breast cancer shall occur at least 5 years after last night-shift
- Or 15 years of ”night shift-work” if more frequent
- Other causes of breast cancer must not be more probable
  - HRT 5 years years before BC diagnosis
  - No (extreme) obesity after menopause

Describing occurrence

- CI5 - Cancer Incidence in Five Continents
- GLOBOCAN
  Incidence, Mortality, Prevalence
  and Disability-adjusted life years

GLOBOCAN 2012
ESTIMATED CANCER INCIDENCE, MORTALITY AND PREVALENCE WORLDWIDE IN 2012

- ACCIS – Automated childhood cancer information system

ACCIS

- CanReg5 – open source software

CanReg 5
IARC IACR

- Training and expert advice
- GICR
  Global Initiative for Cancer Registry development

GICR
GLOBAL INITIATIVE FOR CANCER REGISTRY DEVELOPMENT
INITIATIVE MONDIALE POUR LE DEVELOPPEMENT DES REGISTRES DU CANCER
INICIATIVA MUNDIAL PARA EL DESARROLLO DE REGISTROS DE CÁNCER

International Agency for Research on Cancer
World Health Organization

Highlights from Volume 100

- Further research often finds **additional cancer sites** for known human carcinogens
- New research continues to find **additional human carcinogens,** e.g. aristolochic acid
- The use of **mechanistic data** to identify carcinogens is **accelerating**, e.g. dioxin-like substances
- Further research has confirmed carcinogenic potential under **conditions of lower exposure**, e.g. radon

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

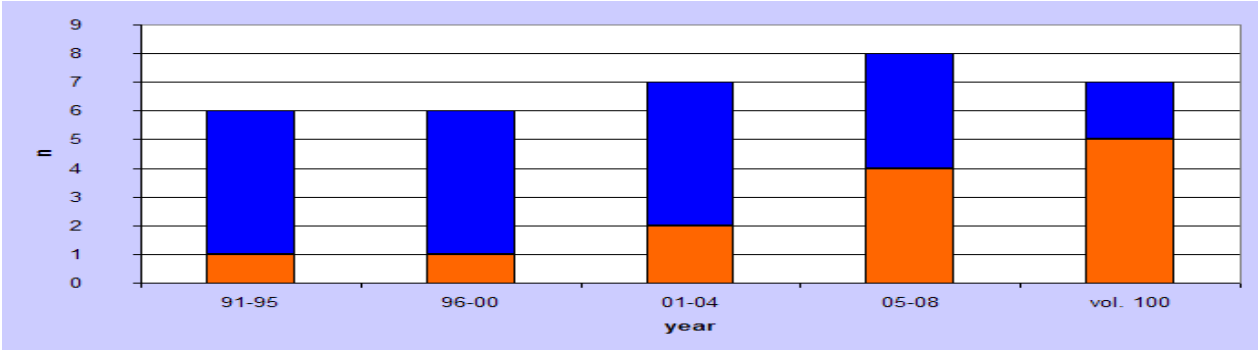
Animal Only

International Agency for Research on Cancer

World Health Organization

Mechanisms Involved in Human Carcinogenesis

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.

Benzo[a]pyrene: Genotoxic mechanism involves its metabolism to highly reactive species that form covalent adducts to DNA that induce mutations in K-Ras and the TP53 genes in both human and mouse lung tumours. K-RAS mutations have been found in nonsmokers exposed to coal smoke

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

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

Zdenko Herceg*, Marie-Pierre Lambert, Karin van Veldhoven[1], Christiana Demetriou[1], Paolo Vineis[1], Martyn T.Smith[2], Kurt Straif and Christopher P.Wild

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

Group-1 agents with less than *sufficient evidence* in humans

- *Ethylene oxide (vol 60, 1994, Vol 97, 2007)*
- 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (vol 69, 1997)
- Neutron radiation (vol 75, 2000)
- Gallium Arsenide (Vol 86, 2003)
- Benzo[*a*]pyrene (vol 92, 2005)
- Dyes metabolized to benzidine (Vol 99, 2007)
- MOCA (Vol 99, 2007)
- 2,3,4,7,8-pentachloro-dibenzofuran and 3,3',4,4',5-pentachloro-biphenyl (Vol 100F, 2009)
  Dioxin-like PCBs (Vol 107)

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

Review

Research Recommendations for Selected IARC-Classified Agents

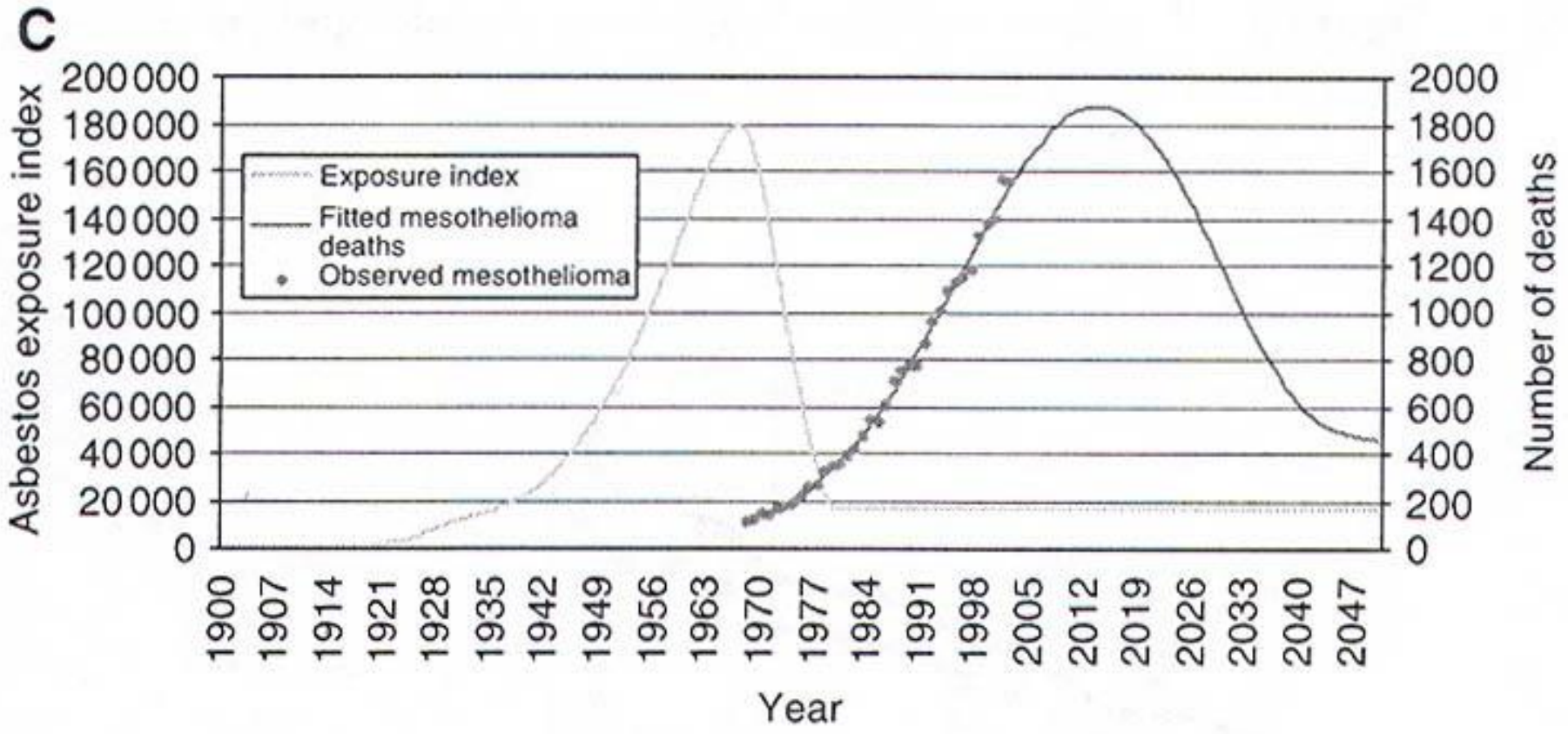
Elizabeth M. Ward,[1] Paul A. Schulte,[2] Kurt Straif,[3] Nancy B. Hopf,[4] Jane C. Caldwell,[5] Tania Carreón,[2] David M. DeMarini,[5] Bruce A. Fowler,[6] Bernard D. Goldstein,[7] Kari Hemminki,[8] Cynthia J. Hines,[2] Kirsti Husgafvel Pursiainen,[9] Eileen Kuempel,[2] Joellen Lewtas,[10] Ruth M. Lunn,[11] 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

International Agency for Research on Cancer

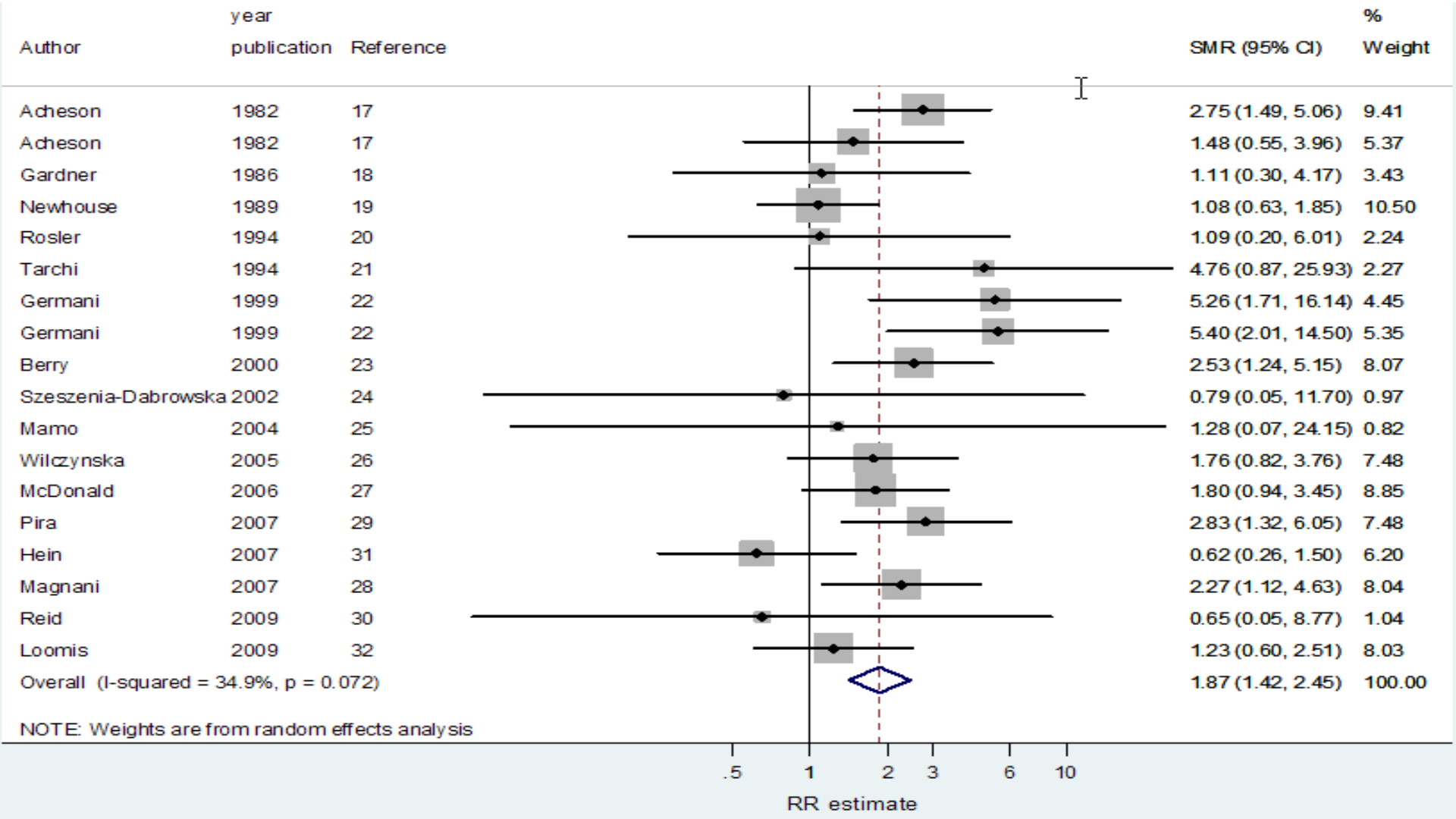
World Health Organization

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



Adapted from Hodgson et al, 2005

Asbestos and Ovarian Cancer



Camargo et al. Env Health Perspectives (2011)

World Health Organization

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.**

Asbestos: open questions

- Lung cancer potency varies by fiber type?
  pro review by Hodgson & Darton 2000 (10x),
  con review by Stayner et al. 1996
- Lung cancer potency varies by fiber size?
  indirect epidemiologic evidence (textile industry) supports belief that fibers > 10 μm have higher carcinogenic potency for lung cancer
- Mesothelioma potency varies by fiber type?
  chrysotile < amphiboles, amosite may be < crocidolite, but: mesothelioma among Chinese workers exposed to “pure” chrysotile (Yano 2001)
- Mesothelioma potency varies by fiber size?
  pro: mesothelioma at South Carolina > Quebec miners
  con: South Carolina textile < New Orleans cement plant

Asbestos and Ovarian cancer, Vol.100C

- **Five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos.**
- **Supported by studies showing that women with environmental exposure to asbestos had non-significant increases in both ovarian cancer incidence and mortality.**
- **Modest support from the findings of non-significant associations between asbestos exposure and ovarian cancer in two case-control studies.**
- **Finding is consistent with laboratory studies documenting that asbestos can accumulate in the ovaries of women with occupational and household exposure to asbestos.**

IARC Monographs V111, Fluoro-edinite

- Fluoro-edenite fibrous amphibole first identified around Etna volcano, Biancavilla, Italy; similar mineral reported from the Kimpo volcano in Japan.
- Unpaved roads made from local quarry products from Biancavilla, since the 1950s,
- Several surveillance studies reported excess of mesothelioma in region of Biancavilla (Bruno et al., 2014).
- Rate ratios for mesothelioma large & stable,
- Excess similar in men and women, most prominent in young adults, suggesting environmental cause.
- Increased incidences of mesotheliomas observed in male and female rats given fibrous fluoro-edenite by i.p. & i. pl. injection (Belpoggi et al., 2011).
- Fluoro-edenite classified as *carcinogenic to humans* (Group 1)

IARC Monographs Vol. 111, CNT

- MWCNT-7 caused peritoneal mesotheliomas in male & female rats in 1 intraperitoneal injection study 1 intrascrotal injection study, in male *p53*$^{+/-}$ mice in 2 intraperitoneal injection studies, inhalation of MWCNT-7 promoted 3-methylcholanthrene-initiated bronchioloalveolar adenoma and carcinoma in male mice.
- 2 other types of MWCNTs with physical dimensions similar to those of MWCNT-7 caused mesotheliomas in male and female rats in one intraperitoneal study.

Overall evaluation of carcinogenicity

- *sufficient evidence* for MWCNT-7, *Group 2B*
- *limited evidence* for the two other types of MWCNTs with dimensions similar to MWCNT-7, Group 3
- *inadequate evidence* for SWCNTs, Group 3.

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.

Diesel engine exhaust: Exposure

- 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.
- 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.
- Emission standards in non-road applications are lagging and therefore are still largely uncontrolled today.

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.
- There is "strong evidence" for the ability of whole diesel-engine exhaust to induce cancer in humans through genotoxicity.

Overall evaluation

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

International Agency for Research on Cancer

World Health Organization

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.

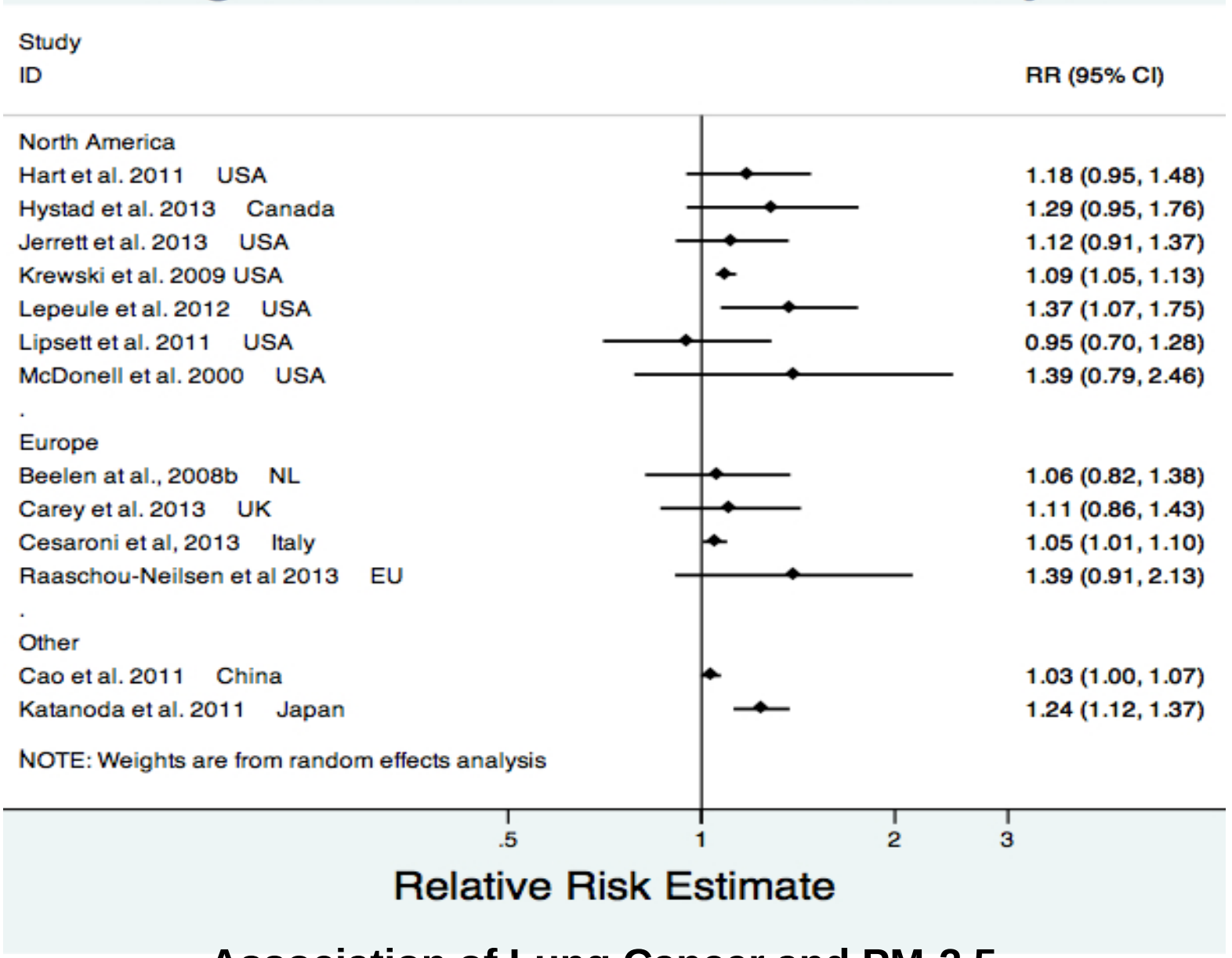
The Working Group concluded that there is "strong evidence" for the ability of whole diesel-engine exhaust to induce cancer in humans through genotoxicity.

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 µg/m^3



Association of Lung Cancer and PM-2.5

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)

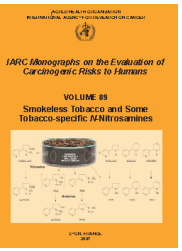
Other relevant data

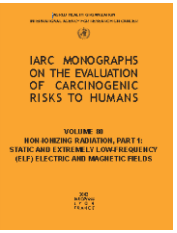
- Studies of people exposed occupationally to outdoor air pollution have demonstrated **enhanced frequencies of chromosome aberrations and micronuclei** in lymphocytes
- Studies of people exposed to polluted outdoor air in occupational settings or urban and industrial areas show **altered expression 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**.

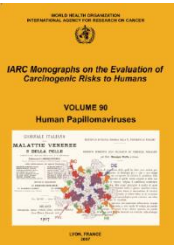
Overall evaluation

- **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**.

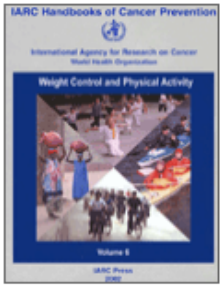
IARC Handbooks of Cancer Prevention

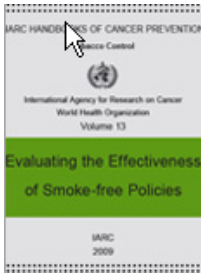






- Launch in 1995 to complement the IARC Monographs' evaluations of carcinogenic hazards with evaluations of cancer-preventive agents.
- Working procedures and evaluation scheme closely mirror those of the Monographs.
- Cancer Prevention HBs re-launched in 2014 with initial broader scope on primary and secondary prevention





International Agency for Research on Cancer

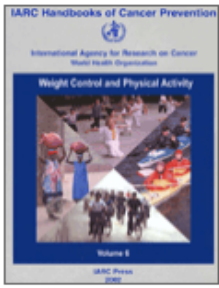
World Health Organization

History of IARC Handbooks of Cancer Prevention

IARC Sc Pub #139 Principles of Chemoprevention (Nov 1995)

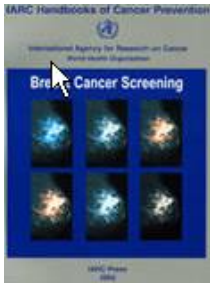
Preventive Agents

Vol 1 NSAIDs
Vol 2 Carotenoids
Vol 3 Vitamin A
Vol 4 Retinoids
Vol 5 Sunscreens
Vol 6 Weight Control & Physical Activity
Vol 8 Fruit and Vegetables
Vol 9 Cruciferous Vegetables,Isothiocyanates and Indoles
Vol 16 Avoidance of Body Fatness (amended Working Procedures)



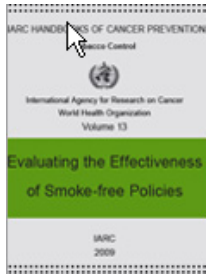
Screening

Vol 7 Breast Cancer Screening (Working procedures)
Vol 10 Cervix Cancer Screening
Vol 15 Breast Cancer Screening (amended Working Procedures)



Tobacco Control

Vol 11 Reversal of Risk after Quitting Smoking
Vol 12 Methods for Evaluating Tobacco Control Policies
Vol 13 Evaluating the Effectiveness of Smoke-free Policies
Vol 14 Effectiveness of Price and Tax Policies for Control of Tobacco



IARC Handbooks of Cancer Prevention

- Re-launch of the IARC Handbooks of Cancer Prevention Serie
  - Updated Working Procedures for Handbooks on Screening
  - Dedicated website – www.handbooks.iarc.fr

Future Opportunities:

- Screening
  - Cervical cancer
  - Others (prostate, lung, oral)
- Preventive agents
  - Weight control and physical inactivity
  - NSAIDS
  - Sunscreens
  - Vitamin D, Vitamin B

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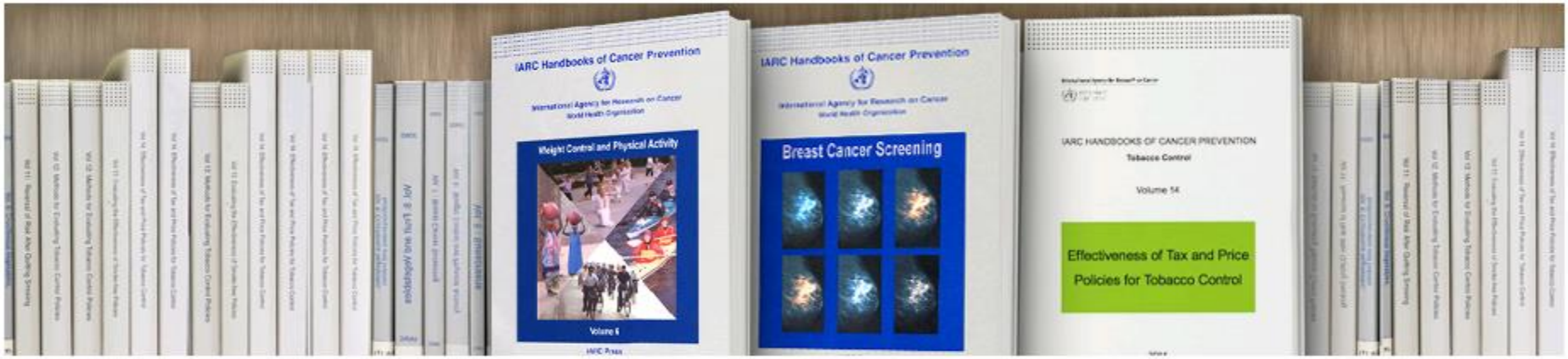


AGENTS AND ACTIVITIES EVALUATED BY THE IARC HANDBOOKS, VOLUMES 1-14

Agents (CAS Registry No.)	Volume (year)	Cancer-preventive activity		Overall evaluation	Organ site(s)
		Humans	Animals		
- Avoidance of weight gain		Sufficient	Sufficient		Oesophagus (adenocarcinoma), colon, breast (postmenopausal), endometrium, kidney (renal cell)
- Dietary restriction (reduction of all dietary components but with vitamin supplements)			Limited[f]		
- Intentional weight loss		Inadequate			
- Regular physical activity		Sufficient			Colon, breast (sufficient) Endometrium, prostate (limited)

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Breast-Cancer Screening — Viewpoint of the IARC Working Group

Béatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, Ph.D., Dana Loomis, Ph.D., Lamia Benbrahim-Tallaa, Ph.D., Véronique Bouvard, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D., for the International Agency for Research on Cancer Handbook Working Group

In November 2014, experts from 16 countries met at the International Agency for Research on Cancer (IARC) to assess the cancer-preventive and adverse effects of different methods of screening

was written or reviewed by someone who was not associated with the study being considered. All studies were assessed and fully debated, and a consensus on the preliminary evaluations was

Lauby-Secretan *et al*. (2015) *New England Journal of Medicine*
On-line publication, June 3rd
Print publication, June 11th

International Agency for Research on Cancer
World Health Organization

http://handbooks.iarc.fr/

Future Handbooks of Cancer Prevention

Cancer screening

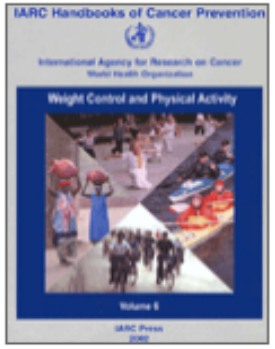
- **Cervical cancer screening** new approaches such as HPV testing, implementation of screening in the context of HPV vaccination.
- **Screening for cancers of the lung, and colon, prostate**

Preventive activities and agents

- **Physical activity**
- **Aspirin**
- **Sunscreens**
- **Vitamin D** and **vitamin B**

Tobacco Control Handbooks

- **Betel quid and areca nut control**



International Agency for Research on Cancer

World Health Organization

Why a new IARC Handbook on Breast Cancer Screening ?

- Previous IARC evaluation from 2002
  - Based mostly on randomized controlled trials (evidence on efficacy)
- Many new studies of organized screening programmes (evidence on effectiveness)
- Recent improvements in treatment outcomes for late-stage breast cancer
- Concerns regarding overdiagnosis
- Evaluation of other imaging techniques
- Evaluation of screening of women at high-risk
- New studies on screening by physical examinations (clinical or self examination)

Screening with mammography
(A) Beneficial effects

Age range (years)	Reduction in breast cancer mortality	
	Efficacy	Effectiveness
40–44	*Inadequate*	*Limited*
45–49		*Limited*
50–69	*Sufficient*	*Sufficient*
70–74	*Inadequate*	*Sufficient*
Optimal screening interval	*Inadequate*	

Screening with mammography (B) Adverse effects

Possible adverse effects

Mammography screening detects breast cancers that would not have been diagnosed if the women had not been screened (overdiagnosis).	*Sufficient*
The risk of radiation-induced cancer from mammography in women aged 50 years and older is substantially outweighed by the reduction in breast cancer mortality from mammography screening.	*Sufficient*
Having a false-positive mammogram has short-term negative psychological consequences.	*Sufficient*

- EUROSCREEN, 1-10%
- RCTs, 4-11%
- Higher in other studies

- 1-10 / 10 000
- 100 x smaller than deaths prevented by screening

Conclusions

- Screening by mammography
  - Sufficient evidence for reduced mortality for age 50-74 years
  - Limited evidence for women age 49 or below
  - No possible determination of the optimal screening interval
  - Sufficient evidence for adverse effect of overdiagnosis
- Other imaging techniques
  - No clear benefit from adjunct ultrasound
  - Sufficient evidence for beneficial effects of tomosynthesis radiation dose needs to be reduced (2D/3D)
- High-risk women
  - No clear evidence for any procedures in any type of high-risk

Breast cancer screening by physical examination

No data available (on-going studies)

- Positive results in 3 studies
- Not evaluated in WHO guidelines

	Reduction in breast cancer mortality	Shift in the stage distribution of tumours detected towards a lower stage	Reduction in the rate of interval cancers
Clinical breast examination	*Inadequate*	*Sufficient*	*n.d.*
Teaching breast self-examination	*Inadequate*	*n.d.*	*Inadequate*
Practicing breast self-examination competently and regularly	*Inadequate*	*n.d.*	*n.d.*

- Same studies as for vol. 7
- Too low compliance to allow evaluation of effectiveness

Impact of Monographs & Handbooks

Collaboration of Monographs 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 2010/2013
- National Agencies, e.g. NTP Report on Carcinogens, ANSES

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)
- Implementation of national screening programs

Increase Capacity

- Training linked to research
- Fellowships
  - IARC post-doctoral fellowships; bilateral partnerships
  - Senior Visiting Scientists
  - Expertise Transfer Fellowships
- Training courses
  - IARC Summer School in Cancer Epidemiology
  - Other courses in Lyon and regionally
  - E-Learning